Tetrahedron Letters,Vol.26,No.40,pp 4887-4890,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

AN UNUSUAL DICHOTOMY IN THE REGIOSELECTIVITY OF A METAL CATALYZED VERSUS THERMAL ENE REACTION

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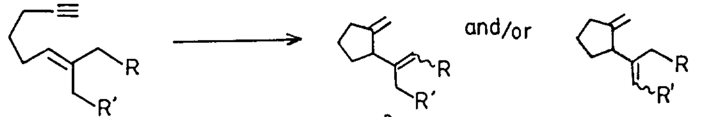
SUMMARY: A Pd(+2) catalyzed cyclization of a 1,6-enyne complements a thermal Alder ene reaction; a rationale invoking a remote binding site is proposed.

In the isomerization of enynes such as 1 to 1,4-dienes (eq. 1) two possible regioisomeric products 2 and 3 may result. Because of the importance of this question in utilizing such methodology in five membered ring synthesis, we explored what factors may affect the regioselectivity. We wish to report that



1 2 3 (1)

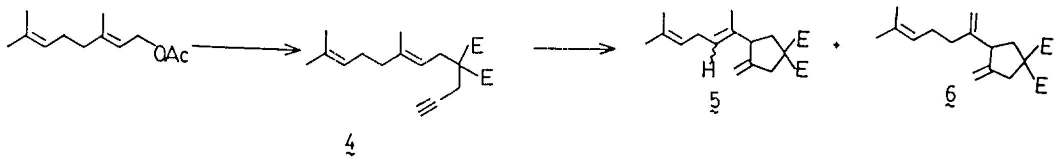
quite different regioselectivity arises in a thermal versus a metal catalyzed[1] isomerization. Furthermore, in the latter case, there is a very subtle dependence of regioselectivity on the structure of the substrate.

To probe this question, we prepared dienyne 4,[2] which was easily obtained from the palladium(O) catalyzed alkylation of geranyl acetate with dimethyl propargylmalonate [5 mol % $(Ph_3P)_4Pd$,THF,NaH,reflux,16 h].[3] This substrate competes a methyl and a methylene group in such an isomerization.

Thermally induced cyclization was examined to determine the intrinsic selectivity toward the types of hydrogens. Surprisingly,[4] flash vacuum thermolysis (FVT) at 625^{o} provided triene 5,[2] which was derived through abstraction of the hydrogen from the methylene group exclusively. In marked contast, palladium(+2) catalyzed cyclization (5 mol % catalyst, C_6D_6, 66^{o}, 1 h) gave, as the principal product, the triene derived from abstraction of the hydrogen from the methyl group, i.e. 6,[2] as summarized in Scheme 1. Furthermore, the ratio of the regioisomers was found to be highly influenced by the presence of phosphine ligands. The presence of any phosphine ligand decreased the regioselectivity. Reaction in the absence of any additional ligands provided very high ratios of triene 6 to 5.

A very slightly different substrate, enyne 7,[2] prepared by palladium(O) catalyzed alkylation of (E)-1-acetoxy-3,7-dimethylhept-2-ene with dimethyl propargylmalonate (5 mol $Pd(PPh_3)_4$, NaH, THF, 20 h reflux) as in Scheme 2, was

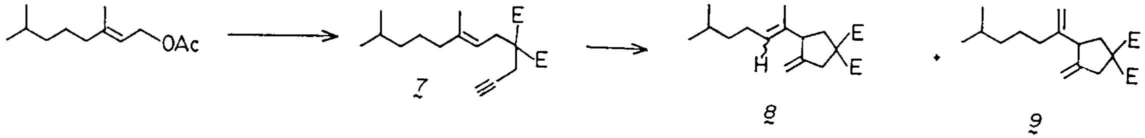
Scheme 1



Conditions	Yield	Ratio(5:6)[5]
625°/FVT	83%	1.0[6a]: 0.0
5 mol%[(o-tol)$_3$P]$_2$Pd(OAc)$_2$	-	1.0[6b]: 2.4
5 mol%(Ph$_3$P)$_2$Pd(OAc)$_2$	73%	1.0[6b]: 2.9
5 mol%Pd(OAc)$_2$	80%	1.0[6b]: 16.9

also examined. The thermally induced cyclization again proved to be highly selective. Only, 8[2] was obtained. In contrast to the cyclizations of 4,

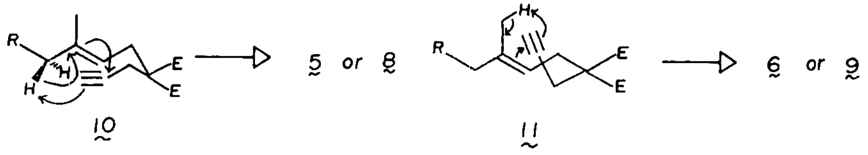
Scheme 2



Conditions	Yield	Ratio (8:9)[7]
575°/FVT	80%	1.0[8a]: 0.0
5 mol%[(o-tol)$_3$P]$_2$Pd(OAc)$_2$	70%	1.0[8b]: 1.4
5 mol%(Ph$_3$P)$_2$Pd(OAc)$_2$	70%	1.0[8c]: 2.7
5 mol%Pd(OAc)$_2$	70%	1.0[8d]: 1.5

palladium (+2) catalyzed cyclizations of 7 exhibit low selectivity. The ratio of 8 to 9[2] was nearly statistical. Furthermore, phosphine ligands had little or no effect on regioselectivity.

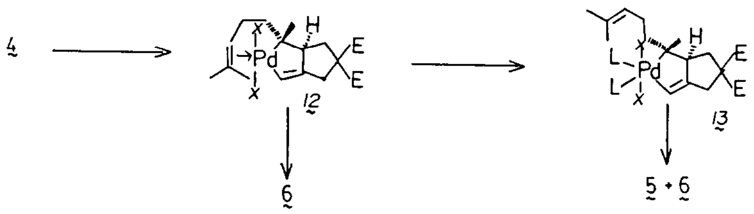
The exceptional regioselectivity of the thermal reaction may be understood on the basis of the two reacting conformations 10 and 11 in which the envelope conformation depicted in 10 minimizes non-bonded interactions compared to 11. On the other hand, the metal catalyzed reaction shows a striking dependence on



substrate. Any explanation of these latter reactions must account for 1) the identical reactivity of 4 and 7 in the thermal reactions but not in the metal catalyzed reactions, 2) the metal catalyzed reactions showing a regioselectivity that does not reflect the intrinsic conformational bias to form 5 and 8 as demonstrated by the thermal reactions, 3) the bias for 4 to generate 6 whereas 7, which only lacks a double bond far from the reaction center, shows no selectivity, and 4) the role of phosphines in affecting the regioselectivity in the case of 4 but showing no effect in the case of 7.

These results are explained if one considers the proposed metallocyclopentene intermediates 12 or 13 (see Scheme 3). Whereas, the thermal reaction only reflects the conformational constraints of the reaction centers and the tether connecting them (and thus the lack of dependence of regiochemistry on substrate 4 or 7), the metal opens the possibility that distant functionality as present in 4 but not 7 may also become involved. In the absence of phosphines, the coordinatively unsaturated metal may complex with the remote double bond as in 12 which both stabilizes the metal and decreases the flexibility of the methylene side chain. The β-hydride elimination which follows is known to be a *cis* process.[7] In the complexed form 12 the methylene hydrogens cannot properly align themselves and thus elimination occurs toward the methyl group. However, upon addition of more strongly coordinating external ligands, such as phosphines,

Scheme 3



competitive coordination may disrupt the chelate as in 13. The additional rotational freedom created allows for correct alignment of the methylene as well as the methyl hydrogens.

Extrapolation of the notion of conformational control by remote binding sites, an important aspect of enzymes, to transition metal catalyzed reactions offers additional opportunities for controlling subtle selectivities. In the present case, not only has the metal catalyst significantly enhanced the rate of reaction but it has possibly also altered the reactive conformation and thereby the regioselectivity. The possibility that other distal binding sites may affect the selectivity of such processes forms the basis for future studies.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs. Mark Lautens thanks NSERC of Canada for a postgraduate scholarship.

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5. Ratio determined by VPC (5% SE-30, 8 ft x 1/8", 150^{o} - 5 min programmed at 10^{o}/min to 200^{o}) with retention times of 10.1, 10.3 and 10.9 min for 5 E (or Z), 6 and 5 Z (or E) respectively. E and Z isomers have not been differentiated. Ratios are kinetic distributions.

6. a) Ratio of geometrical isomers = 1.2:1; b) Only one isomer.

7. Ratios determined by VPC as in ref. 5 with retention times of 8E (or Z), 9, and 8Z (or E) of 6.1, 6.5 and 6.8 min. E and Z isomers have not been differentiated.

8. a) Ratio of geometrical isomers = 1.2:1; b) ratio = 4:1; c) ratio = 2:1; d) ratio = 1.5:1.

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10. Spectral data for 5 (1:1.16 ratio of Z:E or vice versa): NMR (270 MHz, $CDCl_3$) δ5.29 (1H, m), 5.10 (1H, m), 4.97 (0.55 H, m), 4.93 (0.45 H, m), 4.75 (0.55 H, m), 4.71 (0.45 H, m), 3.74 (2.35 H, s), 3.72 (3.30 H, s), 3.71 (1.35 H, s), 3.20-3.00 (2H, m), 2.90 (1H, m), 2.70 (2H, m), 2.46 (1H, m), 2.12 (1H, m), 1.70 (3H, s), 1.65 (1.65 H, s), 1.64 (1.35 H, s), 1.58 (1.65 H, s), 1.52 (1.35 H, s). IR ($CDCl_3$): 1730, 1655 cm^{-1}. Calcd. for $C_{18}H_{26}O_2$: 306.1834. Found: 306.1830.

Spectral data for 6: ^{1}H NMR: δ5.18 (1H, bt, J=6.4 Hz), 5.00 (1H, s), 4.95 (1H, s), 4.91 (2H, s), 3.50 (1H, m), 3.31 (3H, s), 3.28 (3H, s), 3.50-2.70 (3H, m), 2.35 (1H, Z,J=9.5 Hz), 2.18 (2H, m), 2.05 (2H, m), 1.65 (3H, s), 1.54 (3H, s). ^{13}C NMR: 167.9, 149.7, 148.9, 131.7, 124.1, 111.5, 108.2, 58.7, 52.7, 50.8, 41.0, 39.3, 32.4, 26.7, 25.6, 17.7. IR ($CDCl_3$): 1731 cm^{-1}. Calcd. for $C_{18}H_{26}O_2$: 306.1824. Found: 306.1838.

(Received in USA 3 June 1985)