PALLADIUM(0)- AND NICKEL(0) CATALYZED "METALLO-ENE-TYPE" CYCLIZATIONS: STEREODIRECTING RESIDENT CHIRALITY.

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<u>Abstract</u>: Trans-cyclization products were selectively formed from C-6-substituted acetoxy-octadienes only via Ni(0) catalysis ($1 \rightarrow 2$) and from C-4-substituted analogs under Pd(0)- and Ni(0) catalysis ($7, 8 \rightarrow 9$). C-5-Substituted precursors gave mixtures of diastereoisomers. Nickel(0) catalyzed allylation/methoxycarbonyl-ation of iodo diene 11 afforded 2-oxa-bicyclo[3.3.0]octanone 12 with highly diastereoselective generation of three stereogenic centers.

Recently developed intramolecular Pd(0)- and Ni(0) catalyzed alkene allylations (I, II \rightarrow III and/or IV), coupled with β -elimination (III, IV \rightarrow V) or methoxycarbonylation (III \rightarrow VI, IV \rightarrow VII), show interesting potential for the stereocontrolled synthesis of various carbo- and heterocycles (Scheme 1).¹



In this context, we studied the topological influence of pre-existing (C-6, C-5 or C-4) over developing (C-3, C-7) stereogenic centers in the carbometalation step $\underline{\text{VIII}} \rightarrow \underline{\text{IX}}$ (Scheme 2).

Scheme 2



So far only a few scattered reports have dealt with this issue.² For example, Pd(0) catalyzed cyclization of allylacetal ether <u>1a</u>, (X=OTHP) gave a 1:1-mixture of *cis*-and *trans* disubstituted tetrahydrofurans <u>2a</u> and <u>3a</u> (Scheme 3, Table 1). ^{2a}

Scheme 3



Table 1 Cyclizations of C(6)-Substituted Acetoxy (Tetrahydropyranyloxy) octadienes $1 \rightarrow 2 + 3^{3}$

		x	Y	R	"Catalyst" ^{a)} (mol %)	Solvent	Temp [°C] (Time [h])	Yield [%] 2 + 3	Ratio 2 / 3
1	a	OTHP	0	n-C ₆ H ₁₃	Pd (5)	AcOH	80 (2)	75	50 : 50
2	a	OAc	ο	n-C6H13	Pd (5)	AcOH	80 (3)	62	52:48
3	a	OAc	0	n-C6H13	Ni (10)	THF	20 (15)	79	>99 : <1
4	b	OAc	СH ₂	CH ₂ OBn	Pd (10)	AcOH	80 (4)	67	72:28
5	b	OAc	СН ₂	CH ₂ OBn	Ni (10)	THF	20(1)/51(24)	88	97.3 : 2.7

a) Catalyst prepared in situ from Pd(dba)₂, PPh₃(1:3) or from Ni(COD)₂, dppb (1:1) except entry 1 where Pd(PPh₃)₄ was used; the listed mol % refer to the metal.

This disappointing lack of stereoselectivity was also observed on subjecting acetate <u>la</u> (X=OAc) to similar reaction conditions (entry 2). However, we were pleased to find exclusive transformation of the same precursor <u>la</u> (X=OAc) to the *trans* product <u>2a</u> when employing a nickel(0) catalyst (entry 3).^{1b} Comparison of entries 4 and 5 also shows a drastically improved "1,4-stereodirecting effect" of a C-6 substituent (CH₂OBn) in the nickel- *versus* palladium-ene cyclization of 1-acetoxy-2,7-octadiene <u>lb</u>, to provide *trans*-cyclopentane <u>2b</u> as the predominant product (97.3%, entry 5).

We then examined the related ring closure reaction of C-5 substituted 1-acetoxy-2,7-octadienes 4. Previously, an *all-cis*-stereoselective catalytic Pd-ene cyclization of 1-acetoxy-5-phenylsulfonyl-2,7,9-decatriene has been reported.^{2b} In contrast, no, or only marginal, topological control was exerted by the phenylsulfonyl group in the Pdand Ni catalyzed processes $4a \rightarrow 5a + 6a$ (Scheme 4, Table 2).



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Table 2	Cyclizations (of C(5)-	Substituted	Acetoxy	yoctadienes	4 → 5	5+6	2

		R	"Catalyst" ^{a)} (mol %)	Solvent	Temp [°C] (Time [h])	Yield [%] 5 + 6	Ratio 5 / 6
6	a	SO ₂ Ph	Pd (5)	AcOH	80 (1)	73	51 : 49 ^{b)}
7	a	SO ₂ Ph	Ni (10)	THF	20 (24)	78	68:32 ^{b)}
8	b	CH ₂ OBn	Pd (7)	AcOH	80 (6)	67	52:48
9	b	CH ₂ OBn	Ni (43)	THF	20(2)/52(24)	73	77:23

a) Comments as in Table 1; b) Stereoisomers not assigned.

Slightly better results were obtained with the CH_2OBn -substituted precursor <u>4b</u> giving cyclopentanes <u>5b</u> + <u>6b</u> in a ratio which increased from 52:48 to 77:23 when replacing Pd- by Ni catalysis (entries 8,9).

C-4-substituted acetoxydienes 7 and 8, on the other hand, cyclized with significantly higher stereochemical control (Scheme 5, Table 3).





Table 3 Cyclizations of C(4)-Substituted Acetoxydienes 7 or $8 \rightarrow 9 + 10^{-3}$

		Starting Diene	Y	R	"Catalyst" ^{»)} (mol %)	Solvent	Temp [°C] (Time [h])	Yield [%] 9 + 10	Ratio 9 / 10
10	a	7	0	n-C ₆ H ₁₃	Pd (10)	AcOH	80 (1)	83	88:12
11	a	7	0	n-C6H13	Ni (10)	THF	20 (8)	85	97.4 : 2.6
12	b	8	CH ₂	CH ₂ OBn	Pd (7)	AcOH	80 (6)	72	92.6 : 7.4
13	b	8	СН ₂	CH ₂ OBn	Ni (40)	THF	20(1)/53(23)	74	97.7 : 2.3
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a) Comments as in Table 1.

Thus, trans-tetrahydrofurans and cyclopentanes 2 were predominantly obtained even via the palladium catalyzed protocol (entries 10,12). Preferential formation of 2 over 10 was further enhanced (up to a ratio of 97.7/2.3) in the corresponding "nickel-ene" reactions (entries 11, 13).

The above mentioned studies have ignored the chirality of developing center C-7 given its planarization in the final β -elimination step IX \rightarrow X (Scheme 2). Nevertheless, considering previous reactions of achiral substrates we expected "nickel-ene cyclization"/carbonylation sequences <u>VIII</u> \rightarrow IX \rightarrow XI to provide a stereocontrolled, synthetically useful approach to bicyclic ring systems.

Indeed, stirring 6-hexyl-1-iodo-5-oxa-2,7-octadiene (11) with Ni(COD)₂/dppb (1:1, 25 mol%) under CO (1 atm, THF/MeOH-4:1, RT, 17 h) afforded exclusively 2-oxa-bicyclo[3.3.0]octanones 12 and 13 in a 89:11-ratio (68%) (Scheme 6).

Scheme 6



It thus follows that bicyclization of 11 involves a ~100% stereocontrolled nickel-ene step.

The observed stereodirecting effects are consistent with two mechanistic alternatives: allylation of the alkene unit by a (E)- σ -allyl- ("ene-reaction", A, C), or syn- π -allylmetal partner (B, D, Scheme 7). ^{1d}

Scheme 7



Comparison of $exo-(\underline{A}, \underline{B})$ versus endo-orientations $(\underline{C}, \underline{D})$ reveals a steric crowding which is opposite with the C-6- $(\mathbb{R}^6, \mathbb{R}^6)$ but parallel with the C-4- (\mathbb{R}^4) and unpredictable with the C-5- substitutents $(\mathbb{R}^5, \mathbb{R}^5)$. In this respect, it is noteworthy that most "palladium-ene" cyclizations exhibit low endo/exo preferences,⁴ different to the nickel-catalyzed reactions which proceed generally in a clean exo-manner (e.g., $11 \rightarrow 12 + 13$). ^{1b,1d} Therefore it does not surprise that synthetically useful inductions were here observed <u>only</u> with C-4- substituents when employing Pd-catalysis but with C-4- and C-6- substituents in the nickel-catalyzed version.

The scope and implications of these results are being further explored in our laboratories.

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REFERENCES AND NOTES

- Examples and definitions of Pd- and Ni catalyzed "metallo-ene cyclizations": a) W. Oppolzer, J.-M. Gaudin, Helv. Chim. Acta <u>1987</u>, 70, 1477; W. Oppolzer, R.E. Swenson, W. Pachinger, *ibid.*, <u>1989</u>, 72, 14; W. Oppolzer, J.-M. Gaudin, T.N. Birkinshaw, Tetrahedron Lett. <u>1988</u>, 29, 4705; b) W. Oppolzer, M. Bedoya-Zurita, C.Y. Switzer, *ibid.*, <u>1988</u>, 29, 6433; W. Oppolzer, T.H. Keller, M. Bedoya-Zurita, C. Stone, *ibid.*, <u>1989</u>, 30, 5883; c) K. Yamamoto, M. Terakado, K. Murai, M. Miyazawa, J. Tsuji, K. Takahashi, K. Mikami, Chem. Lett. <u>1989</u>, 955; d) Review: W. Oppolzer, Angew. Chem. <u>1989</u>, 101, 39; Angew. Chem. Int. Ed. Engl. <u>1989</u>, 28, 38.
- a) W. Oppolzer, J.-M. Gaudin, M. Bedoya-Zurita, J. Hueso-Rodriguez, T.M. Raynham, C. Robyr, *Tetrahedron Lett.* <u>1988</u>, 29, 4709; b) B.M. Trost, J.I. Luengo, J. Am. Chem. Soc. <u>1988</u>, 110, 8239; c) E. Negishi, S. Iyer, C.J. Rousset, *Tetrahedron Lett.* <u>1989</u>, 30, 291; d) K. Hiroi, Y. Kurihara, J. Chem. Soc. Chem. Commun. <u>1989</u>, 1778; e) c.f., a stereodirecting effect of a C-6-methyl group on a magnesium-ene cyclization: W. Oppolzer, E.J. Jacobsen, *Tetrahedron Lett.* <u>1986</u>, 27, 1141.
- 3) All <u>new compounds</u> were <u>characterized</u> by IR, ¹H-NMR, ¹³C-NMR and MS. Racemic acyclic <u>precursors</u> were <u>prepared</u> as follows. *Reaction sequences*: <u>1a</u> (X=OAc) from <u>1a</u> (X=OTHP) ^{2a} via a,b). <u>1b</u> from methyl cyanoacetate via c-k,f,b). <u>4a</u> from the corresponding gem-disulfone ^{1b} via 1). <u>4b</u> from dimethyl malonate via m-p,i,a,b). <u>7a</u> from heptanal via q,m,r,s,b). *Reaction conditions*: a) PPTS/MeOH; b) Ac₂O/Et₃N/DMAP/CH₂Cl₂; c) NaH/2-(2-bromoethyl)-1,3-dioxolane/DMF; d) NaBH₄/t-BuOH/MeOH; e) TBDMSOTf/Et₃N; f) DIBAL-H/Et₂O; g) Ph₃PMeI/t-BuOK/THF; h) Bu₄NF/THF; i) NaH/BnI/THF or DMF; j) PPTS/acetone; k) (MeO)₂POCH₂COOMe/DBU/LiCl/MeCN; 1) Na/Hg 5%/AcOH/THF/MeOH/-10°C; m) NaH/allyl bromide/DMF; n) NaH/Pd(PPh₃)₄/1-chloro-4-tetrahydropyranyloxy-2-butene/THF; o) NaCl/aq DMSO/160°C; p) LiAlH₄/THF; q) 1,3-dithiane/BuLi/THF; r) MeI/aq MeCN/ s) vinylmagnesium bromide/Et₂O. The <u>configurations of cyclization products</u> were assigned by means of NOE evidence.
- 4) For highly endo-selective "palladium-ene" cyclizations see ref 1b,2a