Tetrahedron Letters,Vol.30,No.43,pp 5883-5886,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

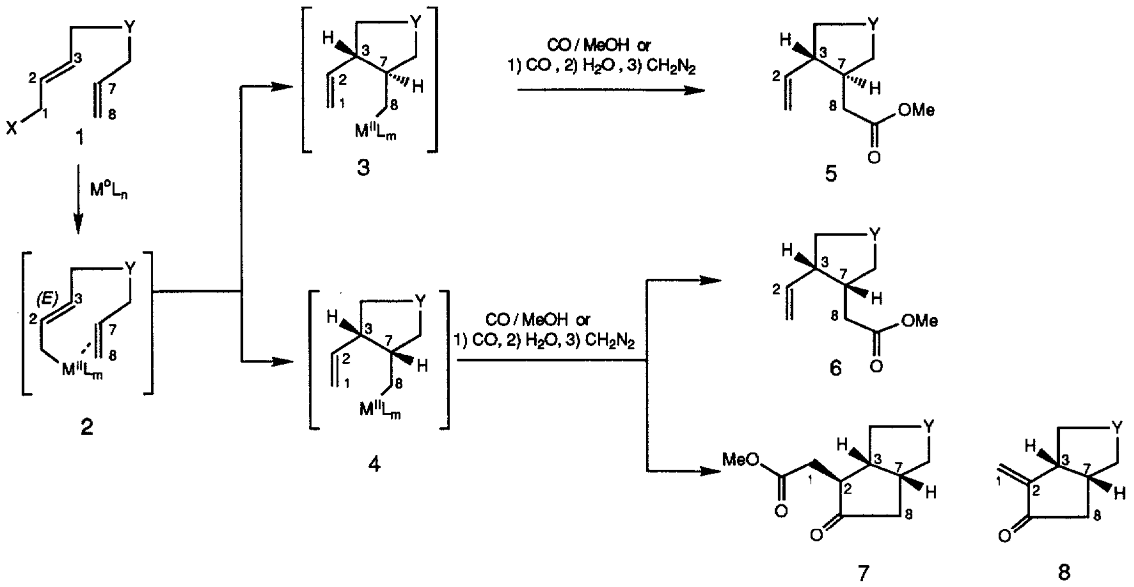
DIASTEREOCONTROLLED NICKEL(0)- AND PALLADIUM(0) CATALYZED "METALLO-ENE-TYPE" CYCLIZATIONS/CARBONYLATIONS

Wolfgang Oppolzer*, Thomas H. Keller, Manuel Bedoya-Zurita and Charles Stone
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Abstract: Treatment of 1-iodo{acetoxy}-2,7-octadienes 1 and 1-iodo{acetoxy}-2-en-7-ynes 12 with $Ni(COD)_2$/dppb (THF/MeOH) or $Pd(dba)_2/PPh_3$ (AcOH, then CH_2N_2) under carbon monoxide furnished chemo- and stereoselectively either bicyclic ketoesters 7 (from 1) and 15 (from 12) or *trans*-substituted monocyclic products 5 (from 1) and 14 (from 12), but *all-cis*-hexahydroindole 11 (from acetoxycyclohexene 9).

Previously we have reported $Ni(CO)_3PPh_3$-catalyzed "metallo-ene cyclization"/carbonylation sequences 1a (X = I) → 6a+7a, 12a (X = I) → 14a and 12c (X = I) → 14c+15c (Schemes 1, 3; Tables 1, 2, entries 1, 9 and 12) [1,2].

Scheme 1



A more recent communication described the related palladium(0)-catalyzed conversion of 1 (Y = CH_2, X = OAc) into the free carboxylic acid of 5 (Y = CH_2, 50%) together with bicyclic enone 8 (Y = CH_2, 20%) and a regioisomer (10%) [3].

Before employing the "metallo-ene"/carbonylation protocol in synthesis we addressed the following issues:

1) verify if the nickel catalyzed process (2 → 4) is generally *cis*-stereoselective;
2) improve the *trans*-diastereoselectivity of the "palladium-ene" step 2 → 3 [4];
3) direct the reaction sequence more distinctly either towards monocyclization (1 → 6, 12 → 14) or, bicyclization (1 → 7, 12 → 15).

Table 1 Ni(0)- and Pd(0) Catalyzed Allylation/Carbonylation of 1-Iodo{Acetoxy}-2,7-octadienes 1

		Y	X	Catalyst a)5)	Reaction conditions b)5) (Time [h])	Product 6) Yields [%] 5	6	7 c)	8
1	a	NTs	I	$Ni(CO)_3PPh_3$	A (20)	1	28	47 (4:1)	-
2	a	NTs	I	$Ni(COD)_2$/dppb	A (12)	-	-	80 (10:1)	-
3	a	NTs	OAc	$Pd(dba)_2/PPh_3$	B (12)	52.5	0.5	16 (8:1)	-
4	a	NTs	OAc	$Pd(dba)_2$/dppb	B (12)	16 (87) d)	-	-	-
5	b	$NCOCF_3$	OAc	$Pd(dba)_2/PPh_3$	B (6)	70	-	-	-
6	c	$C(CO_2Me)_2$	I	$Ni(CO)_3PPh_3$	A (36)	3.2	14.8	62 (4:1)	-
7	c	$C(CO_2Me)_2$	I	$Ni(COD)_2$/dppb	A (30)	3.7	4.3	66 (4:1)	-
8	c	$C(CO_2Me)_2$	OAc	$Pd(dba)_2/PPh_3$	B (20)	62.4	0.6	10 (3:1)	5

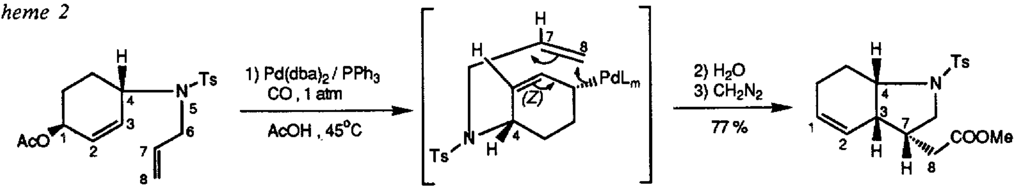
a) $Ni(CO)_3PPh_3$ prepared before use 7); other catalysts formed *in situ* from $Pd(dba)_2$, PPh_3 (1:3) and dppb (1:1) under CO or, by addition of dppb to $Ni(COD)_2$ (1:1) under CO. b) A : 25 mol% Ni(0), THF/MeOH 4:1, CO (1 atm r.t.; B : i) 10 mol% Pd(0), HOAc, CO (1 atm), 45°C; ii) addition of H_2O, 40°C, 1 h., evaporation; iii) CH_2N_2, CH_2Cl_2. c) Ratio of 7 and its C(2)-epimer in parenthesis. d) Yield based on recovered **1a** in parenthesis.

Indeed, changing the ligands around the nickel atom improved significantly the product ratio 7/6. Thus, stirring iodide 1a with a catalyst, prepared *in situ* from $Ni(COD)_2$ and dppb (0.25 mol-equiv. each), in THF/MeOH (4:1) under carbon monoxide (1 atm) at r.t. gave bicyclic ketoester 7a 6) (10:1-mixture of C(2)-epimers) in 80% yield and no trace of pyrrolidines 5 or 6 (entry 2). Analogous treatment of acetate 1a with $Pd(dba)_2/PPh_3$ in acetic acid under CO at 45°C, addition of water and esterification (CH_2N_2) yielded a mixture of products 5/6/7 (76 : 0.8 : 23.2); after chromatography, pyrrolidines 5a/6a (97 :1) were obtained in 53% yield (entry 3). Exclusive formation of the *trans*-substituted pyrrolidine 5a 6) was achieved on using $Pd(dba)_2$/dppb (0.1 mol-equiv. each) but with low conversion (entry 4). However, subjecting the *N*-trifluoroacetyl precursor 1b to the usual "$Pd(dba)_2/PPh_3$-catalyzed" reaction conditions furnished *trans*-pyrrolidine 5b 6) (70%) as a single product.

Similar (although less dramatic) trends were observed with malonates 1c i.e., predominant formation of either bicyclic product 7c 6) (66%) employing $Ni(COD)_2$/dppb or, monocyclic *trans*-cyclopentane 5c 6) (62%) using $Pd(dba)_2/PPh_3$ (entries 7, 8). The favoring of the C(8)/C(2)-*trans* relation (1 → 2 → 3 → 5) in the Pd(0)-catalyzed process reflects the *(E)*-configuration of the allylpalladium species 2 8).

A *(Z)*-allylpalladium intermediate, on the other hand, was expected to provide only C(8)/C(2)-*cis* products 8). Indeed, treatment of acetate 9 2) with $Pd(dba)_2/PPh_3$ under CO in AcOH, addition of water and esterification afforded exclusively *all-cis*-hexahydroindole 11 6) (Scheme 2).

Scheme 2



9 10 11

Intramolecular allylnickel or -palladium/alkyne insertion-carbonylation sequences (Scheme 3, Table 2) resulted in a highly stereoselective generation of the C(7)/C(8) olefinic bond regardless of the metal and consistent with a suprafacial metallo-allylation of the acetylene unit. However, the product ratio 14/15 was clearly dependent on the choice of metal and ligands.

Scheme 3

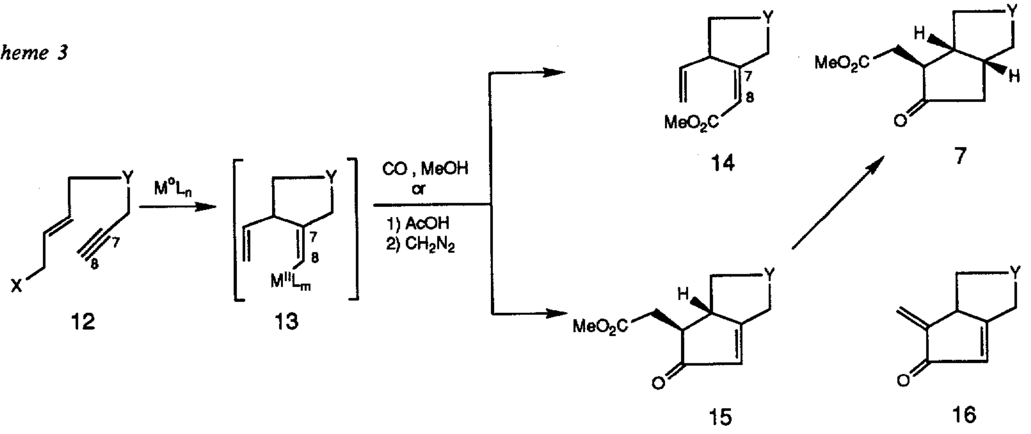


Table 2 Nickel(0)- and Palladium(0) Catalyzed Allylation/Carbonylation of 1-Iodo{Acetoxy}octa-2-en-7-ynes 12

		Y	X	Catalyst[a]	Reaction conditions[a] (Time [h])	Product Yields [%]		
						14	15[a]	16
9	a	NTs	I	Ni(CO)$_3$PPh$_3$	A (20)	69	-	-
10	a	NTs	I	Ni(COD)$_2$/dppb	A (12)	23	57 (20:1)	-
11	a	NTs	OAc	Pd(dba)$_2$/PPh$_3$	B (2)	13	50 (7:1)	16
12	c	C(CO$_2$Me)$_2$	I	Ni(CO)$_3$PPh$_3$	A (20)	41	36 (>25:1)	-
13	c	C(CO$_2$Me)$_2$	I	Ni(COD)$_2$/dppb	A (15)	-	87 (27:1)	-
14	c	C(CO$_2$Me)$_2$	OAc	Pd(dba)$_2$/PPh$_3$	B (7)	-	74 (11:1)	3

a) Comments as in Table 1.

Thus, Ni(CO)$_3$PPh$_3$-catalyzed allylation/methoxycarbonylation furnished pyrrolidine 14a (69%) as the sole product from iodide 12a [2)] which, on the other hand, employing Ni(COD)$_2$/dppb provided bicyclic enone 15a [6)] as the major product (57%) (entries 9, 10). Bicyclization of acetate 12a to 15a was also favored over monocyclization (12a → 14a) using Pd(dba)$_2$/PPh$_3$ in acetic acid (entry 10). More strikingly, malonates 12c (X = I) and 12c (X = OAc) gave only bicyclization product 15c [2)] utilizing Ni(COD)$_2$/dppb and Pd(dba)$_2$/PPh$_3$, respectively.

It follows that *cis/trans*-diastereoselectivities (2 → 3 or 4) as well as monocyclization/bicyclization product ratios (6/7 or 14/15) depend on the nature of the bridge moiety Y but more prominently on the catalyst. For controlling the relative configuration of stereogenic centers C(2)/C(3) in products 7 and 15 it seems that the Ni(COD)$_2$/dppb protocol is superior over the Pd(dba)$_2$/PPh$_3$ alternative. Stereoselective functionalizations of the enone moiety in products 15 offers interesting perspectives as indicated by the catalytic hydrogenation of 15c (Pd/C, H_2, EtOH) yielding bicyclo[3.3.0]octanone 7c (95%). Simple 2,7-dienes or 2-en-7-ynes are thus readily converted into annulated 5-membered ring systems involving the regio- and stereoselective formation of four carbon-carbon bonds and of three stereogenic centers which may be of value in synthesis.

Acknowledgements: Financial support of this work by the *Swiss National Science Foundation*, *Sandoz AG*, Basel, and *Givaudan SA*, Vernier is gratefully acknowledged. We also thank Mr. *J.P. Saulnier*, Mr. *A. Pinto* and Mrs. *D. Clément* for NMR and MS measurements.

REFERENCES AND NOTES

1) Examples and definition of transition-metal catalyzed "metallo-ene cyclizations": a) W. Oppolzer, J.-M. Gaudin, *Helv. Chim. Acta* 1987, *70*, 1477; W. Oppolzer, *Pure & Appl. Chem.* 1988, *60*, 39; W. Oppolzer, R.E. Swenson, W. Pachinger, *Helv. Chim. Acta* 1989, *72*, 14; b) Review: W. Oppolzer *Angew. Chem.* 1989, *101*, 39; *Angew. Chem. Int. Ed. Engl.* 1989, *28*, 38.

2) W. Oppolzer, M. Bedoya-Zurita, C.Y. Switzer, *Tetrahedron Lett.* 1988, *29*, 6433.

3) K. Yamamoto, M. Terakado, K. Murai, M. Miyazawa, J. Tsuji, K. Takahashi, K. Mikami, *Chem. Lett.* 1989, 955. We thank Professor K. Yamamoto for kindly communicating to us this work prior to publication.

4) For the first examples of kinetically controlled *cis/trans*-selectivities of "palladium-ene" cyclizations see: W. Oppolzer, J.-M. Gaudin, M. Bedoya-Zurita, J. Hueso-Rodriguez, T.M. Raynham, C. Robyr, *Tetrahedron Lett.* 1988, *29*, 4709.

5) The following procedures are representative: Procedure A: To avoid handling toxic $Ni(CO)_4$ the latter was prepared *in situ* as follows. A solution of freshly prepared $Ni(COD)_2$ (0.25 mol-equiv.) in degassed THF/MeOH (4:1) was stirred under CO (1 atm) at 0°C for 30 min. The colorless solution of $Ni(CO)_4$ was warmed to r.t.. Addition of dppb (0.25 mol-equiv. in THF/MeOH), stirring for 30 min, followed by addition of allyl iodide 1 or 12, stirring under CO (1 atm) at r.t. for 12-30h, workup and flash chromatography yielded cyclized product(s). Procedure B: A solution of allyl acetate 1, 9 or 12 in degassed AcOH was added to a mixture of $Pd(dba)_2$ (0.1 mol-equiv.) and PPh_3 (0.3 mol-equiv.) [or dppb (0.1 mol-equiv.)] under argon. After evacuation at <0°C the flask was filled with CO (1 atm). Stirring the mixture at 45°C for 2-36h (until disappearance of starting material), addition of water, stirring at 45°C for 1h, evaporation and treating the residue with CH_2N_2 (excess) in CH_2Cl_2, r.t., evaporation and chromatography gave cyclized product(s).

6) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. The configuration of cyclization products was established *via* NOE measurements [2,4] as exemplified by that of 11 ($CDCl_3$): $\delta H_7 = 2.10$(*m*, 1H, spin saturation at $\delta = 3.07 \rightarrow$ NOE: 12.2%); $\delta H_3 = 3.07$(*m*, 1H); $\delta H_4 = 3.75$(*m*, 1H, spin saturation at $\delta = 3.07 \rightarrow$ NOE: 11.2%)

7) W.F. Edgell, M.P. Dunkle, *Inorganic Chem.* 1965, *4*, 1629

8) "Metallo-ene-type" insertion of an olefinic bond into a *(Z)*-allylpalladium unit, linked by a bridge of three atoms is unlikely to give a *trans*-substituted five-membered ring since this would imply a strained transition state c.f., ref.[4].

(Received in Germany 28 August 1989)