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Palladium-Catalyzed Intramolecular Zinc-Ene Reactions [1)]

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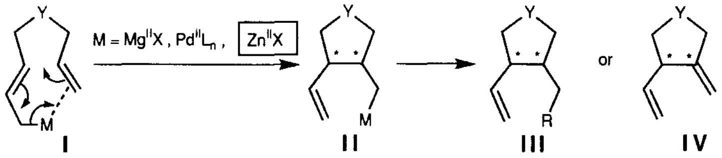
Abstract: Cyclizations of acetoxydienes **1** with $Pd(PPh_3)_4/Et_2Zn$ (0.05/4-5 mol-equiv.) in Et_2O at reflux, followed by either protonation, iodination or cyanation, provide *cis*-disubstituted cyclopentanes and pyrrolidines **5**, **7** or **9**. These tandem reactions, as well as the conversions **15** → **17** or **18** and **20** → **22** show good to excellent regio- and stereocontrol, which is compared to those of Pd-ene ring closures of **1** and **20**.

The intramolecular allylmetalation (metallo-ene reaction) of alkene (and alkyne bonds) **I** → **II** (Scheme 1) has proven to be a synthetically powerful process. [2)]

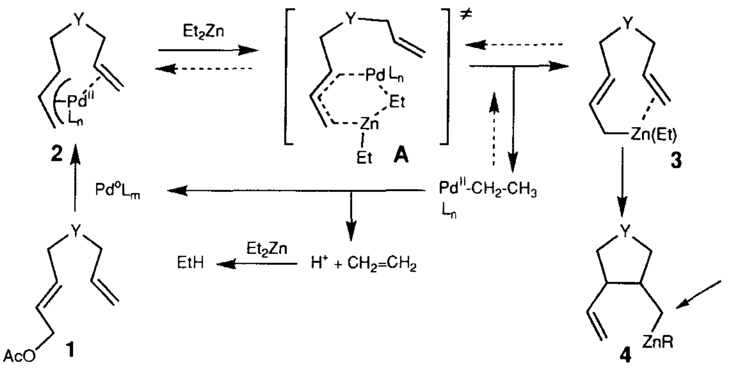
Scheme 1



Mg-ene reactions, for instance, excel at the possibility to trap cyclized intermediates **II**, $M = Mg^{II}X$ with numerous electrophiles, [2a)] whereas Pd- and Ni-catalyzed cyclizations **I** → **II**, $M = Pd^{II}L_n$ or $Ni^{II}L_n$ are stereospecific and compatible with various functionalities. [2b)]

Reactions **I** → **II**, M = ZnR, on the other hand, have the potential to embrace several of these features. Allylzincations, however, are only scarcely described, [3)] probably due to the tedious preparation of the allylzinc precursors **I** (e.g. by transmetallation of allylic Grignard reagents with $ZnBr_2$ [3d)]).

Scheme 2



We now envisaged a practical allylzincation protocol involving *in situ* generation of olefinic allylzinc intermediates **3** from dienyl acetates **1** *via* transmetallation of allylpalladium intermediate **2** with diethylzinc (Scheme 2) [4)] This tandem reaction should require only catalytic amounts of Pd(0) and ≥2 mol-equiv. of Et_2Zn (for the transmetallation **2** → **3** and for proton-scavenging). Relative to the palladium-ene cyclizations of **2**, it can be expected that 1) both the transmetallation **2** → **A** → **3** and the Zn-ene cyclization **3** → **4** ar faster, 2) the cyclization **3** → **4** proceeds with a different stereochemistry and 3) the cyclized product **4** is susceptible to a different range of derivatizations.

Our results are summarized in Schemes 3-5 and Tables 1-2.

Scheme 3

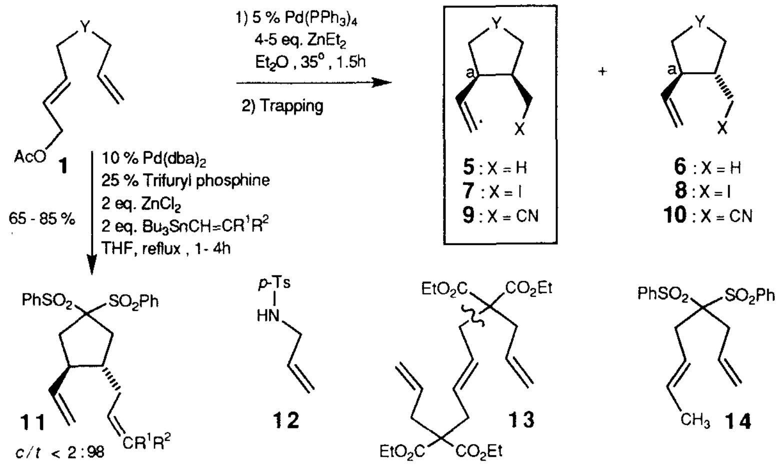
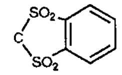
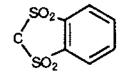


Table 1 : Pd-Catalyzed Zinc-Ene Cyclization/Trapping Reactions of 1-Acetoxy-2,7-Octadienes 1 [5]

Entry	Series	Y	Mol-equiv. $ZnEt_2$	Trapping Agent (mol-equiv.)	Ratio (crude) *cis/trans*	Major Product [a]	Yield [%]	M.p.[°C]
1	a	$C(SO_2Ph)_2$	5	aq. NH_4Cl	86 : 14	5a	(79)	solid
2	b		5	aq. NH_4Cl	92 : 8	5b	45	119
3	c	$N-CPh_3$	5	aq. NH_4Cl	98 : 2	5c	(79)[b]	oil
4	d	N-Phenylfluorenyl	5	aq. NH_4Cl	>99.8 : 0.2	5d	(88)	oil
5	e	N-Ts	4	aq. NH_4Cl	96 : 4	5e[c]	44	47
6	f	$C(CO_2Et)_2$	3	aq. NH_4Cl	-	13	(83)	oil
7	a	$C(SO_2Ph)_2$	5	I_2 (7)	83 : 17	7a	62	160
8	b		5	I_2 (8.5)	92 : 8	7b	43	143
9	d	N-Phenylfluorenyl	5	I_2 (9)	>98 : 2	7d	(87)	oil
10	e	N-Ts	5	I_2 (4.5)	96 : 4	7e[c]	(51)	oil
11	a	$C(SO_2Ph)_2$	4	1) $CuCN(LiCl)_2$ (1.0) 2) TsCN (6)	83 : 17	9a	58	157
12	d	N-Phenylfluorenyl	4	1) $CuCN(LiCl)_2$ (1.0) 2) TsCN (6)	>98 : 2	9d	(73)	oil

a) Yields after crystallization (FC). *Cis*-configuration assigned based on δ-C(a) (^{13}C-NMR).[6a] D.r. >98:2, except entry *1* (5a/6a = 86:14), entry *10* (7e/8e = 96:4) and entry *11* (9a/10a = 96:4). b) Partial decomposition of 5c during FC (SiO_2). c) Separated (FC) from *N*-allylsulfonamide 12 (19-28% from 1).

$Pd(PPh_3)_4$ (0.05 mol-equiv.) was added to a stirred 0.05 M solution of acetoxydiene **1a** [Y = $C(SO_2Ph)_2$] in Et_2O under Ar. After 3 min, Et_2Zn (5 mol-equiv.) was added dropwise to the yellow solution which became colorless. Heating of the mixture at reflux until reappearance of the yellow color (1 h), quenching with sat. aq. NH_4Cl at 0°C and flash chromatography (FC) furnished an 86:14-mixture **5a**/**6a** in 79% yield (Scheme 3, Table 1, entry *1*). Under otherwise identical reaction conditions, similar reaction rates, yields and ratios of **5a**/**6a** were observed when replacing the acetoxy group in **1a** by a $PhCO_2$-, $MeOCO_2$-, *t*-$BuOCO_2$-, or Cl group. Only unchanged educt **1a** was isolated when replacing the Et_2Zn by Me_2Zn or in the absence of Pd(0). Whereas the Et_2Zn-mediated cyclization **1a** → **5a**/**6a** proceeded smoothly at 35°C allylpalladations of the same substrate **1a** required temperatures above 60° C whether in tandem with β-elimination [AcOH, reflux giving **IV**, Y = $C(SO_2Ph)_2$] [6d] or 1-alkenyltin coupling (THF, reflux, yielding **11**, Scheme 3 [6a]). While these results are consistent with the postulated catalytic cycle (Scheme 2), they should not be taken as a rigorous proof. [7]

Neverthless, it is clear that the diastereoselectivities of the Pd- and Zn-ene reactions (**1a** → **11**, **1a** → **5a**) are reversed. The *cis*-selectivity of the allylzincation becomes even more pronounced and even complete in the $ZnEt_2$-mediated cyclizations of the 1,3-benzodithiol,1,1,3,3,-tetraoxide derived acetoxydiene **1b** (yielding **5b**/**6b** = 92:8, 55%, entry *2*), the *N*-trityl-*N,N*-dienylamine **1c** (affording **5c**/**6c** = 98:2, 79%, entry *3*) and the *N*-phenylfluorenyl-protected *N,N*-dienylamine **1d** (giving pure **5d**, 88%, entry *4*).

With increased leaving group ability of the bridge constituent Y, intermediates **3** are prone to elimination. [8] For instance, during the transformation **1e** → **5e**/**6e** (96:4, 53%) allylzinc intermediate **3e** underwent partial elimination giving *N*-tosylallyl amide **12** (19%, entry *5*). A similar process became predominant with malonate **1f** giving solely the elimination/allylation product **13** (83%, entry *6*).

We then explored synthetically more relevant derivatizations of cyclized alkylzinc species **4**. Quenching the above described allylzincation mixture of **1a** by addition of a 1 M solution of I_2 in THF until the violet color persisted (7 mol-equiv.) followed by work up with sat. aq. $Na_2S_2O_3/Et_2O$ and FC gave an 83:17 mixture of iodomethylvinylcyclopentanes **7a**/**8a** (78%) from which the pure *cis*-isomer **7a** was isolated by crystallization (62% from **1a**, entry *7*). The crude product mixture contained minor amounts of **14** (3%, ^1H-NMR) and **5a** (7%), corresponding to protonolysis of organozinc intermediates **3** and **4**, respectively. The same protocol but employing less Et_2Zn (2.2 mol-equiv.) yielded more **14** (12%) and **5a** (12%) at the expense of **7a**/**8a** (47%), reflecting the role of diethylzinc as a proton scavenger (Scheme 2). Allylzincation/iodination of substrates **1b**, **1d** and **1e** also gave mixtures of iodides **7**/**8** (43 to 87%, entries *8*-*10*) with identical *cis*/*trans* ratios as observed in entries *2*, *4*, and *5*.

Cyanation [9] of the cyclized alkylzinc intermediates **3a** and **3d** was accomplished after transmetallation with Cu(I) giving *cis*-nitriles **9a** (58% after crystallization) and **9d** (73%), respectively (entries *11*, *12*). [10]

In view of the bimolecular addition of allylzinc bromides to silyl-1-alkynes [3c] (THF, 60°C), it was not surprising that acetoxyenynes **15** underwent efficient intramolecular zinc-ene reactions (Scheme 4, Table 2).

Scheme 4

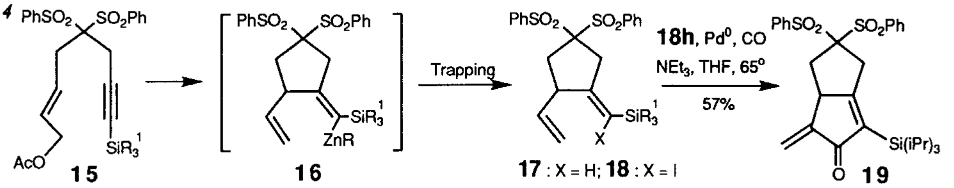


Table 2: Pd-Catalyzed Zinc-Ene Cyclization / Trapping Reaction of 1-Acetoxy-2-en-7ynes **15**. [5]

Entry	Series	R^1	Mol-equiv. $ZnEt_2$	Trapping Agent (Mol-equiv.)	Product [a]	Yield [%]	M.p. [°C]
13	**f**	Me	5	aq. NH_4Cl	**17f**	87	oil
14	**g**	Et	5	aq. NH_4Cl	**17g**	88	oil
15	**f**	Me	5	I_2 (8.5)	**18f** [b]	55 [b]	oil
16	**h**	*i*-Pr	5	I_2 (6.5)	**18h**	81	156

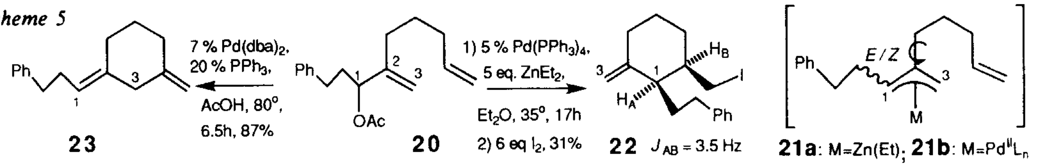
a) Olefinic configuration determined *via* NOESY measurements. b) Separated (FC) from **17f** (23% from **15f**).

Protonation of the transient 1,1-dimetalloalkenes **16f** and **16g** (aq. NH_4Cl) provided exclusively (*E*)-alkenylsilanes **17f** and **17g** (87 - 88%), respectively, corresponding to clean *cis*-additions **15** → **16**. Iodination of cyclized trimethylsilyl intermediate **16f** produced ~ 100% selectively (*Z*)-1-iodo-1-(trimethylsilyl)alkene **18f** in 55% yield, accompanied by the protonolysis product **17f** (23%). Whatever the origin of this side reaction, it was efficiently suppressed in the allylzincation/iodination of triisopropylsilylalkyne **15h** giving crystalline (*Z*)-1-iodo-1-TIPS-alkene **18h** (81%). The bulky silyl group in **18h** is perfectly compatible with

Pd-mediated carbonylation (as previously described for an acyclic iodosilyldiene 3c)) providing multifunctional *exo*-methylene bicyclooctenone **19** (57%). 11)

Finally, it is worth noting that intramolecular allylmetalation of a 4-butenyl chain which is attached at the allylic center C(2) (type-II metallo-ene process) showed an interesting metal dependent reversal of regio- and stereo-selection (Scheme 5).

Scheme 5



Pd-catalyzed zinc-ene ring closure of acetoxydiene **20** was relatively slow and gave, after iodination, *cis*-iodomethylcyclohexane **22** as a single isolable product (31%). This result corresponds to a C-C-bond formation at the more substituted terminal C(1) of allylzinc precursor (*Z*)-**21a**. Conversely, Pd-ene cyclization/β-elimination of the same acetoxydiene **20** 12) provided solely (*E*)-alkylidenecyclohexane **23** (87%) indicating bond formation at the less substituted C(3) of the *syn*-η^3 (*E*-η^1)-allylpalladium unit in **21b**.

We conclude that Pd-catalyzed cyclizations of acetoxy-dienes and -enynes, either in the presence or absence of Et$_2$Zn, can give complementary results which may be put to advantage in organic synthesis.

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5) Preparation of starting materials: **1a** 6a); **1b** *c.f.* 6b); **1c** 6c); **1d** treatment of (*E*)-*t*-butyl *N*-[4-(acetoxy)but-2-enyl]-*N*-(prop-2-enyl)carbamate 6c) with i) TFA/MeOH 2:1, r.t., 1 h; ii) 9-PhFlBr, K$_3$PO$_4$, Pb(NO$_3$)$_2$, MeCN. For PhFl-*N*-protection in synthesis see: B. D. Christie, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 1239; **1e** *c.f.* 6c); **1f** *c.f.* 6d); **15** i) desilyl-**15** 6a), LiHMDS, -78°C; ii) R$^1_3$SiCl, THF.
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7) R in **4** is uncertain, particularly in view of the equilibration 2 R-Zn-R' $\rightleftharpoons$ R$_2$Zn + R'$_2$Zn: K. Nützel in 'Houben-Weyl, Methoden der Organischen Chemie', Ed. E. Müller, Thieme, 1973, Vol.13/2a, p. 655.
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10) A 0.2 M soln. of CuCN(LiCl)$_2$ (1 mol-equiv., THF) was added to the allylzincation mixture, obtained from **1a** or **1d**, at -50°C. Warming of the mixture to 0°C within 5 min, rapid cooling of the resulting dark blue soln. to -78°C, dropwise addition of a 1 M soln. of TsCN (6 mol-equiv., THF), stirring at -78°/1 h, then at -30°C/16 h, work up (aq. NH$_4$Cl/Et$_2$O) and FC (crystallization) gave **9a** or **9d**.
11) Stirring a mixture of iodoalkene **18h** (0.05 mmol), Pd(PPh$_3$)$_4$ (1 mol-equiv.) and NEt$_3$ (1 mol-equiv.) under CO (1.1 atm) at 65° for 12 h, workup (aq. NH$_4$Cl/Et$_2$O) and FC (SiO$_2$, hexane/Et$_2$O) gave **19**.
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