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OXYGEN AND NITROGEN HETEROCYCLES BY INTRAMOLECULAR MAGNESIUM- AND ZINC-ENE REACTIONS; METHYLENECYCLOPENTANES BY Pd(0) - CATALYZED ISOMERIZATION OF 5-(BROMOZINCMETHYL)-3-METHYLENEOXACYCLOALKANES

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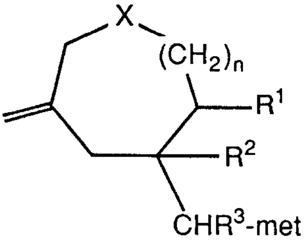
Summary: 2-(Alkenyloxymethyl)-2-propenylzinc bromides **2a-e** and 2-(allylmethylaminomethyl)-2-propenylzinc (or magnesium) halides **2g** rearrange thermally to 5-(1-bromozincalkyl)-3-methyleneoxa-cycloalkanes **1a-e** and 5-(bromozinc[or chloromagnesium]methyl)-3-methylene-*N*-methylpiperidine **1g**; some of the former can be isomerized by $Pd(PPh_3)_4$ to methylenecyclopentanes **3**.

Intramolecular magnesium-ene reactions have proven a valuable tool for the synthesis of carbocycles.[1] Our interest in synthetic applications of functionalized 2-alkenylmetal compounds[2] led us to explore the feasibility of constructing heterocyclic systems **1** by intramolecular metallo-ene reactions of **2**. We were also aware of the potential of organometallics **1** (X = O), being allylic ethers, to undergo Pd(0)-catalyzed isomerization to methylenecyclopentane derivatives **3**.



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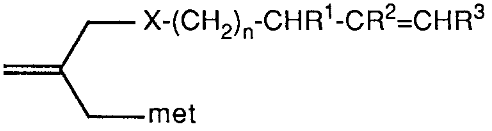

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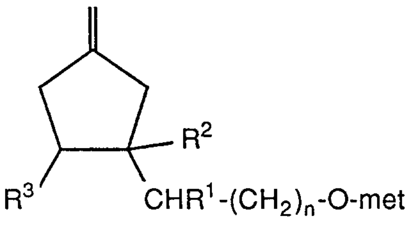

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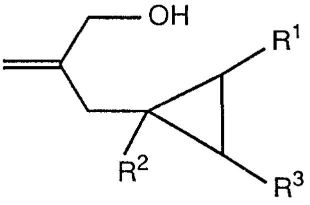
	X	n	R^1	R^3	R^2
a :	O	0	H	H	H
b :	O	0	H	H	CH_3
c :	O	0	H	CH_3	H
d :	O	0	C_6H_5	H	H
e :	O	1	H	H	H
f :	O	0	— $(CH_2)_3$ —		H
g :	NCH_3	0	H	H	H

Starting from 3-chloro-2-chloromethyl-1-propene and the appropriate sodium alkoxides, THF solutions of **2a-f** (met = MgCl) were prepared according to standard procedures.[2] The Grignard reagents **2a-f** (met = MgCl) were heated to 100 -130 °C for 23 - 86 hours,[3] whereafter the reaction mixtures were quenched, either with $ClSnMe_3$ or with aqueous NH_4Cl, and analyzed by GLC. Only in the case of Grignard reagent **2e** (met = MgCl) a compound of type **1**, **1e** (met = MgCl), was indicated by its stannylation product.[4] The latter, though, was obtained in low yield (15%)[5] and was accompanied by many by-products whose structures were not determined. Breaking of the C-O bond was involved in the formation of the three types of product obtained from the Grignard reagents **2a-d,f** (met = MgCl). Cyclopropanes **4** (0-35%) result from 1,3-elimination subsequent to the magnesium-ene reaction anticipated. The dienes **5** (0-20%) and the trienes **6** (3-26%) are derived from intramolecular and intermolecular S_N2' processes, respectively.



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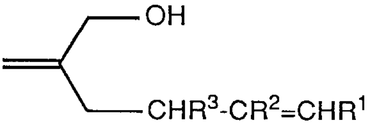

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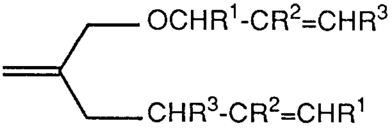

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The predicaments of the oxygen containing Grignard reagents were absent in the nitrogen compound **2g** (met = MgCl).[6] Under relatively mild conditions and after quenching with $ClSnMe_3$, *N*-methyl-3-methylene-5-(trimethylstannylmethyl)piperidine **1g** (met = $SnMe_3$) was obtained in 76% yield. No by-products were present. Magnesium-ene reactions hold promise as routes to nitrogen heterocycles !

Searching for means to effect cyclization in the case of oxygen systems the Grignard compounds **2a-f** (met = MgCl) were converted *in situ* [2] into their less nucleophilic zinc derivatives **2a-f** (met = ZnBr), which were then subjected to thermal rearrangement. It was gratifying to note that at 80 °C after 24 hours the simple allyl and homoallyl ethers **2a** and **2e** (met = ZnBr) gave only **1a,e** (met = ZnBr) in reasonable yield as indicated by the amounts of the respective tin derivatives obtained after $ClSnMe_3$ quench. The methyl substituted (**2b,c**, met = ZnBr) and phenyl substituted (**2d**, met = ZnBr) allyl ethers required longer reaction times or higher temperatures. The neopentyl type zinc compound **1b** (met = ZnBr) reacted only slowly with $ClSnMe_3$, giving rise to a low yield of its stannylated derivative (31%). **1c** (met = ZnBr), having a secondary carbon-zinc bond, did not react at all with $ClSnMe_3$. As far as we know, the reactions of **2b,c** (met = ZnBr) are the first cases of metallo-ene reactions, in which a disubstituted carbon-carbon double bond, unactivated by strain[7], conjugation[8] or an intramolecular Lewis base group[9], is the ene part. However, no reaction could be effected with the cyclohexenyl ether **2f** (met = ZnBr).

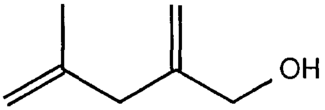
The amine **2g** (met = ZnBr) also afforded the product of intramolecular carbometallation **1g** (met = ZnBr) in fair yield. Reaction conditions and results for **2a-g** (met = ZnBr) are compiled in Table 1.

Table 1. Reaction conditions and products (%)[5] of zinc-ene reactions of **2a-g** (met = ZnBr) after quench and aqueous work-up.

Structural pattern	T(° C)	t(h)	Quench[a]	2(met=H)[b]	1(met=$SnMe_3$)	1(met=H)
a	80	23	A	-	57	-
b	80	45	A[c]	23	31	18
			B	18	-	80
c[d]	130	22	B	-	-	50[e]
d	80	48	B	16	-	51 *trans*, 25 *cis*
e	80	24	A	24	62	-
f	130	24	A	21	0	0
g	80	24	A	16	64	-

a) A = $ClSnMe_3$ quench (1.5 equiv., added as 1 M solution in *n*-pentane, room temperature,1 h stirring), B = NH_4Cl quench. b) Presumably formed during preparation of the Grignard reagents and manipulation of the small-size samples. c) In this instance, **1b** (met = ZnBr) was stirred for 22 h with $ClSnMe_3$. d) 93% *trans*, 7% *cis* . e) Only one isomer.

Having found[2] that allyl ethers bearing a 1-alkenylzinc bromide moiety undergo Pd(0)- catalyzed cyclization, we treated the THF solutions containing **1a-e,g** (met = ZnBr) with 5 mol % $Pd(PPh_3)_4$ at 65 °C. While **1g** (met = ZnBr) remained unchanged and **1c,d** (met = ZnBr) gave unidentified mixtures, **1a**, **b**, **e** (met = ZnBr) after 24 (**a**,**e**) and 45 (**b**) hours followed by aqueous work-up gave **3a**, **b**, **e** (met = H) in yields of 49, 65 and 71%[5]. **3a** (met = H) was accompanied by 15% of its isomer **7** and **3b** (met = H) was accompanied by 12% of **1b** (met = H). By contrast, **3e** (met = H) was the sole compound detectable, **2e** (met = H) present in the solution containing **1e** (met = ZnBr) apparently having been destroyed under the conditions of the isomerization reaction.



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In summary, type-II metallo-ene reactions in which the reacting allylmetal and ene parts are interconnected by a chain containing an oxygen (met = ZnBr) or an NCH_3 link (met = MgCl, ZnBr) can be used for the construction of oxygen and nitrogen heterocycles. The rates of these cyclizations are much higher than those of their intermolecular counterparts.[10] This has permitted, for the first time, the use of disubstituted carbon-carbon double bonds lacking any kind of activation as the ene part. Some of the 5-(1-bromozincalkyl)-3-methyleneoxacycloalkanes generated in this way can be isomerized by Pd(0) to 3-methylenecyclopentylalkanols. To our knowledge this is the first case of Pd(0)-catalyzed coupling between a saturated organozinc compound and an allylic ether.

References and notes

1 *Cf.* The work of W. Oppolzer and coworkers: W. Oppolzer and A. Nakao, Tetrahedron Lett. **27**, 5471 (1986); W. Oppolzer and A.F. Cunningham, *ibid.* **27**, 5467 (1986) and earlier papers cited there.

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3 A Carius tube with valve and N_2-inlet was used, see: A.R. Forrester and G. Soutar, Chem. Ind. **1984**, 772.

4 All new compounds gave satisfactory NMR and mass spectral data.

5 Yields are based on the starting chlorides.

6 Generated from the corresponding chloride [preparation: 3-chloro-2-chloromethyl-1-propene *plus* sodium *N*-methyl-2-propenamide (1:1), THF, reflux, 11 h, 36%] following our standard procedure.[2]

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