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Metal catalyzed hydrometalations and their applications in synthesis

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Abstract: We report that palladium catalyzed hydrostannation of allenes leads to allylstannanes or vinylstannanes depending on the choice of catalyst. Hydrostannation of 1,6-diynes has also been investigated and shown to give 1,2-alkylidenecyclopentanes bearing a tin group with (*Z*) stereochemistry. The effect of metal and ligand is discussed. Finally, an enantioselective nickel catalyzed reductive ring opening of three classes of oxabicyclic substrates has been developed and the methodology has been applied to the synthesis of sertraline, a commercially important antidepressant.

INTRODUCTION

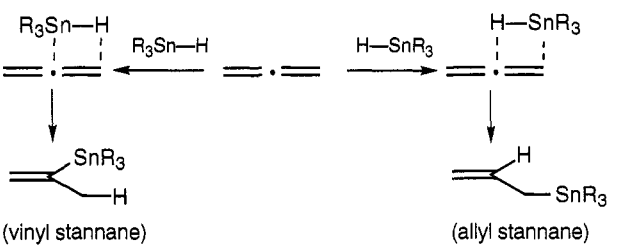
Metal catalyzed hydrometalations are of significant interest due to the synthetic utility of the resulting organometallic products. We now describe two different transition metal catalyzed hydrometalation reactions. Palladium catalysts have been shown to promote the hydrostannation of allenes and diynes while nickel catalyzes the hydrometalation-ring opening of oxabicyclic substrates. These reactions open up new approaches to synthetically useful intermediates and precursors to bioactive compounds.

REGIOSELECTIVE HYDROSTANNATION OF ALLENES

We recently reported the palladium catalyzed hydrostannation of alkenes and showed that $Pd(OH)_2/C$ catalyzes the reaction of strained and unstrained alkenes whereas palladium complexes bearing phosphines react exclusively with strained alkenes (ref. 1).

The hydrostannation of allenes was of interest because there are two modes with which the H–Sn moiety can add across an allene (Scheme 1) and both classes of products are of significant synthetic utility. Addition of the tin to the central carbon of the allene gives a vinyl stannane, while addition to the terminal carbon gives an allyl stannane. Previous reports from the literature indicate that allylstannanes are the most commonly formed products (refs. 2,3).

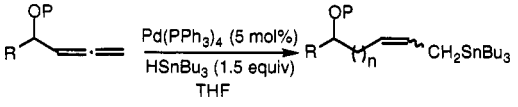
SCHEME 1. Possible modes of addition of H-Sn to an allene



Hydrostannation of Allenic Alcohols and Ethers

A series of allenes were subjected to "ligandless" and ligand-containing palladium complexes and the results are shown in Tables 1 and 2 and equation 1. Remarkably the two catalysts give different products with $Pd(Ph_3P)_4$ favoring the production of allylstannanes and $Pd(OH)_2/C$ generating predominantly vinylstannanes. In both cases slow addition of Bu_3SnH to a mixture of the allene and catalyst in THF gave the best yields. Neither the nature of the oxygen substituent nor the R group had any measurable effect on the outcome of the reactions. Reaction with a soluble catalyst lacking phosphine ligands, Pd_2dba_3, gave a very complex mixture of products containing several olefinic residues.

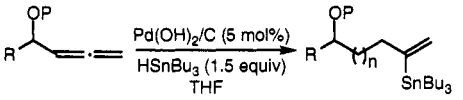
TABLE 1. Hydrostannation using $Pd(PPh_3)_4$



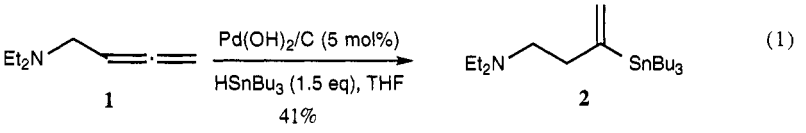
Entry[a]	R	P	n	Yield(%)[b]
1	Chx	H	0	56
2	Chx	MEM	0	56
3	H	*t*-Bu	2	67

[a] All reactions carried out at room temperature, 0.1 M in THF, syringe pump addition of $HSnBu_3$ over 1.5h. [b] Isolated yield of a mixture of stereoisomers. [c] Isolated yield.

TABLE 2. Hydrostannation using $Pd(OH)_2/C$



Entry[a]	R	P	n	Yield(%)[c]
1	Chx	H	0	57
2	Chx	MEM	0	57
3	Chx	TBDPS	0	55
4	*n*-C_7H_{15}	H	0	57
5	Ph	H	0	58
6	*t*-Bu	H	2	67



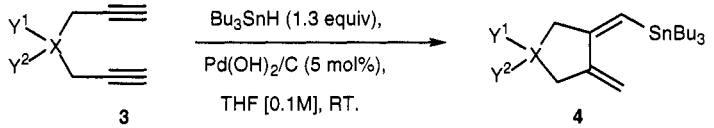
1 2 (1)

PALLADIUM CATALYZED HYDROSTANNATION-CYCLIZATION OF 1,6-DIYNES

We also investigated the reactions of 1,6-diynes to determine if hydrostannation of the individual alkynes occurred or if a cyclization-hydrostannation would be possible. We see remarkable differences between ligandless catalysts and phosphine-containing palladium catalysts but have found conditions to generate synthetically useful 1,2-dialkylidenecycolpentanes containing a (*Z*)-tributylstannane moiety. 1,2-Dialkylidenecycloalkanes are useful building blocks in organic synthesis and other approaches including the cyclizations of 1,*n*-enynes or diynes using Zr, Ti, Ni or Pd have been reported (refs. 4-8).

The hydrostannation-cyclization is applicable to a range of substrate types (Table 3) including those with a heteroatom in the propargylic position (entries 4-7) giving in each case, good to excellent yields of the corresponding cyclized products **4a-g**. Of particular note is the cyclization of dipropargyl sulfide **3f** (entry 6) and sulfone **3g** (entry 7) as it has been reported that substrates containing sulfur at the propargylic position are incompatible with homogeneous palladium catalysts (ref. 9).

TABLE 3. The stannylative-cyclization of 1,6-diynes catalyzed by $Pd(OH)_2/C$.



3 4

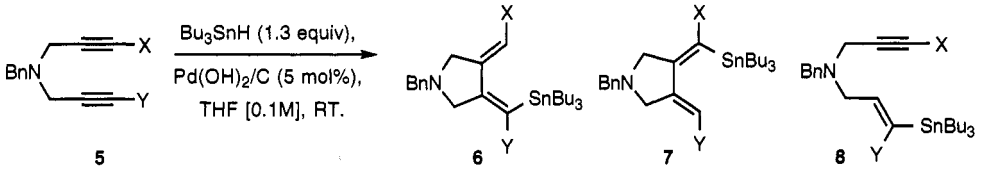
Entry[a]	Substrate		Product[b]		Yield (%)
1	X=C, Y^1=Y^2=MeO_2C	**3a**	X=C, Y^1=Y^2=MeO_2C	**4a**	95
2	X=C, Y^1=Y^2=$HOCH_2$	**3b**	X=C, Y^1=Y^2=$HOCH_2$	**4b**	61
3	X=C, Y^1=Y^2=$PhCO_2CH_2$	**3c**	X=C, Y^1=Y^2=$PhCO_2CH_2$	**4c**	60
4	X=N, Y^1=$PhCH_2$	**3d**	X=N, Y^1=$PhCH_2$	**4d**	85
5	X=O	**3e**	X=O	**4e**	68
6	X=S	**3f**	X=S	**4f**	58[c]
7	X=S, Y^1=Y^2=O	**3g**	X=S, Y^1=Y^2=O	**4g**	77

(a) Conditions: Reactions carried out with Bu_3SnH (1.3 equiv, addition over 1 h), $Pd(OH)_2/C$ (5 mol%) in THF [0.1M]. (b) The (*Z*) geometry of vinyl stannane **4** was proved by ^1H-^1H NOESY. (c) In addition to **4f**, the product arising from mono-hydrostannation of **3f** (with Sn terminal) was isolated in 9% yield.

When 1,6-diyne **3a** was treated with various palladium catalysts several important observations were made. Phosphine-free catalysts such as $Pd(OH)_2/C$, Pd/C, $Pd(OAc)_2$ and $Pd_2(dba)_3$ all gave >75% yield of the cyclized product **4a**. Conversely, the use of $Pd_2(dba)_3$ in the presence of 1 or 2 equivalents of PPh_3 or 1 equivalent of dppb results in a complex reaction mixture containing less than 15% of **4a**. Non-regioselective hydrostannylation of **3a** was the major reaction pathway in the presence of phosphine ligands (hydrostannylation:stannylative-cyclization = approx. 7:1). These results suggest that the phosphine ligand occupies one of the coordination sites in a proposed Pd(II) intermediate thereby preventing formation of a chelate between the diyne and the metal bearing a hydride and tributylstannyl group.

Terminally substituted 1,6-diynes also undergo the cyclization although the nature of the substituent had a dramatic effect on the course of the reaction, Table 4. Thus, alkynone **5a** undergoes hydrostannation-cyclization to furnish exclusively the α,β-unsaturated ketone **6a** in 64% yield. In contrast, alkynol **5b** gives a mixture of regioisomers **6b** and **7b** in 42% and 14% yield respectively (small quantities of **8b** were also observed), pointing to electronic effects influencing the reaction pathway. Monosilylacetylene **5c** undergoes regioselective hydrostannylation as the major reaction pathway to give terminal vinylstannane **8c** in 59% yield (as opposed to stannyl-cyclization) while disilane **5d** gave mostly recovered starting material.

TABLE 4. Terminally substituted 1,6-diynes as substrates for hydrostannation-cyclization



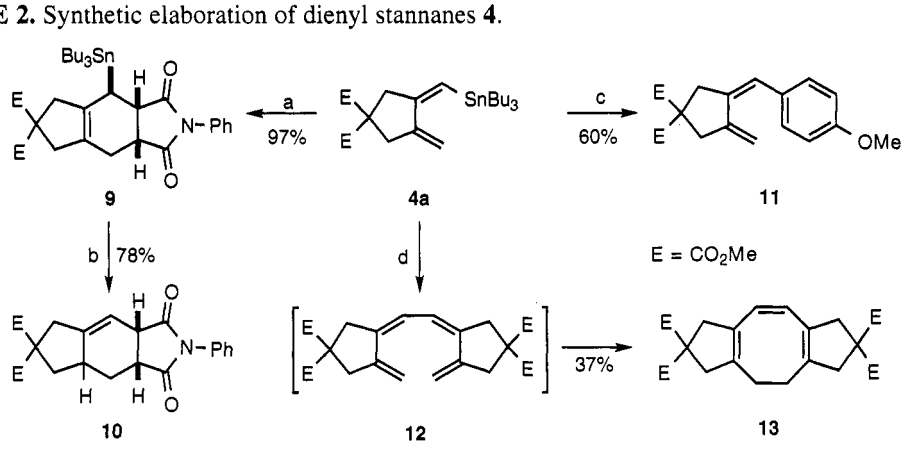
5 6 7 8

Entry	Substrate		Product	Isolated Yield (%)[b]
1	Y=H, X=C(O)CH_2CH_3	**5a**	**6a**	64%
2	Y=H, X=CH(OH)$CH_2CH_2CH_3$	**5b**	**6b/7b/8b** = 9/2/1[a]	**6b**: 42% **7b**: 14%
3	Y=H, X=TMS	**5c**	**8c**	59%
4	Y=TMS, X=TMS	**5d**	Recovered **5d**	-

(a) Ratio determined by ^1H NMR of the crude reaction mixture. (b) Purification carried out by column chromatography on Et_3N washed silica gel.

Dienyl stannanes **4** are useful synthetic intermediates as illustrated by the transformations shown in Scheme 2. Thus, Diels-Alder cycloaddition of **4a** with N-phenylmaleimide gave **9** in 97% yield which upon treatment with $BF_3{\bullet}Et_2O$ underwent proto-destannylation with allylic rearrangement to give non-symmetrical tricycle **10** in 78% yield. A modified Stille-type coupling converted **4a** into **11** in 60% yield although extended reaction times and low temperature were required to prevent isomerization of the aryl group to the thermodynamically favored (*E*)-stereoisomer (ref. 10). Homocoupling of stannyl diene **4a** with $Cu(NO_3)_2{\bullet}3H_2O$ gave **13** *via* a thermally allowed 8π electron conrotatory electrocyclization of **12** (ref. 11).

SCHEME 2. Synthetic elaboration of dienyl stannanes **4**.

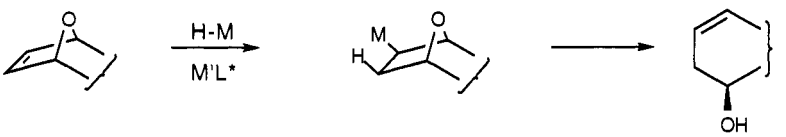


9 4a 11 10 12 13

Conditions: (a) N-phenyl maleimide, PhMe, RT. (b) $BF_3{\bullet}Et_2O$ (5 equiv), CH_2Cl_2, RT. (c) $Pd_2(dba)_3$ (10 mol%), $AsPh_3$, *p*-iodoanisole, NMP, RT, 6 days. (d) $Cu(NO_3)_2{\bullet}3H_2O$, THF, RT→ 40 °C.

DEVELOPMENT OF AN ASYMMETRIC REDUCTIVE RING OPENING

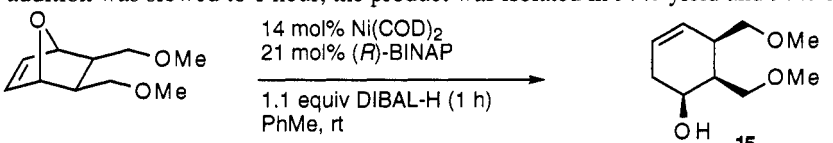
As part of our efforts to control stereochemistry using rigid bicyclic precursors as templates (ref. 12), we sought a method of performing an enantioselective hydrometalation-ring opening on oxabicyclic substrates. Meso oxabicyclic alkenes are readily available via [4+3] or [4+2] cycloaddition reactions between furan and a suitable partner, and hydrometallation-ring opening would regenerate the alkene in enantiomerically enriched cycloalkenols, eq. 2.



(2)

Cyclohexenes from [2.2.1] Systems

We have reported that diisobutylaluminum hydride (DIBAL-H) and heat or DIBAL-H and nickel complexes at room temperature catalyzes the reductive ring opening of oxabicyclic compounds (ref. 13). In the presence of a chiral phosphine such as BINAP, $Ni(COD)_2$ efficiently catalyzed the reductive cleavage reaction and gave enantiomerically enriched products. Interestingly, we found that the rate of addition of DIBAL-H to be crucial to the outcome of the reaction. When DIBAL-H was added over 1-2 min to **14** in the presence of a catalytic amount of $Ni(COD)_2$/BINAP, the ee of **15** was 56%. When the rate of addition was slowed to 1 hour, the product was isolated in 97% yield and 97% ee, eq. 3.

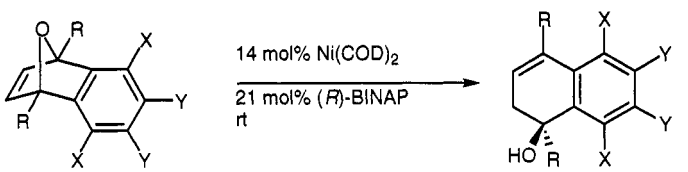


14 97% yield, 97% ee **15**

(3)

We have recently extended this investigation to the labile oxabenzonorbornadiene class of substrates which are much more sensitive than previously examined substrates. For example, reaction of **16** under our optimized conditions in toluene gave **6** in a 33% yield and 60% ee in addition to naphthalene and naphthol, Table 5 entry 1. By changing the solvent to THF, which would reduce the Lewis acidity of DIBAL-H, **16** could be ring opened to give **17** in 98% ee and 88% yield. A number of other oxabenzonorbornadienes were similarly studied to determine the scope of the reaction. The reaction was found to be quite sensitive to sterics but insensitive to electronic effects. Both the electron donating dioxolane, entry 5, and the electron withdrawing difluoro compound, entry 6, gave the products in 94% and 96% ee respectively.

TABLE 5. Enantioselective Ring Opening Oxabenzonorbornadienes



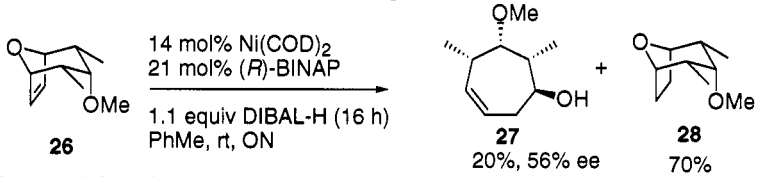
Entry	Substrate	Solvent	Time[a]	Product	Yield[b]	ee[c]
1	**16** R,X,Y=H	PhMe	1	**17** R,X,Y=H	33	60
2	**16**	THF	2	**17**	88	98
3	**18** R=Me, X,Y=H	THF	16	**19** R=Me, X,Y=H	66	73
4	**20** R,Y=H, X=Me	THF	2	**21** R,Y=H, X=Me	73	88
5	**22** R,X=H, Y=OCH_2O	THF	3	**23** R,X=H, Y=OCH_2O	58	94
6	**24** R,X=H, Y=F	THF	3	**25** R,X=H, Y=F	84	96

[a] Addition of DIBAL-H to a solution of $Ni(COD)_2$, (*R*)-BINAP and the alkene *via* syringe pump. [b] Isolated yield. [c] Measured by capillary GC (Chiraldex G-TA or B-TA column) or chiral HPLC (Chiracel OD or OJ column).

Cycloheptenes from [3.2.1] Systems

We found that the corresponding oxabicyclo[3.2.1]octenes were significantly more difficult to open than the [2.2.1] systems. For example, treatment of **26** with DIBAL-H in the presence of the

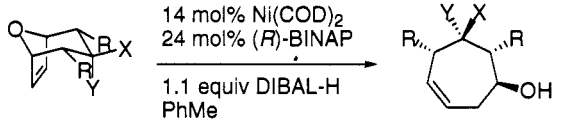
$Ni(COD)_2$/BINAP complex gave the cycloheptene **27** in only 20% yield and 56% ee. The major product was typically the oxabicyclo[3.2.1]octane **28**, eq. 4.



26 **27** 20%, 56% ee **28** 70% (4)

We made the surprising discovery that conducting the reaction at 60 °C rather than at room temperature had a profound effect on the yield and enantioselectivity of the reaction. The ee's improved to 91-99.35% and the yields were in excess of 80% with many different substrates, Table 6. While inverse temperature effects of this kind have previously been observed in catalytic asymmetric processes (ref. 14), the effect was particularly dramatic effect with these substrates.

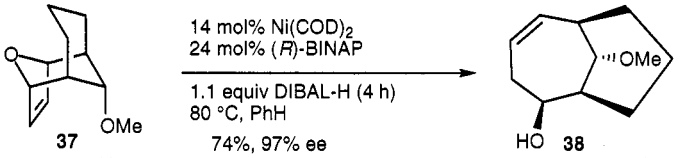
TABLE 6. Enantioselective Ring Opening of Oxabicyclo[3.2.1]alkenes



Entry[a]	Substrate	Product	Yield[c]	ee[d]
1	**26** R=Me, X=H, Y=OMe	**27** R=Me, X=H, Y=OMe	83-95	97
2	**29** R=Me, X=H, Y=OTIPS	**30** R=Me, X=H, Y=OTIPS	87	>95
3[e]	**29**	***ent*-30**	95	91
4	**31** R,X=H, Y=OMe	**32** R,X=H, Y=OMe	67	95
5[f]	**33** R,X=H, Y=OH	***ent*-34** R,X=H, Y=OH	89	99.3
6	**35** R,Y=H, X=OBn	**36** R,Y=H, X=OBn	88	95

[a] For all reactions, DIBAL-H was added over 4 h at 60 °C (oil bath), unless otherwise noted. [b] DIBAL-H added over 16 h. [c] Isolated yield. [d] Measured by CGC (Chiraldex G-TA or B-TA column) or HPLC (Chiralcel OD or OJ column) or Mosher's ester. [e] 4 mol% $Ni(COD)_2$, 8 mol% (*S*)-BINAP was used and DIBAL-H was added over 12 h at 65 °C. [f] 4 mol% $Ni(COD)_2$, 8 mol% (*S*)-BINAP was used and the substrate was pretreated with one equiv. of DIBAL-H.

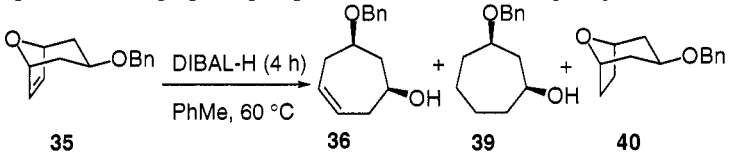
The effect of temperature on the ee in [3.2.1] systems is most dramatically illustrated by substrate **37**. At ambient temperature, the ee of the product **38** is 56%. At 60 °C, the ee improves to 81% while at 80 °C **38** is obtained in 97% ee.



37 74%, 97% ee **38** (5)

This temperature effect is not limited to the asymmetric reaction, but it does require the presence of a phosphine, Scheme 3. Reaction of **35** at 60 °C in the absence of a phosphine ligand has no effect on the ring opening as compared to the reaction at room temperature. However, in the presence of either dppb or BINAP, the hydrogenated alkene is not observed.

SCHEME 3. Comparison of ring opening in presence and absence of phosphine.



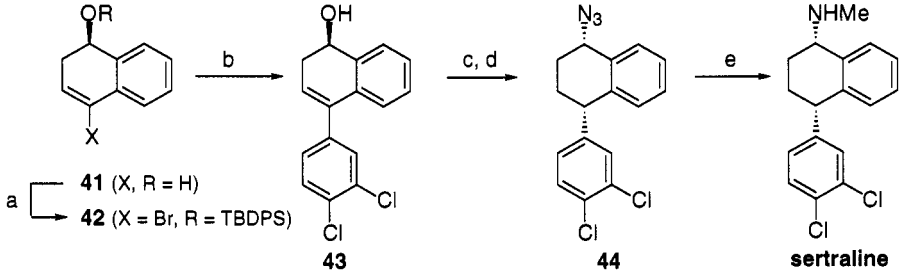
35 **36** **39** **40**

	36	**39**	**40**
$Ni(COD)_2$	15	10	75
$Ni(COD)_2$/(*R*)BINAP	88 (95% ee)	-	-
$Ni(COD)_2$/dppb	90	-	-

Total Synthesis of Sertraline

We have applied the enantioselective reductive ring opening reaction in the synthesis of the clinically important antidepressant agent sertraline (ref. 15). Silylation, bromination and dehydrobromination of the alcohol **41** gave the vinyl bromide **42** in >85% yield over three steps. A Stille coupling under Farina's conditions (ref. 16) followed by desilylation provided the alcohol **43** in 64% yield over two steps. Crabtree's catalyst (ref. 17) was employed to effect a directed reduction of the olefin providing the desired epimer with 28:1 selectivity and 88% isolated yield. The alcohol was converted to the azide **44** (ref. 18) in 88% yield and reduction and methylation provided sertraline in 86% yield over three steps. The synthesis required 8 steps and gave an overall yield of 33%, Scheme 4.

SCHEME 4. The Synthesis of sertraline



[a] Reagents and conditions: (a) i)TBDPSCl, imidazole, CH_2Cl_2, DMAP; ii) Br_2, CH_2Cl_2, Et_3N, 0°C then DBU, PhH, 88%, 2 steps. (b) i) 5% $(MeCN)_2PdCl_2$, 20% $AsPh_3$, (3,4-diCl)$C_6H_3SnMe_3$, NMP, 80 °C, 1.5 h; ii) TBAF, THF, AcOH, 3 d, 64%, 2 steps. (c)10 mol% [Ir(COD)pyPCy_3]PF_6, H_2 (1000 psi), CH_2Cl_2, 88%, 28:1; (d)dppa, DBU, THF, 88%, 98:2; (e) i) H_2, Pd-C, EtOH. ii) $ClCO_2Et$, MeCN, K_2CO_3. iii) $LiAlH(OMe)_3$, THF, reflux, 40 h, 86%.

CONCLUSIONS

Palladium catalyzed hydrostannation reactions of allenes and 1,6-diynes have been shown to lead to synthetically useful tin-containing products in moderate to excellent yields. Issues relating to mechanism and the nature of the catalytically important species are the subjects of our ongoing experiments. Our work on nickel catalyzed hydrometalation reactions has yielded a new approach to enantiomerically pure cyclohexenols, cycloheptenols and hydroxydihydronaphthalenes. We continue to search for information on the sequence of events which lead to the final ring opened products.

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