

## Metal-directed stereoselective functionalizations of alkenes in organic synthesis

Wolfgang Oppolzer

Département de Chimie Organique, Université de Genève, CH-1211 Genève, Switzerland

**Abstract**- The critical role of metals in  $\pi$ -face selective alkene functionalizations is exemplified by Diels-Alder reactions, osmylations, hydrogenations, conjugate additions (hydride, organocopper reagents, alkyllmagnesium halides) of N-enoyl-bornane-10,2-sultams as well as by protonations, alkylations and aldolizations of "enolates" derived from the same auxiliary. In extension of the magnesium-ene process catalytic intramolecular palladium-ene reactions are presented. Thus, Pd(dba)<sub>2</sub>/PPh<sub>3</sub>- or Pd(PPh)<sub>3</sub>-catalyzed stereoselective cyclizations of acetoxy-2,7(8)-dienes gave 1-vinyl-2-methylene- or 1,2-divinyl-substituted cyclopentanes (or cyclohexanes) consistent with a *cis*-insertion/ $\beta$ -elimination process.

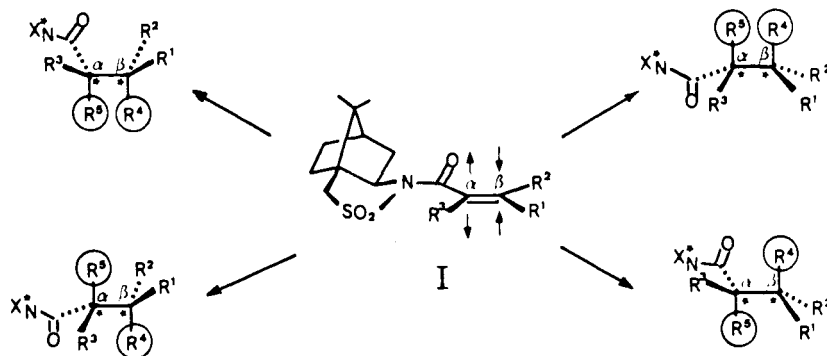
### INTRODUCTION

The last years have witnessed enormous progress in the crucial use of metal templates for  $\pi$ -face selective functionalizations and cyclizations of alkenes. These two issues shall be also addressed in the following presentation.

### $\pi$ -FACE-SELECTIVE FUNCTIONALIZATIONS OF ALKENES

Thus, carbon-, hydrogen- and oxygen substituents may be introduced at C $\beta$  and C $\alpha$  of enoyl sultams **I** by a variety of reactions with high, "metal-dependent" face stereodifferentiation featuring either one of the four depicted topocities (ref. 1)(Scheme 1).

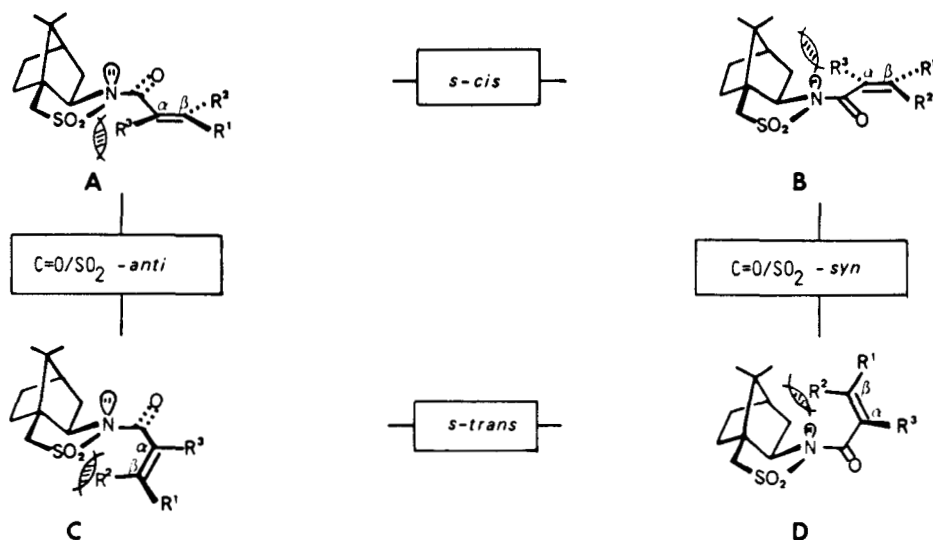
Scheme 1



To predict and understand the topology of these additions to enoyl sultams **I** an X-ray-diffraction study of the non-coordinated (*E*)-crotonoyl sultam **I** was carried out (ref. 2). It shows ( in contrast to an acyclic N-acylsulfonamide (ref. 3)) a pyramidal nitrogen as well as *anti*-disposed SO<sub>2</sub>- and C=O groups and *s-cis*-related C=O/C $\alpha$ -C $\beta$ -bonds which correspond to conformation **A** (Schemes 2,7). We thus propose as a general working hypothesis the following topocities for addition reactions to **I** (Scheme 2).

- (1) Disposition of the C=O and SO<sub>2</sub> groups *anti* (**A**, **C**) in the absence but *syn* (**B**, **D**) in the presence of coordinating metals.
- (2) *s-Cis*-relation of the C=O/C $\alpha$ , C $\beta$ - bonds when the  $\alpha$ -substituent R<sup>3</sup>=H (**A**, **B**) but *s-trans* when R<sup>3</sup>=alkyl and R<sup>4</sup>=H.
- (3) Preferential attack of the reagents to **A**, **B**, **C**, and **D** from the bottom face (opposite to the lone electron pair on nitrogen).

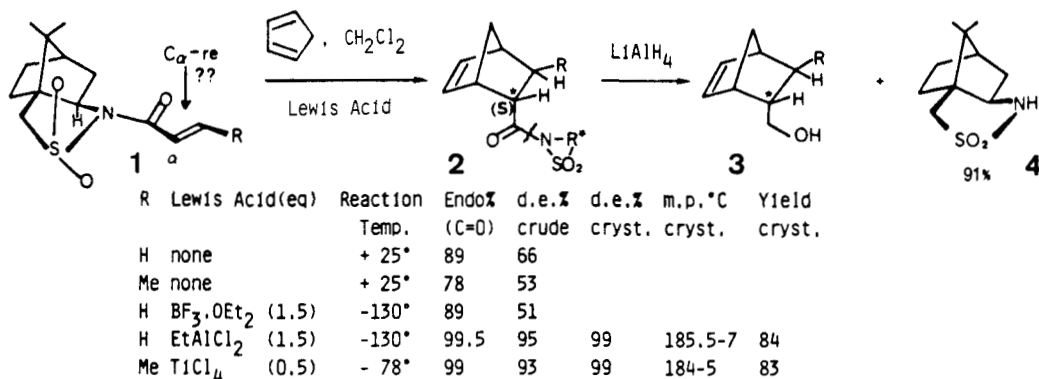
## Scheme 2



## Diels-Alder reactions

The sultam moiety **4** serves as an excellent dienophile auxiliary as exemplified by the cycloadditions of 1,3-dienes to its acryloyl- and (*E*)-crotonoyl derivatives **1** (ref. 2), (Scheme 3).

## Scheme 3

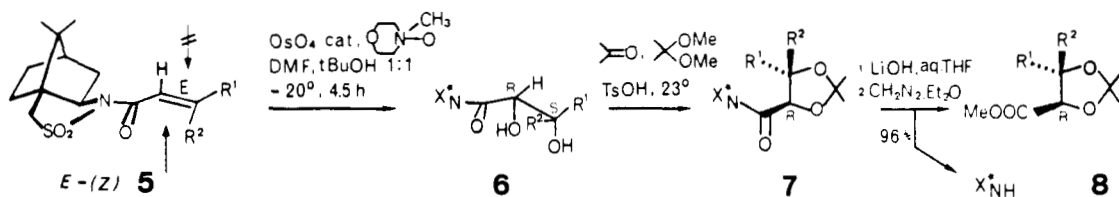


The striking reactivity and topological control of the EtAlCl<sub>2</sub>- or TiCl<sub>4</sub>-promoted Diels-Alder reactions **1** → **2** are consistent with a chelation of the SO<sub>2</sub>- and C=O-groups by the metal which directs the diene to the less hindered C<sub>α</sub>-Re-face of the rigid conformation **B** (Scheme 2); this agrees with the poor results obtained with the monocoordinating Lewis acid BF<sub>3</sub>·OEt<sub>2</sub>.

## Osmylations

An analogous topicity was observed on oxidation of β-substituted α,β-enoyl sultam **5** with *N*-methyl morpholine-*N*-oxide/OsO<sub>4</sub> (ref. 4), (Scheme 4).

## Scheme 4

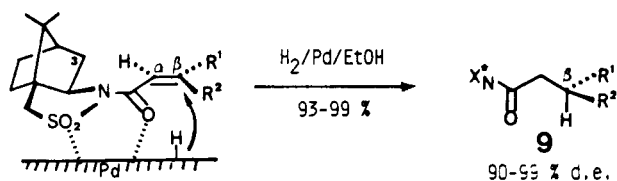


The resulting glycols **6** were converted into the more stable acetals **7**, obtained after crystallization in <99% d.e. and in 63-74% yield from **5**. Again we assume a metal-directed approach of the reagent from the less hindered C<sub>α</sub>-Re (bottom) face of conformation **B** (Scheme 2).

### Hydrogenations

High (91-98%) topological control was also achieved on simple hydrogenations (100 psi H<sub>2</sub>, 4 mol% Pd/C, EtOH, r.t.) of  $\beta,\beta$ -disubstituted enoyl sultams (ref. 5), (Scheme 5).

**Scheme 5**

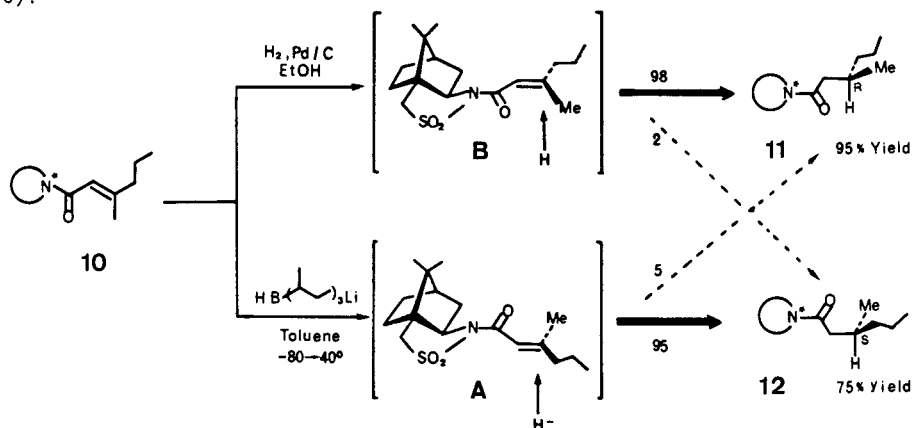


The  $\pi$ -face differentiation may be attributed to a coordination of the metal surface with the *syn*-disposed SO<sub>2</sub>- and C=O groups followed by H-transfer to the bottom face of conformation B.

### Conjugate hydride additions

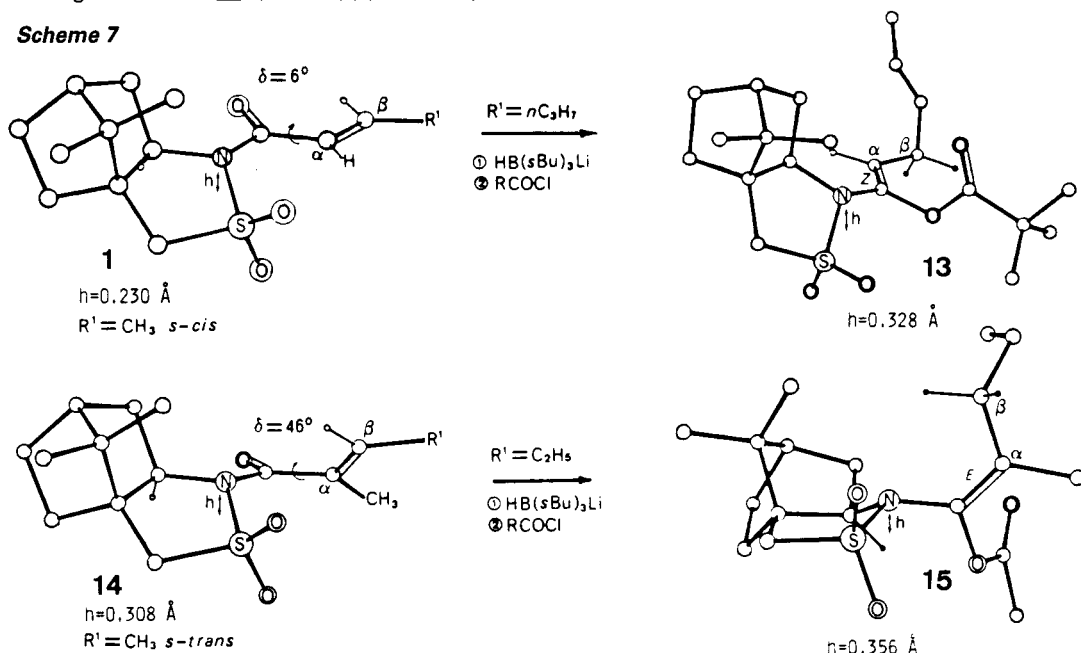
In surprising contrast,  $\beta,\beta$ -disubstituted enoyl sultams underwent efficient 1,4 hydride additions (on treatment with tri-*s*-butylborohydride) from the opposite  $\pi$ -face (ref. 6), (Scheme 6).

**Scheme 6**



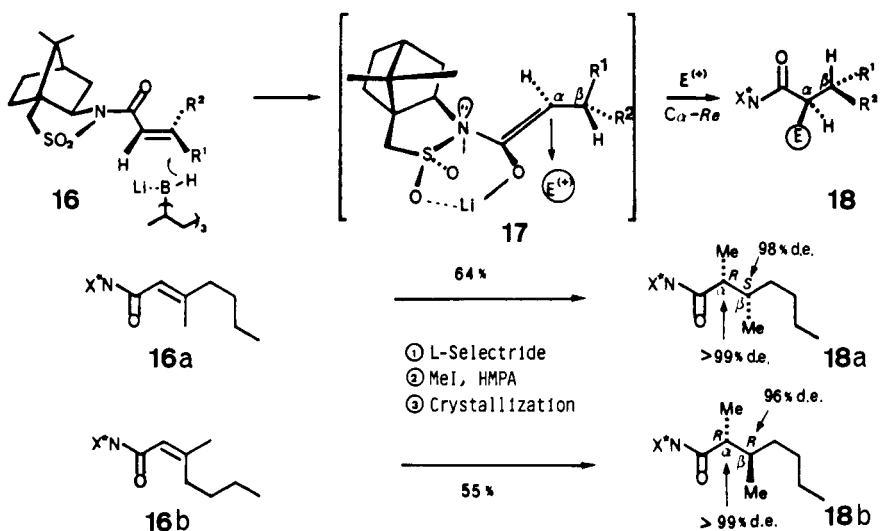
This agrees with a reactive conformation A of the  $\alpha$ -unsubstituted enoyl sultam. Experimental support for this postulate and for part of our working hypothesis (Scheme 2) relies on 1,4-addition of *L*-Selectride followed by O-acylation of the resulting "enolates". X-ray diffraction comparison of enoyl sultam **1** with O-pivaloyl-ketene acetal **13** indicates that the *s-cis*-conformation of the enoyl sultam "translates" into the (*Z*)-configuration of the enolate. Similar comparison of the ( $\alpha$ -substituted) tigloyl sultam **14** with O-acetyl-ketene acetal **15** reveals an (out of plane) *s-trans* conformation of **14** related to the (*E*)-configuration of **15** (ref. 7), (Scheme 7).

**Scheme 7**



The enolate intermediate **17** could be protonated (aq.  $\text{NH}_4\text{Cl}$ ) or methylated ( $\text{MeI}$ ,  $\text{HMPA}$ ) to generate conveniently two centers of asymmetry (at  $\text{C}_\alpha$  and  $\text{C}_\beta$ ) in one synthetic operation (**16**  $\rightarrow$  **17**  $\rightarrow$  **18**, Scheme 8).

Scheme 8

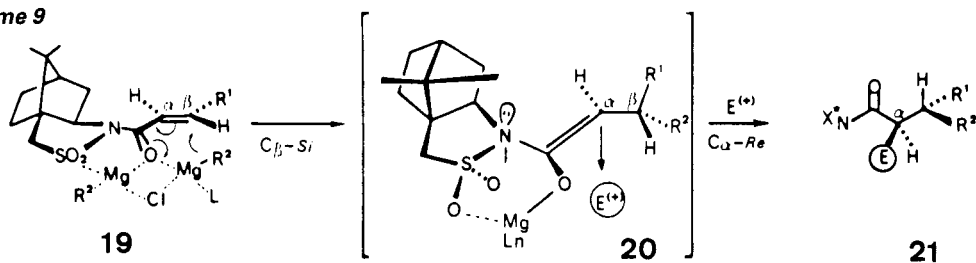


The  $\text{MeI}$  seems to approach the bottom face of enolate **17** (opposite to the lone electron pair on the nitrogen) owing to the steric or stereoelectronic bias of the auxiliary which overrides that of the preexisting center  $\text{C}_\beta$ . As expected, the topological situation changes on subjecting  $\alpha$ -substituted enoyl sultams (such as **14**) to the tandem hydride addition/protonation.

#### Conjugate additions of Grignard reagents

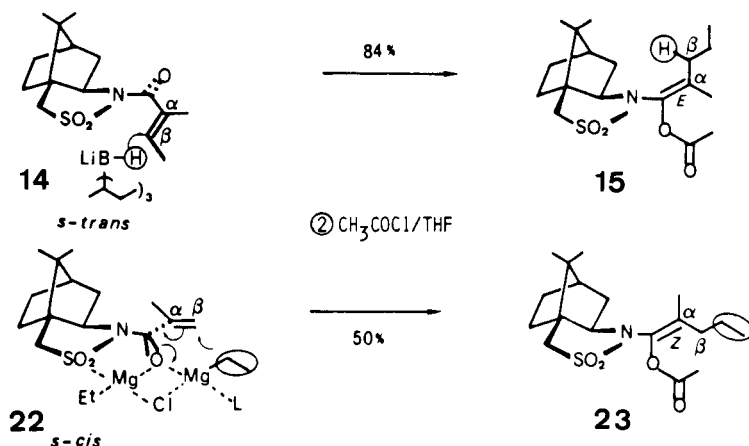
Most conveniently, simple alkylmagnesium chlorides (2.2 equiv) added smoothly in a 1,4-fashion to  $\beta$ -*trans*-substituted enoyl sultams **19** (77-90% d.e.), (ref. 8), (Scheme 9).

Scheme 9



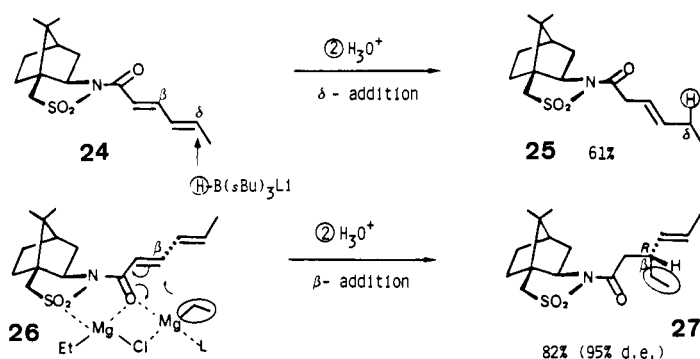
Protonation or methylation of the transient (*Z*)-enolates **20** gave after crystallization virtually pure (*2R,3R*)-imides **21**. The stereochemistry of the addition at  $\text{C}_\beta$  agrees with the postulate that a chelation by the magnesium and the operation of a six-membered cyclic mechanism requires the  $\text{C}=\text{O}/\text{C}_\alpha, \text{C}_\beta$ -*s-cis*-conformation **B** in **19**. For the methylation of (*Z*)-magnesium "enolates" **20** the same topicity was observed as with the lithium enolate **17**. As shown in Scheme 10 the cyclic transition state  $\text{C}=\text{O}-\text{Mg}-\text{R}^2-\text{C}_\beta$  enforces the  $\text{C}=\text{O}/\text{C}_\alpha, \text{C}_\beta$ -*s-cis*-conformation **B** of **22** regardless of the  $\alpha$ -methyl substituent to give **23** in contrast to the hydride addition **14**  $\rightarrow$  **15** (proceeding by conformation **C**).

Scheme 10



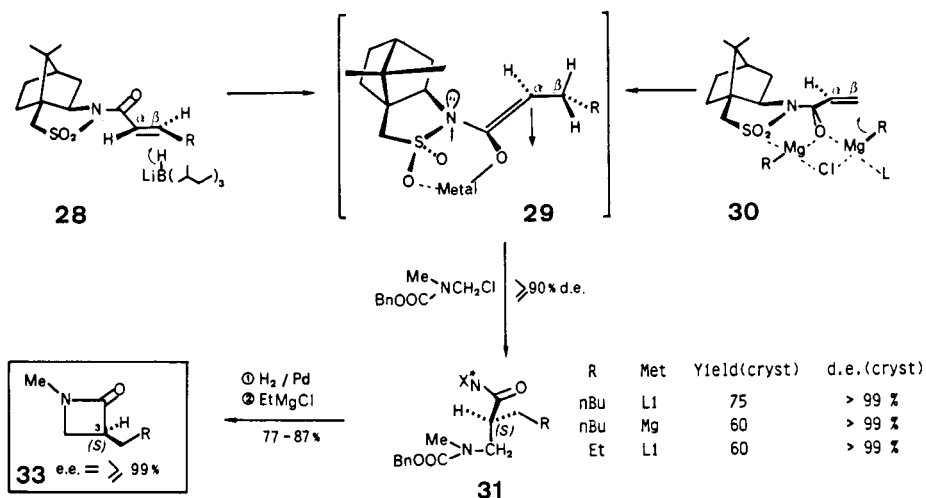
Probably for the same reason dienoyl sultam **24** underwent exclusive 1,4-addition of ethylmagnesium chloride (**24** → **26** → **27**) as compared to the 1,6-hydride addition **24** → **25** (Scheme 11).

Scheme 11



Conjugate additions of *L*-Selectride or Grignard reagents to enoyl sultams **28** and **30**, respectively, followed by *N*-methylamidoalkylation of the resulting (*Z*)-"enolates" **29** opened a new route to enantiomerically pure 3-substituted  $\beta$ -lactams **33** (ref.9), (Scheme 12).

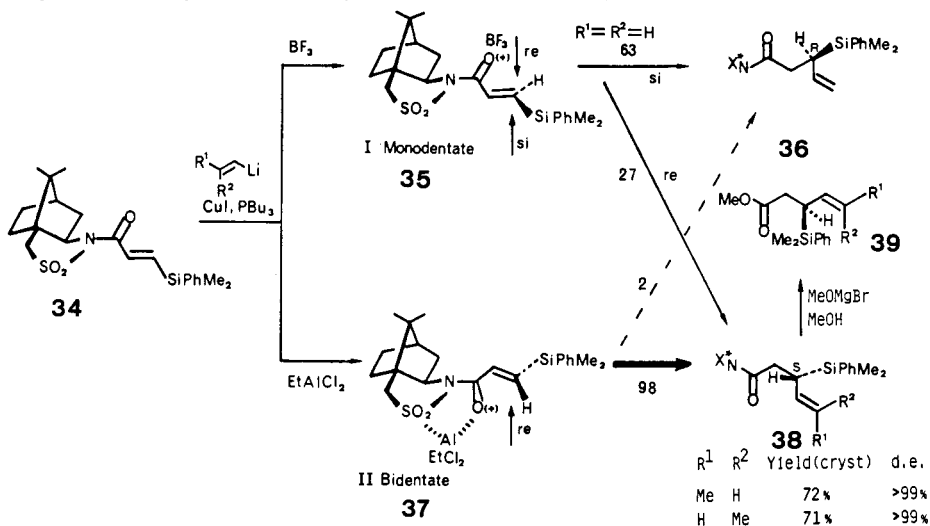
Scheme 12



### Organocopper additions

The importance of metal chelation is also exemplified by conjugate additions of phosphine-stabilized alkyl and alkenyl copper reagents to *N*-( $\beta$ -silylenoyl)sultams **34** (ref. 10), (Scheme 13).

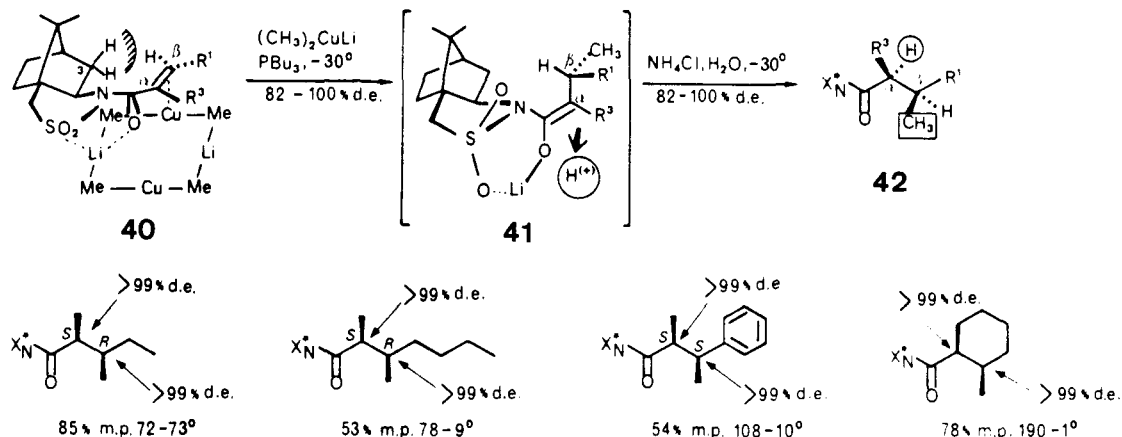
Scheme 13



Thus, opposite face stereodifferentiations were observed on  $\text{BF}_3 \cdot \text{OEt}_2$ - ( $34 \rightarrow 35 \rightarrow 36$ ) versus  $\text{EtAlCl}_2$ -mediated ( $34 \rightarrow 37 \rightarrow 38$ ) reactions. The latter conditions furnished crystalline adducts  $39$  and via their mild methanolysis ( $\text{MeOMgBr}$ ,  $\text{MeOH}$ ,  $60^\circ\text{C}$ ) enantiomerically pure (*E*)- and (*Z*)- $\beta$ -silyl- $\gamma,\delta$ -alkenyl carboxylates  $39$  which are valuable building blocks owing to the topological bias of the silyl substituent (ref. 11).

A further topicity (**D**, Scheme 2) was observed on  $\pi$ -face-selective 1,4-additions of dimethylcopper lithium to (*E*)- $\alpha,\beta$ -disubstituted enoyl sultams (ref. 8), (Scheme 14).

#### Scheme 14

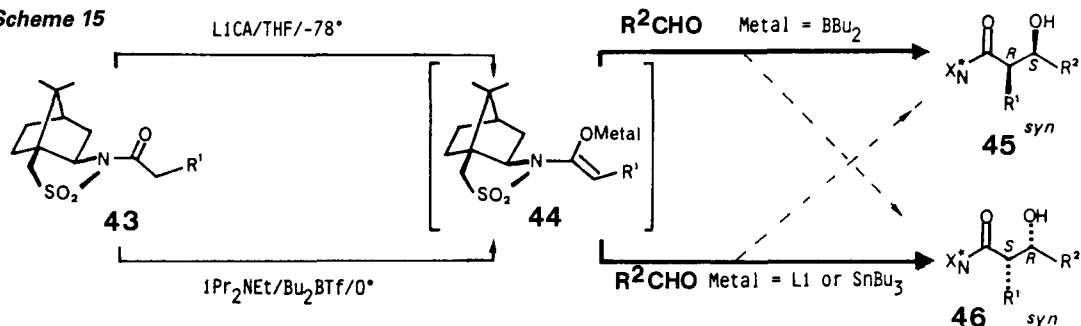


Protonation of the transient "enolates"  $41$  followed by crystallization yielded enantiomerically pure  $\alpha,\beta$ -disubstituted carboxyl derivatives  $42$ .

#### Aldolizations

Chiral "enolates"  $44$  may be also generated stereoselectively from saturated acyl sultams  $43$  (ref. 12), (Scheme 15).

#### Scheme 15



$R^1$	$R^2$	Metal	Ratio <sup>1)</sup>		Major Product Yield % <sup>2)</sup>	Major Product d.e. % <sup>2)</sup>
			45	46		
Me	Ph	$\text{BBu}_2$	>95 : <5 (0)	45	78	45 >99
Me	1Pr	$\text{BBu}_2$	>99 : <1 (0)	45	48	45 >99
Me	Me ( $-100^\circ\text{C}$ )	$\text{BBu}_2$	>99 : <1 (0)	45	48	45 >99
Et	Me ( $-100^\circ\text{C}$ )	$\text{BBu}_2$	>95 : <5 (0)	45	69	45 >95
Et	Ph	$\text{BBu}_2$	>95 : <5 (0)	45	63	45 >95
Et	1Pr	$\text{BBu}_2$	>95 : <5 (0)	45	72	45 >95
Me	Ph	Li	8 : 85 (7)	46	72	46 >99
Me	1Pr	Li	6 : 86 (8)	46	70	46 >95
Et	Ph	Li	9 : 88 (3)	46	51	46 >95
Me	tBu	Li	7 : 88 (8)	46	51	46 >95
Me	Ph	$\text{SnBu}_3$	11 : 89 (0)	46	66	46 >99

1) Crude reaction product (percentage of *anti* -products) 2) Purified product

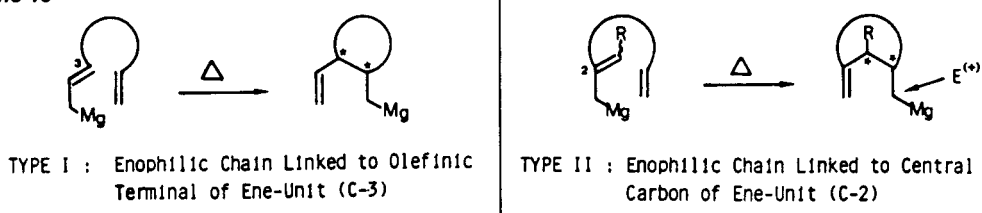
Thus, treatment of  $43$  with  $\text{Bu}_2\text{BTF}/i\text{Pr}_2\text{NEt}$  followed by addition of aldehydes at  $-78^\circ\text{C}$  gave the crystalline *syn*-aldols  $45$  in high diastereomeric excess. In comparison, deprotonation of  $43$  with LICA and aldolization of the lithium (or tin-) enolates  $44$  resulted in the formation of the diastereomeric *syn*-aldols  $46$  with surprisingly good face discrimination. Notably, aldols  $45$  and  $46$  could be purified to <99% d.e. by flash chromatography and/or crystallization.

### Practical considerations

For practical reasons it is worth mentioning that the sultam auxiliary provides not only a versatile, predictable and strong topological bias to its enoyl- and "enolate" derivatives. Both antipodes are also (1) easily accessible from the inexpensive camphor-10-sulfonyl chlorides (2) readily transformed to their N-acyl derivatives which (3) are stable and (4) can be readily purified by crystallization, (5) directly analyzed by  $^1\text{H-NMR}$  and/or GC to determine their stereochemical purity and, last but not least, (6) cleaved (e.g. with  $\text{LiAlH}_4$ ,  $\text{LiOH}$ ,  $\text{MeOMgBr}$ ,  $\text{Ti}(\text{OEt})_4/\text{EtOH}$ ) under mild conditions without loss of the induced chirality and with efficient recovery of the auxiliary (ref. 1,13).

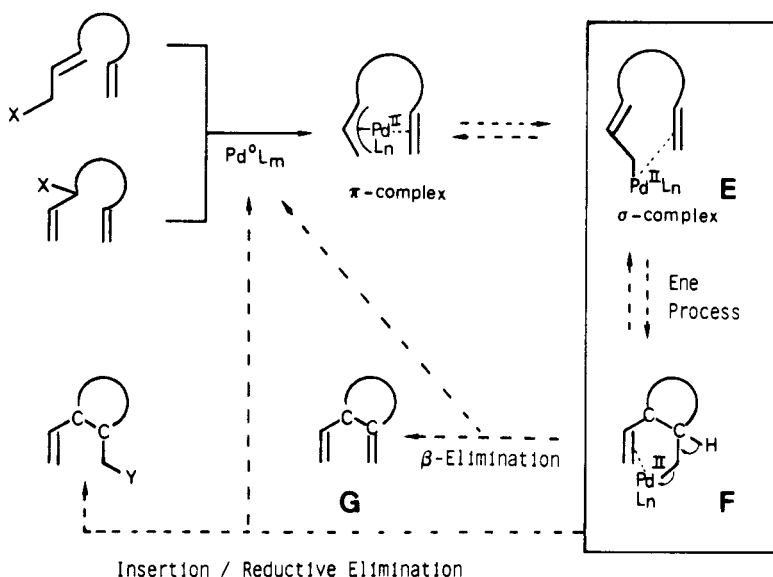
### CATALYTIC INTRAMOLECULAR PALLADIUM-ENE REACTIONS

Scheme 16



In conjunction with our previous studies of the magnesium-ene cyclization (ref. 14), (Scheme 16) we envisaged the extension of this concept to catalytic intramolecular palladium-ene reactions (ref. 15), (Scheme 17).

Scheme 17

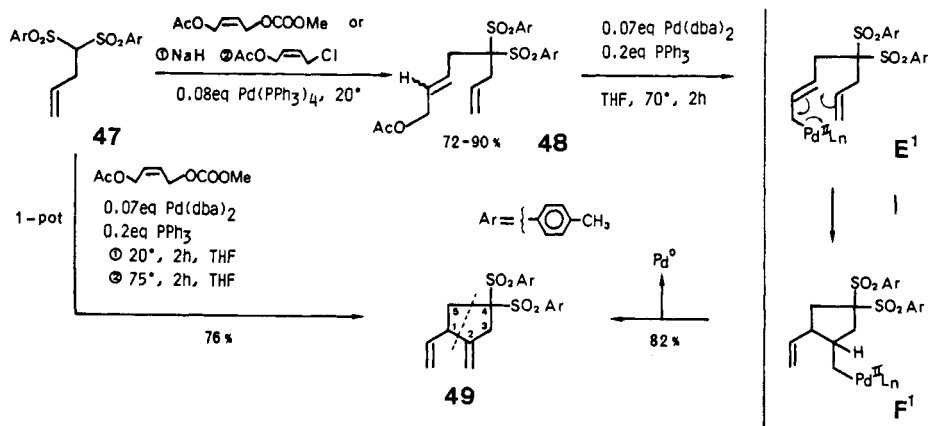


Whereas norbornadiene, norbornene and 1,3-dienes were reported to insert into stoichiometric amounts of allylpalladium complexes, simple olefins (e.g. styrene, cyclohexene, 1,4-cyclohexadiene and 1,5-cyclooctadiene) did not undergo this reaction under similar conditions (ref. 16). Nevertheless, we assumed the intramolecular ene process  $\text{E} \rightarrow \text{F}$  to be entropically facilitated and a subsequent irreversible  $\beta$ -elimination  $\text{F} \rightarrow \text{G}$  to withdraw the ene product  $\text{F}$  from the equilibrium  $\text{E} = \text{F}$ .

In situ-preparation of the olefinic allylpalladium intermediates could be accomplished by oxidative addition of  $\text{Pd}^0$ -complexes to allylacetates (ref. 17). The required 1-acetoxy-2,7(8)-dienes were readily obtained, predominantly as their *E*-isomers via  $\text{Pd}(\text{PPh}_3)_4$ -catalyzed alkylation of 1-acetoxy-4-chloro-2-butene or, preferably, (4-acetoxy-2-butenyl)-methylcarbonate with a 3(4)-alkenyl-1,1-disulfone or with 3-alkenylmalonates as exemplified by the transformation  $\underline{47} \rightarrow \underline{48}$ . (Scheme 18).

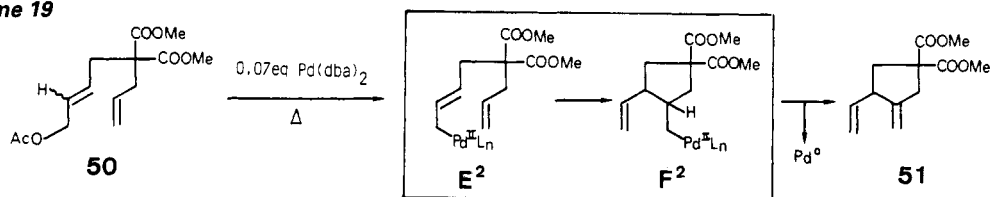
Heating diene  $\underline{48}$  with  $\text{Pd}(\text{dba})_2$  (0.07 equiv) and  $\text{PPh}_3$  (0.2 equiv) in THF at  $+70^\circ\text{C}$  for 2h gave the expected cyclized 1,4-diene  $\underline{49}$  in 83% yield. Even more conveniently, product  $\underline{49}$  was obtained in one operation from disulfone  $\underline{47}$  by treatment with (4-acetoxy-2-butenyl)-methylcarbonate (1.0 equiv),  $\text{Pd}(\text{dba})_2$  (0.07 equiv) and  $\text{PPh}_3$  (0.2 equiv) in THF at  $+20^\circ\text{C}$  (2h) and then at  $+75^\circ\text{C}$  (2h). Accordingly bonds C4-C5 and C1-C2 of cyclopentane  $\underline{49}$  may be efficiently formed by this simple combined alkylation/cyclization procedure.

Scheme 18



Solvent effects influence significantly this novel ene process as illustrated by the cyclization of malonate **50**. Whereas no reaction took place in toluene, dichloromethane or *N,N*-dimethylformamide the rate and yield increased on proceeding from THF to methanol to acetic acid. Interestingly the presence of the phosphine turned out to be indispensable (Scheme 19).

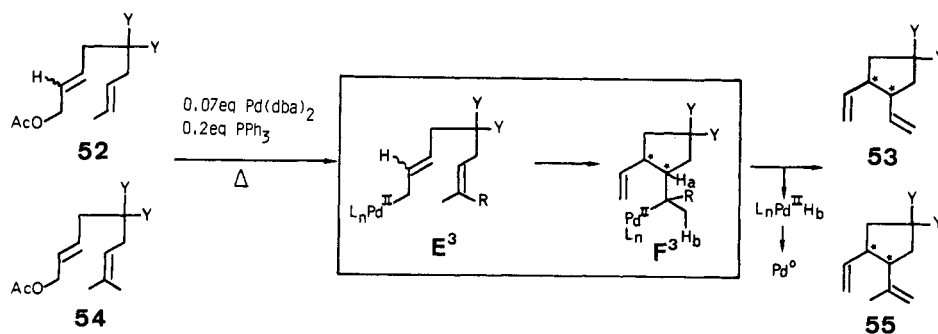
Scheme 19



Solvent	Phosphine (Equiv.)	Reaction Temp. (Reaction Time)	Yield % of <b>51</b>
Toluene	$\text{PPh}_3$ (0.2)	80°C (24h)	-
$\text{CH}_2\text{Cl}_2$	$\text{PPh}_3$ (0.2)	80°C (24h)	-
DMF	$\text{PPh}_3$ (0.2)	80°C (24h)	-
THF	$\text{PPh}_3$ (0.2)	80°C (40h)	20
MeOH	$\text{PPh}_3$ (0.2)	80°C (8h)	65
AcOH	$\text{PPh}_3$ (0.2)	80°C (1.5h)	77
AcOH	-	80°C (3h)	-

In striking contrast to 8-alkyl-substituted 2,7-dienylmagnesium halides which did not cyclize, the allylpalladium unit of  $\text{E}^3$  inserted readily into a terminally mono- and even di-methyl-substituted olefinic bond ( $\text{E}^3 \rightarrow \text{F}^3$ ) (Scheme 20).

Scheme 20



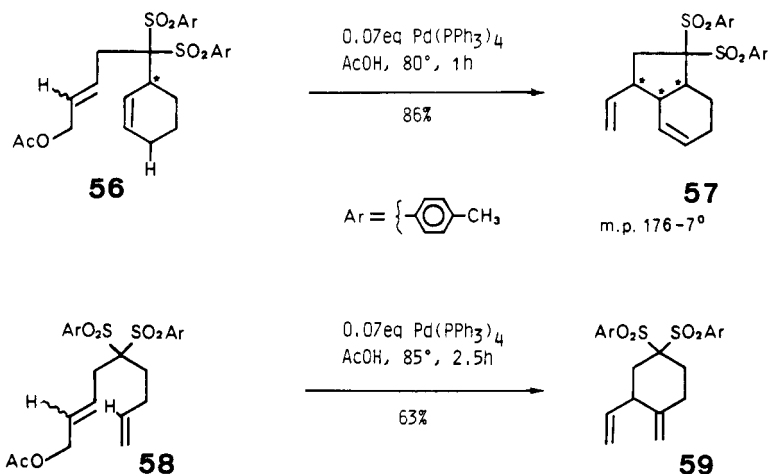
Starting Diene	Y	Solvent	Additive	Reaction Temp. (Reaction Time)	Product	Yield %
<b>52</b>	$\text{SO}_2\text{PhMe}$	THF	$\text{Na}_2\text{CO}_3$	80°C (24h)	<b>53</b>	-
<b>52</b>	$\text{SO}_2\text{PhMe}$	THF	-	75°C (15h)	<b>53</b>	80
<b>52</b>	$\text{SO}_2\text{PhMe}$	AcOH	-	75°C (1.5h)	<b>53</b>	91
<b>54</b>	$\text{SO}_2\text{PhMe}$	THF	-	85°C (40h)	<b>55</b>	40
<b>54</b>	$\text{SO}_2\text{PhMe}$	AcOH	-	75°C (1.5h)	<b>55</b>	71



Thus, Pd<sup>0</sup>-catalyzed cyclizations of 1-acetoxy-2,7-dienes **52** and **54** gave in each case a single 1,5-diene product **53** and **55**, respectively (to which the configurations are not yet assigned). It follows that the ene-step  $E^3 \rightarrow E^3$  is highly stereoselective and that the intermediate  $F^3$  eliminates the exocyclic  $H_b$  preferentially over  $H_a$  in agreement with the conformational constraints of a *syn*- $\beta$ -elimination process. Again, the cyclizations **52**  $\rightarrow$  **53** and **54**  $\rightarrow$  **55** proceeded significantly faster in acetic acid as compared to THF without change of the stereochemical outcome. In contrast, attempts to effect a Pd<sup>0</sup>-catalyzed cyclization of **52** in THF, while trapping the generated acetic acid by finely powdered Na<sub>2</sub>CO<sub>3</sub>, gave only unchanged **52**.

As expected, Pd(PPh<sub>3</sub>)<sub>4</sub> (0.07 equiv) turned out to be an equally efficient catalyst for intramolecular palladium ene reactions (Scheme 21).

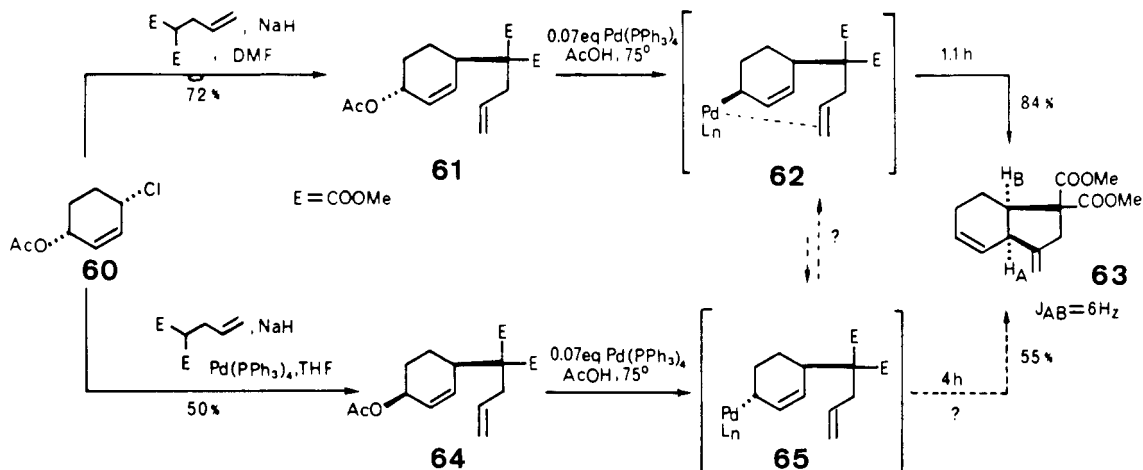
### Scheme 21



Thus, 1-acetoxy-2,7-diene **56** containing a cyclic "enophile" unit furnished stereoselectively the bicyclic product **57** in 86% yield. Similar conversion of the 1-acetoxy-2,8-diene **58** to **59** illustrates the feasibility of this method for 6-membered ring formation.

The palladium ene-unit may be also part of a ring as shown by the smooth Pd(PPh<sub>3</sub>)<sub>4</sub> catalyzed cyclization of the *trans*-acetoxydiene **61** which was complete after 1.1 h to give the *cis*-fused hydrindene **63** in 84% yield (Scheme 22).

### Scheme 22



Under similar conditions the *cis*-substituted acetoxydiene **64** reacted slower affording after 4h the identical *cis*-product **63** in only 55% yield. These results indicate that the olefin inserts into the allylpalladium unit preferentially *cis* relative to the Pd consistent with the intermediacy of **62**. However, in the epimeric complex **65** coordination of the Pd with the *trans*-disposed enophile is excluded. Therefore, the slower conversion of **64** to **63** may imply that **65** isomerizes to **62** (e.g. via the corresponding  $\pi$ -allyl complex), or that **65** undergoes a relatively slow "enophile"-insertion *trans* to the palladium.

