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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 π-face selective alkene functionalizations is exemplified by Diels-Alder reactions, osmylations, hydrogenations, conjugate additions (hydride, organocopper reagents, alkylmagnesium 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, $Pd(dba)_2/PPh_3$- or $Pd(PPh)_3$-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/β-elimination process.

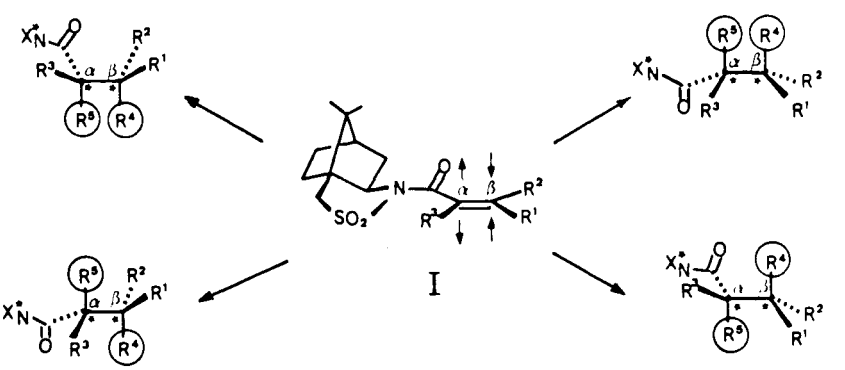
INTRODUCTION

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

π-FACE-SELECTIVE FUNCTIONALIZATIONS OF ALKENES

Thus, carbon-, hydrogen-and oxygen substituents may be introduced at Cβ and Cα of enoyl sultams I by a variety of reactions with high, "metal-dependent" face stereodifferentiation featuring either one of the four depicted topicities (ref. 1)(Scheme 1).

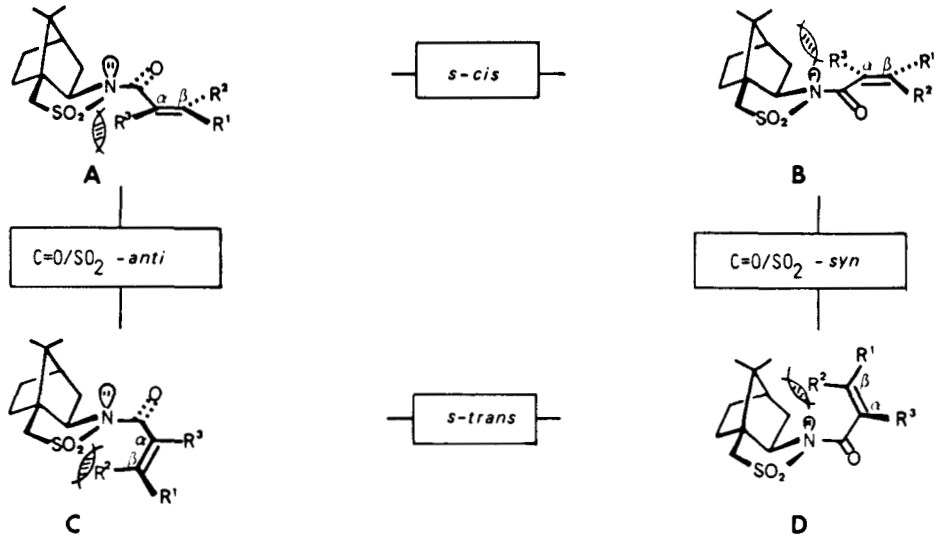
Scheme 1



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_2- and C=O groups and *s-cis*-related C=O/Cα-Cβ-bonds which correspsond to conformation A (Schemes 2,7). We thus propose as a general working hypothesis the following topicities for addition reactions to I (Scheme 2).

(1) Disposition of the C=O and SO_2 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/Cα, Cβ- bonds when the α-substituent R^3=H (A, B) but *s-trans* when R^3=alkyl and R^2=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).

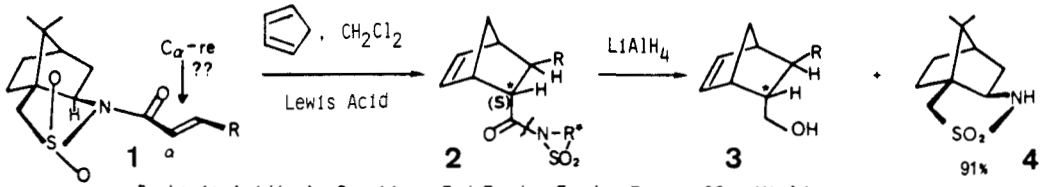
Scheme 2



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



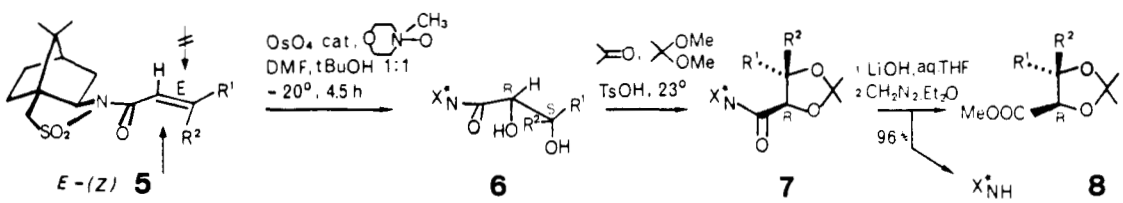
R	Lewis Acid(eq)	Reaction Temp.	Endo% (C=O)	d.e.% crude	d.e.% cryst.	m.p.°C cryst.	Yield cryst.
H	none	+ 25°	89	66			
Me	none	+ 25°	78	53			
H	$BF_3.OEt_2$ (1.5)	-130°	89	51			
H	$EtAlCl_2$ (1.5)	-130°	99.5	95	99	185.5-7	84
Me	$TiCl_4$ (0.5)	- 78°	99	93	99	184-5	83

The striking reactivity and topological control of the $EtAlCl_2$- or $TiCl_4$-promoted Diels-Alder reactions 1 → 2 are consistent with a chelation of the SO_2- and C=O-groups by the metal which directs the diene to the less hindered Cα-*Re*-face of the rigid conformation B (Scheme 2); this agrees with the poor results obtained with the monocoordinating Lewis acid $BF_3.OEt_2$.

Osmylations

An analogous topicity was observed on oxidation of β-substituted α,β-enoyl sultam 5 with N-methyl morpholine-N-oxide/OsO_4 (ref. 4),(Scheme 4).

Scheme 4

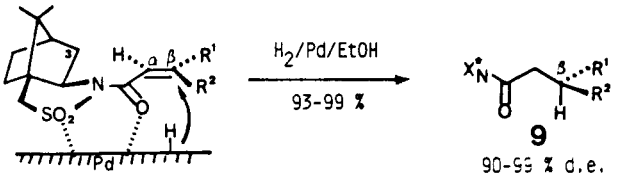


The resulting glycols 6 were converted into the more stable acetals 7, obtained after crystallization in <99% d.e. and in 63-74% yield from 5. Again we assume a metal-directed approach of the reagent from the less hindered Cα-*Re* (bottom) face of conformation B (Scheme 2).

Hydrogenations

High (91-98%) topological control was also achieved on simple hydrogenations (100 psi H_2, 4 mol% Pd/C, EtOH, r.t.) of β,β-disubstituted enoyl sultams (ref. 5),(Scheme 5).

Scheme 5

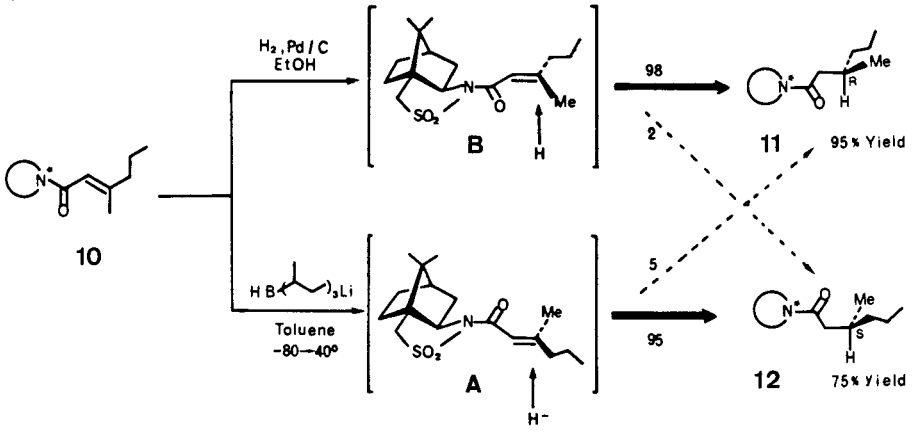


The π-face differentiation may be attributed to a coordination of the metal surface with the *syn*-disposed SO_2- and C=O groups followed by H-transfer to the bottom face of conformation B.

Conjugate hydride additions

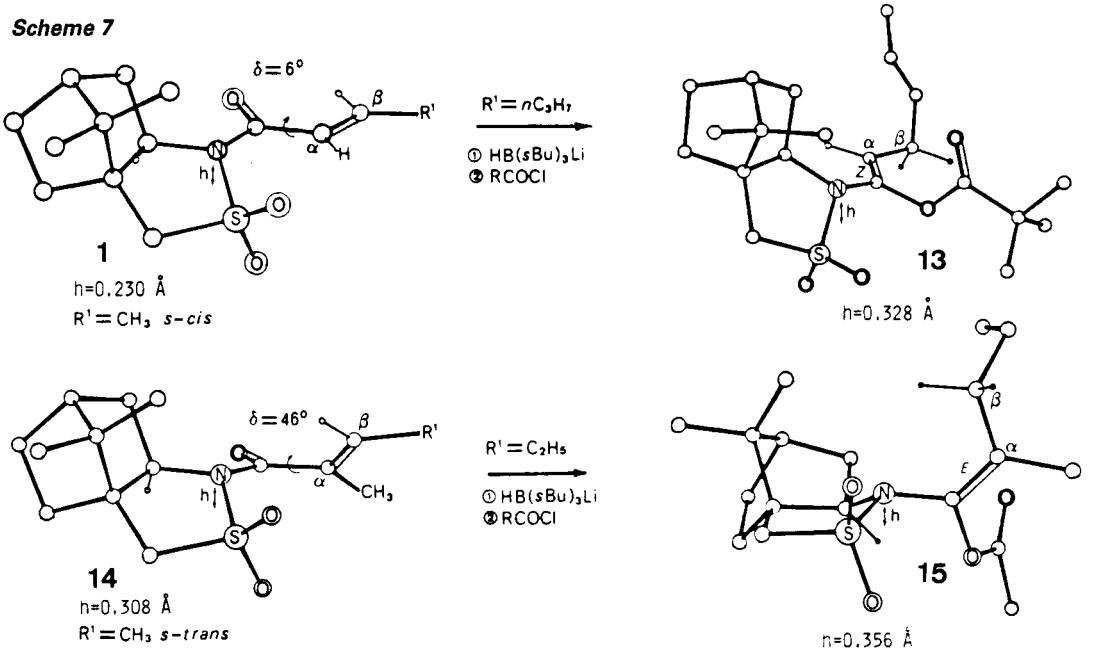
In surprising contrast, β,β-disubstituted enoyl sultams underwent efficient 1,4 hydride additions (on treatment with tri-*s*-butylborohydride) from the opposite π-face (ref. 6),(Scheme 6).

Scheme 6



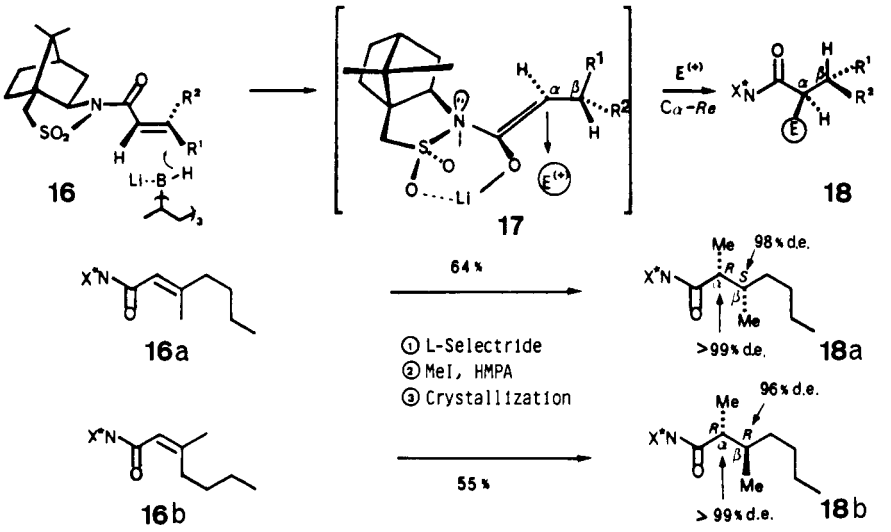
This agrees with a reactive conformation A of the α-unsubstituted enoyl sultam. Experimental support for this postulate and for part of our working hypothesis (Scheme 2) relies on 1,4-addition of *L-Selectride* followed by O-acylation of the resulting "enolates". X-ray diffraction comparison of enoyl 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 (α-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. NH_4Cl) or methylated (MeI, HMPA) to generate conveniently two centers of asymmmetry (at Cα and Cβ) in one synthetic operation (16 → 17 → 18, Scheme 8).

Scheme 8

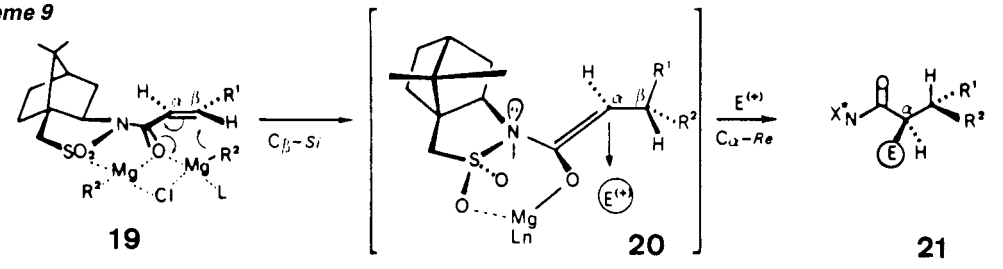


The MeI seems to approach the bottom face of enolate 17 (opposite to the lone electron pair on the nitrogen) owing to the steric or stereoelectronic bias of the auxiliary which overrides that of the preexisting center Cβ. As expected, the topological situation changes on subjecting α-substituted enoyl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

Conjugate additions of Grignard reagents

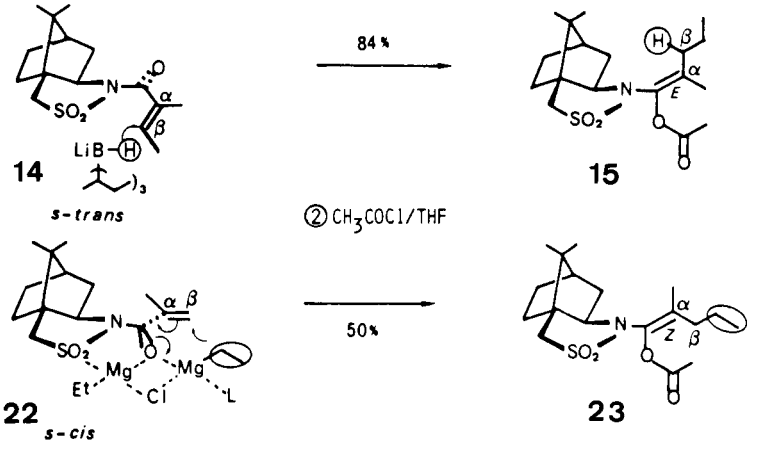
Most conveniently, simple alkylmagnesium chlorides (2.2 equiv) added smoothly in a 1,4-fashion to *β-trans*-substituted enoyl sultams 19 (77-90% d.e.), (ref. 8),(Scheme 9).

Scheme 9



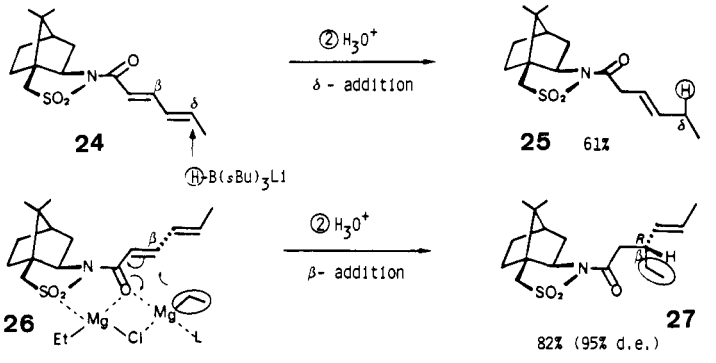
Protonation or methylation of the transient (*Z*)-enolates 20 gave after crystallization virtually pure (2*R*,3*R*)-imides 21. The stereochemistry of the addition at Cβ agrees with the postulate that a chelation by the magnesium and the operation of a six-membered cyclic mechanism requires the C=O/Cα,Cβ-*s*-*cis*-conformation 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 C=O--Mg-R^2--Cβ enforces the C=O/Cα,Cβ-*s*-*cis*-conformation B of 22 regardless of the α-methyl substituent to give 23 in contrast to the hydride addition 14 → 15 (proceeding by conformation C).

Scheme 10



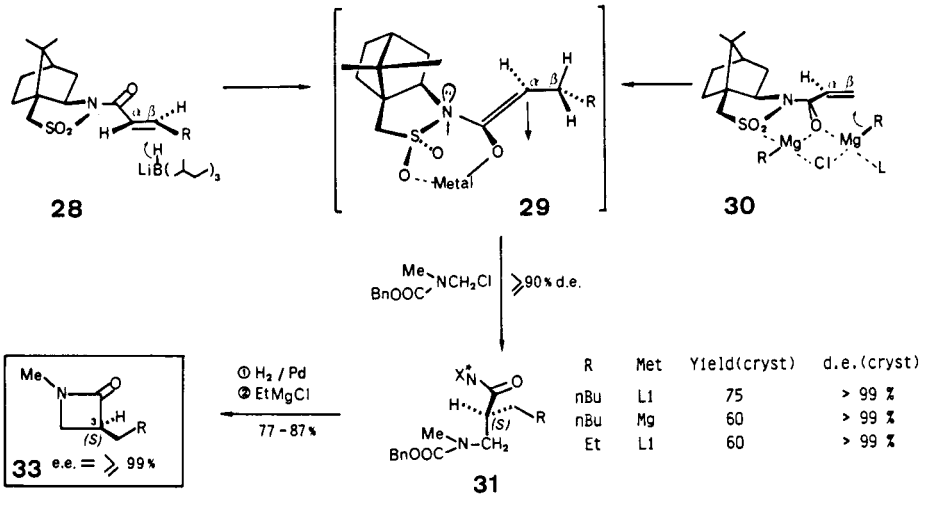
Probably for the same reason dienoyl sultam 24 underwent exclusive 1,4-addition of ethylmagnesium chloride (24 → 26 → 27) as compared to the 1,6-hydride addition 24 → 25 (Scheme 11).

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 β-lactams 33 (ref.9), (Scheme 12).

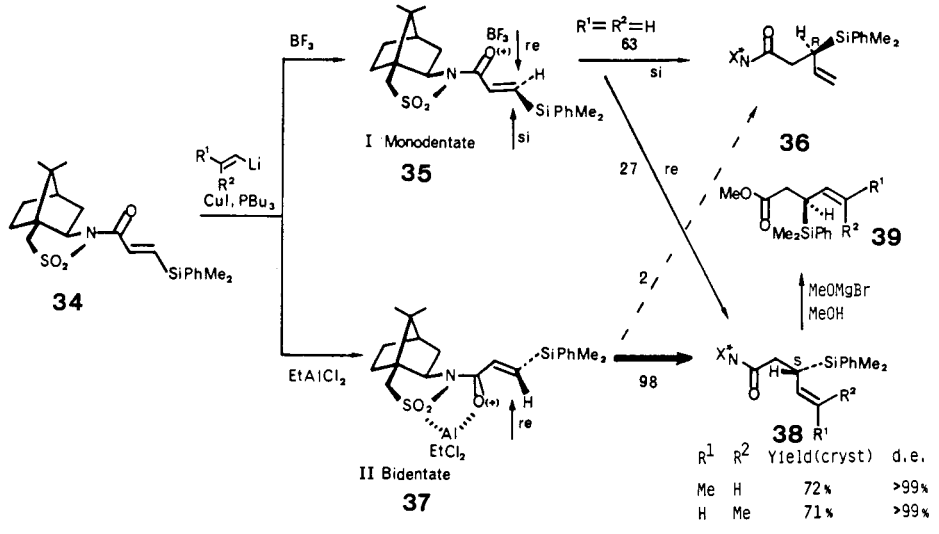
Scheme 12



Organocopper additions

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

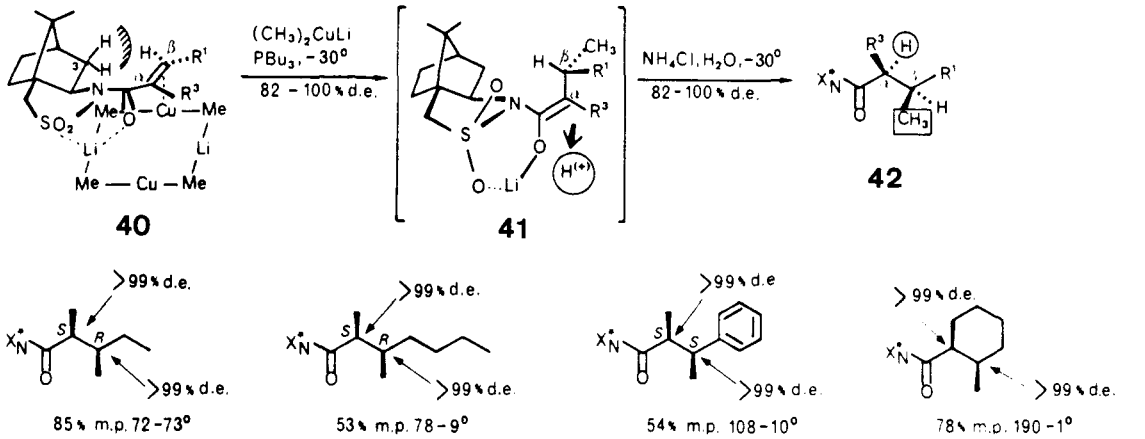
Scheme 13



Thus, opposite face stereodifferentiations were observed on $BF_3.OEt_2$-(34 → 35 → 36) versus $EtAlCl_2$-mediated (34 → 37 → 38) reactions. The latter conditions furnished crystalline adducts 39 and *via* their mild methanolysis (MeOMgBr, MeOH, 60°C) enantiomerically pure (*E*)- and (*Z*)- β-silyl-γ,δ-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 π-face-selective 1,4-additions of dimethylcopper lithium to (*E*)-α,β-disubstituted enoyl sultams (ref. 8), (Scheme 14).

Scheme 14

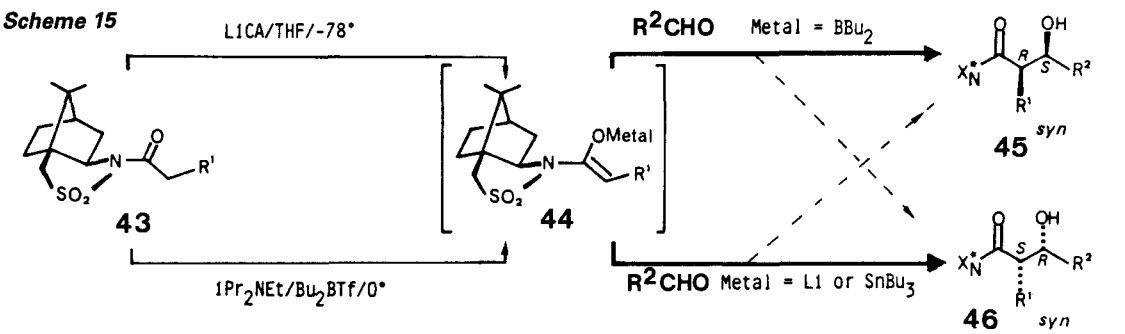


Protonation of the transient "enolates" 41 followed by crystallization yielded enantiomerically pure α,β-disubstituted carboxyl derivatives 42.

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[1] 45 : 46	Major Product Yield %[2]		Major Product d.e. %[2]	
Me	Ph	BBu_2	>95 : <5 (0)	45	78	45	>99
Me	iPr	BBu_2	>99 : <1 (0)	45	48	45	>99
Me	Me (-100°C)	BBu_2	>99 : <1 (0)	45	48	45	>99
Et	Me (-100°C)	BBu_2	>95 : <5 (0)	45	69	45	>95
Et	Ph	BBu_2	>95 : <5 (0)	45	63	45	>95
Et	iPr	BBu_2	>95 : <5 (0)	45	72	45	>95
Me	Ph	Li	8 : 85 (7)	46	72	46	>99
Me	iPr	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	$SnBu_3$	11 : 89 (0)	46	66	46	>99

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

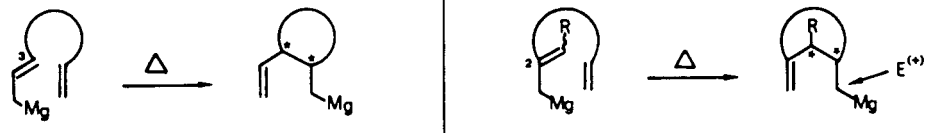
Thus, treatment of 43 with Bu_2BTf/iPr_2NEt followed by addition of aldehydes at -78°C gave the crystalline *syn*-aldols 45 in high diastereomeric excess. In comparison, deprotonation of 43 with LICA and aldolization of the lithium (or tin-) enolates 44 resulted in the formation of the diastereomeric *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, predictible 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}H-NMR and/or GC to determine their stereochemical purity and, last but not least, (6) cleaved (e.g. with $LiAlH_4$, LiOH, MeOMgBr, $Ti(OEt)_4$/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

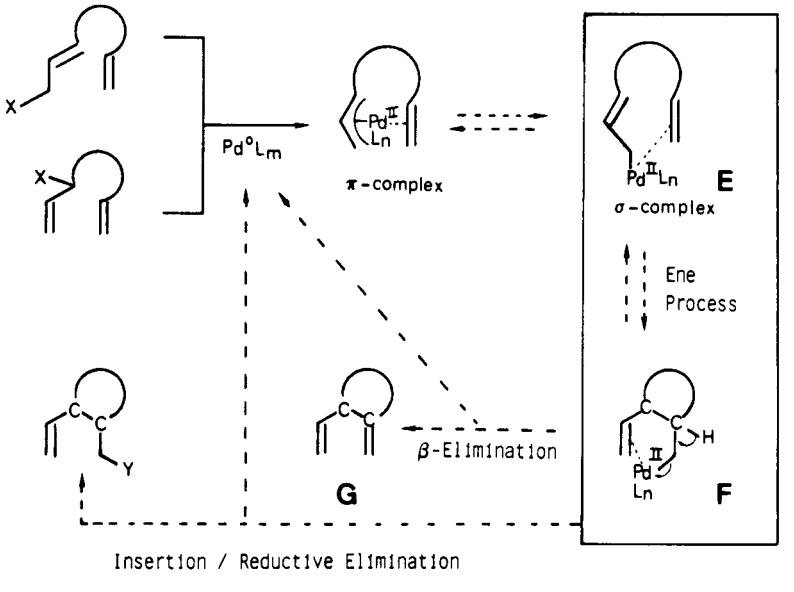


TYPE I : Enophilic Chain Linked to Olefinic Terminal of Ene-Unit (C-3)

TYPE II : Enophilic Chain Linked to Central Carbon of Ene-Unit (C-2)

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

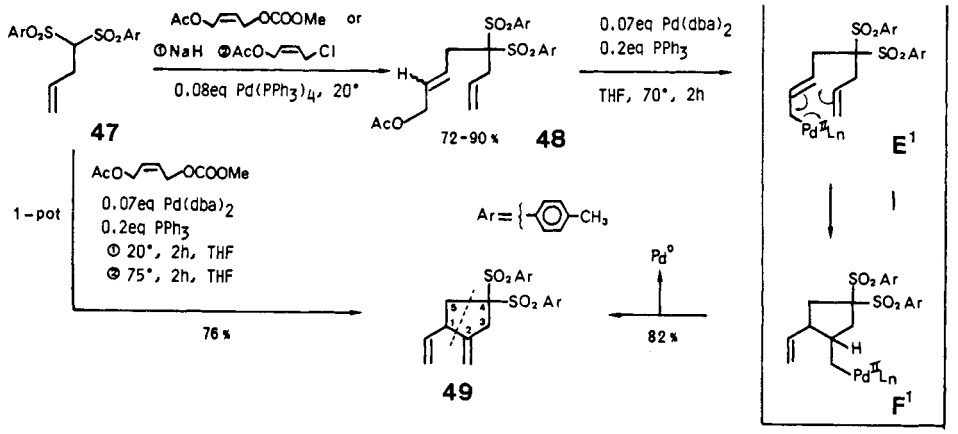


Whereas norbornadiene, norbornene and 1,3-dienes were reported to insert into stoichiometric amounts of allylpalladium complexes, simple olefins (e.g. styrene, cyclohexene, 1,4-cyclohexadiene and 1,5-cyclooctadiene) did not undergo this reaction under similar conditions (ref. 16). Nevertheless, we assumed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

In situ-preparation of the olefinic allylpalladium intermediates could be accomplished by oxidative addition of Pd^0-complexes to allylacetates (ref. 17). The required 1-acetoxy-2,7(8)-dienes were readily obtained, predominantly as their *E* -isomers *via* $Pd(PPh_3)_4$-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 47 → 48. (Scheme 18).

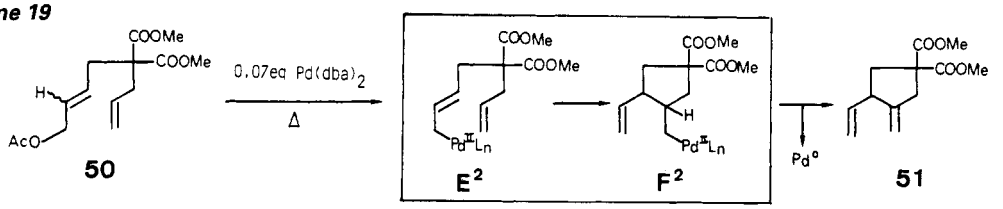
Heating diene 48 with $Pd(dba)_2$ (0.07 equiv) and PPh_3 (0.2 equiv) in THF at +70°C for 2h gave the expected cyclized 1,4-diene 49 in 83% yield. Even more conveniently, product 49 was obtained in one operation from disulfone 47 by treatment with (4-acetoxy-2-butenyl)-methylcarbonate (1.0 equiv), $Pd(dba)_2$ (0.07 equiv) and PPh_3 (0.2 equiv) in THF at + 20°C (2h) and then at +75°C (2h). Accordingly bonds C4-C5 and C1-C2 of cyclopentane 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).

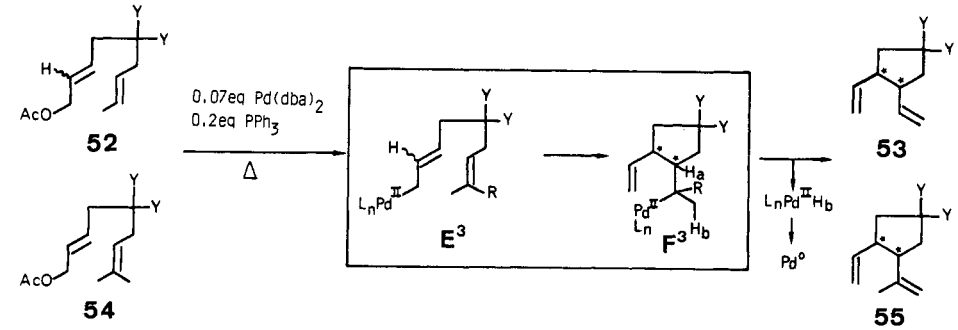
Scheme 19



Solvent	Phosphine (Equiv.)	Reaction Temp. (Reaction Time)	Yield % of 51
Toluene	PPh_3 (0.2)	80°C (24h)	-
CH_2Cl_2	PPh_3 (0.2)	80°C (24h)	-
DMF	PPh_3 (0.2)	80°C (24h)	-
THF	PPh_3 (0.2)	80°C (40h)	20
MeOH	PPh_3 (0.2)	80°C (8h)	65
AcOH	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 E^3 inserted readily into a terminally mono- and even di-methyl-substituted olefinic bond ($E^3 \rightarrow F^3$) (Scheme 20).

Scheme 20

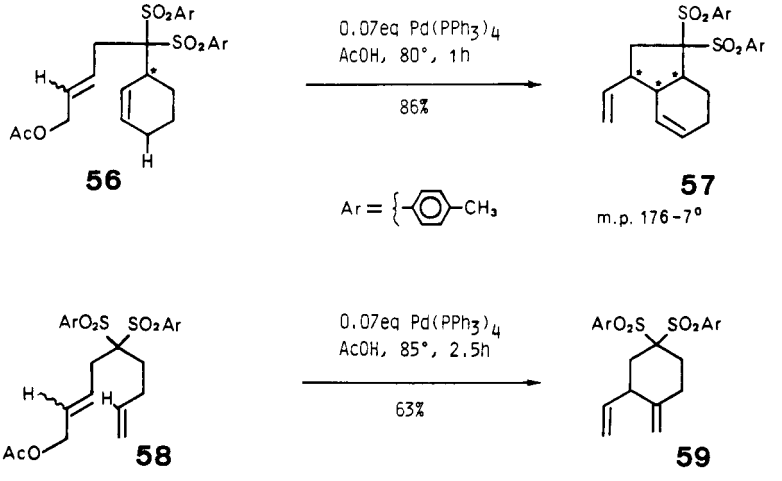


Starting Diene	Y	Solvent	Additive	Reaction Temp. (Reaction Time)	Product	Yield %
52	SO_2PhMe	THF	Na_2CO_3	80°C (24h)	**53**	-
52	SO_2PhMe	THF	-	75°C (15h)	**53**	80
52	SO_2PhMe	AcOH	-	75°C (1.5h)	**53**	91
54	SO_2PhMe	THF	-	85°C (40h)	**55**	40
54	SO_2PhMe	AcOH	-	75°C (1.5h)	**55**	71

Thus, Pd^0-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 $E^3 \rightarrow F^3$ 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*-β-elimination process. Again, the cyclizations 52 → 53 and 54 → 55 proceeded significantly faster in acetic acid as compared to THF without change of the stereochemical outcome. In contrast, attempts to effect a Pd^0-catalyzed cyclization of 52 in THF, while trapping the generated acetic acid by finely powdered Na_2CO_3, gave only unchanged 52.

As expected, $Pd(PPh_3)_4$ (0.07 equiv) turned out to be an equally efficient catalyst for intramolecular palladium ene reactions (Scheme 21).

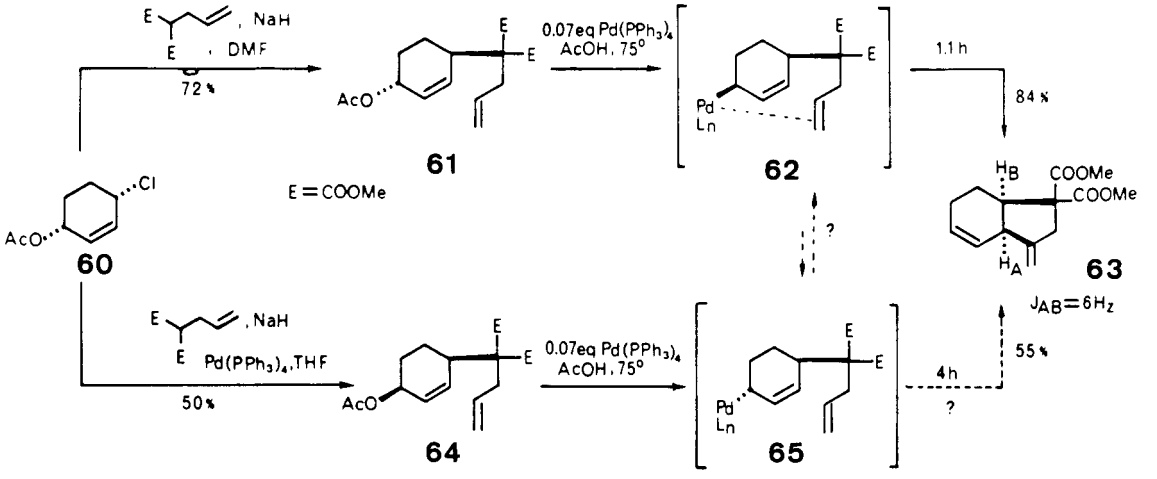
Scheme 21



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 $Pd(PPh_3)_4$ 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).

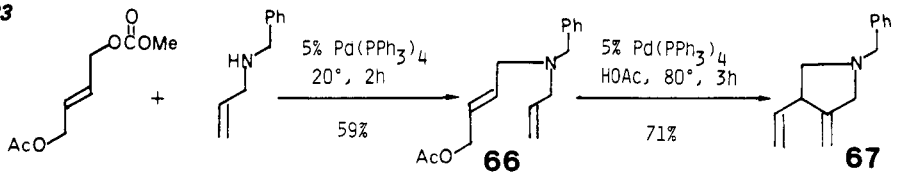
Scheme 22



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 π-allyl complex), or that 65 undergoes a relatively slow "enophile"-insertion *trans* to the palladium.

This process may also open new perspectives in alkaloid synthesis considering the smooth formation of a pyrrolidine: 66 → 67 (Scheme 23).

Scheme 23



In summary, we have shown here that catalytic intramolecular palladium-ene reactions are simple to carry out, compatible with various functional groups as well as applicable to 1,2-dialkyl-, trialkyl- and cyclo- alkenyl enophiles thus complementing advantageously the analogous magnesium-ene process. Further extensions and applications of this novel methodology are presently under investigation in our laboratories.

It is a privilege to acknowledge the crucial contribution of my coworkers whose names appear in the references. We thank the *Swiss National Science Foundation*, *Sandoz AG*, Basel and *Givaudan SA*, Vernier, for generous support of this work.

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