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Camphor as a natural source of chirality in asymmetric synthesis

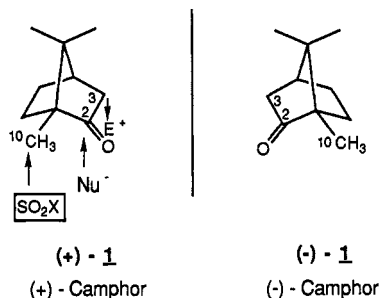
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Abstract: The readily available enantiomers of bornane[10,2]sultam serve as efficient, versatile and practical chiral auxiliaries. A selection of highly π -face-selective reactions of their *N*-enoyl derivatives (Diels-Alder additions, dihydroxylations, 1,4-additions) as well as of their *O*-metalated *N,O*-ketene acetals (aldolizations, alkylations, brominations, "aminations") are described. Applications to the syntheses of natural products and, particularly, of enantiomerically pure α -amino acids demonstrate their preparative potential.

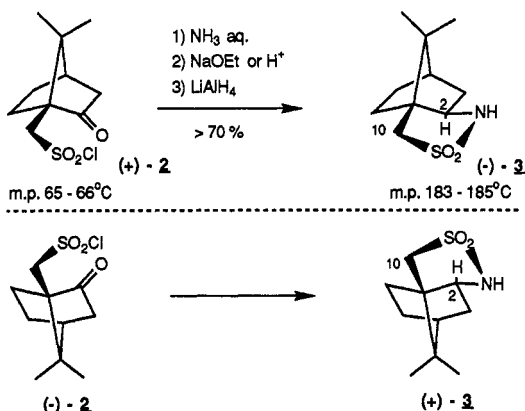
The abundance, crystallinity and manifold transformations of camphor (+)-**1** (Scheme 1) have attracted considerable interest throughout the history of organic chemistry. By means of various rearrangements and functionalizations at C(3), C(5), C(8), C(9) and C(10), as well as cleavage of the C(1)/C(2) and C(2)/C(3) bonds, camphor has served as a fascinatingly versatile starting material for the syntheses of enantiomerically pure natural products. This chemistry, which entails incorporation of the camphor topicity into the target molecules, has been reviewed (ref. 1).

Scheme 1



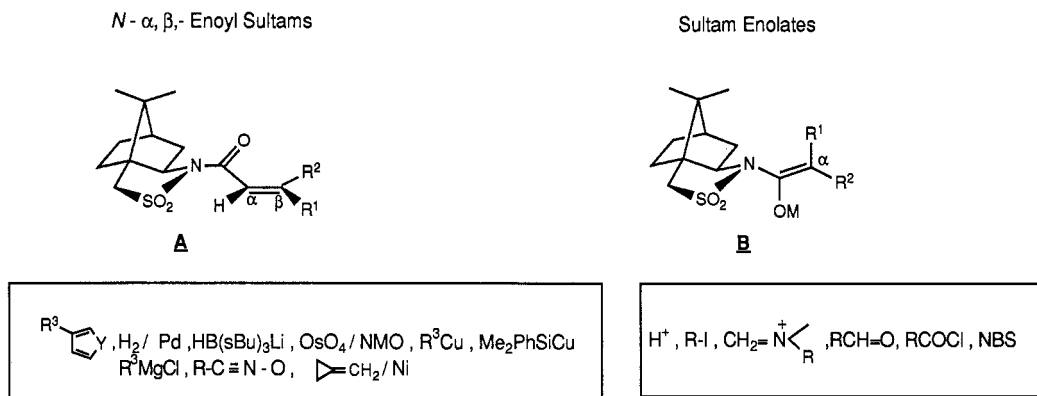
Here we address the issue of non-destructive chirality transfer from derivatives of (+)- and (-)-camphor which serve as covalently bound auxiliary groups. Particularly, the venerable C(10)-sulfonation of camphor, combined with the conformational rigidity of the bornane skeleton have spawned the most successful development of this field. Thus, bornane-10,2-sultam (-)-**3** and its antipode (+)-**3**, accessible from inexpensive (+)- and (-)-camphorsulfonic acids in two simple operations were introduced in 1984 and rank today among the most practical auxiliaries (Scheme 2) (ref. 3). Both chirophore enantiomers are commercially available in kg-quantities (ref. 3c).

Scheme 2

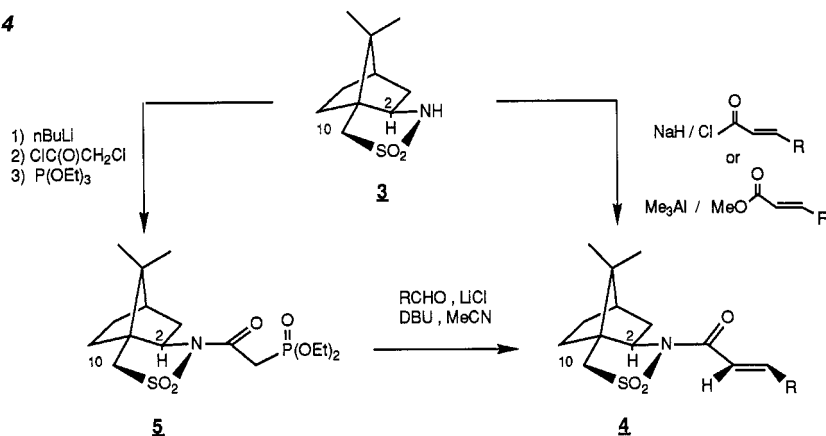


Addition reactions to *N*-enoyl derivatives **A**, as well as reactions of "enolates" **B** with electrophiles, proceed in high yield and with good to excellent π -face discrimination (Scheme 3).

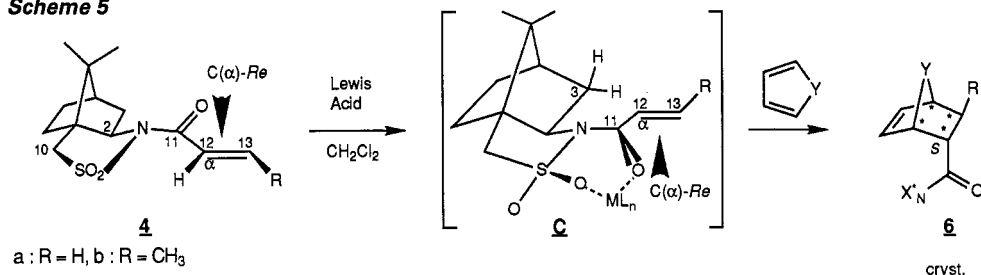
Almost all of the *N*-acyl products are stable and can be (1) readily purified by crystallization, (2) directly analyzed by ^1H -NMR and/or GC to determine their stereochemical purity, and (3) cleaved (e.g. with LiAlH_4 , LiOH , LiOOH , MeOMgI etc.) under mild conditions without loss of the induced chirality and with easy recovery of the auxiliary.

Scheme 3

The strongly dienophilic *N*-enoyl compounds **4** are readily prepared by direct *N*-acylation (NaH , RCOCl or Me_3Al , RCO_2Me) or *via* phosphonates **5** by means of a modified Wittig-Horner reaction (Scheme 4).

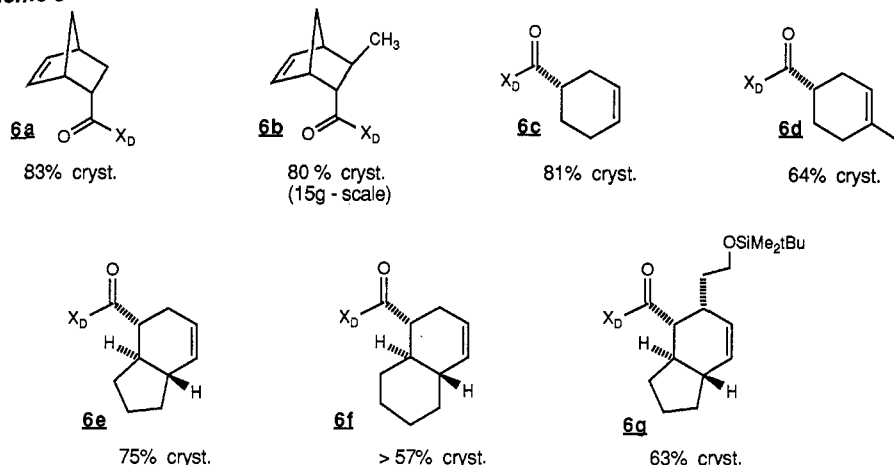
Scheme 4

Sultams **3** were in fact conceived as dienophile auxiliaries to extend the scope of asymmetric Diels-Alder reactions. In the presence of TiCl_4 , EtAlCl_2 or Me_2AlCl , cyclopentadiene added smoothly to the acryloyl sultam **4a** and to the less reactive crotonoyl sultam **4b** at -150 to -78°C (ref. 3, Scheme 5).

Scheme 5

Adducts **6a** or **6b** were formed with excellent *endo*- as well as π -face selectivities and obtained pure in good yields after crystallization. EtAlCl_2 - or Me_2AlCl promoted Diels-Alder addition of butadiene or isoprene to **4** also proceeded readily at -78°C or -94°C to give, after recrystallization, $\sim 100\%$ pure (*S*)-cyclohexenes **6c** or **6d** in 81 and 53-60% yield, respectively (Scheme 6).

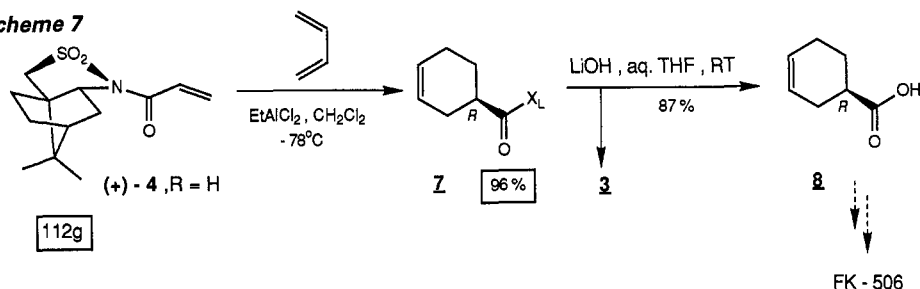
Scheme 6



Extension of the sultam-directed bias to intramolecular Diels-Alder reactions has proved equally successful as exemplified by the preparation of **6e**, **6f** and **6g**. Cycloadduct **6g** served as the key precursor for the enantioselective total synthesis of (-)-pulo'upone (ref. 3d).

The sense of asymmetric induction could be easily reversed by exploiting the readily available enantiomeric auxiliary (+)-**3**. It is worth noting that several of these sultam-controlled [4+2]-cycloadditions were smoothly carried out with 10g-, 15g-, and 112g batches of dienophile (e.g., Scheme 7).

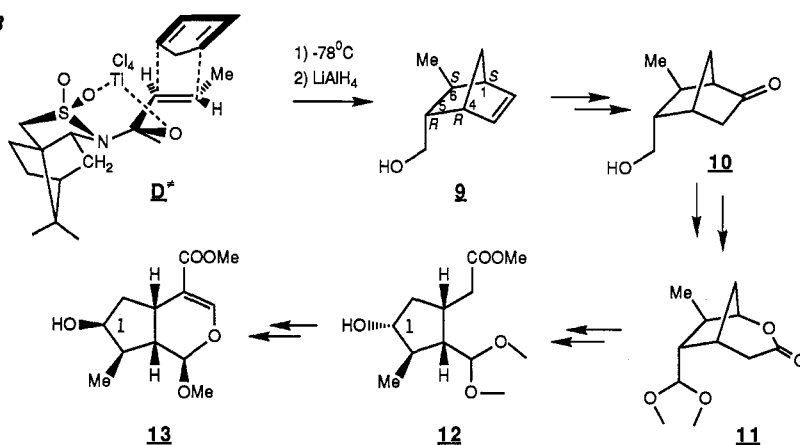
Scheme 7



Saponification of adduct **7** with LiOH afforded acid **8** (a potential precursor for a synthesis of the immunosuppressor FK-506) without epimerization (ref. 3e).

Alternatively, addition of cyclopentadiene to the antipode of **4** (R=Me), followed by reductive cleavage (LiAlH₄) furnished enantiomerically pure alcohol **9** which was transformed into (-)-1-*O*-methyl loganin aglucone **13** (ref. 3f, Scheme 8).

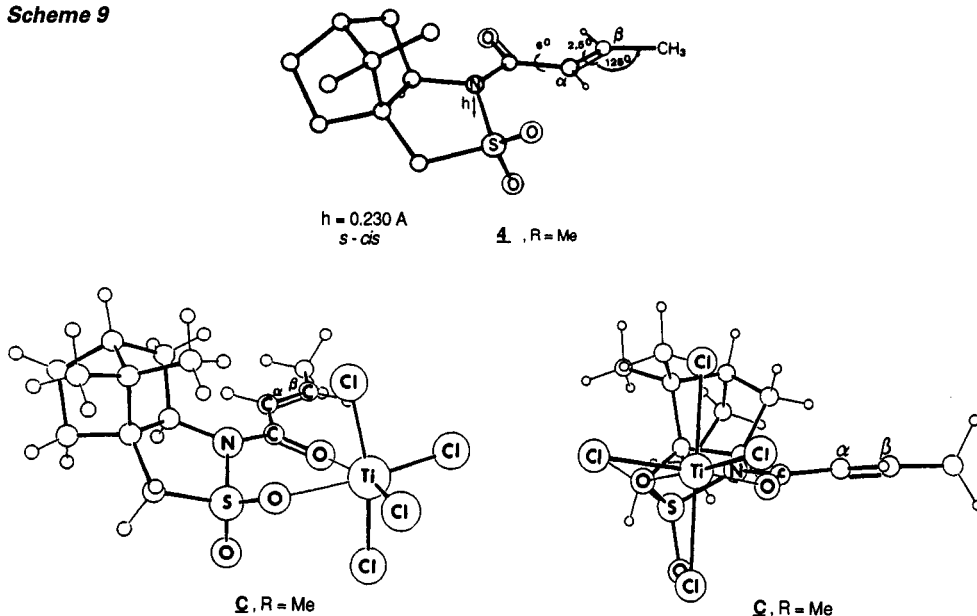
Scheme 8



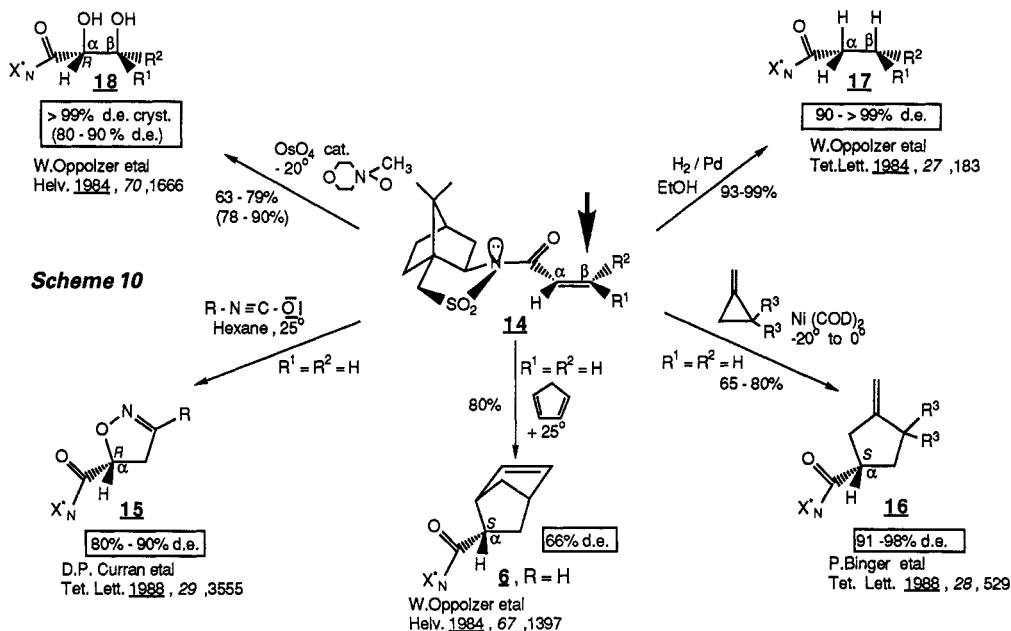
This synthesis illustrates the potential of asymmetric Diels-Alder reactions which in one step (**D***) created four stereogenic centers, of which all but C-1 (requiring C,O-inversion) possess the desired absolute configuration.

The remarkable TiCl_4 -, EtAlCl_2 - and Me_2AlCl enhanced rate and π -face differentiation of [4+2]-cycloadditions to *N*-enoylsultams **4** was rationalized in terms of chelates **Q** (Scheme 9), involving the di-coordinating Lewis acid ML_n , the carbonyl O-atom and the upper sulfonyl O-atom, which are attacked by dienes from the π -face opposite to the C-3 methylene group. Indeed, X-ray crystal-structure analyses of non-coordinated **4** ($\text{R}=\text{Me}$) (ref. 3a) and TiCl_4 -chelated *N*-crotonylsultam **Q** ($\text{R}=\text{Me}$) (ref. 3g) show in both cases *s-cis*-disposed $\text{C}=\text{O}/\text{C}(\alpha)=\text{C}(\beta)$ bonds but an $\text{NSO}_2/\text{C}=\text{O}$ -*s-trans* arrangement of **4** ($\text{R}=\text{Me}$) in the absence of TiCl_4 (Scheme 9). In the TiCl_4 -chelate **Q** ($\text{R}=\text{Me}$) the NSO_2 and $\text{C}=\text{O}$ groups are locked into a rigid *s-cis* conformation where the H_{exo} -C-3 apparently plays a major rôle in blocking the $\text{C}(\alpha)$ -*Si*-face (c.f., Scheme 9).

Scheme 9

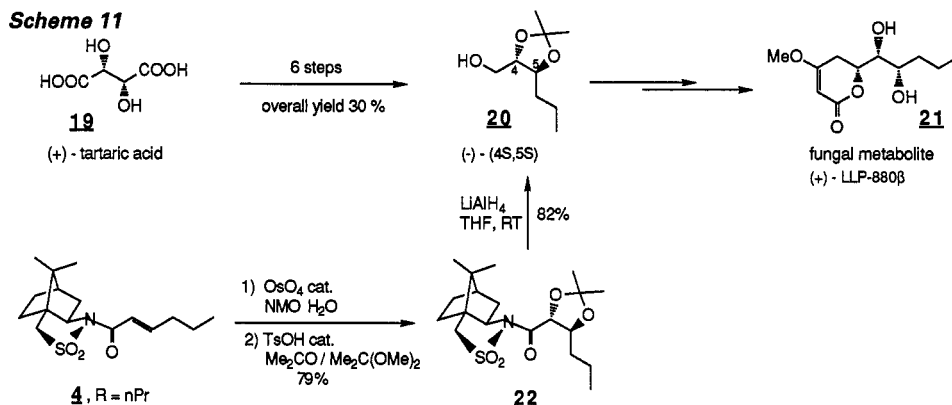


Surprisingly, even non-coordinated *N*-enoyl sultams underwent several addition reactions selectively from the $\text{C}(\alpha)$ -*Re*-face (Scheme 10).



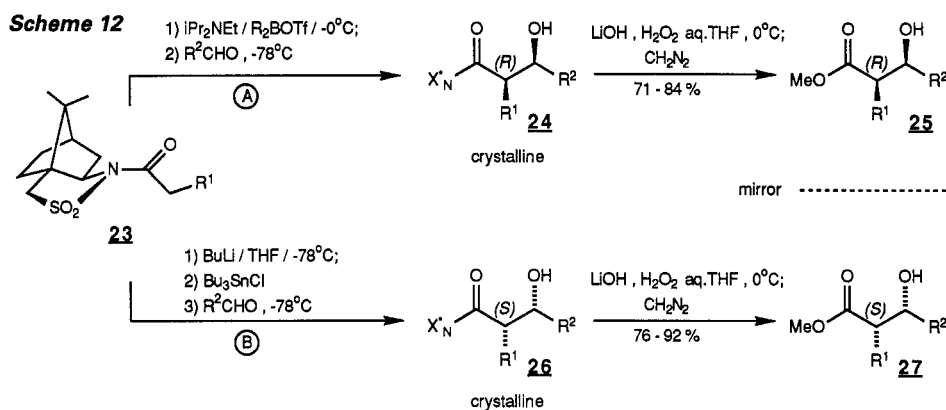
Assuming that the reactive conformation of **14** resembles that of **4** ($\text{R}=\text{Me}$), as found in the solid state, the conjugated alkene bond appears to be rather remote from the bornane skeleton. We, therefore, believe that the chiral information, provided by the bornane moiety is transmitted to the distant prochiral centers $\text{C}(\alpha)$ and $\text{C}(\beta)$, perhaps *via* the pyramidal nitrogen atom. Studies are underway to clarify the origin of this stereoelectronic effect by means of structure/induction correlations with analogous chiral sultams.

A synthetic application of the dihydroxylation $14 \rightarrow 18$ is depicted in the Scheme 11 (ref. 4). Thus, OsO_4 -promoted oxidation of **4** ($R=n\text{-Pr}$) with *N*-methylmorpholine-*N*-oxide, followed by acetalization, crystallization and reduction (LiAlH_4) provided enantiomerically pure hydroxydioxolane **20**, an otherwise much less easily available intermediate for a synthesis of the fungal metabolite **21**.

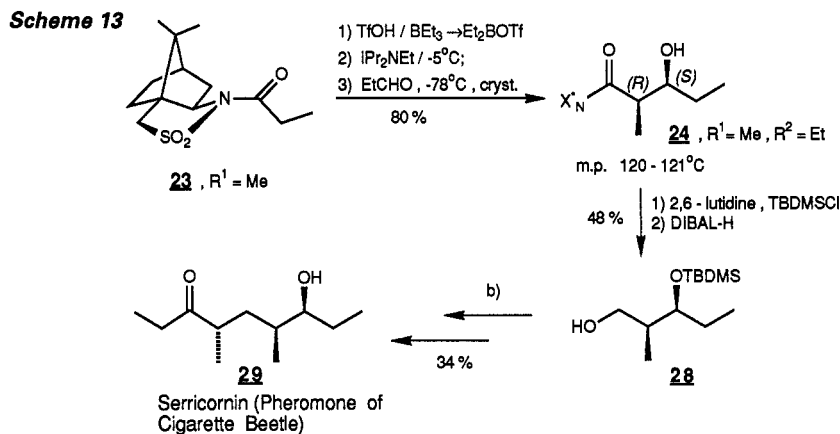


The use of chiral enolates **B** (Scheme 3) in asymmetric aldol reactions has ample precedent (ref. 5a). Nevertheless, sultam-directed aldolizations compare very favorably with other methods.

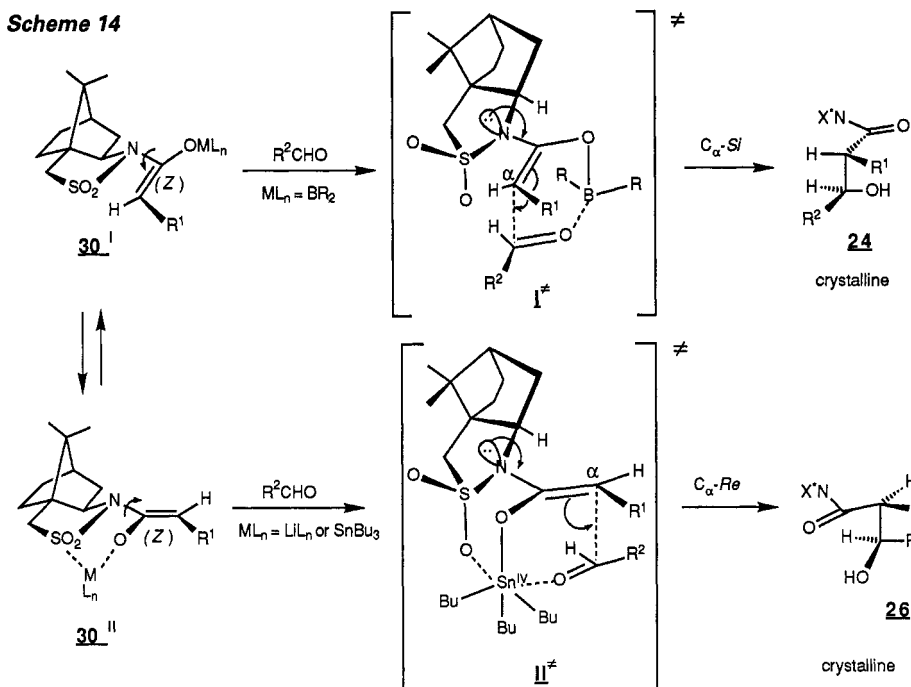
Thus, diastereomerically pure 'syn'-aldols result from *N*-acylsultams **23** via aldolization of their 'enolates' with aromatic and aliphatic aldehydes and subsequent crystallization. The absolute product configuration is controlled by the choice of the 'enolate counterion': Method A: boron $\rightarrow$ aldols **24**; method B: lithium or tin(IV) $\rightarrow$ aldols **26**. Hydroperoxide assisted hydrolysis/esterification provided enantiomerically pure methoxycarbonyl aldols (**25**, **27**) with recovery of auxiliary **3** (ref. 3b,5b, Scheme 12).



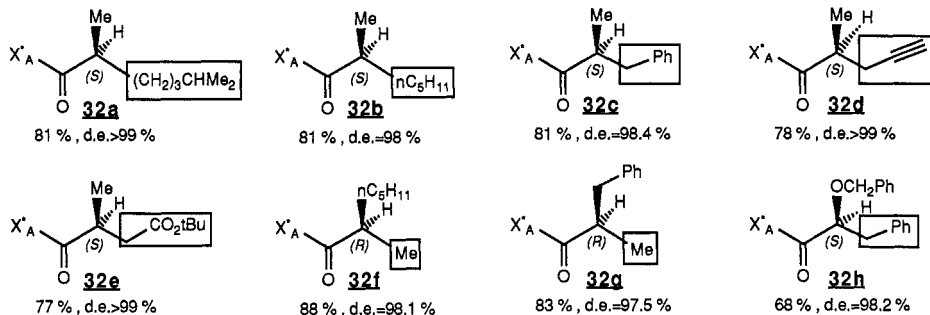
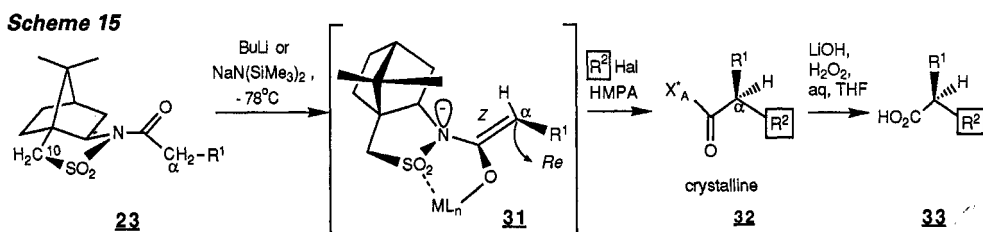
The borylenolate protocol (method A) seems to benefit from the *in situ* preparation of diethylboryl triflate. To illustrate the preparative value of this method, crystalline aldol **24** ($\text{R}^1=\text{Me}$, $\text{R}^2=\text{Et}$), obtained in 80% yield from **23** ($\text{R}^1=\text{Me}$), was silylated and cleaved with DIBAL-H to provide alcohol **28**, a precursor for the synthesis of the cigarette beetle pheromone serricornin **29** (ref. 5b, Scheme 14).



The stereochemical dichotomy between boron- and tin(IV) mediated aldolizations was rationalized by invoking 'closed' transition states $I^\ddagger$ or $II^\ddagger$. Both imply a coordination of aldehyde R^2CHO with the counterion of (*Z*)-enolate **30**. Li(I) and $Bu_3Sn(IV)$ can, furthermore, coordinate with a SO_2 oxygen atom ($II^\ddagger$) in contrast to the coordinatively saturated $R_2B(III)$ in $I^\ddagger$. Consequently, the enolate $C=C/N-SO_2$ conformation is either *s-cis* ($I^\ddagger$) or *s-trans* ($II^\ddagger$) which orients either the $C(\alpha)-Si$ -face ($I^\ddagger$) or $C(\alpha)-Re$ -face ($II^\ddagger$) opposite to the lone electron pair on the nitrogen atom (Scheme 14).



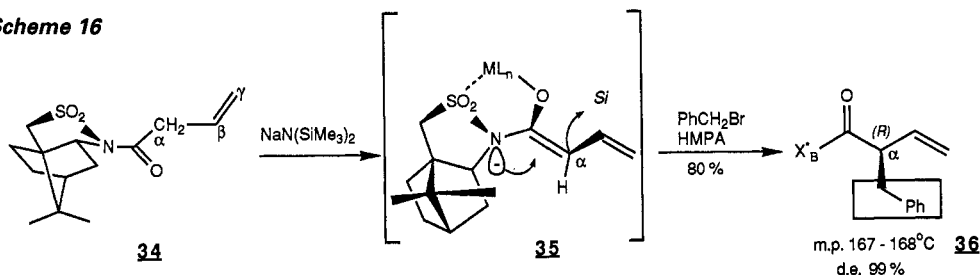
Electrophilic attack to the latter face was also observed on alkylations of chelated lithium- and sodium (*Z*)-enolates **31** (ref. 6, Scheme 15).



Thus, deprotonation of **23** with either $nBuLi$ or $NHDMs$ in THF, followed by alkylation with benzylic, allylic, propargylic, $C(\alpha)$ -alkoxycarbonyl halides and even with non-activated primary alkyl iodides, followed by crystallization, gave products **32** in high yield and diastereomeric purity. Non-destructive hydroxyperoxide-assisted saponification provided sultam **3** and enantiomerically pure carboxylic acids **33**. The absolute configuration at $C(\alpha)$ of **32** was easily directed in either sense by interchanging R^1 with R^2 or by using the antipodal auxiliaries **3**.

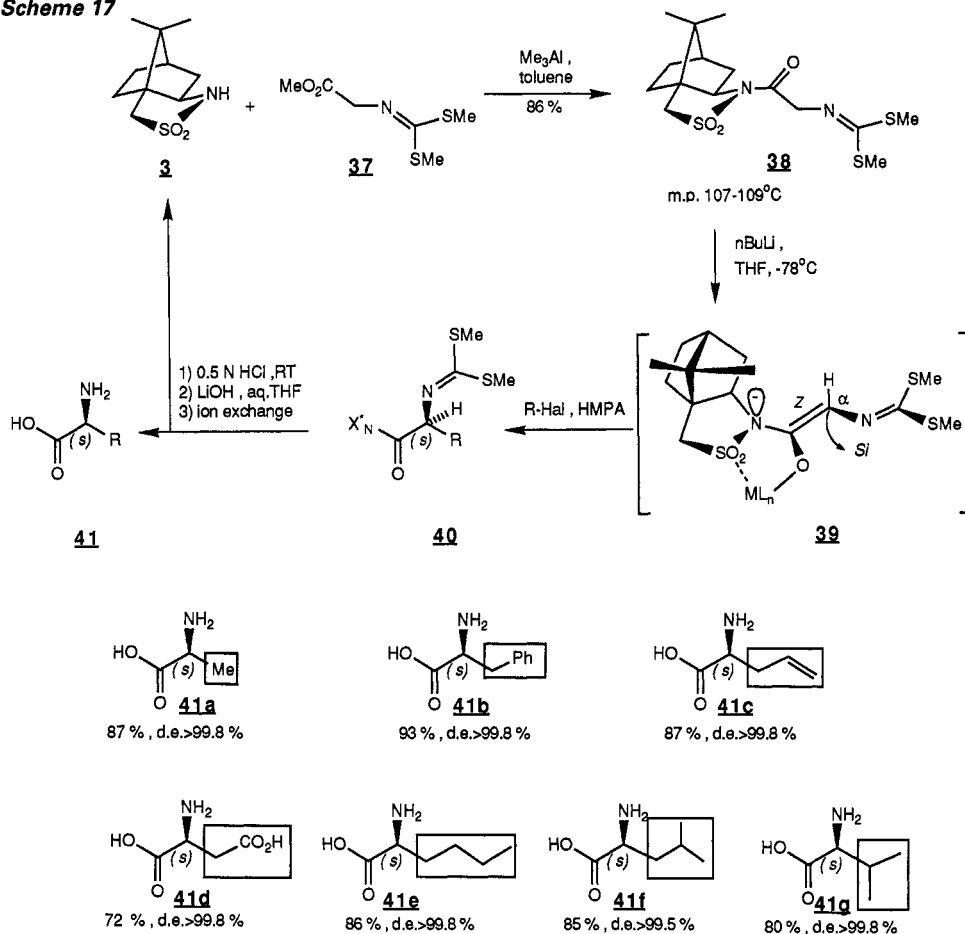
For example, benzylation of *N*-(3-butenyl)sultam **34** provided, via the transient dienolate **35**, pure (*R*)-product **36** (Scheme 16).

Scheme 16



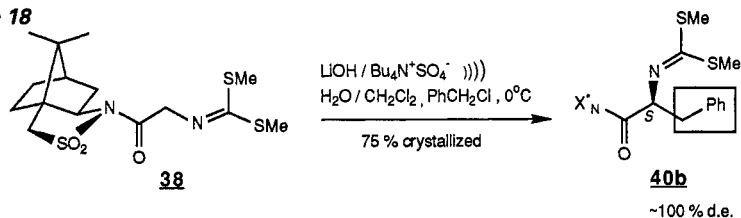
Analogous alkylation of easily available 'glycinate equivalent' **38** afforded a variety of α -amino acids **41**. The common crystalline precursor **38** reacted smoothly even with non-activated primary and secondary alkyl iodides. *N*-deprotection by mild acidic hydrolysis and gentle saponification gave the readily separable sultam **3** and the free amino acids **41** in high overall yield (ref. 7, Scheme 17).

Scheme 17



Intriguingly, simple deprotonation/alkylation at 0°C using phase transfer catalysis furnished crystallized **40b** in 75% yield without cleavage of the *N*-acyl moiety (Scheme 18).

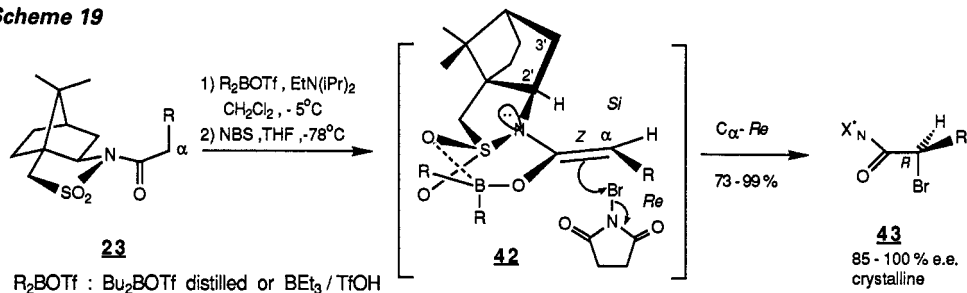
Scheme 18



Furthermore, heteratoms can be attached to C(α) of *N*-acylsultams **23** in a highly π -face-selective manner which provides alternative routes to enantiomerically pure α -amino acids.

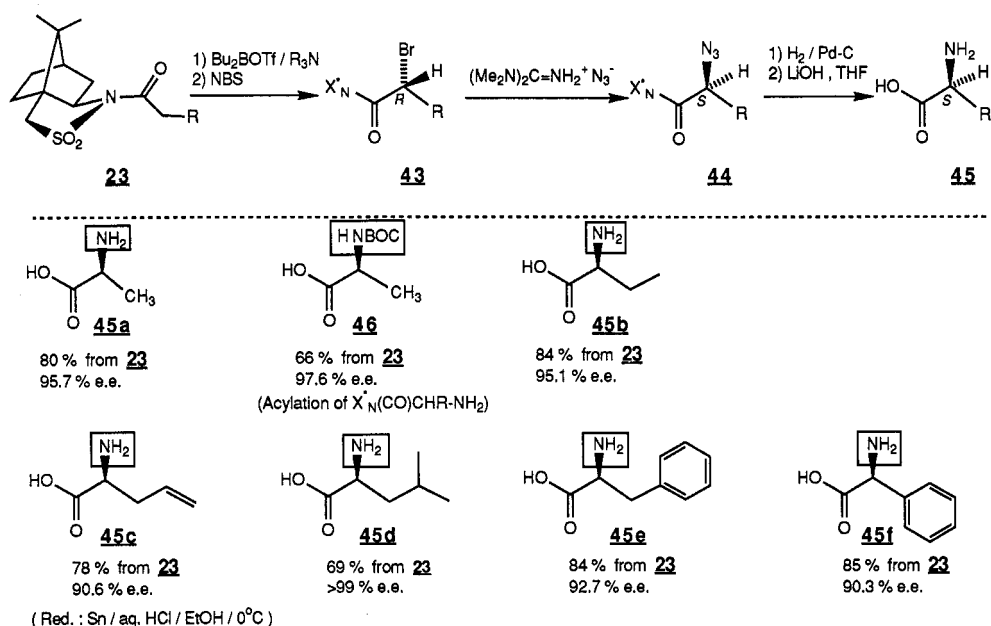
For example, treatment of *in situ* prepared boryl enolates **42** with NBS furnished (*R*)-bromides **43**, consistent with a bromination of chelated (*Z*)-enolates **42** at their C(α)-*Re*-face (Scheme 19).

Scheme 19



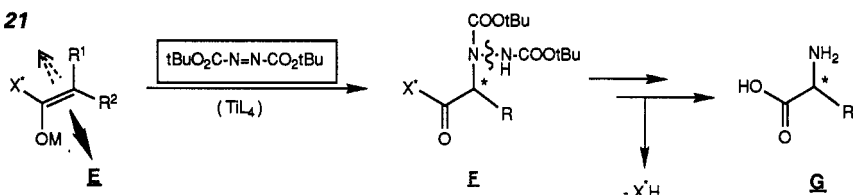
S_N2-displacement of the bromide with azide, followed by hydrogenolysis of the azide group and cleavage of the sultam moiety (LiOH, aq. THF, RT) furnished (*S*)-amino acids **45** in good overall yields from **23**. *N*-Acylation of the primary amino group prior to the final saponification step may lead to *N*-protected amino acids e.g., to **46** (ref. 8, Scheme 20).

Scheme 20



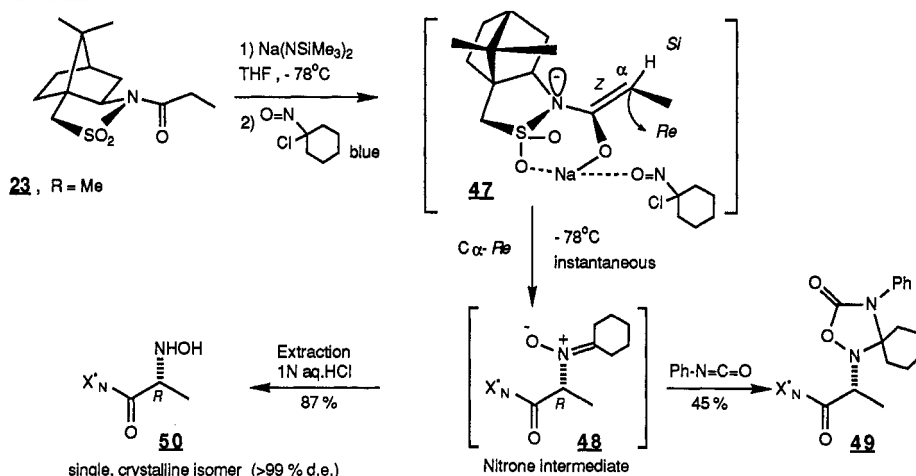
Asymmetric syntheses of α -amino acids from chiral enolates by direct electrophilic C-N bond formation have been so far restricted by the limited choice of "amination" reagents such as di-*t*-butylazodicarboxylate (ref. 9a-9d, Scheme 21) or 2,4,6-triisopropylbenzenesulfonyl azide (ref. 9e).

Scheme 21



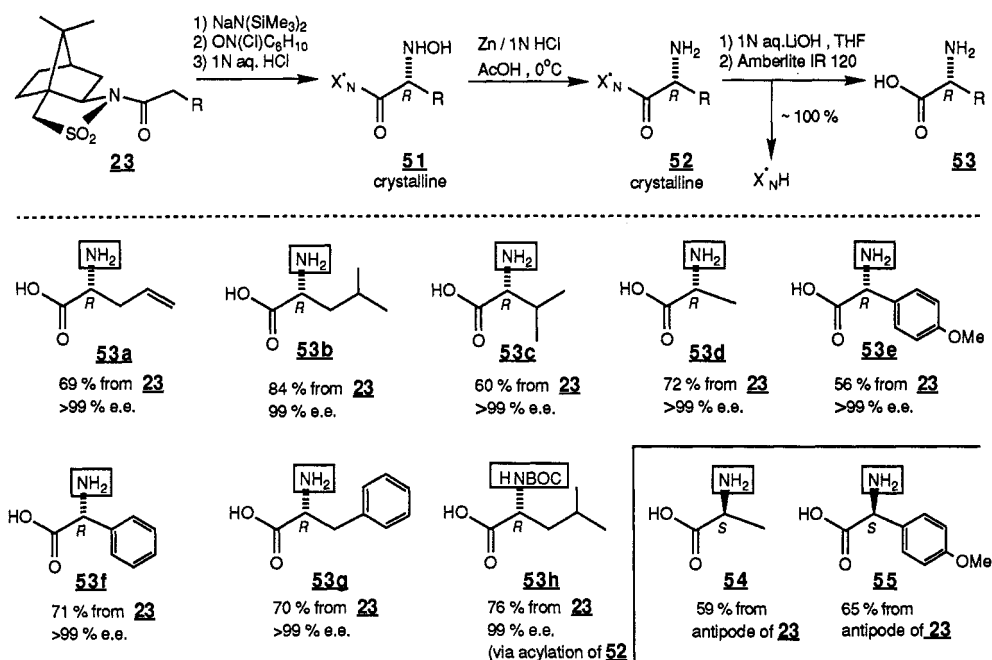
More advantageously, 1-chloro-1-nitrosocyclohexane (ref. 10) was used as an [NH₂⁺]-equivalent which attacked the (*Z*)-enolate **47** exclusively from the C(α)-*Re*-face to give (*R*)-hydroxylamine **50** on acidic workup (ref. 11). The transient nitron **48**, was identified as [3+2]-cycloaddition product **49**, (Scheme 22).

Scheme 22



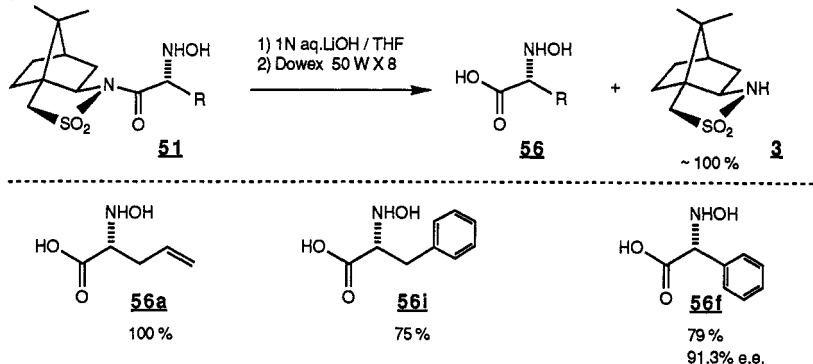
A variety of crystallized hydroxylamines **51** was subjected to *N/O*-hydrogenolysis (Zn/H^+) to afford amines **52** which, after saponification, gave enantiomerically pure (*R*)-amino acids in good overall yield from **23** (Scheme 23).

Scheme 23



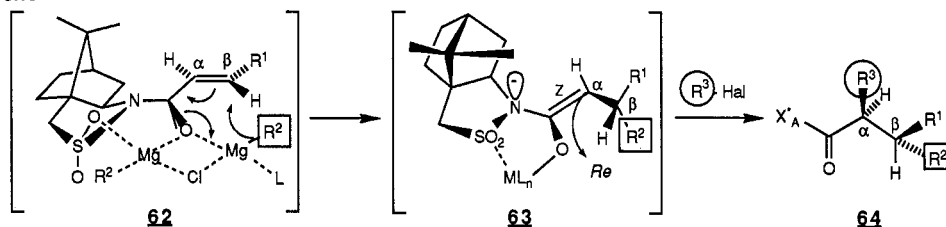
The mildly basic removal of the sultam moiety offers several advantages such as the ready access to *N*-protected amino acids (e.g., **53h**) or to α -*N*-hydroxyamino acids **56** (ref. 11, Scheme 24). α -*N*-Hydroxyamino acids are known as components of naturally occurring metabolites and of therapeutically interesting peptides.

Scheme 24



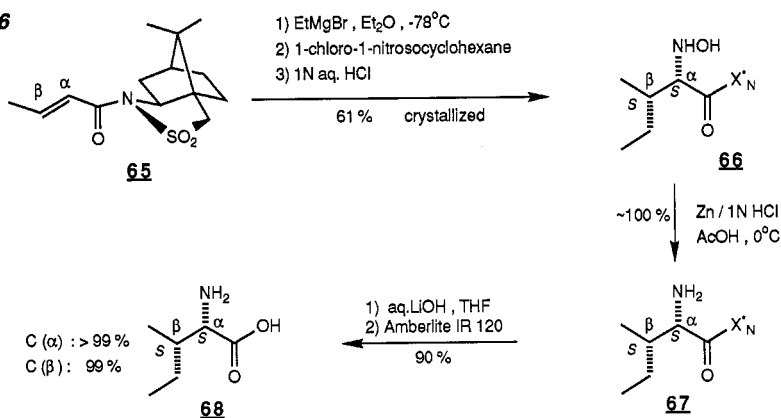
1,4-Additions of organomagnesium halides to *N*-enoylsultams are an attractive alternative for obtaining chiral enolates **63** since they allow for the highly selective generation of two stereogenic centers ($C(\alpha)$ and $C(\beta)$) in one synthetic operation (ref. 12, Scheme 25).

Scheme 25



Thus, the 1,4-addition/enolate "amination" tandem **65** $\rightarrow$ **66** was the key transformation in the efficient synthesis of (*S,S*)-isoleucine **68** from *N*-crotonoylsultam **65** (ref. 11, Scheme 26).

Scheme 26



The potential of this approach for the asymmetric synthesis of further β -branched α -amino acids is under current investigation.

In conclusion, compared to a plethora of auxiliaries so far developed for asymmetric synthesis, sultams **3** are among the most practical and universal. Extensions of their utility are to be expected.

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

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