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Asymmetric Thermal Reactions with Oppolzer's Camphor Sultam

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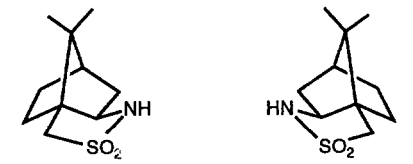
1. Introduction. Over the past four years, Oppolzer's camphor sultam[2] (Figure 1) has rapidly emerged as one of the most useful chiral auxiliaries for thermal reactions conducted in the absence of metals. Oppolzer has also convincingly shown that this sultam is a powerful auxiliary for all sorts of reactions involving metals.[2] As a consequence, Oppolzer's camphor sultam is one of the most generally useful chiral auxiliaries yet developed. Because of this general usefulness, it is especially worthwhile to try and understand why Oppolzer's sultam works so well. In this review, we will summarize the asymmetric thermal reactions of Oppolzer's camphor sultam and a few related auxiliaries. We will then put forth a model that rationalizes why Oppolzer's sultam gives reasonable levels of asymmetric induction in reactions where many other classes of chiral auxiliaries do not. We will also integrate our model for thermal reactions with Oppolzer's models for reactions in the presence of metals. A rather simple picture then emerges. We will suggest that Oppolzer's camphor sultam is a "2,5-dialkylpyrrolidine in disguise".

Figure 1. Oppolzer's Camphor Sultam.

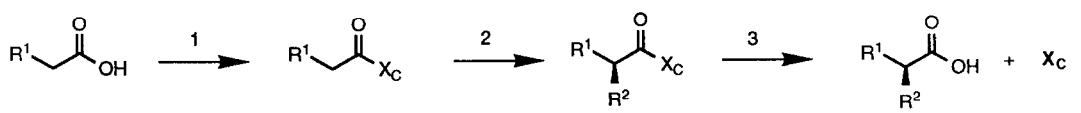


(–)-D-camphor sultam (+)-L-camphor sultam

A bornane-10,2-sultam

1.1 Chiral Auxiliaries: The use of chiral auxiliaries to control absolute stereochemistry is now a indispensable tactic in organic synthesis.[3] Figure 2 shows a schematic example of a typical strategy for controlling absolute stereochemistry in the formation of a bond adjacent to a carbonyl. An optically active chiral auxiliary is: 1) introduced into a substrate, 2) used to control stereochemistry in a subsequent bond-forming reaction, and 3) removed. If the initial substrate is achiral (as shown), the net result is formation of a chiral product, ideally with good control of absolute stereochemistry. Sometimes, the initial substrate is chiral, and the auxiliary is used to dictate stereochemistry at a given stereocenter relative to existing stereocenters.

Figure 2. Control of Stereochemistry with Chiral Auxiliaries.



achiral X_C = chiral auxiliary chiral, optically active

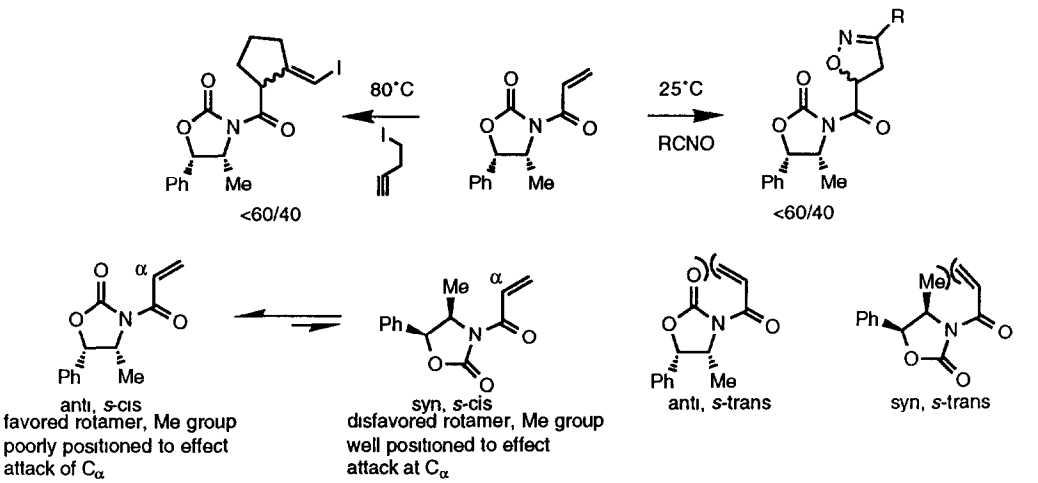
Most early reactions of chiral auxiliaries involved metals in one way or another.[3] In some reactions, such as enolate alkylations, the metal is a part of the reagent itself. In other reactions, such as Diels-Alder cycloadditions, the metal is a Lewis acid promotor (sometimes a catalyst), and the actual reactant is a complex of the metal and the chiral auxiliary. More recently, purely thermal reactions of chiral auxiliaries have come under scrutiny. Typically, these reactions involve no metal at all (radical

reactions,[4] dipolar cycloadditions[5]), but they may also involve metal reagents that do not form complexes with the chiral auxiliaries.

Recently, the asymmetric catalysis approach has begun to both supplement and complement the chiral auxiliary approach to controlling absolute stereochemistry.[6] However, to develop an asymmetric catalysis approach to a given reaction first requires a knowledge of how to catalyze the reaction. For large classes of reactions like radical additions and dipolar cycloadditions, general methods of catalysis are not yet available. Thus, the use of covalently bonded chiral auxiliaries is currently the only practical method to control absolute stereochemistry in such reactions.

1.2 Problems with Thermal Reactions of Chiral Auxiliaries: It is by no means safe to assume that chiral auxiliaries that are useful for enolate reactions and metal-catalyzed Diels-Alder reactions will be useful for thermal reactions in which no metals are involved. For example, Evans' chiral oxazolidinones are a powerful class of chiral auxiliaries that dictate stereochemistry in a wide variety of important reactions.[7] In contrast, we have observed that they exert virtually no stereocontrol in radical cyclizations or in dipolar cycloaddition reactions. Two representative examples are shown in Figure 3 (upper half).[8]

Figure 3. Thermal Reactions of Oxazolidinones.



We suspect that this inability to control relative stereochemistry is not unique to oxazolidinones. Many other imide- and amide-based chiral auxiliaries may also be ineffective in such reactions. Based on the conformational behavior of imides,[7] the problem with the oxazolidinones can be identified. We discuss this problem with the acrylimide derivatives used in the nitrile oxide cycloaddition; the analysis of the radical reactions is very similar (because radicals adjacent to carbonyls adopt very similar geometries to acrylates[4]). Taking into account the benefits of overlapping π-orbitals, the acrylimide has four reasonable rotamers (Figure 3, lower half): two about the imide C–N bond (syn, anti) and two about the acryloyl (O)C–C(=C) bond (*s*-cis, *s*-trans). The two planar *s*-trans rotamers are significantly raised in energy because there is a severe interaction between one amide substituent and the alkene. (For the same reason, Z-amide enolates are much more stable than E-amide enolates [9])

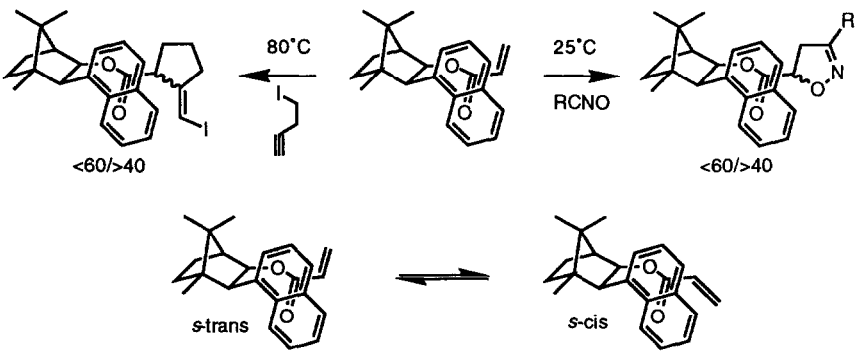
This phenomenon is not unique to oxazolidinones, but instead is shared by all acrylate derivatives of 3'-imides and amides. Between the two *s*-cis rotamers, the syn, *s*-cis rotamer is destabilized by an unfavorable dipole alignment. Thus, the anti, s-cis rotamer is highly populated in the ground state.

Despite this good level of ground state conformational control, the acrylimide still gives poor selectivity in the reactions shown in Figure 3. This is because the resident stereochemistry in the anti, *s*-cis rotamer is now too far away from the attacking reagent to significantly influence facial selectivity. In contrast, the syn, *s*-cis rotamer has the resident stereochemistry well placed to control face selectivity. However, the unfavorable dipolar interactions that operate in the ground state of the syn, *s*-cis rotamer persist in the transition state. Since there is no obvious stabilizing interaction to compensate for this destabilizing one, we believe that transition states resembling the syn, *s*-cis rotamer will be higher in energy that those resembling the anti, *s*-cis rotamer. Likewise, transition states resembling both *s*-trans rotamers should be even higher in energy.

The problem with these imides then is that the favored rotamer has a poor location of the face shielding group, but that the unfavored rotamer has a good location. This problem is not unique to oxazolidinones; it applies to other imides as well. By adding a chelating metal, the rotamer ordering can be changed; bidentate chelation can now favor the syn, *s*-cis rotamer.[7] This chelation strategy has been highly effective for Diels-Alder reactions,[7] but it has not yet been implemented in dipolar cycloadditions or radical reactions.

Typical ester-based chiral auxiliaries have a different problem. Take for example the chiral borneol-based auxiliary used by Taber in asymmetric Rh-catalyzed C–H insertions[10] (related auxiliaries are useful for a variety of reactions[3b]). Once again, this auxiliary gives dismal induction (Figure 4) in the same pair of reactions used in Figure 3.[8] The problem here is not the location of the face shielding group; we assume that the "back" face of this molecule is very efficiently shielded. Instead, it seems likely that reactions occur with both *s*-cis and *s*-trans rotamers of the acylate ester. These two rotamers are probably not far apart in energy in the ground state, and we presume that the related transition states are not far apart in energy either.[11] Because the *s*-cis and *s*-trans rotamers present different faces of the alkene to the attacking reagent, diasteromeric mixtures result. Once again, the introduction of a metal can solve this problem; it is generally thought that metal chelation with acrylate esters favors *s*-trans rotamers.[11]

Figure 4. Thermal Reactions of Borneol Esters.



In the absence of a metal, control of *both* rotamer population and face shielding must be "built-in" to the chiral auxiliary. Many acrylimides and acrylamides have good rotamer control, but place the stereodirecting elements in a poor location. In contrast, acrylic esters can present problems of rotamer control, and may give poor selectivity even though spectacular shielding groups are both present and well located.

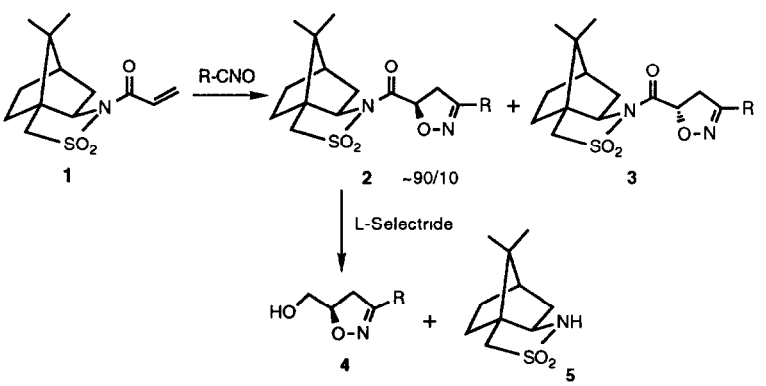
The examples presented in Figures 3 and 4 illustrate another common problem with asymmetric thermal reactions: temperature. The radical annulations are sequential chain reactions[12] that do not propagate well at room temperature or below (however, rapid radical reactions can proceed at low temperatures). Nitrile oxide cycloadditions also proceed at drastically reduced rates as the temperature is lowered. The simple expedient of lowering the temperature to increase selectivity is then limited by the rates of some reactions. Auxiliaries that effect useful levels of asymmetric induction at room temperature and above are desirable.

1.3. Oppolzer's Camphor Sultam: As the name implies, Oppolzer's camphor sultam (Figure 1) was first prepared by Oppolzer and coworkers in 1984.[13] Reactions of this sultam in the presence of metals (enolate alkylations, conjugate additions, Lewis acid catalyzed Diels-Alder reactions) have been extensively investigated by the Oppolzer group with excellent success.[2] In 1988, back-to-back papers by Oppolzer[14] and ourselves[15] indicated that the sultam might be generally useful for controlling stereochemistry in the absence of chelating metals. Since then, contributions to the thermal chemistry of acryloyl derivatives of Oppolzer's sultam have come from quite a number of groups.

Oppolzer's camphor sultam is easy to prepare from camphor, and both enantiomers are currently commercially available at identical prices. It is typically introduced by standard acylation reactions. Reductive or hydrolytic removal of the auxiliary is relatively easy because it is a sulfonimide (see examples below). Recycling of the auxiliary after removal is often practical.

2. Examples of Reactions. The following section provides a review of all the thermal reactions of derivatives of Oppolzer's camphor sultam reported through early 1992. The presentation is organized by reaction class. Reactions of metals are included where we suspect that the metal plays no role in chelation; that is, the stereochemistry is controlled by the uncomplexed auxiliary.

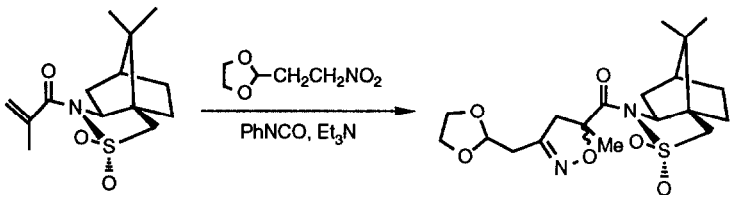
2.1 Dipolar Cycloadditions: 2.1.1 Nitrile Oxides: Among several 1,3-dipolar cycloadditions with Oppolzer's camphor sultam, nitrile oxide cycloadditions have been studied the most (eq 1). The



eq 1

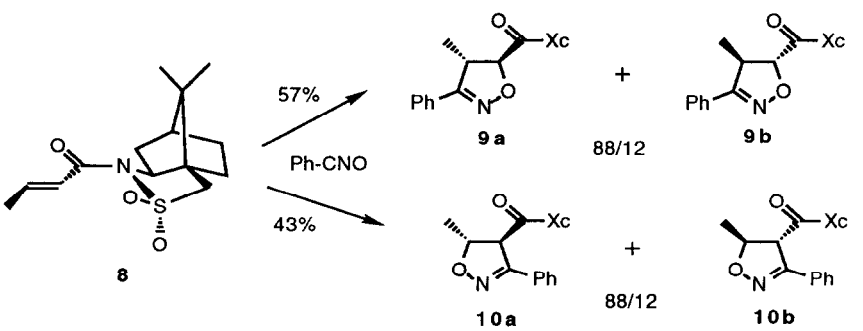
cycloadditions of various nitrile oxides with *N*-acryloyl camphor sultam **1** produced mixtures of diastereomers **2** and **3** with good diastereoselectivity (90/10).[15] After flash chromatography, the major diastereomer **2** was isolated in pure form in good yields (59-85%). Reduction of **2** with L-selectride™ provided easily separable mixtures of optically pure 2-isoxazoline **4** and recovered camphor sultam **5**. The absolute configuration of **4** was assigned by both chemical correlation and X-ray crystallography. The diastereoselectivity in these nitrile oxide cycloadditions is useful, if not spectacular. Indeed, the discovery that Oppolzer's sultam provides good levels of selectivity was important because several other chiral auxiliaries were already known to be relatively ineffective.[16]

Recently, the scope of asymmetric nitrile oxide cycloadditions was extended by using *N*-methacryloyl camphor sultam **6** and *N*-crotonoyl sultam **8**.[17] The *N*-methacryloyl camphor sultam **6** was prepared in 96% yield by acylation of L-camphor sultam, and was reacted with 2-(2-nitroethyl)-1,3-dioxolane under Mukaiyama conditions.[18] A mixture of diastereomers **7** (stereochemistry unassigned) was produced in 86% yield in a ratio of only 65/35 (eq. 2). Not only is *N*-methacryloyl camphor sultam **6** less selective than *N*-acryloyl camphor sultam **1**, it is also significantly less reactive.



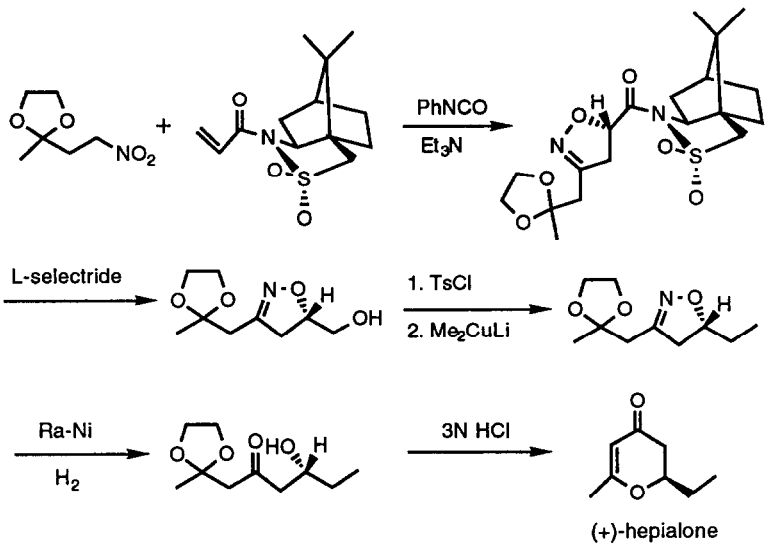
The cycloaddition of *N*-crotonoyl camphor sultam **8** with benzonitrile oxide gave a mixture of four products. The regioisomers **9a/b** and **10a/b** were formed in a ratio of 57/43. Within each regioisomeric pair, there was a pair of stereoisomers (**a/b**) that was formed in a ratio of 88/12 (Scheme 1). Regioselectivity in nitrile oxide cycloadditions with crotonates is usually poor, and the crotonoyl camphor sultam **8** is no exception. However, there is a reasonable level of facial selectivity that is independent of the regiochemical orientation of the approaching nitrile oxide.

Scheme 1. Xc = L-camphor sultam



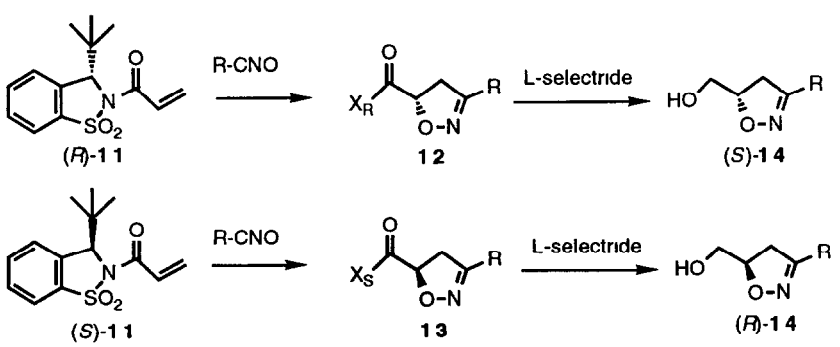
Curran and Heffner[17] demonstrated the synthetic utility of asymmetric nitrile oxide cycloadditions with Oppolzer's camphor sultam by achieving the total syntheses of three natural products: (+)-hepialone, (–)-(1*R*, 3*R*, 5*S*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane, and (-)-(1*S*)-7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane. These syntheses served to show that the optically active isoxazolines could be converted into a variety of common functionalities. The synthesis of (+)-hepialone is outlined in Scheme 2.

Scheme 2

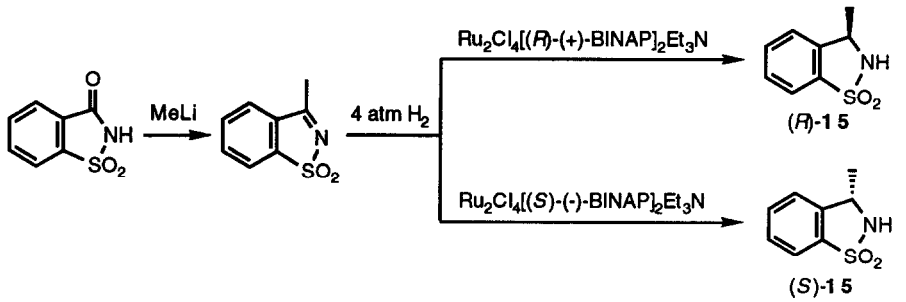


In 1991, Oppolzer and coworkers[19] reported asymmetric nitrile oxide cycloadditions with new *N*-acryloyl toluene sultam dipolarophiles (Scheme 3). Thus, cycloadditions of 2,2-dimethyl-propionitrile oxide, benzonitrile oxide, acetonitrile oxide and propionitrile oxide with (*R*)-**11** gave isoxazolines **12** and their diastereomers (not shown) in ratios >95:5. This level of selectivity is comparable to the highest levels previously reported for nitrile oxide cycloadditions (with acrylimide

Scheme 3

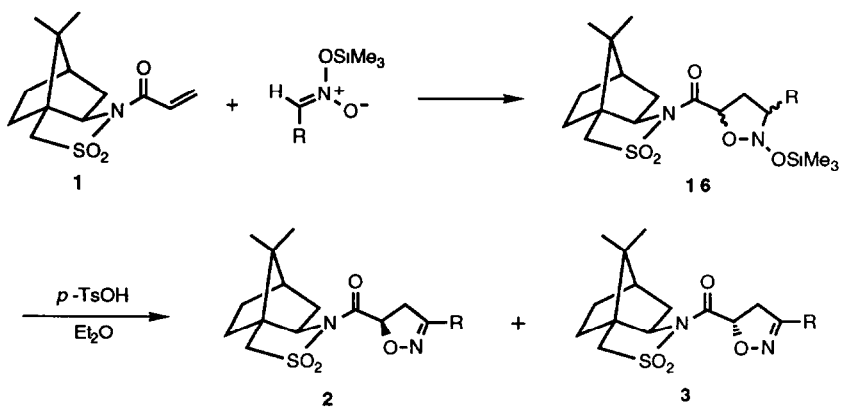


derivatives of Kemp's triacid[20]). The sense of induction was easily reversed by employing the antipodal substrate (*S*)-**11**. The absolute configuration of alcohols **14** was assigned by chiroptic comparison with published values. Sultam **11** is a relative of Oppolzer's toluene sultam **15**, which was introduced in 1990.[21] Starting from relatively inexpensive saccharine, each antipodal sultam **15** was prepared in two steps in 53% overall yield (eq. 3). The observed position of the proton on the nitrogen atom in the X-ray crystallographic structure of toluene sultam **15** shows the nitrogen atom is pyramidal.[22]



eq 3

2.1.2 Silyl Nitronates: Asymmetric silyl nitronate cycloadditions with *N*-acryloyl (2*R*)-camphor sultam (**1**), *N*-acryloyl(2*S*)-camphor sultam (ent-**1**), and *N*-methacryloyl (2*R*)-camphor sultam (ent-**6**) were studied by Kim and coworkers (eq 4).[23] The cycloadditions of **1** with in situ-generated silyl nitronates, followed by *p*-toluenesulfonic acid catalyzed elimination of trimethylsilyl alcohol from *N*-trimethylsilyloxyisoxazolidine cycloadducts **16**, produced the diastereomeric mixtures of 2-isoxazolines (**2** and **3**) in good diastereoselectivity (90/10). The asymmetric silyl nitronate cycloaddition/elimination methodology provides a general route for the asymmetric synthesis of 2-isoxazolines, and it is used as a key element in the asymmetric synthesis of (+)-methyl nonactate and (–)-methyl 8-*epi*-nonactate.[24]

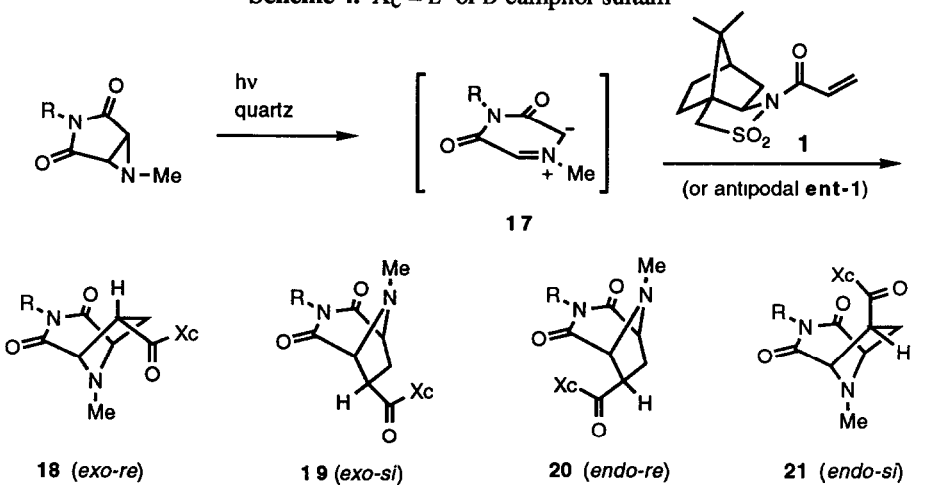


1 16 2 3

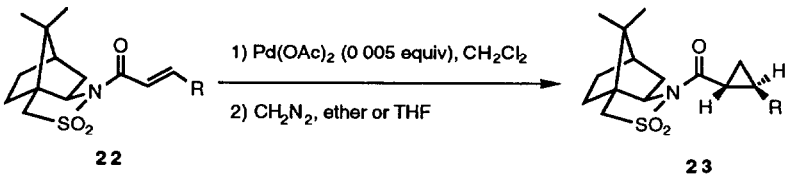
eq 4

2.1.3 Azomethine Ylides: Garner and coworkers observed that cycloadditions of photochemically generated azomethine ylides **17** with *N*-acryloyl camphor sultams **1** and ent-**1** showed uniformly excellent diastereofacial selectivity (>25:1) (Scheme 4).[25] The major product **18** derived from an "exo-re" attack. Like the nitrile oxides, dipole **17** reacted with an assortment of other chiral acrylates with little or no facial selectivity. This asymmetric azomethine ylide cycloaddition set the stage for a concise enantioselective synthesis of quinocarcin and related substances.

Scheme 4. X_C = L- or D-camphor sultam

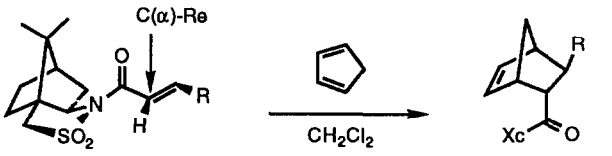


2.1.4 Cyclopropanation with Diazomethane: Vallgarda and Hacksell showed that cyclopropanations of *N*-enoyl camphor sultams **22** with diazomethane in the presence of catalytic amounts of $Pd(OAc)_2$ provided the cyclopropanated products **23** with good diastereoselectivity (85/15 to 95/5) (eq. 5).[26] Chemical correlation was used to determine that the products **23** had the *1R, 2R* stereochemistry.



eq 5

2.2 Diels-Alder Reactions: Thermal Diels-Alder reactions of *N*-enoyl camphor sultams **1** or **24** with cyclopentadiene gave endo selective (R = H, 89%, R = CH_3, 79%) Diels-Alder adducts **25a** or **25b** in moderate diastereoselectivity (R = H, 83/17, R = CH_3, 76/24) (eq 6).[27] Rate enhancement and high selectivity were obtained by Lewis acid-promoted Diels-Alder reactions. Cyclopentadiene predominantly added from the C(α)-Re-face in both the thermal and Lewis acid promoted reactions.

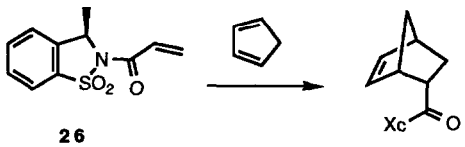


1 R=H
24 R=CH_3

25a R=H
25b R=CH_3
Xc = D-camphor sultam

eq 6

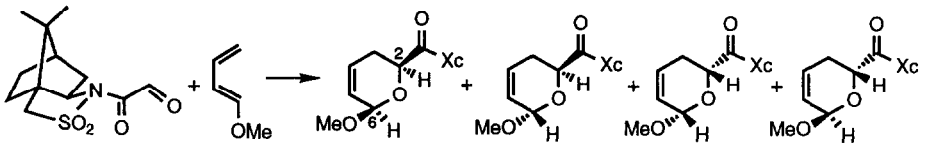
Thermal Diels-Alder reaction of *N*-acryloyl toluene sultam **26** with cyclopentadiene occurred smoothly (eq 7).[28] The endo/exo selectivity was high (96:4), but diastereomeric excess of the endo products was modest (81/19).



26

eq 7

Jurczak and coworkers observed that the [4+2] cycloaddition of 1-methoxybuta-1,3-diene to *N*-glyoxyloyl camphor sultam **27** gave rise to the cycloadducts **28-31** (eq. 8).[29] The uncatalyzed reaction at ambient temperature and pressure afforded the diastereomeric cycloadducts in a good yield, but with rather low face selectivity (**28** + **29**/**30** + **31** = 73/27). The approach of the diene to the dienophile **27** occurred from the same face as that observed for non-catalyzed cycloaddition of cyclopentadiene to *N*-enoyl camphor sultams **1** and **24**.



27

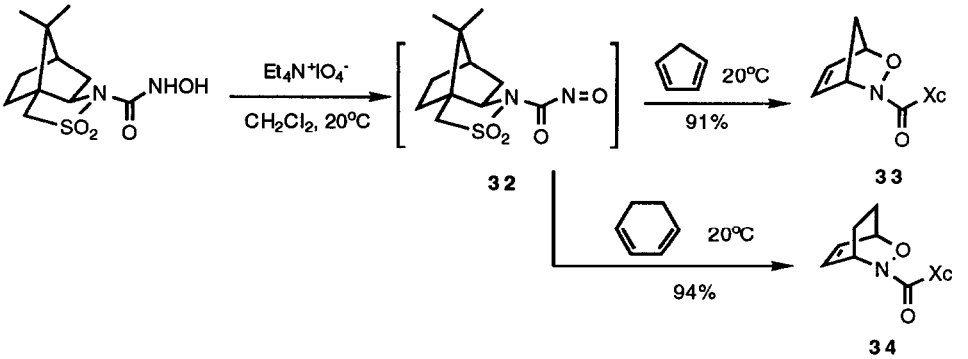
28 (2*S*, 6*R*) **29** (2*S*, 6*S*) **30** (2*R*, 6*S*) **31** (2*R*, 6*R*)

Xc = D-camphor sultam

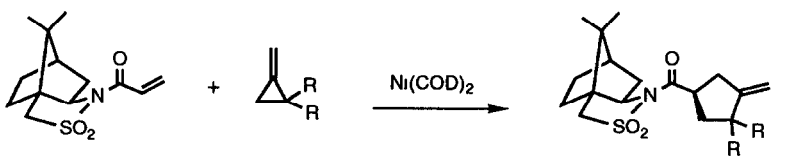
eq 8

Thermal Diels-Alder reactions of acylnitroso camphor sultam **32** with several dienes have been studied by Ghosez and coworkers.[30] In the presence of a five-fold excess of cyclopentadiene or cyclohexadiene, cycloadducts **33** or **34** were obtained in excellent yields and with excellent selectivity (>99/1) (Scheme 5). Relative to the camphor sultam, the face selectivity of this reaction is ambiguous because the nitrogen atom does not become a stereogenic center. Attack from one face through an endo transition state gives the same product as attack of the other face in an exo transition state.

Scheme 5. Xc = D-camphor sultam

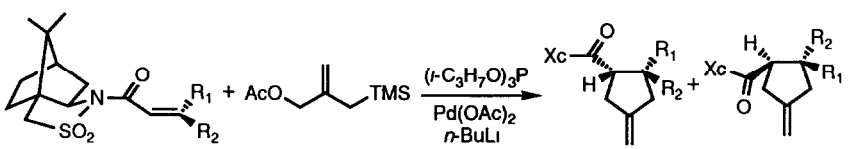


2.3 Annulations with Metals: Binger and coworkers[31] reported asymmetric nickel (0)-catalyzed [3+2] cycloadditions of methylenecyclopropanes with chiral derivatives of acrylic acid. Thus, Ni(0)-catalyzed cycloaddition of *N*-acryloyl camphor sultam **1** with methylenecyclopropane (**35a**) or 2,2-dimethylmethylenecyclopropane (**35b**) led to 3-methylenecyclopentanecarboxylic amides **36** with selectivities as high as 99/1 (eq 9). Oppolzer's sultam was the best auxiliary of the six that were surveyed in this reaction.



eq 9

In contrast, asymmetric palladium-catalyzed cycloaddition of 2-((trimethylsilyl)methyl)-3-acetoxy-1-propene with *N*-enoyl camphor sultams **37** showed rather disappointing results (eq 10).[32] Diastereofacial selectivity amounted to 4-26%, and the Z acceptor **37b** exhibited the higher selectivity. For this reaction, Trost and coworkers observed that other auxiliaries were superior to the camphor sultam.

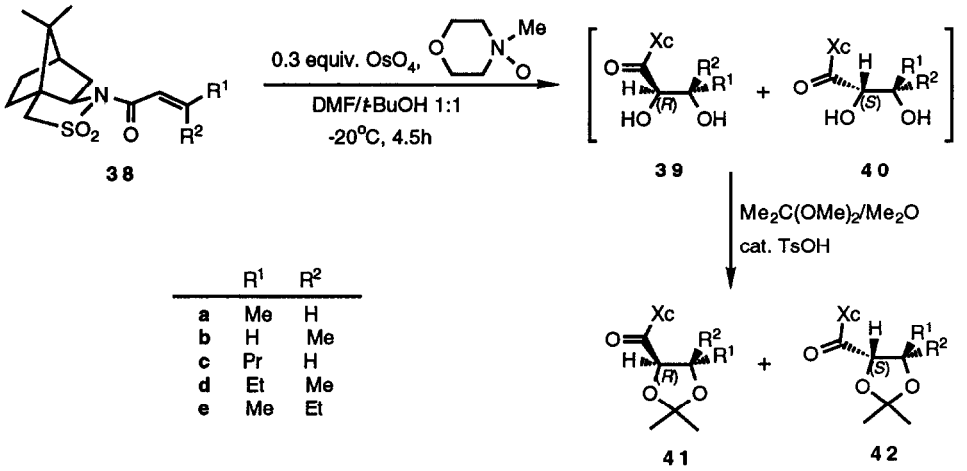


37a R_1 = H, R_2 = i-C_3H_7
b R_1 = i-C_3H_7, R_2 = H

eq 10

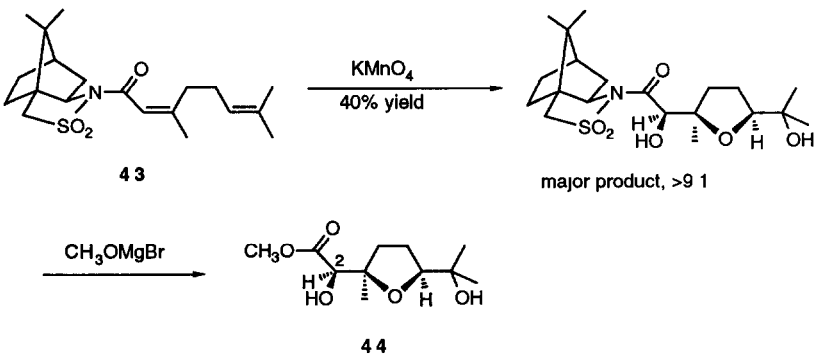
2.4 Oxidation. 2.4.1 Osmium Tetroxide: Asymmetric dihydroxylations of β-substituted *N*-enoyl camphor sultams **38** with OsO_4/*N*-methylmorpholine *N*-oxide provided glycols **39/40**. These diols were converted to the corresponding dimethyl acetals **41/42** in ratios ranging from 90:10 to 95:5 (Scheme 6).[33]

Scheme 6. Xc = D-camphor sultam



	R^1	R^2
a	Me	H
b	H	Me
c	Pr	H
d	Et	Me
e	Me	Et

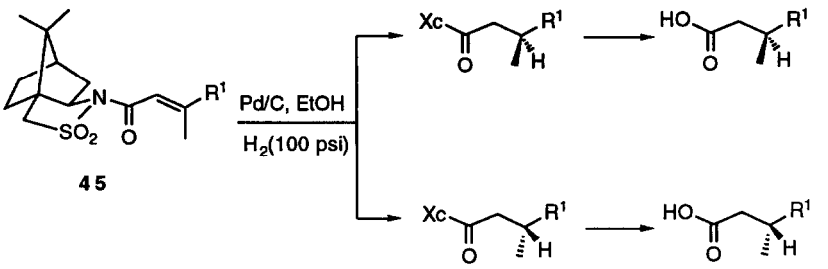
2.4.2 Potassium Permanganate: Walba and coworkers showed that asymmetric oxidative cyclization of *N*-dienoyl camphor sultam **43** with $KMnO_4$ gave a >9:1 mixture of diastereomers. After separation of the major diastereomer, treatment of this compound with MeOMgBr provided a sample of nonracemic diol **44**, shown to possess the 2*R* absolute configuration (eq 11).[34] The major diastereomer results from attack on the Re face of the conjugated double bond, and this is the same facial bias that was observed in the osmylation.



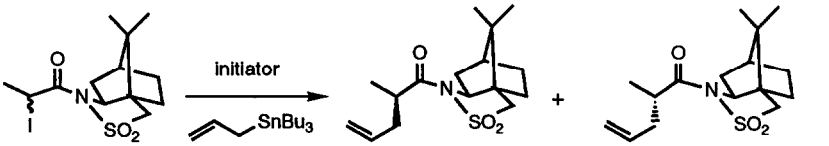
eq 11

2.5 Hydrogenation: Olefinic bonds of *N*-enoyl camphor sultams **45** were hydrogenated in the presence of Pd/C often with a diastereofacial discrimination of >95/5 (Scheme 7).[35]

Scheme 7. Xc = D-camphor sultam

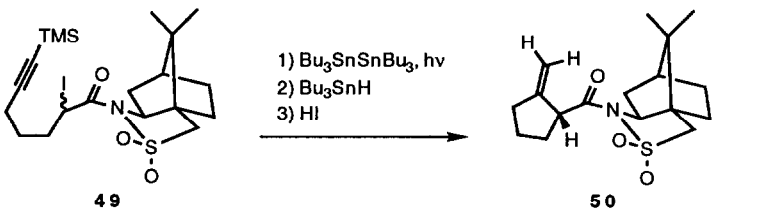


2.6 Radical Reactions: Recently, Curran and coworkers[36] demonstrated that chiral radicals derived from Oppolzer's camphor sultam gave high levels of asymmetric induction in radical addition, cyclization, and annulation reactions with achiral alkenes and alkynes. Reaction of iodosultam **46** with allyltributylstannane in the presence of AIBN or triethylboron gave a mixture of the allylated products **47** and **48** in ratios ranging from 25/1 at –20°C to 12/1 at 80°C (eq 12).



eq 12

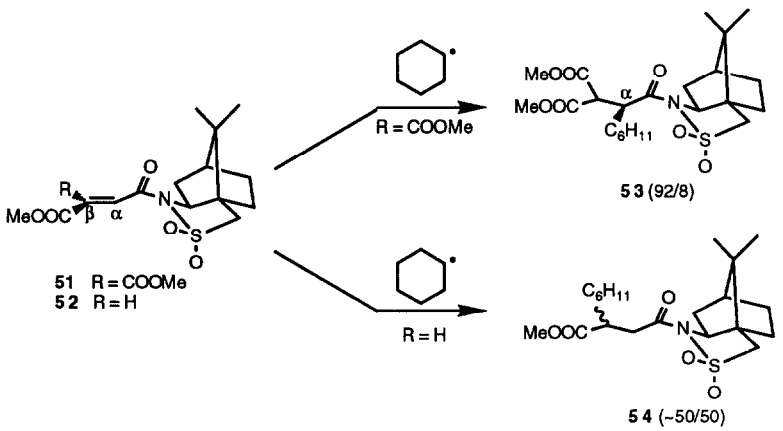
Atom transfer cyclization of iodosultam **49** by the standard ditin procedure,[37] followed by reductive deiodination with tributyltin hydride and desilylation gave the cyclized product **50** and its diastereomer in a ratio of 9/1 (eq. 13). This reaction involves an asymmetric radical cyclization. Very recently, modest selectivity (3/1) has also been reported in radical cyclizations Oβ-keto sulfurimide derivatives of Oppolzer's sultam.[38]



eq 13

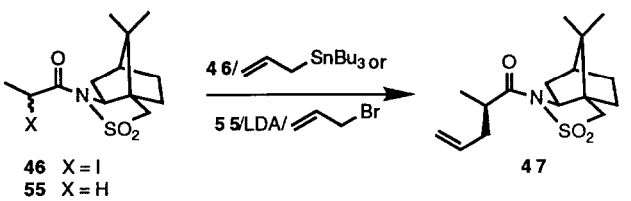
Oppolzer's camphor sultam is also effective in controlling radical addition reactions when attached to the alkene component of the reaction rather than the radical component (eq 14).[39] However, the location of the sultam relative to the site of radical attack is crucial. If the radical adds to the alkene carbon closer to the auxiliary (Cα), then selectivity is good. For example, addition of

cyclohexyl radical to alkene **51** gives **53** with good stereoselectivity. However, if the radical adds to the carbon further from the auxiliary (Cβ), then selectivity is very poor. Addition of cyclohexyl radical to **52** gives **54** with no stereoselectivity.[40]



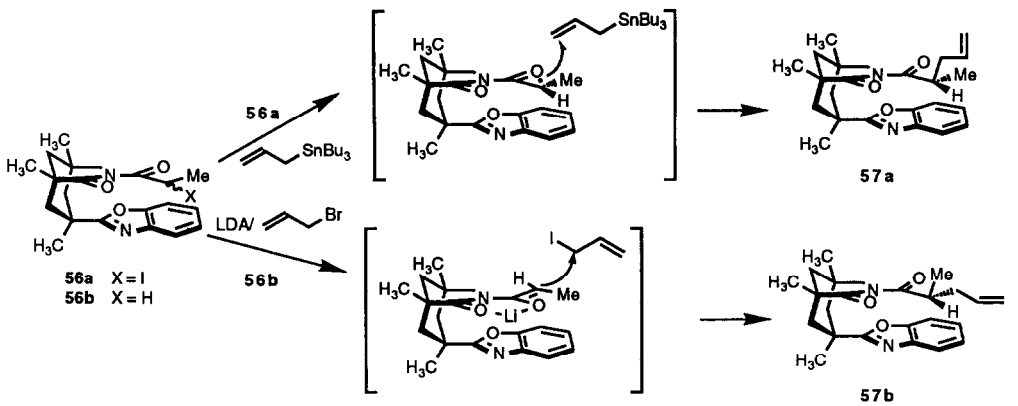
eq 14

3. Models for Stereoselectivity. Though degrees of facial selectivity differ, virtually all of the reactions in Section 2 proceed with attack on the same face of the π-system (alkene, carbonyl, or radical). Furthermore, Oppolzer has shown that metal-promoted reactions (Lewis acid-catalyzed Diels-Alder reactions, enolate allylations) typically give the same face selectivity as the thermal reactions.[2] For example, enolate allylation[41] of the propionoyl sultam **55** (eq 15) provides the same major product **47** as the radical allylation. At comparable temperatures, the selectivity of the radical and enolate allylations are comparable.



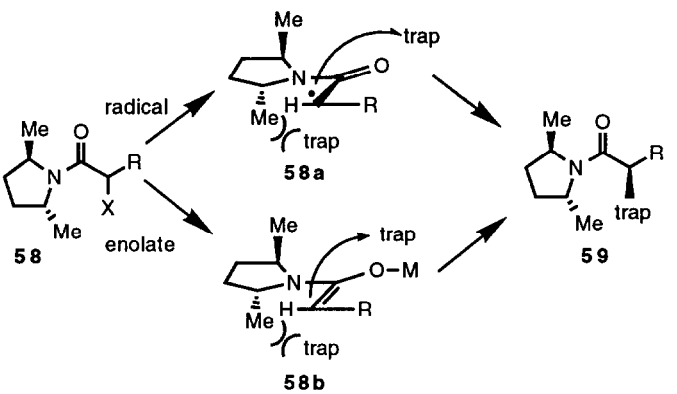
eq 15

That the metal (enolate) and non-metal (radical) processes give the same face selectivity is counterintuitive. If attack of a reagent always occurred from the same face, then one might expect to obtain opposite products from these reactions. This is because opposite faces of the reagent are exposed in non-chelated (dipole-opposed) and chelated rotamers. For example, the Rebekian auxiliaries **56a,b** provide *opposite* stereoisomers in radical (**56a** → **57a**) and enolate (**56b** → **57b**) allylations (eq 16).[42] This is concisely rationalized by postulating attack of the allylating reagent from the same face in either dipole-opposed (radical) or chelated (enolate) rotamers.



eq 16

However, the formation of the same stereoisomers from metal and non-metal reactions is reminiscent of the reactions of 2,5-dialkylpyrrolidines. For example, radical reactions of **58a**[43] and enolate alkylations of **58b**[44] give the same stereoisomer **59** (eq 17). Because the pyrrolidine has C2 symmetry, there is only one amide C–N rotamer. Face selectivity is then interpreted as the result of a "cis, 1,4" interaction between one of the methyl groups and the approaching reagent. This retards attack from one face. On the other face, the "trans, 1,4" methyl group is too remote to have a significant effect. Porter has provided excellent kinetic support for this model in the related additions of radicals to acryloyl pyrrolidines.[45]



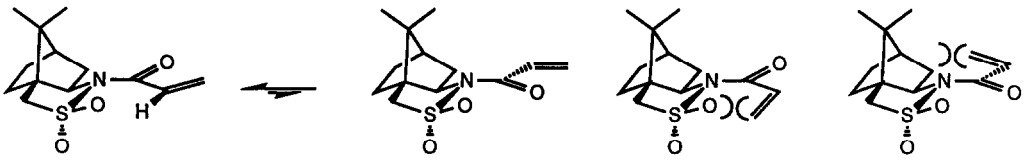
eq 17

A comprehensive model for the reactions of Oppolzer's camphor sultam should then explain why the same face selectivities are observed in chelated and non-chelated reactions, and it should also explain why the sultam gives good levels of asymmetric induction in thermal reactions where other (apparently) related imides do not (see Figure 3).

3.1 Conformations of Acryloyl Derivatives: Just like the imide in Figure 3, Oppolzer's acryloyl sulfonimide has four possible planar rotamers that are generated by rotating the sulfonimide C–N bond (syn, anti) and the acryloyl (O)C–C(=C) bond (*s*-cis, *s*-trans).[2] These four rotamers are shown in

Figure 5. By analogy to imides, *s*-trans rotamers are expected to be quite high in energy due to severe steric interactions, and syn rotamers will be disfavored relative to anti because of unfavorable dipolar interactions. The anti, s-cis rotamer of the acryloyl sultam then stands alone as the ground state energy minimum.

Figure 5. Rotamers of Acryoyl Sultam 1.



In support of this analysis, there are now crystal structures of all sorts of derivatives of Oppolzer's sultam, and all exhibit rotamers with the carbonyl and sulfonyl groups opposed.[46] More recently, crystal structures of the actual acryloyl derivatives also show the expected *s*-cis orientation of the acryloyl group. Thus, though the differences in energy between the various rotamers are not well quantified, the qualitative picture is straightforward.

3.2 Transition State Models: If one accepts that the transition state (TS) conformations of acryloyl derivatives of Oppolzer's sultam are similar to those of the ground state (GS), then a model for addition reactions is defined simply by the stereochemical outcome of these reactions. This model is shown in Figure 6a. For radical reactions, the model shown in Figure 6b results. The close parallel between reactions of acrylate derivatives and those of radicals arises because the geometries of the two species are very similar.[4] In these models, reagents attack the "top face" of the favored GS rotamer of either the acryloyl derivative or the radical.

Figure 6. Transition State Models for Acrylates (6a) and Radicals (6b).

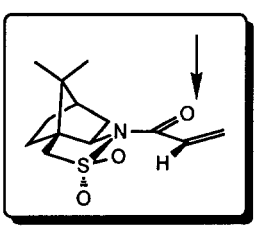


Figure 6a. Acrylate TS Model

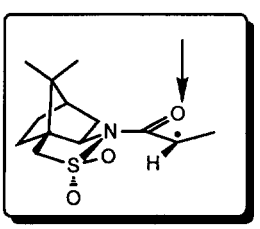
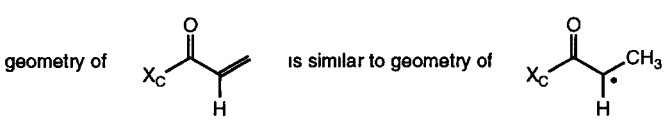


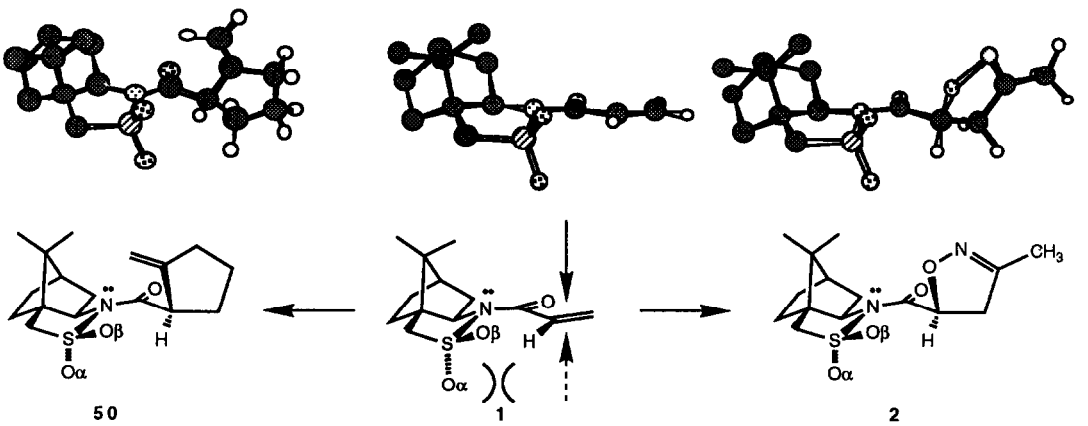
Figure 6b. Radical TS Model



Is it reasonable to suppose that TS conformational preferences parallel the GS? For these kinds of reactions, we think that it is. Cycloadditions and radical reactions are generally thought to have

early, reactant-like transition states.[11b] Thus, large unfavorable steric or dipolar interactions in the GS should still be significantly reflected in the TS. Strong, if circumstantial, evidence for the TS/GS parallel comes from crystal structures of reactants and products. Figure 7 shows the x-ray crystal structure of acryloyl sultam **1** and the products of nitrile oxide cycloaddition (**2**) and radical annulation (**50**). The conformations of the two products are dominated by dipolar interactions (two carbonyls anti) and by Oβ, whose size and location dictate that the smallest group (H) adjacent to the carbonyl reside in its vicinity. The structures of these products bear a striking resemblance to that of the precursor **1**, and it is easy to imagine a reaction coordinate where starting materials are converted to products with only small changes in geometry accompanying rehybridization of sp^2 centers to sp^3. Given the ground state similarities in the reactants and products, why should the transition states look different?

Figure 7. Crystal Structures Support a TS Resembling the GS.

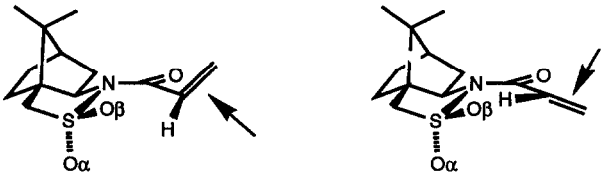


The Curtin-Hammett principle cautions that TS energies of **1** need not directly parallel GS energies.[47] Is there some (electronic?) factor that could dramatically increase the reactivity of a higher energy conformer of **1** relative to its lower energy counterpart? Probably not. There is no reason to believe that *s*-trans rotamers should be more reactive than *s*-cis, and we think it is unlikely that syn (dipole-aligned) rotamers are much more reactive than anti (dipole opposed ones).

Just what are the factors that promote "top side" attack in the thermal reactions of Opplozer's camphor sultam? Even though we are reasonably confident that the model is realistic, the answer to this question is not immediately obvious. We consider here three possible factors for facial selectivity: 1) twisting of the acrylate, 2) pyramidalization of sulfonimide nitrogen, and 3) asymmetric disposition of the two sultam oxygens.

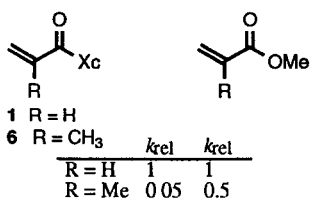
Oppolzer has suggested that twisting of the acryloyl (O)=C–CH=CH_2 might be important in stereocontrol.[48] If this bond twists down, then one face of the alkene is more exposed to reagents, and if this twists up, then the other is exposed (Figure 8). One must propose the "twisted down" model to fit the results. Clearly some twisting will occur in the transition state as sp^2 centers rehybridize to sp^3, with attendant loss of conjugation of the acryloyl group.

Figure 8. Twisted Models

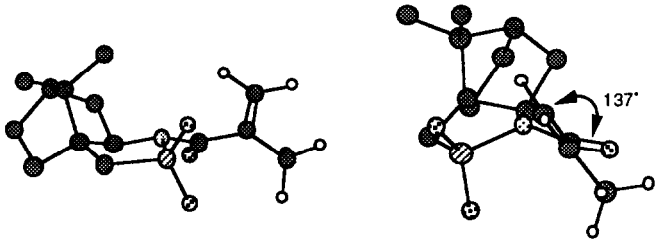


Given that significant twisting away from conjugation should presumably cost energy, is there any compensating factor that might make twisted conformers more reactive? Our experiments suggest that precisely the reverse is true. Figure 9 shows k_{rel} for reactions of four alkenes with *t*-butyl nitrile oxide.[17] The methacrylate derivative of Oppolzer's camphor sultam **6** shows an abnormally low reactivity compared to a methacrylate ester. This low reactivity is also coupled with low stereoselectivity. Abnormally low reactivity of the methacrylate derivative of Oppolzer's sultam is also exhibited in radical additions[49] and other reactions. This phenomenon is probably very general; methacrylate derivatives of imides and amides will frequently show reduced reactivity in such thermal addition reactions.[33,35] Why do methacrylate derivatives of amides and imides (but not esters) show low reactivity? Once again, x-ray structures suggest an answer; the acryloyl groups of these compounds are not planar. The crystal structure of the methacrylate derivative of Oppolzer's camphor sultam (**6**) is shown in Figure 9.[17] Due to the large size of the amide substituent trans to the carbonyl (SO_2), neither planar rotamer (*s*-trans or *s*-cis) of the methacrylate can be accommodated. Therefore, the methacrylate adopts a twisted conformation that is closer to *s*-trans than *s*-cis. The acrylate derivative **1** adopts an *s*-cis conformation (see Figure 7) because the small hydrogen can be accommodated in the region near the SO_2.

Figure 9. Reactivity and Structure of the Methacrylate Sultam.



	k_{rel}	k_{rel}
R = H	1	1
R = Me	0 05	0.5



"Front" and "side" views of methacryloyl sultam 6 (crystal structure)

It seems likely then that the twisted conformations of the methacrylate derivatives of Oppolzer's sultam are responsible for their abnormally low reactivity in dipolar cycloadditions and radical additions. This suggests that highly twisted transition state models for acrylate reactions are not realistic because the twisted conformers are both higher in energy and less reactive than planar ones. Small amounts of twisting are expected in these cycloaddition transition states, but it can be difficult to evaluate whether such twisting is a cause or an effect of the stereoselective reaction.

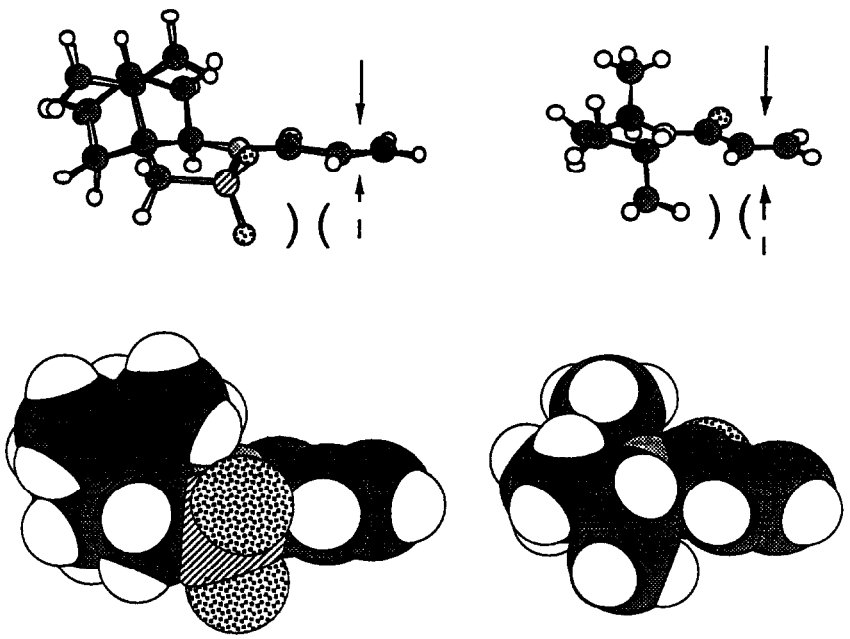
X-ray structures of derivatives of Oppolzer's sultam (including acryloyl derivatives) show that the sultam nitrogen is somewhat pyramidalized in the direction indicated in Figure 7.[2,14,15] This pyramidalization may be caused by steric factors (pyramidalization probably reduces the interaction between Oβ and the substituents adjacent to the carbonyl and it may reduce angle strain in the five-membered ring) or stereoelectronic factors (the N-lone pair is antiperiplanar to the S–Oα bond). Nitrogen atoms in acyclic sultams are not significantly pyramidalized; however, the ring prevents Oppolzer's sultam from attaining the geometry observed for acyclic sultams[50] (N-lone pair staggered between SO_2). Pyramidalization has often been noted in enamines and amide enolates (which are derivatives of enamines).

Does nitrogen pyramidalization dictate face selectivity in Oppolzer's camphor sultam? Both we and Oppolzer[48a] now suspect that it does not. Compared to enamines (or amide enolates),[22] the nitrogen of Oppolzer's sultam is not directly attached to the alkene (or radical) whose face selectivity it must influence; instead it is separated by a C=O group. Taking into account that face selectivity in the reactions of this sultam seems to be independent of the electronic nature of the attacking reagent (see section 2), it is not clear what kind of information the nitrogen might transmit to influence face selectivity or how this information might be transmitted. In short, while there is no experimental evidence to cite against the importance of N-pyramidalization, there is currently no theoretical evidence to cite in support of it.

In 1988, we suggested that the disposition of the sultam oxygens relative to the plane of the acryloyl group might be important in controlling face selectivity.[15] Over the past several years, our confidence in this suggestion has grown. The basic idea can be seen in the crystal structures and transition state models of Figure 7. The plane of the acryloyl group is not symmetrically disposed between the two oxygens of the sultam. Instead, Oβ is "in front of" the acryloyl group, and is not well positioned to impede a reagent approaching from the β (top) face. In contrast, Oα is "below" the acryloyl group, and it is well positioned to impede a reagent approaching from the α (bottom) face. Furthermore, as a reagent attacks the top face, the vinyl hydrogen moves away from Oβ, thus decreasing this steric interaction.

Support for the idea that a "cis 1,4" interaction between Oα and an incoming reagent controls stereochemistry comes from the stereochemical parallel between the reactions of Oppolzer's sultam and 2,5-dimethylpyrrolidine,[51] and also from exercises in modeling. Figure 10 compares ball-and-stick and space filling models of acrylate derivatives of 2,5-dimethylpyrrolidine (DMP) and Oppolzer's camphor sultam. The conformation of the DMP derivative is dominated by A-strain; the two methyl groups are "axial-like" to avoid interactions with the amide oxygen or nitrogen. Visual and mathematical comparisons of these two models[4] show that Oα of the sultam is in the same region of space as the cis 1,4-methyl group of the DMP while Oβ is in the same region as an "equatorial-like" hydrogen. Just as the trans 1,4-methyl group exerts little effect on the reactions of the DMP acrylate, we suggest that the whole camphor ring of the sultam exerts little effect on the reactions of the anti, *s*-cis rotamer of the sultam. Though it does not directly control face selectivity, the camphor ring is, of course, indispensable; it folds the five-membered sultam ring so that Oα and Oβ are oriented differently with respect to the acrylate.

Figure 10. Comparison of Sultam (left) and DMP (right) Acrylates.



Very recently, PM3 calculations of transition states in nitrile oxide cycloadditions have provided good support for this model.[52] These TSs (Figure 11) resemble very closely the crystal structures of the starting acrylate and the product isoxazoline (Figure 7). Indeed, attack from the bottom face is calculated to be about 1 kcal/mol higher in energy than attack from the top, and unfavorable interactions between the nitrile oxide oxygen and Oα appear to be primarily responsible for this energy difference.

Figure 11. Computed Major (left) and Minor (right) TSs for Cycloaddition of CH_3CNO with 1.

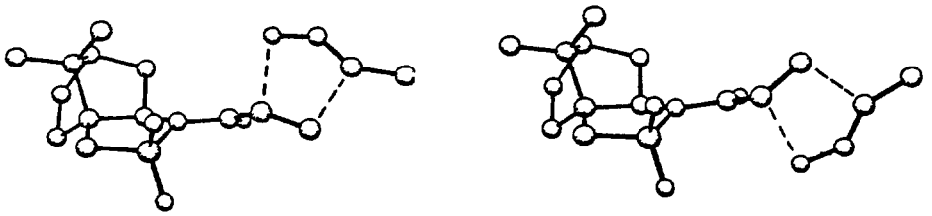
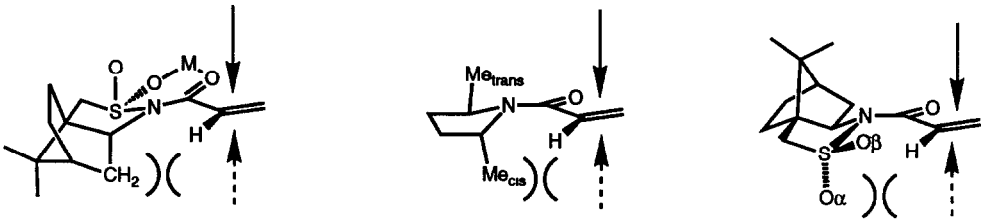


Figure 12 shows Oppolzer's model for the reactions of chelated derivatives of the sultam.[2] In this model, chelation enforces a syn arrangement of the CO and SO_2 groups, the acryloyl group is *s*-cis

(*s*-trans rotamers are again high in energy), and reagents attack the top face. Very similar models can be constructed for the reactions of enolates.[2] In this chelate model, the relationship between the sultam and the DMP is evident; the CH–CH_2 bond of the camphor ring plays the role of the cis 1,4-methyl group of DMP. The SO_2 group is no longer a player because it is in the trans 1,4-position.

Figure 12. Analogy Between the Camphor Sultam and DMP.



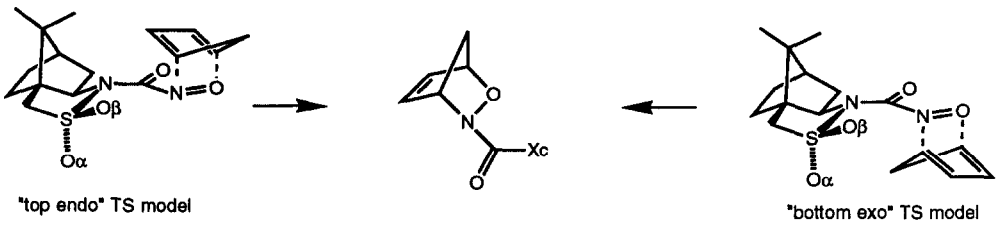
Oppolzer's chelate model | 2,5-dimethylpyrrolidine model ")(" signifies cis 1,4-interaction | non-chelate model

We propose then the simple notion that Oppolzer's camphor sultam is a "2,5-dimethylpyrrolidine in disguise". As summarized in Figure 12, metal-chelated reactions proceed through transition states with the CO and SO_2 syn, and the CH_2 group of the camphor (perhaps aided by the rest of the camphor ring) plays the role of the DMP methyl group. In non-chelated reactions, the CO and SO_2 are anti, and Oα of the sultam ring plays the role of the DMP methyl group. As demanded by the results, these two models predict that chelated and non-chelated reactions will produce the same stereoisomers.

We suggest that all of the asymmetric thermal reactions summarized in Section 2 can be rationalized by the non-chelated model in Figure 12. This model should also apply to reactions of non-chelating metals. When chelating metals are used (enolates, Lewis acids), Oppolzer's chelate model then applies. Assignment of metal reactions as chelated or non-chelated is often not trivial and requires more information that just the stereostructures of the products (because both models predict the same stereoisomer). Most importantly, these models rationalize why Oppolzer's sultam is a good chiral auxiliary for radical reactions and dipolar cycloadditions while other imides are not (see Figure 3).

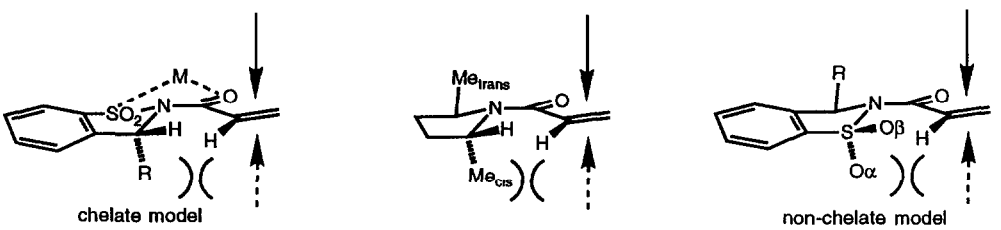
Ghosez's asymmetric Diels-Alder reactions of acyl nitroso derivatives (Scheme 5) merit special comment.[30] In this case, neither of the two sp^2 atoms of the sultam precursor are stereogenic in the product, so a knowledge of the geometry of the acyl nitroso group and the stereostructure of the product does not uniquely define a model. If we assume again that the CO and SO_2 groups are anti and the NO and CO groups are *s*-cis (analogous to an acrylate), then the observed product can arise either from top face attack through an endo transition state or bottom face attack through an exo one (Figure 13). Our analysis suggests that the top/endo transition state should be favored. This suggestion is corroborated by recent calculations of Houk,[53] which predict that endo transition states in nitroso Diels-Alder reactions should be significantly lower than their exo counterparts due to lone-pair/bonded pair repulsions between the nitroso heteroatoms and the diene.

Figure 13. TSs for Acyl Nitroso Diels-Alder Reactions



Given the structural similarities between Oppolzer's camphor sultam and his new toluene sultams (see Scheme 3 and eq 3), it is possible that similar stereocontrol elements are operating. Figure 14 extends the camphor sultam model to the toluene sultams. Once again, the analogy to 2,5-dimethylpyrrolidine can be made. In a chelated model, the R group directly fills the role of the methyl group of DMP, while the SO_2 group is a spectator. In a non-chelated model, transannular repulsion between the R group and Oβ now serves to differentiate Oα (axial-like) from Oβ (equatorial-like).[54] The axial-like Oα then controls facial selectivity. Though this model is consistent with the reaction products of these new sultams, we stress that the attribution of face selectivity to the differential orientation of the SO_2 group is speculative at this early stage. However, PM3 transition state calculations again predict the correct stereoisomer in nitrile oxide cycloadditions with these toluene sultams and lend support to the model in Figure 14.[51]

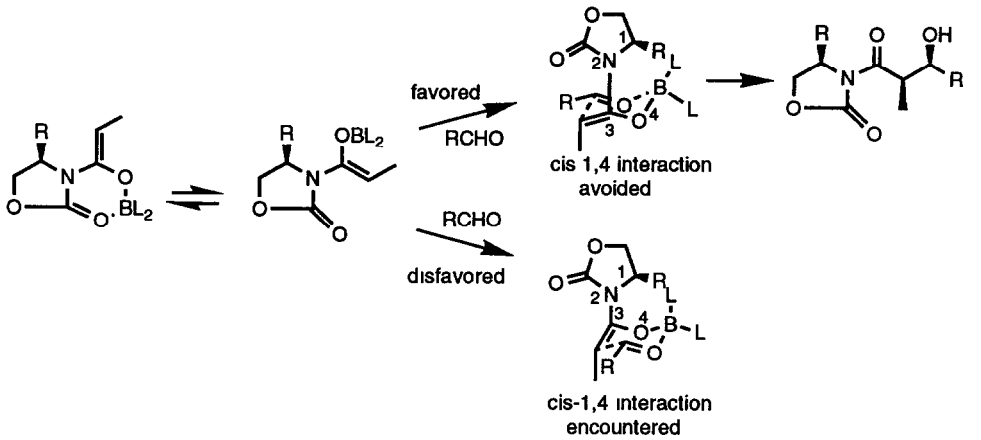
Figure 14. Toluene Sultam Models.



We conclude the discussion of models with some thoughts on thermal reactions of oxazolidinones. In Figure 3, we rationalized poor dipolar cycloaddition and radical selectivities as resulting from the absence of a cis-1,4 interaction in the favored rotamer. In contrast to these poor selectivities, boron aldol reactions of oxazolidinanes often give outstanding selectivities (Figure 15).[55] These reactions are usually rationalized by involving anti rotamers (because the boron cannot simultaneously chelate with the aldehyde and the oxazolidine carbonyl).

In this transition state model, there is no cis,-1,4 interaction between the auxiliary stereocenter and the forming C–C bond. Why then do such reactions often proceed with high stereoselectivity? It seems likely that a cis-1,4 interaction between the auxiliary and the *existing* B–O bond plays a key role.[55] In the favored transition state, this cis-1,4 interaction is avoided, but in the disfavored transition state it is not. Thus aldol reactions have a "two-point" contact between the progressing reactions and the auxiliary (the forming C–C bond and the breaking B–O bond) while the other kinds

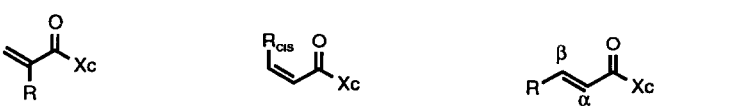
Figure 15. Boron Aldol Reactions of Oxazolidines



of thermal reactions in Figure 3 have only a "one-point" contact (the forming C–C or C–O bond). The two-point contact provides a cis-1,4 interaction in either the syn or the anti rotamer while the one-point contact provides this interaction only in the anti rotamer.

4. Limitations: Though Oppolzer's camphor sultam is applicable to thermal reactions of all sorts, significant limitations exist (Figure 16). The biggest of these is that good asymmetric induction may be limited to 2°-systems like acrylate **1**. Substitution of a group R for H results in decreased reactivity and selectivity probably because this group upsets planar rotamer preferences. Such an analysis suggests this problem is not restricted to Oppolzer's sultam and may be general for many amides and imides. Thus, the development of a chiral auxiliary that effects asymmetric dipolar cycloadditions, radical additions and related reactions at 3°-centers adjacent to carbonyls remains a large, unsolved problem.[56]

Figure 16. Limitations of Oppolzer's Camphor Sultam in Thermal Reactions



poor induction if R ≠ H

poor induction expected as R_{cis} gets larger

poor induction expected for reagents that attack only Cβ

Trans-disubstituted acrylates should pose no problems, but cis-disubstituted acrylate derivatives of Oppolzer's sultam may cause problems; as R_{cis} becomes larger, the preference for planar, *s*-cis rotamers may again be upset. Finally, it is important to point out that Oppolzer's sultam only controls stereoselectivity in reactions directly adjacent (α) to the carbonyl. In cycloaddition reactions that occur at both Cα and Cβ, it is the interactions occurring in the vicinity of Cα that control stereochemistry. Thermal reactions that occur only at Cβ show very low selectivity, presumably

because the approaching reagent is just too far away from the stereocontrol elements. Once again, this failure should not be unique to Oppolzer's sultam, but should instead apply to any auxiliary that relies on this type of cis 1,4-interaction. These limitations are for thermal reactions only; metal-promoted reactions can give good levels of induction in many of the systems shown in Figure 16.[2]

5. Conclusion: Even though it has some significant limitations, Oppolzer's camphor sultam is clearly one of the most generally useful chiral auxiliaries that is currently available. It is effective in a wide variety of metal-promoted reactions, and, more uniquely, it is generally useful in several important classes of thermal reactions where metals are not present. We have argued that, despite its complex structure, Oppolzer's camphor sultam controls stereochemistry for underlying reasons that are really quite simple; it is a 2,5-dialkylpyrrolidine in disguise. We hope that this model will now allow the prediction of which thermal reactions will give good asymmetric induction with Oppolzer's sultam, and which will not. Beyond that, the understanding of when and why good selectivities are observed provides us with a rational footing to use for the design of new, improved chiral auxiliaries.

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