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Asymmetric synthesis using N-sulfonyloxaziridines

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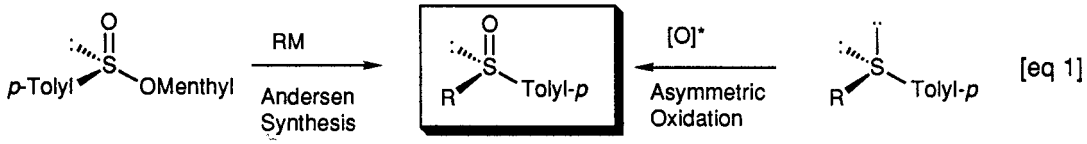
Abstract The development of reagents for the asymmetric oxidation of sulfides to sulfoxides with high stereoselectivities is problematic because these substrates are nonfunctionalized. Nevertheless N-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (**4**) exhibits remarkably high and predictable ee's for the asymmetric oxidation of sulfides to sulfoxides (66->95% ee), selenides to selenoxides (90->95% ee) and sulfenimines to sulfinimines (85-91% ee). While steric effects are primarily responsible for the molecular recognition, an important electronic component is operational for those sulfides having an aryl group directly attached to the sulfur atom. The high ee's associate with this reagent are a consequence of the presence of complementary vacant regions and a molecular cleft or grove on the active site surface.

INTRODUCTION

Enantiopure sulfoxides continue to play prominent roles as auxiliaries in the asymmetric construction of C-C bonds and have been instrumental in studies of the origins of molecular recognition (Ref. 1). The reaction of an organometallic reagent with a diastereomerically pure menthyl *p*-toluenesulfinate, the Andersen synthesis, is the method most often employed for the preparation of nonracemic sulfoxides (Ref. 2) [eq 1]. Despite improvements in method, the commercial availability of both epimers of menthyl *p*-tolylsulfinate and the introduction of modifications by Kagan et. al. (Ref. 3) this methodology is still limited in the synthesis of highly functionalized sulfoxides as well as certain dialkyl sulfoxides. The asymmetric oxidation of a prochiral sulfide, at least in principal, is an attractive alternative because i) the sulfoxide would be available in one step and ii) those sulfoxides not readily accessible by the Andersen procedures could be realized.

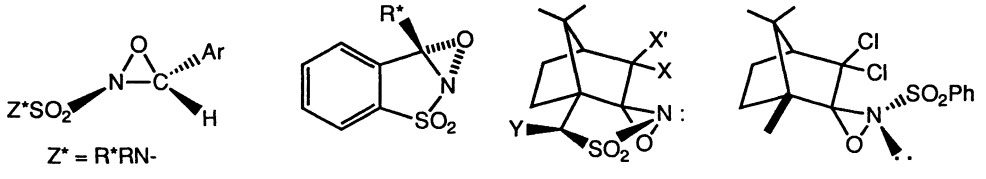


[eq 1]

The difficulty in developing reagents for the asymmetric oxidation of prochiral sulfides to sulfoxides with consistently high ee's is that sulfides are nonfunctionalized substrates. Lacking functional groups these substrates are unable to coordinate with the oxidant to form highly ordered transition state structures that are prerequisites for most stereoselective reactions that occur with high ee's. Nonfunctionalized substrates must rely on noncovalent steric and electronic forces to control the molecular recognition. While the influence of steric forces on molecular recognition is generally well understood the role played by electronic forces is less certain, in part, because they are difficult to distinguish from steric effects. Despite these obstacles two reagent systems have been devised that afford synthetically useful ee's (>90%) for the asymmetric oxidation of sulfides to sulfoxides: Kagan's modified Sharpless reagent, limited to aryl methyl sulfides (Ref. 4) and N-sulfonyloxaziridines (Ref. 5).

Enantiopure N-sulfonyloxaziridines **1-4**, developed in our laboratories, exhibit quite different stereoselectivities in their asymmetric oxidations reflecting their dissimilar active site structures. Oxaziridines types **1** (Ref. 6) and **2**, (Ref. 7) require separation of diastereoisomers in their

preparation and give poor ee's (19-40%) for the asymmetric oxidation of sulfides to sulfoxides. Camphor based oxaziridines, types **3** and **4** are more easily prepared in enantiopure form because diastereoisomer separation is not required. For the oxidation of *n*-butyl or methyl *p*-tolyl sulfides to the corresponding sulfoxides (+)-(camphorylsulfonyl)oxaziridine **3a** (X=H) gave very poor results (< 6 %ee) (Ref. 8). Modification of the active site by introducing halogens (F, Cl, Br) or oxygens into the α-positions (X) of **3** improved the ee's to 50-80% (Ref. 9,10). Although type **3** oxaziridines gave only modest results for the asymmetric oxidation of sulfides to sulfoxides the enantioselectivities for the hydroxylation of enolates to α-hydroxy carbonyl compounds often exceeds 95% (Ref. 5, 11).

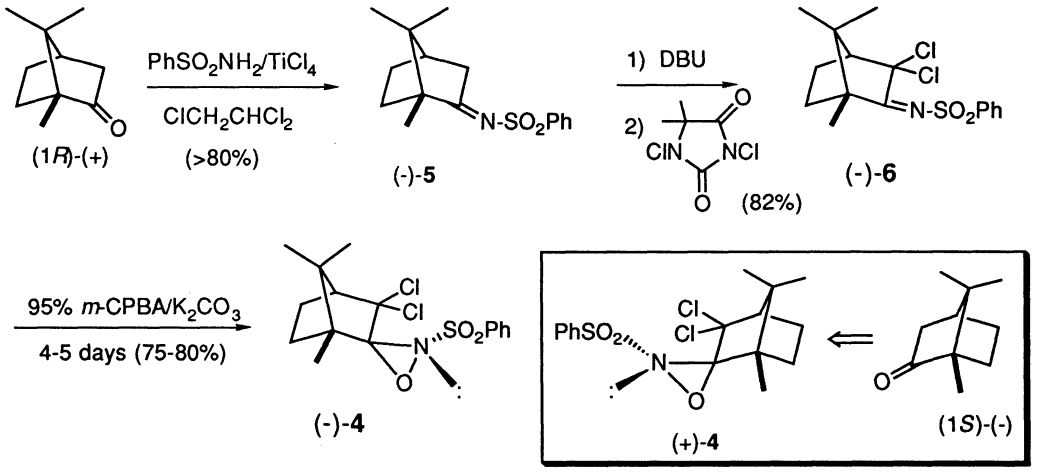


1 **2** **3** **4**

N-(PHENYLSULFONYL) (3,3-DICHLOROCAMPHORYL)OXAZIRIDINE

The most efficient and general reagent yet developed for the asymmetric oxidation of sulfides to sulfoxides is N-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (**4**) (Ref. 12). This oxaziridine is prepared from (1*R*)-(+)-camphor as outlined in Scheme 1. The chlorine atoms are introduced via the sulfonimine azaenolate by treatment of **5** with NaHMDS and NCS or preferable with DBU and 1,3-dichloro-5,5-dimethylhydantoin (Ref. 13). Although oxidation of the dichlorosulfonimine **6** requires >95% *m*-CPBA and 4-5 days for completion the oxidation can be carried out on a multi-gram scale (>60 g). Since the configuration of the oxaziridine three-membered ring controls the absolute stereochemistry of the product the other antipode, (+)-**4** is similarly available from (1*S*)-(-)-camphor.

Scheme 1



The asymmetric oxidation of sulfides to the sulfoxides by (-)-**4** was carried out at 20 °C according to Scheme 2 to give the (*S*)-sulfoxides. Oxidations were generally complete within 1-6 hr, although some sulfides having electron withdrawing or sterically demanding groups may required up to 48 hr for completion. The sulfoxides and the sulfonimine **6** were isolated by prep. TLC in >90% with the latter being recycled. The highest enantioselectivities were observed for oxidations in low dielectric solvents such as CCl_4 and for those sulfides (R_L-S-R_S) where the difference in size of the R_L and R_S group is large. These results are summarized in Figure 1.

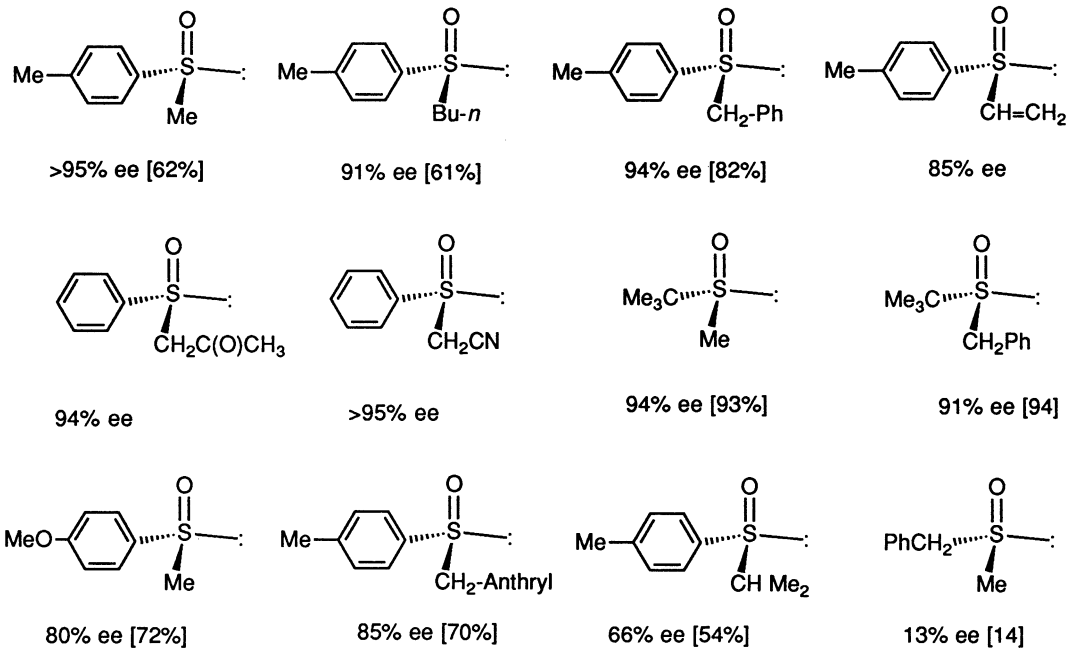


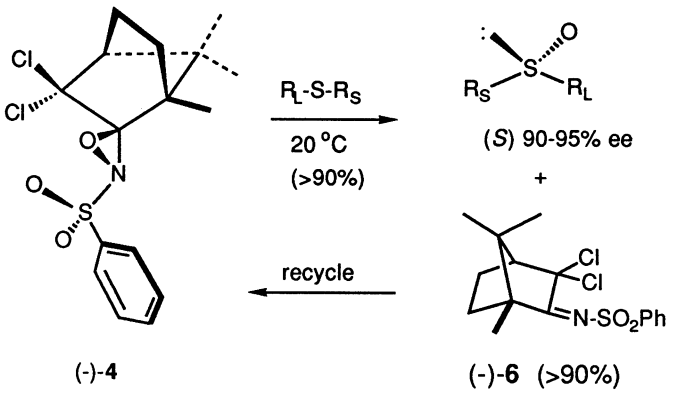
Figure 1. Synthesis of sulfoxides at 20 °C in CCl_4 [CH_2Cl_2] using oxaziridine (-)-**4**.

ORIGIN OF THE MOLECULAR RECOGNITION

The mechanism of oxygen-transfer for N-sulfonyloxaziridines involves an S_N2 type displacement of the sulfonimine by the nucleophile which is facilitated by a relatively weak oxygen-nitrogen bond and the enthalpy of the carbon-nitrogen π-bond (Scheme 2) (Ref. 14). The "electrophilic" nature of oxaziridines is attributed to the fact that these compounds possess a weak σ-bond whose σ* component can readily decrease in energy very early along the reaction coordinate (Ref. 14, 15). For the oxidation of sulfoxides to sulfones by oxaziridines nearly 50% of the net charge transferred to the oxaziridine fragment resides on oxygen in the transition state (Ref. 16). Ab inito calculations indicated that there are no stereoelectronic influences on the transition structures and the molecular recognition or transition state orientation is steric in origin governed by the structures of the substrate and the active site microenvironment of the oxaziridine.

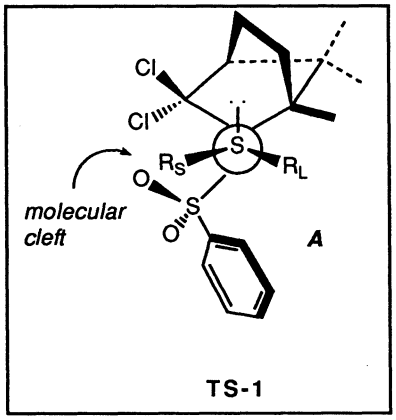
The results summarized in Figure 1 are consistent with steric effects being primarily responsible for the molecular recognition and are predictable using a simple active-site model. In this model

Scheme 2



the nonbonded interactions between the R_L and R_S groups of the sulfide (R_L-S-R_S) and the active site surface are minimized in a planar transition state structure; i.e. **TS-1**. The X-ray structure of (-)-**4** and studies with derivatives where Cl was systematically replaced with H, F, and Br atoms reveal that the exceptional stereoselectivities exhibited by this reagent are a consequence of a molecular groove or cleft defined by the chlorine atoms and the phenyl sulfonyl group and the vacant area **A** on the active site surface (Ref. 12).

The active site model shown in Figure 2 is constant with these considerations and the structure reactivity trends summarized in Figure 1. It predicts that the (*S*)-sulfoxide will be obtained in >90% ee as long as R_L is a bulky *tert*-butyl or aryl group with the R group in pocket **A** having a varied structure. However, the open-end pocket **C** means that this reagent cannot distinguish between methyl and *n*-butyl groups; i.e. methyl and *n*-butyl aryl sulfides give similar ee's (Figure 1) and that lower ee's are observed for those sulfides such as methyl benzyl sulfide where the two groups directly attached to sulfur are similar in size.



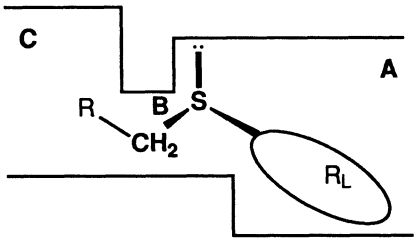
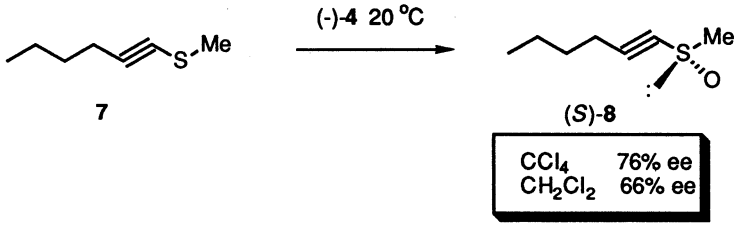


Figure 2: Active site model for (-)-**4** (top view)

Although steric forces are primarily responsible for the molecular recognition the fact that oxidations in non polar solvents (CCl_4) gave higher ee's than in polar solvents (CH_2Cl_2) suggests that there is an electronic component as well. Note also that solvent effects were *only* observed for those sulfides where there was an aryl group directly attached to the sulfur atom. Although the energies of these solvent induced effects are undoubtedly small, 0.3-0.4 kcal/mole, they mean the difference between a reaction of synthetic utility and one that is not. Quantitatively polar solvents increase the rates of oxidation of sulfides to sulfoxides. Faster rates are associated with earlier transition states (Hammond postulate) where nonbonded steric interactions become less important. Faster rates may reflect stabilization of polar transition state by the solvent. Alternatively a polar solvent may disrupt favorable dipole-dipole and/or van der Waals attractive interactions between the sulfide and oxaziridine in the transition state.

There are numerous examples where the presence of a proximal phenyl group is observed to be necessary for high stereoselectivities. Examples included the Diels-Alder (Ref. 17) and ene reactions (Ref. 18). The enhanced molecular recognition is generally discussed in terms of parameters which include differential π-stacking or solvation between phenyl and unsaturated groups and the shape and size of the phenyl group. The difficulty in assigning these effects relates to the problem of dissecting steric forces from electronic forces. For the asymmetric oxidation of sulfides to sulfoxides by oxaziridines and the modified Sharpless reagent the presence of an aryl group directly attached to sulfur not only ensures high ee's but also acts as the sterically most demanding group (Ref. 4, 12). To gain further insights into the influence of unsaturated π-systems on the molecular recognition the asymmetric oxidation of methyl *n*-hexenyl-1 sulfide (**7**) by (-)-**4** explored. Significantly the (*S*)-sulfoxide **8** was obtained in 76% ee indicating that the smaller alkynyl group, like phenyl, acts as a large group. Similar results were reported by Kagan and co-workers (Ref. 4). Thus the enhanced stereoselectivities exhibited by alkyl aryl sulfides likely result from a combination of steric and electronic effects caused by the aromatic π-system.



ASYMMETRIC OXIDATION OF SELENIDES TO SELENOXIDES

The difficulty in preparing enantiopure selenoxides relates to their configurational lability. In 1985 we reported that the configurational lability of selenoxides results from their facile reaction with trace amounts of water in an acid catalyzed reaction to form achiral hydrates [$ArSe(OH)_2R$] (Ref. 19). Hydrate formation could be impeded to some extent by placing bulky blocking groups adjacent to the selenoxide moiety. In order to prepare selenoxides in high enantiomeric purity it is necessary not only to have methods that are highly enantiospecific, but also free of acid and moisture. In this regard oxaziridine (-)-**4** is the reagent of choice because it is predicted to give high ee's (Figure 2), and the oxidation can easily be carried out under rigorously anhydrous conditions (Ref. 20). The asymmetric oxidation of selenides to selenoxides by oxaziridine (-)-**4** is summarized in Figure 3.

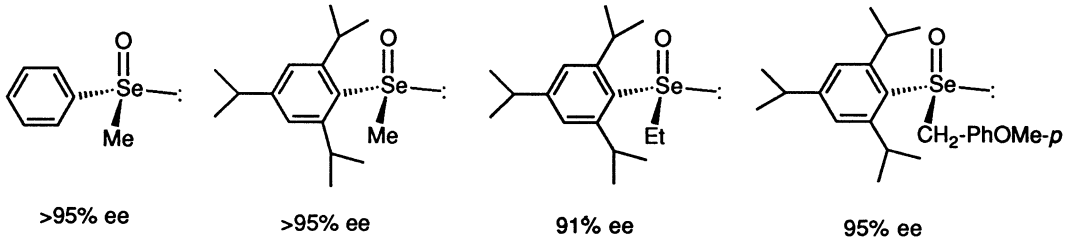
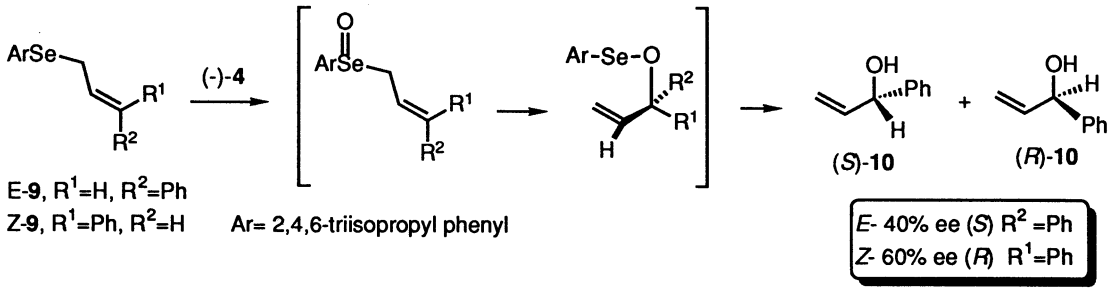


Figure 3: Synthesis of selenoxides at 0 °C in $CHCl_3$ using oxaziridine (-)-**4**.

The selenoxides shown in Figure 3 were obtained in >90% ee and predicted to have the (*S*)-configuration based on the sulfide model (**TS-1**). Chromatography on basic alumina results in nearly complete racemization of methyl phenyl selenoxide (10-15% ee), but the other selenoxides having the bulky *ortho*-isopropyl groups were isolated in good yield and 80-85% ee (Ref. 20). In the presence of trace amounts of acid and moisture these selenoxides racemize completely within a few seconds. The chiral integrity of these selenoxide proved to be less stable in the solid state (complete racemization within several days) than in solution where they were stable for weeks.

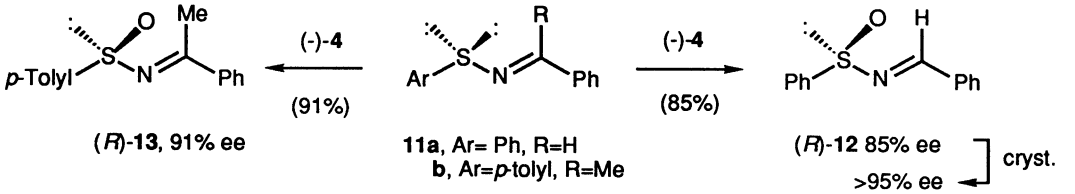
Oxidation of E- and Z-aryl cinnamyl allylic selenides **9** gave 1-phenyl allyl alcohol (**10**) via an allyl selenoxide-selenate [2,3] sigmatropic rearrangement. Since allylic selenoxides can not be isolated, the modest 1→3 chiral transfer is dependent upon the structure of allylic selenide which determines the exo-endo transition state energies. This assumes that the initial oxidation of the selenide to the selenoxide is >90% ee and that racemization is not significant. High chirality transfer has been observed by Reich and Yelm for the rearrangement of a diastereomeric allylic selenoxide (Ref. 21).



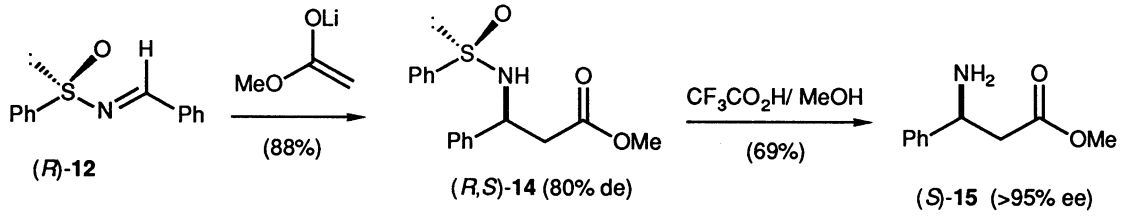
ASYMMETRIC OXIDATION OF SULFENIMINES TO SULFINIMINES

Racemic sulfinimines or N-alkylidene sulfinamides (RS(O)N=C(R)Ar) were first reported by us in 1974, by oxidation of sulfenimines (RSN=C(R)Ar) with *m*-CPBA (Ref. 21). The silver-assisted reaction of ammonia with aliphatic or aromatic disulfides in the presence of aldehydes and ketones gave the sulfenimines in good to excellent yield (Ref. 22) Chiral sulfinimines were reported by Cinquini et. al. using an Andersen type procedure involving the reaction of Grignard reagents with benzonitrile followed by treatment with (-)-*l*-menthyl (*S*)-*p*-toluenesulfinate (Ref. 23). Improved yields were observed with lithium reagents (Ref. 24).

Asymmetric oxidation of sulfenimines **11** with (-)-**4** affords aldehyde derived sulfinimines not available via the nitrile route. Thus oxidation of **11a** affords (*R*)-**12** in 85% ee which on crystallization is obtained in >95% ee (Ref. 25). Sulfinimine **12** is predicted to have the *R*-configuration based on the sulfide model (**TS-1**) and was confirmed by oxidation of **11b** to the known sulfinimine (*R*)-**13** (Ref. 24).



Optically active sulfinimines have application to the asymmetric synthesis of β-amino acids. For example, treatment of enantiopure (*R*)-**12** with the lithium enolate of methyl acetate gave sulfinamide **14** in 80% de and was obtained diastereomerically pure by crystallization. The absolute stereochemistry of the new amino center was established as *S* by hydrolysis to the known β-amino acid **15**.



CONCLUSIONS

N-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (**4**) is the most efficient and general reagent developed to date for the asymmetric oxidation of sulfides to sulfoxides and selenides to selenoxides. High ee's are predictable for those substrates (R_L-X-R_S, X= S, Se) where the R_L group is large, aryl or *tert*-butyl, with R_S having a varied structure. Synthetically useful ee's were also observed for the asymmetric oxidation of sulfenimines to sulfinimines which have applications in the stereoselective synthesis of β-amino acid derivatives.

Acknowledgement

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