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Multiple Stereo selectivity Application in Organic Synthesis

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Abstract – The application of oxiranyl anions in organic synthesis represents a unique means to introduce the epoxide functional group into organic molecules. Unlike simple oxidation procedures, use of these nucleophiles increases molecular complexity in the carbon skeleton at the same time new functionality is created. The generation and utility of trialkylsilyl-substituted oxiranyl anions is highlighted in this paper.

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INTRODUCTION

Stereoselectivity and stereoselective methods in organic synthesis are a problem of fundamental importance and will be even more important in the future as the drug industry is required to supply 100% optically pure compounds. Much progress in this area has been made in the last few years. A number of new, highly stereoselective reactions and methods have been developed and applied in industry. The Nobel Prize in chemistry has been awarded in 2001 to Sharpless, Noyori and Knowles for the development of catalytic asymmetric synthesis, selective processes and chiral catalysts.

One of the methods to increase the stereoselectivity of reactions is multiple stereoselectivity (multiple stereodifferentiation, multiple asymmetric induction), when the stereochemical process proceeds under the control of more than one chiral auxiliary. This kind of chemical transformation occurs in nature because many enzymatic reactions involve the cooperation of several chiral auxiliaries. This type of stereochemical effect, very important froma theoretical and practical standpoint, has not been sufficiently investigated.

In organic chemistry, the earliest attempts to increase the stereoselectivity of a reaction by means of two chiral auxiliaries were described, probably, by Vavon (1950), and Harada and Matsumoto (1966). In 1968, Horeau, Kagan and Vigneron discovered the cumulative effect of two auxiliaries in the reaction of phenyl glyoxalates to mandelate derivatives and named this effect as ‘the double induction’.

In 1977, Izumi has proposed the term ‘double stereodifferentiation’ which is more exact than the term ‘double asymmetric induction’. Articles devoted to the applications of double asymmetric synthesis in different sections of organic chemistry have been published. In 1984, the article of Poulin and Kagan being devoted to asymmetric hydrogenation and the section of Morrison’s monograph written by Heathcock reviewing the aldol condensation.

The following year, Masamune and co-authors described the application of double stereodifferentiation for four crucial reactions of organic chemistry: aldol condensation, hydrogenation, Sharpless epoxidation and Diels–Alder reactions.

During the past 10–15 years, this field of asymmetric synthesis was advanced and studies which allowed a consideration of the problems of stereodifferentiating reactions more widely and exactly have been performed. Multiple stereoselective reactions have found a use in such fields of organic chemistry as Sharpless dihydroxylation, Michael additions, addition to allylmetals, the Reformatsky reaction, the Mukaiyama reaction, photochemical reactions, alkylation, cycloadditions and the synthesis of heteroatom compounds, etc. New versions of multiple stereoselectivity were developed; the substrates, reagents and catalysts bearing several chiral auxiliaries with an additive effect of stereoselectivities, reacting under control of double asymmetric induction. These outstanding achievements require a generalisation of the existing information on the application of multiple asymmetric induction in organic synthesis and a critical consideration of a number of accumulated theoretical problems.

This paper focuses on the synthesis of new organic compounds with specific beneficial biological properties that may be able to be used as antibiotic, antiviral and antitumour drugs or as herbicides and pesticides. In many cases, these properties depend on the different spatial arrangement of the atoms of one molecule, a phenomenon known as stereoselectivity.

The paper also develops new methods for synthesizing already known compounds and

dedicates much of its basic research to providing solutions to specific demands, a field in which it has considerable experience of transfer, particularly to the fine chemical industry.

Oxiranes are critical components of many important, biologically active compounds (e.g., the antitumor antibiotics maytansine and ankinomycin antibiotics asperling and pseudomonic acids A and B and immunosuppressants such as ovalicin). Oxiranes are widely recognized as being extremely versatile synthetic intermediates as well. The high reactivity of epoxides, attributable to ring strain, supports a variety of nucleophilic ring openings, Lewis acid catalyzed rearrangements, and isomerization reactions. Predictable control of regiochemistry and of course stereochemistry in nucleophilic ring-opening reactions of epoxides lends further attraction to their use in selective organic synthesis.

STEREOSELECTIVITY IN DNA

DNA templates are capable of directing chemical reactions without obvious structural requirements or functional group adjacency. The generality of DNA-templated synthesis enables otherwise incompatible reactions to take place in the same solution, multistep small molecule syntheses programmed by DNA sequences, and the selection and amplification of synthetic molecules paralleling key aspects of biological molecule evolution in nature. The chiral nature of DNA raises the possibility that DNA-templated synthesis can proceed stereoselectively without the assistance of chiral groups beyond those present in DNA, thereby transferring not only sequence but also stereochemical information from the template to the product. Previous studies have demonstrated that the chirality of nucleic acid templates can induce a preference for the template-directed ligation of D-nucleotides over L-nucleotides. Stereoselectivity during the DNA-templated synthesis of structures unrelated to the DNA backbone, however, has to our knowledge not been studied. Here, we describe stereoselectivity during DNA-templated organic synthesis and provide insights into its origins.

We examined stereoselectivity in the context of DNA-templated nucleophilic substitution reactions. Hairpin architecture templates conjugated at their 5□□amino termini directly to (*S*)- or (*R*)-2-bromopropionamide were combined with reagent oligonucleotides at 25 □C. The stability of the bromides under the reaction conditions was confirmed by several independent methods (see Supporting Information). Initial rates of thioether product formation were determined by denaturing gel electrophoresis, and products were additionally characterized by MALDI-TOF mass spectrometry (see Supporting Information).

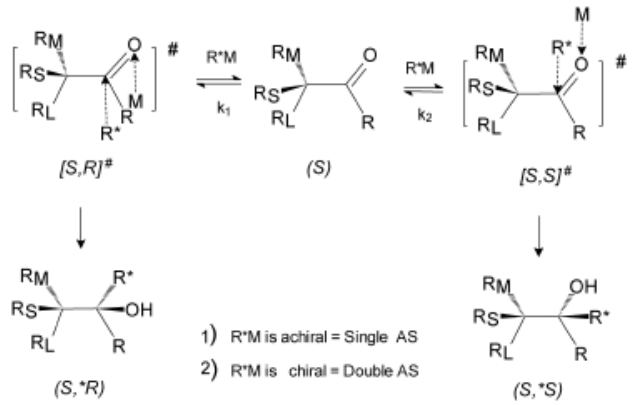
Apparent rates of product formation were 4.0 (0.2-fold higher for (*S*)-bromide-linked templates than for (*R*)-bromide-linked templates. Because template-reagent annealing could be partially rate-determining, this value is a lower limit of the actual ratio of *k*S/*k*R, assuming annealing rates are unaffected by bromide stereochemistry. Surprisingly, similar preferences favoring the (*S*)-bromide were also observed using end-of-helix template architectures1, , even when 12 nucleotides separated the thiol and bromide in the template-reagent complexes. Stereoselectivity also appeared independent of whether the bromide or the thiol was conjugated to the template. Similar selectivities emerged from pseudokinetic resolutions containing both bromide stereoisomers in which thioether products arising from (*S*)- and (*R*)-bromides were distinguished using templates of two distinct lengths (*k*S/*k*R = 4.2 ± 0.4 to 4.9 ± 0.3). Taken together, these findings indicate that the chirality of a DNA template can be transferred to products of DNA-templated synthesis that do not resemble the DNA backbone.

To probe the origins of the observed stereoselectivity, we synthesized a series of template and reagent analogues in which nucleotides near the thiol or bromide were replaced with flexible achiral linkers. Replacing the

template nucleotides separating the bromide and thiol in either of the end-of-helix reactions with an achiral poly(ethylene glycol) linker of similar length (72 bonds) resulted in the loss of stereoselectivity. Stereoselectivity was also abolished when flexible achiral linkers consisting of three or five consecutive methylene or ether oxygens were inserted between the template oligonucleotide and the thiol or bromide groups, or between the reagent oligonucleotide and the thiol or bromide. Chiral linkers between reactants are therefore required for stereoselectivity in this DNA-templated reaction. These results also suggest that both the thiol and the bromide participate in the rate-determining step of the reaction, consistent with an SN^2 mechanism.

STEREOCHEMICAL ANALYSIS OF MULTIPLE STEREOSELECTIVITY

The stereoselectivity can be defined as the preferential formation of one product of several possible products that differ only in their configurations. Stereoselectivity can be further subdivided into enantioselectivity and diastereoselectivity. According to Izumi, when the chirality of participating in differentiation occurs in a reagent, the catalyst or the reaction medium, the reaction is classified as an enantiodifferentiating reaction. When the chirality related to the differentiation is present in the substrate, the reaction is classified as a diastereodifferentiating reaction.



Depending on the structure of a substrate, the diastereoselectivity can be facial, topical or isomeric. The stereoselectivity of reagents can be estimated as a difference of reaction rates or energies of activation leading to two diastereomers. The equilibrium concentrations of activated diastereomeric forms are connected with free energy activations of reactions according to the equation.

$$-RT\ln\frac{k_1^{\#}}{k_2^{\#}} = -RT\ln\frac{[S^*R]^{\#}}{[S^*S]^{\#}} = \Delta G_{SR}^{\#} - \Delta G_{SS}^{\#}$$

In order to obtain the highest stereoselectivity, we need to increase the difference between the concentrations of diastereomers. Thus, we can introduce into the reaction system two or several chiral asymmetric centers. In this case, we obtain the double stereoselectivity or multistereoselectivity if we have several chiral asymmetric centers taking part in the asymmetric synthesis. In the case of multiple asymmetric induction, the activated diastereomeric forms, $[S,R]^{\#}$ and $[S,S]^{\#}$, leading to the diastereomeric products, differ in energies of formation, that determines a difference in their equilibrium concentration.

In all of the approaches, a chiral substrate or agent is acted upon by another chiral entity. This interaction of two chiral agents gives rise to diastereomeric transition states. The difference in energy between the two transition states $(\Delta\Delta G^{\neq})$ determines the degree of selectivity and the lower energy pathway will provide the major antipode, even if the product is not thermodynamically favoured. It is obvious that every additional chiral auxiliary in a reaction system affects asymmetric induction and changes the difference between the activated diastereomeric forms ($\Delta G_{SR}^{\neq}$ – and $\Delta G_{SS}^{\neq}$–). The individual stereochemical properties of chiral auxiliaries, present in a reacting system, as a rule can reinforce one another (matched asymmetric synthesis), or, on the contrary, counteract each other (mismatched asymmetric synthesis).

Several versions of multiple stereoselective reactions are known:

- both reagents, a substrate and a reagent, each bear one asymmetric element;
- a single reaction partner, substrate, reagent or catalyst bears two or more asymmetric centers, and the second reaction partner is achiral;
- reaction of the chiral substrate is carried in the presence of an asymmetric catalyst, chiral phase transfer catalyst, chiral crown-ether, etc;
- reaction of a chiral substrate is carried out in a chiral solvent.

In principle, other versions of multiple stereoselectivity are also possible, e.g. the double asymmetric synthesis with a multifunctional chiral catalyst, polarised light and asymmetric catalysis in a chiral solvent.

The first type of multiple stereoselectivity (substrate–reagent controlled asymmetric synthesis) occurs the most frequently. The asymmetric induction of this type can be explained by example of double asymmetric hydrogenations described by Horeau and Kagan. These authors have found an impressive increase in stereoselectivity in the reduction of chiral ethers of phenylglyoxal acids by optically active reductants in comparison with the case when either the ether or the reducing agent were optically active Chiral groups in the initial compounds 1 and 2 acted in one direction to increase the diastereofacial selectivity of the reagents.

The second version of double stereoselectivity, when a substrate contains two (or more) chiral centers and the reagent is achiral (substrate-controlled asymmetric synthesis), is less studied than the preceding method. This case is very important for biological systems, usually containing several asymmetric centers controlling the stereo course of highly selective processes in living organisms.

MULTIPLE STEREOSELECTIVITY AS A METHOD OF STEREOCONTROL IN ASYMMETRIC ORGANIC SYNTHESIS

Multiple stereoselectivity as a method to increase the stereoselectivity has been more and more widely used in organic synthesis in the last few years, in order to find applications in new areas. During the last two decades, a number of powerful double stereoselective reactions have been developed as a result of the growing need to develop efficient and

practical syntheses of biologically active compounds. Multiple stereoselective reactions provided an especially effective entry to the chiral world due to their economical use of asymmetry-inducing agents. A number of processes have gained wide acceptance, and some of them are even used on an industrial scale. Among the most prominent examples are Sharpless asymmetric epoxidation and dihydroxylation.

Asymmetric reduction : Double asymmetric induction in asymmetric reduction was first demonstrated by Horeaux, Kagan and Vigneron, although in 1950 Vavon and Antonini reported that the reduction of phenylglyoxalic acid derivatives proceeds more stereoselectively if it is required to insert an additional chiral center into a reacting system.

Asymmetric oxidation : The asymmetric oxidation of carbon–carbon double bonds into a variety of functionalised compounds is undoubtedly one of the most useful transformations in synthetic organic chemistry and efforts have been devoted to the development of efficient methods for asymmetric oxidation. The most outstanding achievements in this field are enantioselective methods for asymmetric epoxidation (AE) and asymmetric dihydroxylation (AD) of alkenes, developed by Sharpless, who was awarded the Nobel Prize in Chemistry in 2001.

Other major advances in asymmetric oxidation of olefins followed,namely the Jacobsen and Katsuki salenasymmetric epoxidation, and the Sharpless asymmetric aminohydroxylation.

Asymmetric alkylation : The asymmetric alkylation reaction constitutes one of the most potent methodologies for the stereoselective elaboration of quaternary carbon centers. There are several methods for double asymmetric induction in the alkylation reaction: a chiral substrate reacts with a chiral alkylation agent; a substrate containing two or more chiral auxiliaries reacts with an achiral reagent; deprotonation of a chiral substrate by chiral bases and reaction with an achiral alkylation agent; alkylation of a chiral substrate in the presence of a chiral phase transfer catalyst or chiral crown ether.

Guifa and Lingchong have studied the asymmetric alkylation of carbanions under S–L phase transfer conditions using chiral phase transfer catalysts. The reaction of potassium phthalimide with chiral 2-bromocarboxylates in this case proceeded under the control of double asymmetric induction.

Asymmetric addition reactions : Addition reactions of nucleophiles to unsaturated compounds is one of the most important bond-forming strategies available to the synthetic organic chemist. This is mainly due to the broad spectrum of donor and acceptors that can be employed in these reactions.

The biggest success in the application of the multiple asymmetric induction to increase the stereoselectivity of addition reactions was achieved in the asymmetric conjugate additions, including the Michael reaction, and also in aldol-type reactions, i.e. carbonyl addition reactions to enolates, including zinc enolates (the Reformatsky reaction) and silyl enolates (the Mukaiyama reaction) or to allylmetals.

Asymmetric synthesis of heteroatom compounds : In the last few years, optically active heteroatom compounds have found a wide application in asymmetric synthesis. Examples of double asymmetric synthesis with participation of chiral heteroatom auxiliaries have been described. The chiral heteroatom group that induces optical activity can be easily removed from the molecule, thus presenting an additional advantage in the asymmetric synthesis of chiral compounds. The double stereodifferentiation has been used for the synthesis of optically active phosphorus and organosulphur compounds. Chiral phosphoric acid esters add chiral aldimines with a high asymmetric induction. A matched addition was observed in the case of the addition of dimenthylphosphite to the aldimine derivative (S)-2-methylbenzylamine, furnishing practically a single diastereomer of the aminophosphonic acid esters. In the case of the aldimine derivative of (R)-2-methylbenzylamine, the mismatched asymmetric induction, with a lower diastereomeric ratio, was observed.

CONCLUSION

I hope that this review of multiple stereodifferentiating reactions and their application in organic synthesis will be useful to chemists interested in various aspects of chemistry and stereochemistry. The facts and problems discussed provide numerous possibilities for the study of additional stereochemical phenomena of stereoselective reactions and stereoselectivity.

Looking to the future, it may be said that the multiple asymmetric synthesis will be and should be the subject of future studies. Opportunities lie in the development of the application of reagents and catalysts containing several chiral auxiliaries, studies of the mechanisms and stereochemistry of reactions and studies dedicated to the diastereodifferentiating reactions in biochemical processes.

Today, synthetic organic chemists have several possibilities for the multiple asymmetric induction on an achiral molecule. The broad spectrum of possibilities offered by the developed methodologies therefore covers all types of different substrates. In addition, the manipulation of the introduced functional groups has reached a high level of sophistication in terms of stereo-, regio- and chemoselectivity.

The level of manipulation of the various functional groups can allow the same final compounds to be obtained by different routes and starting from different precursors. The newly introduced methodologies allow shorter synthetic sequences and higher yields in many instances, with respect to the originally developed methodologies. A careful analysis of all the methodologies is still required, however, in planning a synthesis that implies an asymmetric reaction for the introduction of the correct absolute configuration.

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