The Unambiguous Specification of the Steric Course of Asymmetric Syntheses

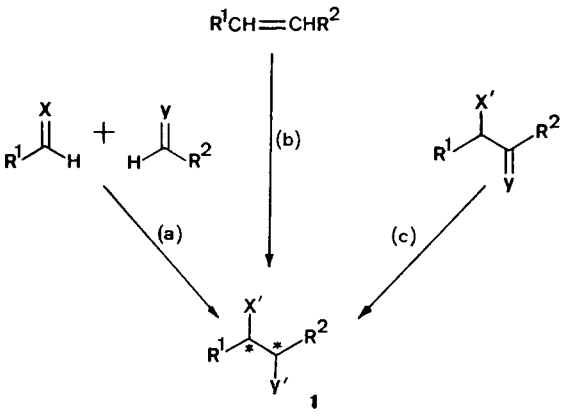
By Dieter Seebach* and Vladimir Prelog

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

The nomenclature of organic chemistry has not kept pace with the staggering advances made in asymmetric syntheses over the last 15 years. Efforts to specify the steric course of stereoselective reactions by use of the terms *erythro* and *threo*, and by other descriptors have led to ambiguous notation and consequently to an almost Babylonic confusion. We propose here a method, based on the CIP-(Cahn-Ingold-Prelog) system, for the unambiguous specification of the steric course and the product configuration of diastereoselective reactions. The reflection-invariant *relative topicity* of approach of reactants is defined as like *(lk)* and unlike *(ul)* if the corresponding descriptor pairs are *Re*,Re** or *R*,Re**, and *Re*,Si** or *R*,Si**, respectively. The descriptor pair notations (*lk* and *ul*) of reactants disclose related steric courses of reactions more often than do the relative configurations of their products, for which the configurational notation $l = R^*,R^*$ and $u = R^*,S^*$ is proposed. The advantage of specifying the relative topicity is demonstrated by means of a series of recent examples of importance to the synthetic organic chemist taken from the literature and from our own work.

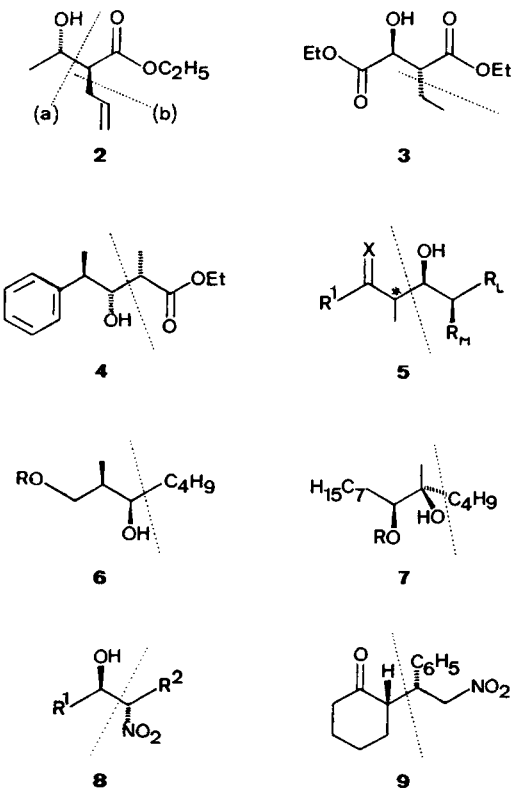
1. Introduction—The Problem

Complex natural products such as macrolides, ionophores, and related compounds have recently become target molecules for synthetic organic chemists[1]. The often formidable array of asymmetric carbon atoms in the structures of these compounds[2] has stimulated the development of highly stereoselective asymmetric syntheses. Foremost amongst these are the aldol[3-5], nitroaldol[6,7], and Michael additions[8]. In all these reactions two planar trigonal carbon atoms are linked together to create a pair of asymmetric tetrahedral carbon atoms [route (a) in Scheme 1]. Stereoselective additions to olefins[9] and to trigonal carbon atoms α to an asymmetric carbon [routes (b) and (c), respectively, in Scheme 1], give the same type of products **1**[7,9-12].



Scheme 1. Three independent routes to structure **1**.

Although these developments represent formidable progress in the art of organic synthesis, attempts to specify the steric course of these reactions have unfortunately led to bizarre nomenclatures, of which the following examples are representative (see Scheme 2): Compound **2** has been termed a "*threo*" aldol product[3,5,17]; **3** an "*erythro*"



Scheme 2. **2a**: *l* by *lk*-aldol addition; **2b**: *l* by *lk*-allylation of an enolate; **3**: *u* by *ul*-ethylation; **4**: *u*, *l* by *ul*-aldol addition with *ul*-1,2-induction; **5**: *lk*-1,2-induction; **6**: *l* by *lk*-addition; **7**: *l* by *lk*-addition; **8**: *u* by *ul*-nitroaldol addition; **9**: *u* by *lk*-Michael addition.

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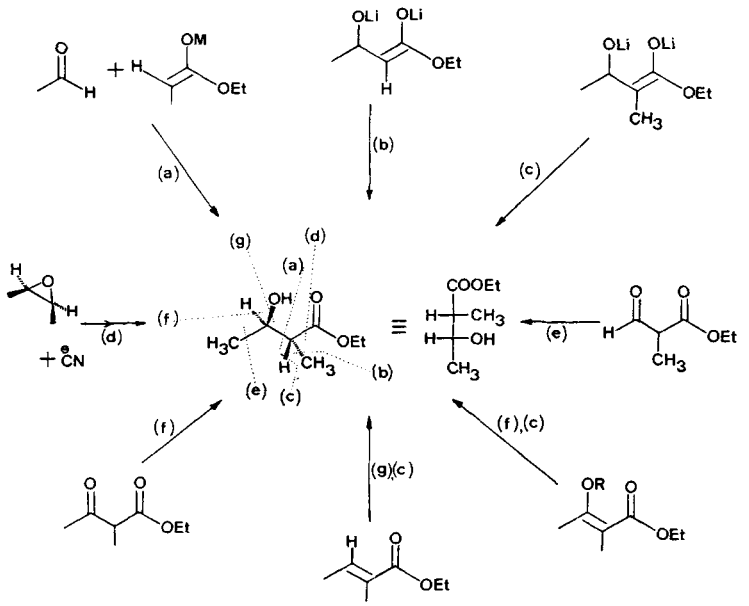
branched malic ester[11]; **4** an "*erythro-anti*-Cram"[3] or "*syn-anti*-Cram" product[4]; **5** a "cram[α- or β-Me]" product, formed in a "CT- (for Cram-*Trans*-enolate) or in a CC (for Cram-*Cis*-enolate)" process[5], respectively; **6** an "*erythro* (Cram steric)" adduct[10a] **7** a "*threo*" glycol derivative[10], **8** an "*erythro*" nitroaldol[7], and **9** an "*erythro*" Michael adduct of an enamine with ω-nitrostyrene[18].

Clearly, there is no agreement about the use of these configurational notations and especially about the meaning of the prefixes *threo* and *erythro*[19]. The attempted redefinition[23] for the purpose of specifying the diastereoselective formation of certain stereoisomers by a particular reaction is certainly not a good basis for configurational notation, because many compounds, such as the β-hydroxyester shown in the center of Scheme 3, can be obtained by



Scheme 3. Formation of *l*-ethyl-3-hydroxy-2-methyl-butanoate with creation of the bonds (a)—(g). (a): *lk*-aldol addition [3–5]; (b): *lk*-methylation of enolate [11, 16]; (c) *ul*-protonation of enolate; (d): opening of *u*-epoxide with inversion (S_N2); (e): *lk*-addition of CH_3-metal derivative [10]; (f) *ul*-hydrogenation of C=O [10b]; (g), (c): *ul*-Michael addition of water to *ul*-olefin; (f), (c): *lk*-hydrogenation of *ul*-enol ether.

several routes [(a—g)], which could well lead to different configurational notations. According to the "aldol-notation"[3,5,17], the (2*R*,3*R*)-3-hydroxy-2-methylbutanoic acid ester in Scheme 3 is specified as "*threo*"; however, according to textbooks of stereochemistry[20] the same compound is specified *erythro*[11].

The present situation in this area is reminiscent of the days when such a simple molecule as dextrorotatory tartaric acid was specified D by European chemists (following *Fischer* and *Freudenberg*) and L by Americans (following *Rosanoff*), because it can be chemically correlated by different reactions with either D- or L-glyceraldehyde[27].

It was in order to avoid such ambiguities that the CIP-system was introduced[28,29]. This specifies the chirality sense of individual two- or three-dimensionally chiral stereogenic atoms (or more generally, stereogenic units, such as centers, axes, planes) by descriptors *Re,Si* or *R,S*, respectively. This system thus specifies not only absolute but also *relative topicities* and configurations by relationships among the descriptors. The duality of diastereomorphic relationships based on combination of two stereogenic atoms and their descriptors leads to two classes which are conventionally specified in the CIP-system (Rule 4[28]) by calling the descriptor pairs with the same first letters (such as *Re,Re*; *R,R etc.*) like (abbreviations *lk* or *l*, respectively) and those with different first letters (such as *Re,Si; R,S* etc.) unlike (abbreviations *ul* or *u*, respectively)[28b,30,31].

We now propose an analogous procedure for the unambiguous specification of the steric course of a single diastereoselective asymmetric reaction or of a class of closely related reactions by specifying diastereomorphic relationships between the two-dimensionally stereogenic trigonal atoms and/or three-dimensionally stereogenic tetrahedral atoms in reactants and in products. This will be explained and illustrated by examples.

2. The *Relative Topicity lk* or *ul* of Reactants and the *Relative Configuration l* or *u* of the Products

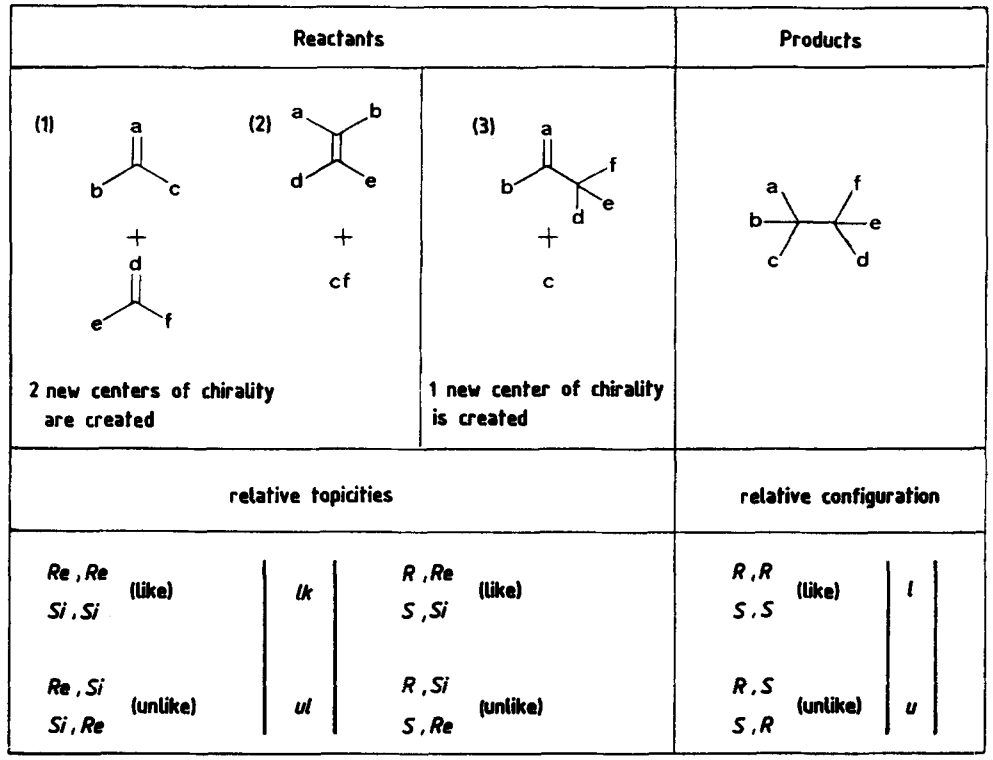
Only one enantiomeric set is shown in all *formulae* representing diastereotopic or diastereomeric relationships. The steric course of reactions leading from reactants with one or two two-dimensionally stereogenic centers to products with two three-dimensionally stereogenic centers is defined by a descriptor pair, and so is the configuration of the product, as shown in Scheme 4. The descriptor pair may be like or unlike. The steric-approach descriptor pairs define *relative topicities*, for instance (*Re,Re*)-approach or addition from the (*Si*)-face of the (*R*)-enantiomer, and are abbreviated as *lk* (like) and as *ul* (unlike), respectively. Similarly, the configurations of the products formed are designated *l* for (*R,R/S,S*) or (*R*,R**) and *u* for (*R,S/S,R*) or (*R*,S**)[30,32]. Procedures for applications to more complex processes or to more complex reactants are given in the legend to Scheme 4.

3. Examples of the Application of the like/unlike Descriptor Pair Notation

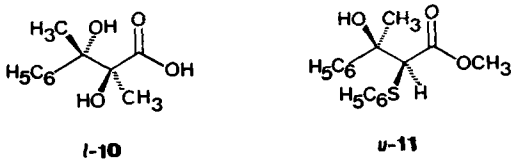
As first examples, the abbreviations *l* and *lk* for like and *u* and *ul* for unlike have been appended for specification of reactions shown in Schemes 2 and 3 (Section 1).

The examples in Scheme 5 show that the *u,l* configurational notation is concise and unambiguous, even in complex cases such as **10**–**12**; in addition, *cis/trans*-diastereomeric olefins, for instance **13** and **14**, can be specified by the same notation[28b].

In Schemes 6–12 a variety of different reactions are specified. Thus, the favored course of aldol and related additions[3–5,8] in nonpolar media turns out to be *ul* with *syn*-enolates and *lk* with *anti*-enolates (see Scheme 6). In Scheme 7 an iodolactonization-type reaction[9], an epoxidation of a homoallylic alcohol[13b], and the conversion of specifically labeled linalol, (*ul,lk*)-1,2,8-trideuterio-3,7-dimethyl-1,6-octadien-3-ol, into terpineol[33] are described with the like, unlike descriptors: the 1,2-induction of the epoxidation in the middle of Scheme 7 is *lk* for all known examples, regardless of the configuration of the atom carrying the hydroxy group[13b]; with the terpineol-forming

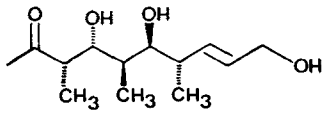


Scheme 4. In complex processes, the relative topicities (1), (2), and (3) are given in this order. The distance between the inducing center of chirality and the reacting atom is specified by 1,2; 1,3; 1,4 ... *etc.* If several centers in the inducing part of the reactant are present, the one which has priority according to the revised CIP system [28] takes precedence.



l-10

u-11



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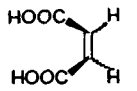
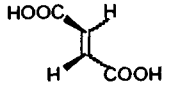


13
ul-diastereomer



14
lk-diastereomer

Scheme 5. **12**: (*u,l,u,l,lk*)-4,6,10-trihydroxy-3,5,7-trimethyl-8-decen-2-one; (order of descriptor pairs according to increasing numbering in IUPAC name).

process, the information content of the relative topicity signs is impressive: the *lk*, *ul*, *ul*-1,3 description specifies (a) that the new CC bond is formed with relative topicity *Re,Re/Si,Si*, (b) that the addition of C and O to the C=C bond occurs with *Re,Si/Si,Re* steric approach, and (c) that the (*R*)- or (*S*)-enantiomeric starting material undergoes CC bond formation with *Si,Si* or *Re,Re* relative topicity, respectively.

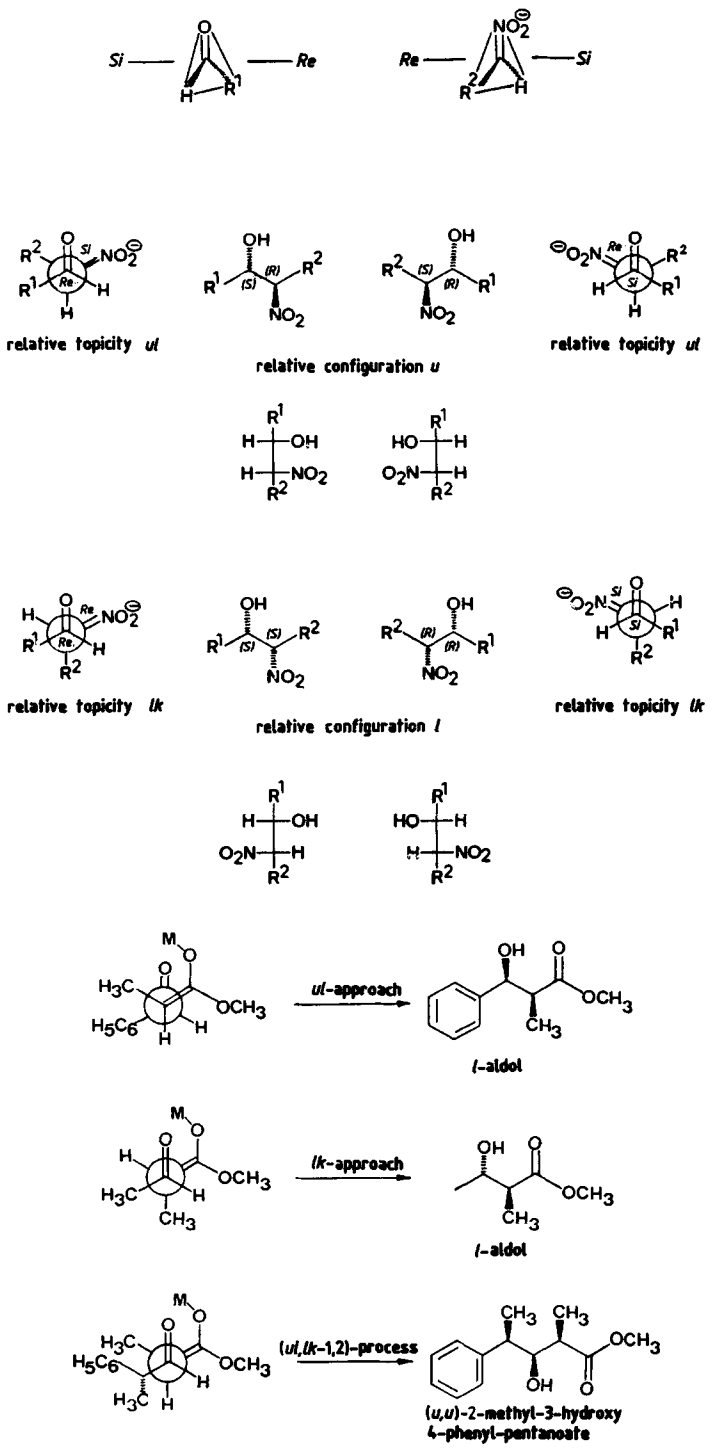
Scheme 8 contains examples of the application of the *lk/ul* descriptor pair abbreviations to reactions following the classical Cram[34], Cornforth[35], and Prelog[36] rules; it is evident, that the acyclic and the cyclic models of the Cram rule are both specified by *lk*. Additions to α-keto-esters of chiral alcohols proceed with *ul*-1,4 induction, irrespective of the priority sequence of the substituents.

In Scheme 9 three examples are shown of reactions which follow a newly established rule for diastereoselective approach of electrophiles to donor double bonds[7, 11, 17].

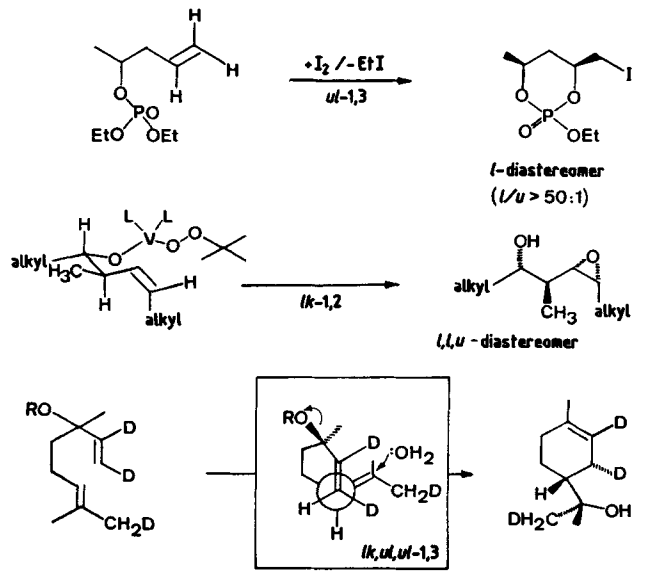
Examples of recently described 1,4- and 1,5-inductions are the reaction sequences (1), (2), and (3) in Scheme 10. The alkylation of the enamine from cyclohexanone and prolinol ether by ω-nitrostyrenes furnishes one of the four possible stereoisomeric 4-nitroketones with >90% selectivity; the first *lk* in the relative topicity specification indicates that the new CC-bond results from a *Re*,Re**-combination of the trigonal centers with formation of the *u*-diastereomer, while the *ul*-1,4 signals that the (*S*)-prolinol ether leads to the (2*S*,1′*R*)-enantiomer of 2-(1′-aryl-2′-nitroethyl)-cyclohexanone[8]. Methylation of the (*S*)-prolinol derivative [see (2) in Scheme 10] occurs from the *Re*-face; a *ul*-1,5 induction[15]. The Michael addition (3) in Scheme 10 can produce[37] (*R*)- or (*S*)-β-branched carboxylic acids, depending upon the sequence in which R^1 and R^2 are attached to the heterocyclic system, with *lk*-1,5 induction.

In Scheme 11, the steric approach in a [2+2]-cycloaddition and in two Diels-Alder reactions is described with the relative topicity notation. Other conversions following the Woodward-Hoffmann rules[38] are of course also amenable to specification by this notation; the intramolecular cycloaddition described in the third equation of Scheme 11 demonstrates the simplicity of the proposed procedure as compared to conventional ways of specification[39].

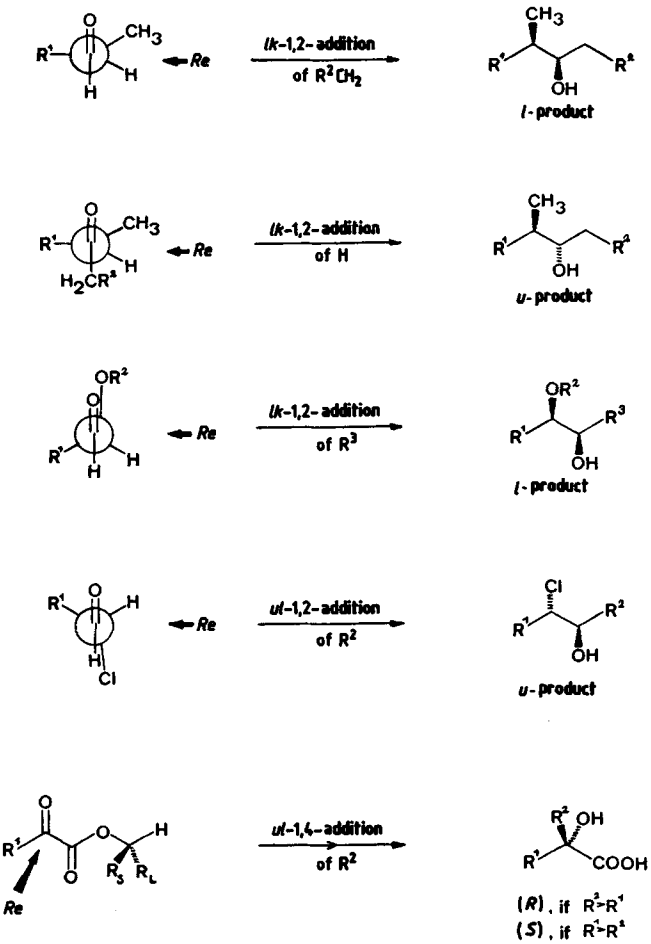
Although not covered by (1), (2), and (3) in Scheme 4, the relative topicities can also be defined in other asym-



Scheme 6. Aldol and nitroaldol additions. Top: Procedure for the specification of the relative topicities of the two possible reactant approaches in the nitroaldol addition and specification of the relative configuration of the products.—Below: Aldol additions of *cis*/*trans*-isomeric enolates to aldehydes. Specification of relative topicities of the first two reactions discloses their different steric course, while specification of the product configurations does not.—The third reaction follows the Cram rule: it exhibits the typical *lk*-relative topicity of the 1,2-induction (see Scheme 8, first three equations).

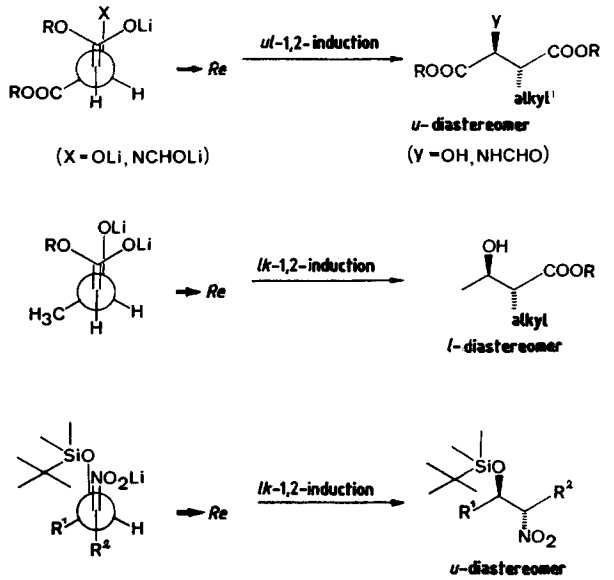


Scheme 7. 1,2- and 1,3-inductions in reactions of substrates with allylic and homoallylic structures.—In the last reaction all three types of processes specified in Scheme 4 occur: (1) formation of a new CC bond between two trigonal centers; (2) addition to a double bond; (3) a 1,3-induction. Notice that the cyclization follows the rule of "antiperiplanar hydrogen atoms" with respect to both double bonds (see 15 in Scheme 11)[8].

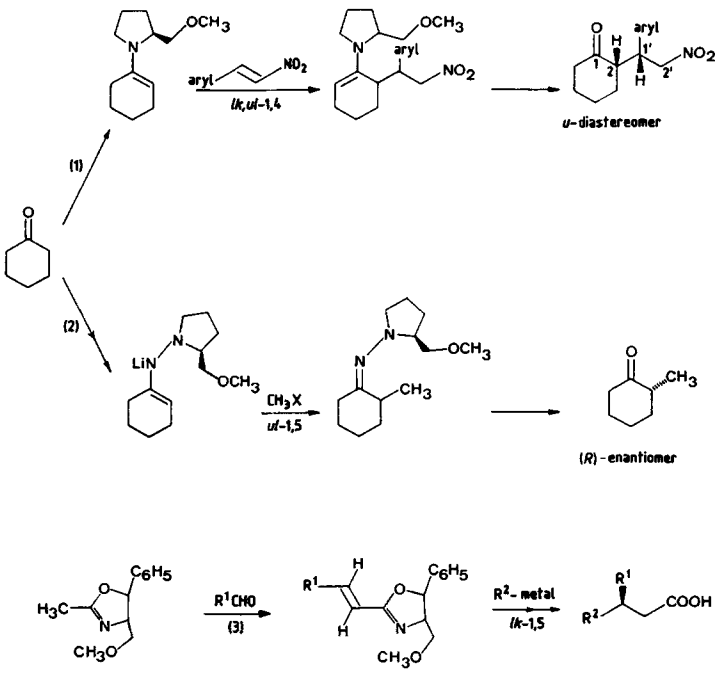


Scheme 8. Specification of reactions following the Cram or Prelog rule. With the normal priority order of substituents at the inducing and at the trigonal centers, both the open-chain [CO > R¹, CH(CH₃)R¹ > CH₂R²] and the cyclic [OR² > CO > R¹] models of the Cram rule have the relative topicity *l* [approach from the *Re*-face of the (*R*)-enantiomer or from the *Si*-face of the (*S*)-enantiomer (see first three equations of the scheme)]. Similarly, the Prelog rule always describes processes with relative topicity *ul* [priority order $R_L > R_S$ (fourth equation)].

metric syntheses. Three such reactions are described by the equations in Scheme 12. In the Horeau method of kinetic resolution[40] an (*R*)-alcohol reacts preferentially with the (*R*)-acylating reagent, a like-selectivity. In the so-called "immolative" asymmetric synthesis[20] of an alcohol by re-

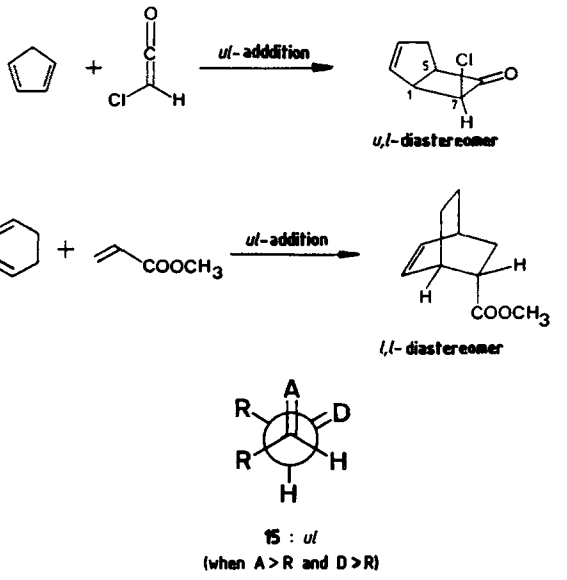


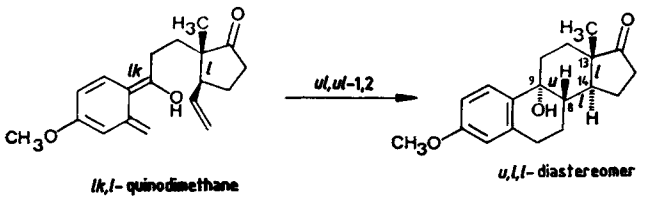
Scheme 9. Specification of three reactions following a rule for electrophilic addition to donor double bonds (cyclic model). On comparison of the second with the third reaction, common features are revealed by the relative topicities rather than by the relative configurations of the products (OLi > C=C > CH_3 and OSi > C=N > R^1); cf. text for a comparison of the first two reactions.



Scheme 10. 1,4- and 1,5-Inductions in the side chain of heterocycles.—The "natural" enantiomers of the prolinol derivatives in reaction (1) and (2) are shown.—The intermediates given do not have to be isolable for specification of relative topicities: formation of (*R*)-methylcyclohexanone under the influence of the (*S*)-center of the heterocycle is a *ul*-process (cf. Scheme 12).—The substrate of reaction (3) contains two 1,5-inducing centers; the route of highest priority leads to the phenyl-substituted center which serves for the purpose of specification (cf. Scheme 4).

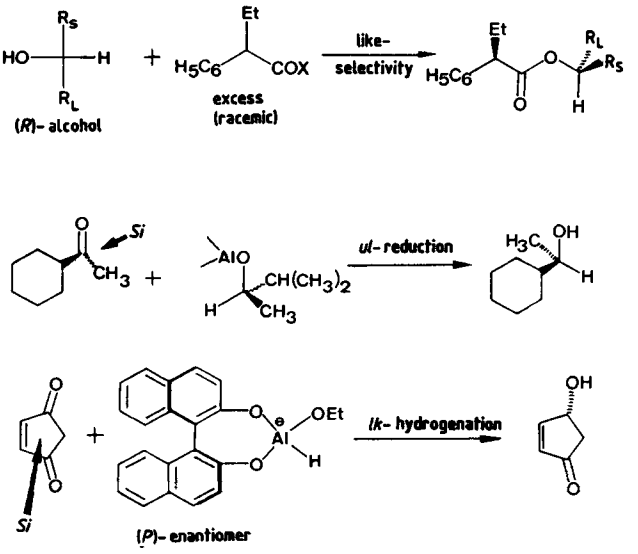
duction of a ketone with an enantiomerically pure aluminum alkoxide, the reducing reagent with (*R*)-configuration approaches the ketone from the *Si*-face[41], *i.e.* with unlike selectivity. If axes or planes of chirality, or helical structures[28] are formed during a reaction or are present in one of the reactants, the convention proposed here can be ap-





Scheme 11. Specification of relative topicities of cycloadditions.—Notice that the *endo*-additions of chloroketene and of acrylic ester turn out to have *ul* relative topicities—just like the preferred mode of nitroaldol and aldol additions (see Scheme 6). All of these reactions are in agreement with the "H-antiperiplanarity rule" [8], see **15** (cf. also third equation in Scheme 7).

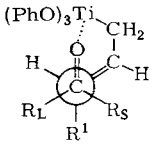
plied by extending the meaning of "like" to the combinations (*R,M*), (*S,P*), (*M,Re*), and (*P,Si*), and of "unlike" to (*R,P*), (*S,M*), (*P,Re*), and (*M,Si*). By means of this extension, the "enantioface differentiation"[42] by an axially chiral aluminate reducing reagent, shown in Scheme 12[43], is *lk*.

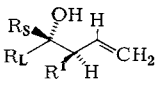


Scheme 12. Application of the like/unlike-specification to asymmetric syntheses, which are not included in the general types (1)—(3) of Scheme 4.

4. Conclusion

Current procedures for specification of the steric course of diastereoselective reactions are often arbitrary and ambiguous. In this paper we propose a slight extension of the CIP-system for specifying the steric course in terms of *relative topicities* and configurations of reactants and for the specification of relative configuration of the product. The advantage of specifying *relative topicity* rather than product configuration is that the former more often discloses similarities and differences in the steric course of reactions (see Scheme 13). The reason is not hard to find: the number of ligands at the stereogenic centers is smaller.





R_L	R_S	R^1	% *ds* [14]	Relative Topicity	Relative Configuration
$CH(CH_3)_2$	H	CH_3	96	*lk*	*u*
$CH(C_2H_5)_2$	H	CH_3	99	*lk*	*u*
$C(CH_3)_3$	H	CH_3	98	*lk*	*l*
$CH_2CH_2C_6H_5$	H	CH_3	95	*lk*	*u*
$CH(C_6H_5)_2$	H	CH_3	93	*lk*	*l*
C_6H_5	H	CH_3	85	*lk*	*l*
C_6H_5	H	C_4H_9	93	*lk*	*l*
C_6H_5	H	$CH(CH_3)_2$	98	*lk*	*l*
p-$CH_3C_6H_4$	H	CH_3	90	*lk*	*l*
p-FC_6H_4	H	CH_3	93	*lk*	*l*
p-$CH_3OC_6H_4$	H	CH_3	98	*lk*	*l*
p-NCC_6H_4	H	CH_3	80	*lk*	*l*
p-$O_2NC_6H_4$	H	CH_3	81	*lk*	*l*
C_6H_5	CH_3	CH_3	88	*lk*	*l*
C_6H_5	CH_3	C_4H_9	87	*lk*	*l*
C_6H_5	CH_3	$CH(CH_3)_2$	87	*lk*	*l*
C_6H_5	C_2H_5	CH_3	74	*lk*	*l*
C_6H_5	$CH(CH_3)_2$	CH_3	55	*lk*	*l*
$C(CH_3)_3$	C_6H_5	CH_3	98	*ul*	*l*
C_6H_5	$C{\equiv}CCH_3$	CH_3	72	*lk*	*u*
C_6H_5	$C{\equiv}CCH_3$	C_4H_9	77	*lk*	*u*
C_6H_5	$C{\equiv}CCH_3$	$CH(CH_3)_2$	77	*lk*	*u*
o-$C_6H_4(CH_2)_3$		CH_3	65	*lk*	*l*
1-Naphthyl	CH_3	CH_3	98	*lk*	*l*
n-C_6H_{13}	CH_3	CH_3	70	*lk*	*u*
Cyclohexyl	CH_3	CH_3	87	*lk*	*u*
Cyclohexyl	C_2H_5	CH_3	60	*lk*	*u*
$C(CH_3)_3$	CH_3	CH_3	96	*lk*	*l*

Scheme 13. Illustration of the usefulness of specifying the relative topicity by means of a further example of practical importance: the addition of 2-alkenyl(triphenoxy)titanium compounds to aldehydes and unsymmetrical ketones proceeds in such a way that the more bulky substituent R_L on the carbonyl C atom is orientated antiperiplanar to the allyltitanium part of the nucleophile which is anchored to the carbonyl O atom. With one exception, in all the cases shown the relative topicity is *lk*, whereas in 19 cases the product configuration is specified as *l*, and in 9 cases as *u* [44].

Different CIP-sequences of ligands will sometimes lead to different descriptors for reactions with analogous diastereoselectivity, but chemists familiar with the CIP-system will easily recognize them.

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tions *n* (negative). We prefer the abbreviations *l* and *u*, because *P* and *p* are reserved for specification of axial, planar, and helical elements of chirality [28].
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Synthetic Membranes—Preparation, Structure, and Application

By Wolfgang Pusch* and Axel Walch*

Dedicated to Professor Klaus Weissermel on the occasion of his 60th birthday

After a long period of dormancy, membrane separation processes have begun to emerge as technically significant and commercially relevant unit operations. Prior to the mid-sixties, synthetic membranes were employed for those few specialized laboratory applications which could tolerate low permeability and poor selectivity or in electrochemical applications excluding, *e.g.*, batteries, fuel cells, chloride-alkali electrolysis, where marginal chemical stability remained a severe limitation. Within the framework of a broad R & D program started in the US in the mid-fifties and devoted to the production of fresh water from brackish and seawater, developments of more suitable membranes arose out of the application of the principles of physical chemistry, modern polymer chemistry (especially surface or interfacial polymerization and polycondensation technology), and electron microscopy. In particular, it was learned that asymmetric membrane structures comprise a very thin consolidated barrier layer (5000 Å or less for membranes with economically practical filtration rates) supported by an integral but less dense substrate which does not participate in the transport process. Later and after much effort, composite membranes were developed in which the salt-rejecting skin (still only 5000 Å thick) was placed atop a supporting matrix formed from a more chemically and mechanically stable polymer.—The main desalination research effort led to several spin-off developments in related membrane fields, *e.g.* the successful preparation and commercialization of ultrafiltration technology in the automobile, food, and chemical industries. Also, ion-exchange membranes prepared from perfluorinated polymers offered the electrochemical industry much better chemical stability than the earlier phenolic-resin-based ion-exchange membranes.—Current efforts are aimed at the improved selectivity and stability required for very specific separation processes (*e.g.* separation of heavy metal salts from waste water or selective enrichment of gases). In the future, the mechanisms of biological processes will have to be exploited for successful development of synthetic membranes suitable for more sophisticated separations.

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1. Introduction

Membranes continue to be the object of intensive research in the fields of physical and polymer chemistry, biology, medicine, and physiology[1-10]. Moreover, synthetic

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