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Communication

Routes to optically-active substances. Rationalization of enantioselectivity and diastereoselectivity*

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Summary — This paper reviews some recent effective methods in asymmetric synthesis exemplified as much in the enantioselective reactions field, by enantioselective protonations and deprotonations, as in the diastereoselective one, by asymmetric halogenation. An explanation is proposed to rationalize asymmetric addition on *E* and *Z* carbon–carbon double bonds.

enantioselective protonation and deprotonation / deracemization / asymmetric halogenation / latent trigonal center concept

Résumé — Voies d'accès aux substances optiquement actives. Rationalisation de l'énantiosélectivité et de la diastéréosélectivité. *Parmi les voies d'accès aux substances optiquement actives décrites récemment, les protonations et déprotonations énantiosélectives constituent un nouveau procédé prometteur permettant, entre autres, de substituer la déracémisation au dédoublement. Par ailleurs, les halogénations diastéréosélectives réalisées avec des auxiliaires chiraux bon marché dérivés du D-(+)-glucose conduisent à des stéréosélectivités élevées. Pour ces procédés et ceux décrits dans la littérature chimique, nous proposons une explication rendant compte des particularités stéréochimiques observées lors des additions asymétriques sur les doubles liaisons carbone-carbone de configuration* Z *et* E.

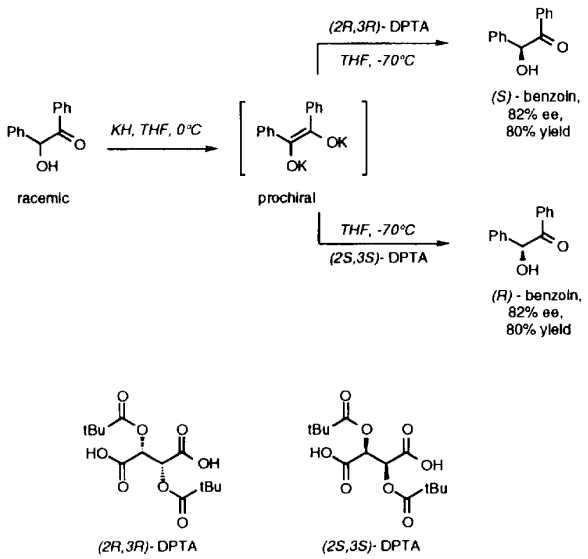
protonation et déprotonation énantiosélective / déracémisation / halogénation asymétrique / concept du centre trigonal latent

Introduction

The development of new routes to optically-active compounds has been one of the main preoccupations of our group in recent years. The enantioselective and diastereoselective reactions which we review here touch upon some important questions concerning the interactions occurring betwen a chiral species and a system containing multiple prostereogenic centres.

We were the first group to employ chiral acids and chiral bases for asymmetric synthesis. In 1976, we published the first examples of kinetically-controlled enantioselective protonations, which were effected by *O*,*O*-dipivaloyltartaric acid (DPTA) upon enolates or enamines having well-defined *E*- or *Z*-configurations [1, 2]. We suggested the term 'deracemization' to define a quantitative enantioselective conversion of a racemic substance into a chosen enantiomer, by variation of the configuration of the chiral acid. Thus benzoin can be deracemized [3] (scheme 1).

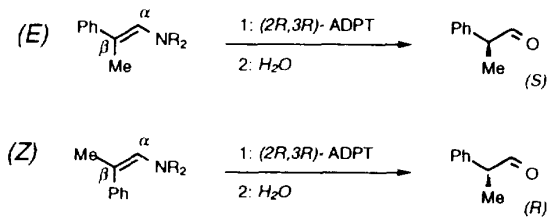
In cases where we employ the same enantiomer of the protonation agent ((2*R*,3*R*)-DPTA), reaction with a *Z*-configured starting material gives one enantiomer of the product, whilst the *E*-isomer gives the other [1, 4] (scheme 2).



Scheme 1

An enantioselective deracemization process developed by C Fehr at Firmenich is now used industrially

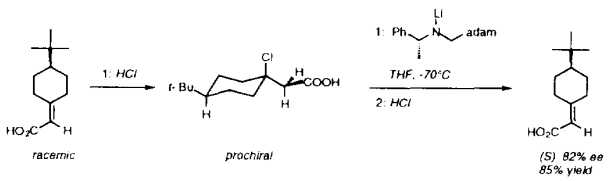
* Presented as a Colloque synthèse asymétrique. Outils chimiques et outils biologiques. ESPCI, Paris, 17 January 1995.



Scheme 2

for the preparation of optically pure (R)-α-cyclogeranic acid. This compound is a key intermediate in the perfume industry [5].

In addition to these studies on chiral acids, in 1980 we and Whitesell simultaneously pursued independent studies which pioneered the use of chiral bases in asymmetric synthesis [6]. Employment of chiral amides allowed us to perform an enantioselective deprotonation sequence which deracemizes axially-chiral molecules [7] (scheme 3).

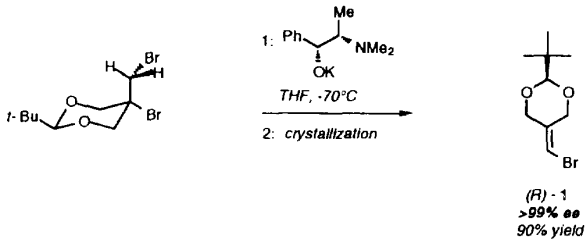


Scheme 3

Since 1980, the literature concerning the use of chiral bases in asymmetric synthesis has developed impressively, with most of the innovations involving the variation of the substituents R^1 and R^2 of chiral amides $LiNR^1R^{2*}$. We recently extended this area by using bases derived from chiral alcoholates. These reagents are particularly efficient generators of optically pure, axially chiral, polyfunctional intermediates [8, 9] (scheme 4).

We have also developed diastereoselective synthetic methodologies, using the cheap and readily available D-(+)-glucose as the chiral auxilliary. These schemes give satisfactory stereoselectivities (90–95%) for the α-halogenation of carboxylic acids. However, unlike the chemistry above, reactions using either the E- or the Z-configured starting material give an identical stereoisomer [10] (scheme 5).

Thus, asymmetric addition reactions at a carbon–carbon double bond demonstrate two different pathways already well defined in the literature. In the first category, addition to an E-configured substrate gives a reaction product which is the mirror image of that



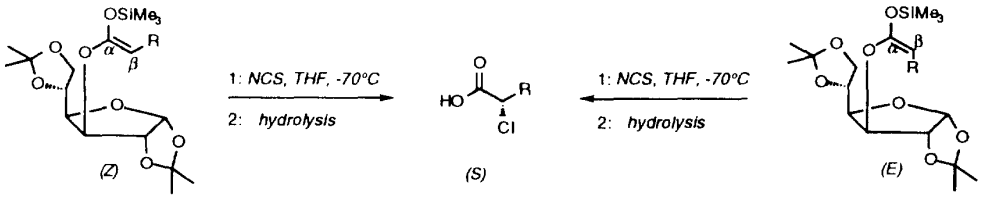
Scheme 4

obtained from the Z-configured stereoisomer. In the second category, the same enantiomer is obtained irrespective of whether the starting material has E- or Z-configuration. These differing results had not previously been discussed, but can be intepreted as follows [11]:

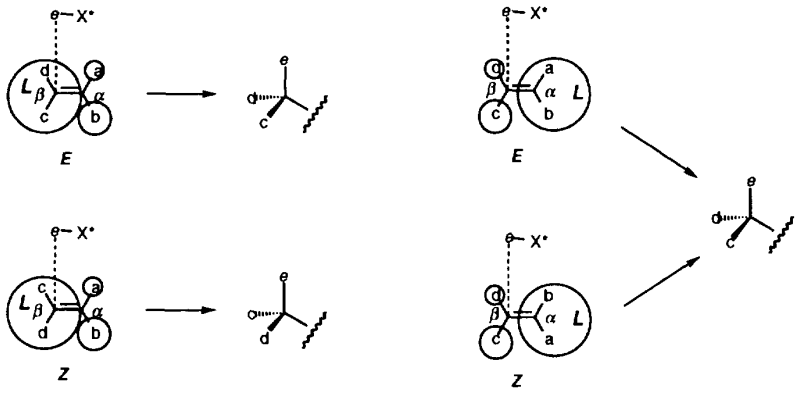
Consider the enantioselective addition of an electrophile e–X* (where e is the electrophilic species and X* is the chiral component) to an electron-rich carbon–carbon double bond, such as an enolate, enamine, ketene acetal, etc. If we label the prostereogenic carbon atom which bears the heteroatom (or heteroatoms, a and b) with the symbol α and the carbon reacting with the electrophile by β, then it is clear that the chiral moiety will have competing interactions with the two prostereogenic carbon atoms α and β. These give rise to two limiting cases (scheme 6).

In the first case, which we term α control, the interaction between the prostereogenic α carbon and the chiral moiety X* overrides any interaction between X* and the prostereogenic β centre. The prostereogenic centre β is then deemed 'latent'. In this case, the site of the reaction (carbone β) is different from the sp^2 prostereogenic centre (α) which is recognized by the chiral moiety. The interactions between the prostereogenic α carbon and X* therefore determine which face of carbon β will bond to the electrophile e. Under such α control conditions, the prostereogenic centre β and its substituents c and d behave simply as a mass, which we represent inside a circle marked L (to indicate that the trigonal centre β is latent). The prostereogenic centre α therefore bears the three substituents a,b, and L. It can be seen that when the interaction of C(α) with the chiral moiety X* favors the introduction of e so as to give a sequence ab$L$, then this preference for the side leading to ab$L$ will give a different enantiomer in the cases of E- and Z-configured starting materials.

The second limiting case, of β control, involves a predominant interaction between the chiral moiety X* and the prostereogenic carbon β. In this case, carbon α and its substituents a and b are represented within the circle



Scheme 5



Scheme 6

L, to denote their latent behavior. The prostereogenic carbon β then bears substituents c, d and L. Should the interactions between carbon β and the chiral group X* lead to the approach of the electrophile e in such a way as to lead to the sequence cd$L$, then this sequence leads imperatively to the same enantiomer, irrespective of whether the starting material has E- or Z-configuration.

In conclusion, if a greater interaction occurs between the chiral moiety X* and substituents a and b than between X* and c and d, then we see a reaction which occurs under α control. In the opposite case, then it will be β control which dominates.

$|a - b| > |c - d|$ α control
$|c - d| > |a - b|$ β control

The same conclusions obviously apply to diastereoselective reactions, where X* is bound to an ethylenic system by a covalent bond. They are equally applicable to aldolizations, where the Zimmerman–Traxler model illustrates a case of α control, whilst the Noyori one provides examples of β-control.

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