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How to build optically active α-amino acids

Review Article

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Summary. Various methodologies published in the literature dealing with α-amino carboxylic acid asymmetric synthesis are presented in a digest form. In each case, only some recent or most typical works are mentioned.

Keywords: α-Amino acid – Asymmetric synthesis – Chiral reagent – Asymmetric auxiliary

1 Introduction

Asymmetric syntheses of organic molecules, particularly those involving α-amino acids, have shown a tremendous development since 1965. Since the publication of various monographs by Kochetkov and Belikov (1987), Duhamel et al. (1988), Williams (1989) and Duthaler (1994), many publications have enriched this field (Davies et al., 1997). In this review we wish to present the various methodologies published in the literature to date dealing with asymmetric syntheses of α-amino-carboxylic acids. Some of these methods are widely used, whilst others are not yet widespread. Our aim is not to comment on the methods already widely reviewed, but rather to present in a shortened form the majority of methods so far published allowing the synthesis of an optically active amino acid, giving in each case the chief chiral auxiliaries. This digest may be considered as a tool facilitating the choice of chemical asymmetric synthesis for a particular amino acid. For each process, we mention only the most typical or recent works rather than all the publications on the subject.

We will not consider syntheses implying a simple modification of the side chain of amino acids, reactions which do not alter the chiral Cα, but only syntheses concerning the asymmetric moiety.

2 From glycine derivatives, by side-chain asymmetric insertion

Glycine derivatives are easily obtained, either from the cheap commercially available natural glycine or from amines and alkyl bromoacetate.

2.1 Electrophilic alkylation of glycine enolates

This is certainly the most widespread method for the asymmetric synthesis of amino acids, being discussed in detail in previous reviews (Williams, 1989 and Duthaler, 1994). We will only recall the main chiral auxiliaries used.

Some well-established methods have been used for asymmetric induction: the chiral auxiliary may be linked to either the amine or the carboxylic function of the glycine derivative (diastereoselective alkylation). Alternatively, it may be situated on the base needed for the enolate formation (enantioselective alkylation) or, in the case of phase-transfer catalyzed reactions, a chiral phase-transfer catalyst may be used. A combination of two chiral auxiliaries (double chiral induction) may also be used in so far as both the inductions are matched.

2.1.1 *via* Schiff base

2.1.1.1 Enantioselective alkylation

In pioneering work O'Donnell (O'Donnell et al., 1989) investigated the enantioselective alkylation of the enolate derived from the *t*-butyl glycinate-benzophenone Schiff base under phase transfer conditions using a chiral catalyst derived from quinine or cinchonine. Quantitative yields were obtained but enantiomeric excess was modest (42–64%). *e.e.* were recently improved (84–97%) by use of cinchonidine or cinchonine derivatives in a homogeneous base system (Schwesinger bases) (O'Donnell et al., 1998). Lygo and Wainwright (Lygo and Wainwright, 1997) and Corey (Corey et al., 1997 and 1998) have obtained very high *e.e.* (up to 99.5%) in the asymmetric alkylation, at −60°C to −78°C, of the same enolate by using solid cesium hydroxide monohydrate as the basic phase and O(9)-allyl-N-(9-anthracenylmethyl) cinchonidinium bromide as chiral catalyst (Fig. 1). The authors explained the excellent results by invoking the rigid structure of the chiral quaternary ammonium salt included in a tight, structured ion pair with the enolate (Corey et al., 1997 and 1998).

2.1.1.2 Diastereoselective alkylation

Chiral Schiff base

Example 1: The chiral carbonyl auxiliaries mainly used are camphor and thiocamphor as first reported by McIntoch (McIntoch et al., 1986 and 1988), the induction efficiency of camphor being improved by replacement with camphorsulfonamides (Yeh et al., 1997), and 2-hydroxy-3-pinanone (now commercially available) as first reported by Yamada (Yamada et al., 1976)

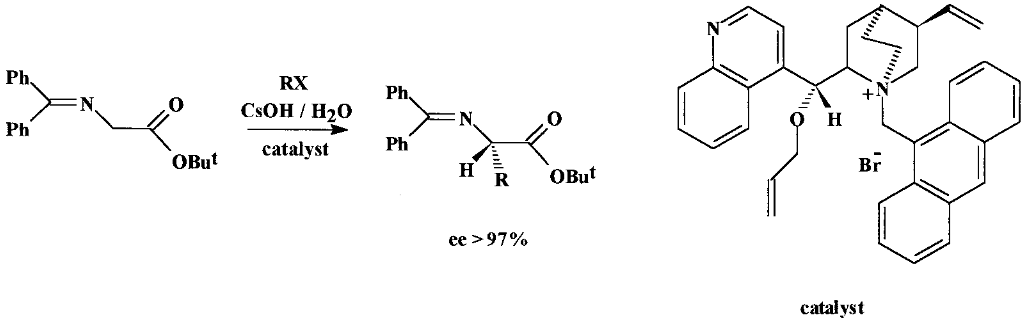


Fig. 1

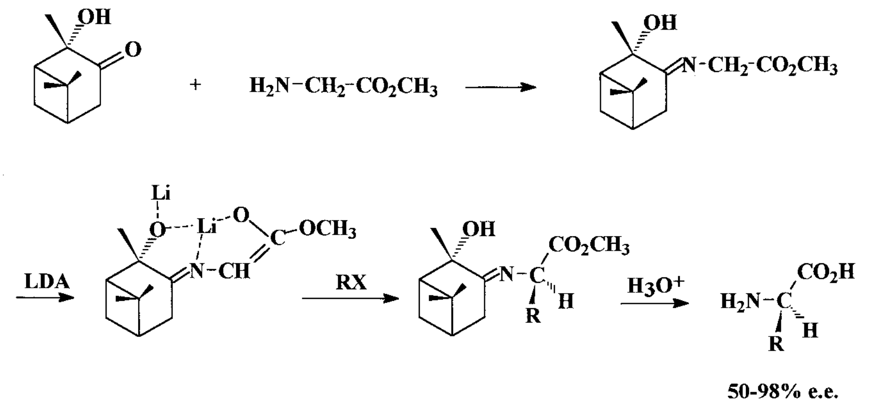


Fig. 2

and for which many applications have been emphasized (Tabcheh et al., 1991). Alkylation of enolates (resulting from the action of LDA, LHMDS, *t*-BuOK or n-BuLi in THF) takes place generally at −78°C, sometimes in the presence of HMPA or DMPU in order to partially deaggregate lithium enolates thus improving chemical yields. The diastereoselectivities are generally good to excellent particularly with 2-hydroxy-3-pinanone (Fig. 2). Hydrolysis of imines is easier in the presence of hydroxylamine in the case of camphor imines and in the presence of citric acid in the case of 2-hydroxy-3-pinanone imines.

Example 2: Both the amine and the acid are chirally derived (double chiral induction, match pair) as chiral Schiff base and as chiral ester, respectively.

The introduction of a second chiral auxiliary on the ester moiety of an already chirally derivatized Schiff base of amino ester (Fig. 3) resulted in high diastereoselectivity (80–99%) in the alkylation of glycine derivatives (Yaozhong et al., 1989 and 1991).

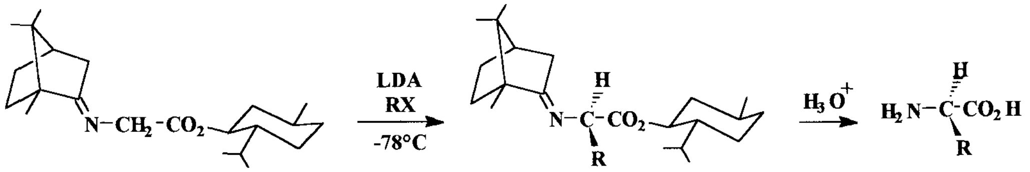


Fig. 3

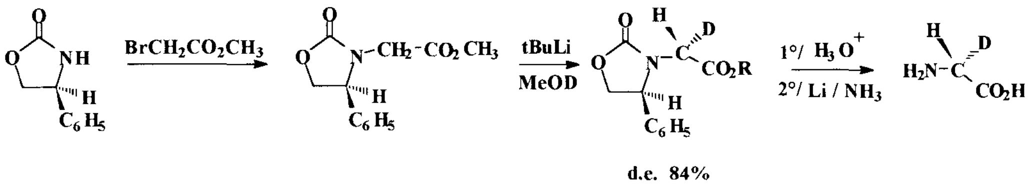


Fig. 4

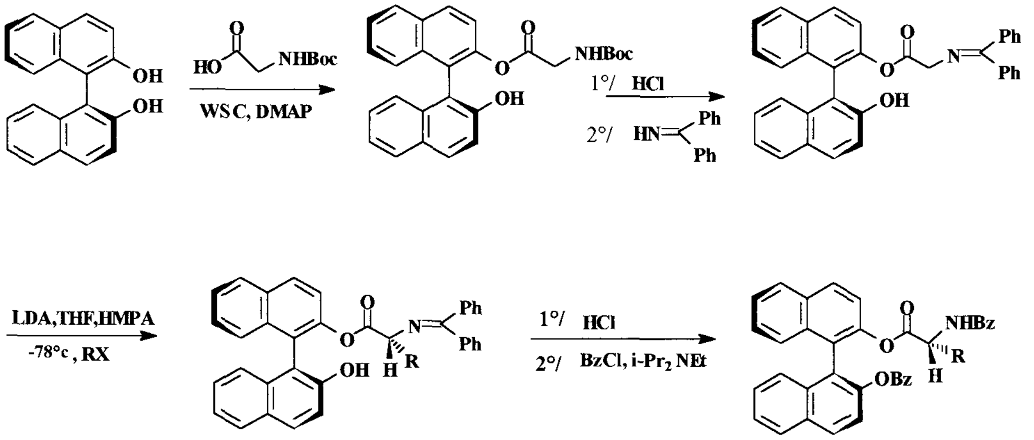


Fig. 5

2.1.2 *via* chiral amine

The N-chirally derived glycine methylester, prepared by action of ethyl bromoacetate on the commercially available Evans's (*R* or *S*)-4-phenyl-2-oxazolidinone, was deuterated, under the same conditions as those reported above, with a good diastereoselectivity (84%) (Hegedus et al., 1992). The N-protecting group was afterwards cleaved with lithium/ammonia (Fig. 4).

2.1.3 *via* chiral ester

The commercially available optically active binaphthol was successfully reported as chiral auxiliary, the amine funtion of glycine being protected as benzophenone imine (Fig. 5). Alkylation proceeded satisfactorily with the

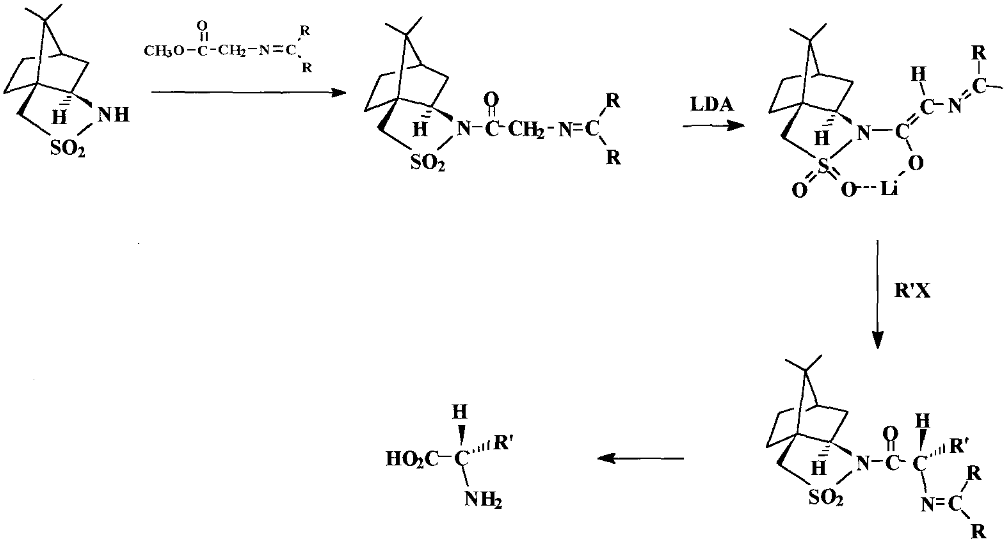
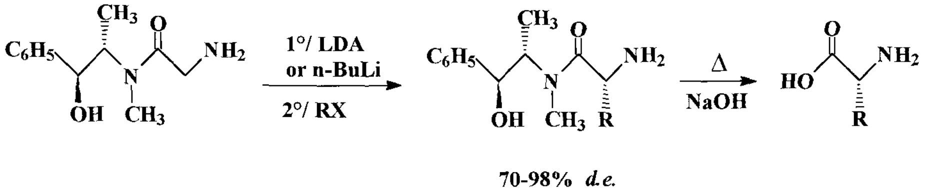


Fig. 6



70-98% *d.e.*

Fig. 7

anion generated with LDA at −78°C in THF containing HMPA (10 equivalents). Because of their instability, alkylated derivatives were not isolated, they had to be converted to N-benzoyl derivatives. These latter were isolated in 62–71% yield with 69–82% *d.e.* (Tanaka et al., 1996).

2.1.4 *via* chiral amide

Example 1: The use of the commercially available bornane[10,2]sultam as chiral auxiliary, first reported by Oppolzer (Oppolzer et al., 1989), afforded very high diastereoselectivities (*d.e.* > 99%) at −78°C, this method being widely used at present (Josien and Chassaing, 1992). The sultam moiety can be easily removed in mildly basic media (Oppolzer et al., 1990) (Fig. 6).

Example 2: N-protected and N-methyl α-amino acids have been recently prepared with high *e.e.* *via* stereoselective alkylation of pseudoephedrine glycinamide or sarcosinamide at 0°C or −78°C and subsequent chiral auxiliary cleavage with NaOH (Myers et al., 1997) (Fig. 7).

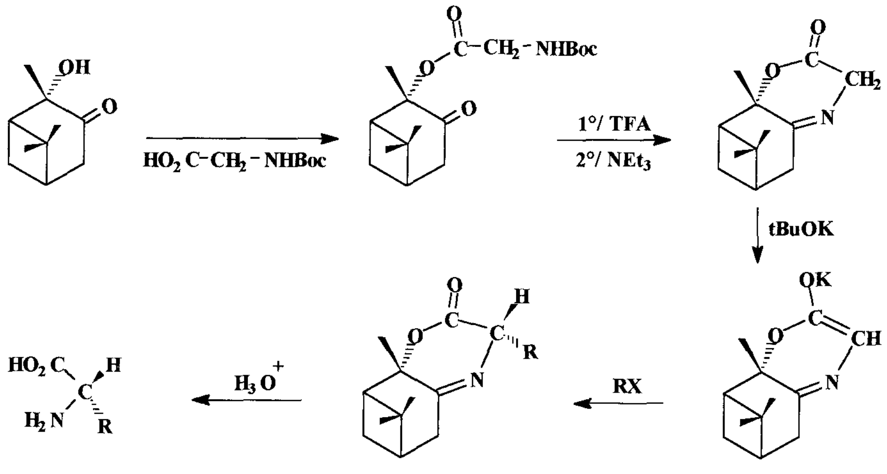


Fig. 8

2.1.5 Simultaneous chiral derivations of both the amine and carboxylic functions

There are many publications in this area. Since most of these chiral auxiliaries are very efficient and have been widely discussed previously (Williams, 1989 and Duthaler, 1994), we only present a selection of them. The advantage of this strategy lies in the fact that there is only one possible configuration of the enolate.

2.1.5.1 Use of 2-hydroxy-3-pinanone to afford the oxazinone ring

The alkylation yield is very dependent on the base used, the best results being obtained at −78°C with tBuOK instead of LDA, in which case *d.e.* always exceeds 95%. 2-Hydroxy-3-pinanone was easily recovered after cleavage of the oxazinone ring with a 2N HCl solution (El Achqar et al., 1988) (Fig. 8). It is generally better to first prepare the ester which afterwards is easily cyclized to the oxazinone rather than first forming the imine which can only be cyclized with difficulty. Oxazoline cleavage was performed with an HCl solution.

Arylation of the same enolate by fluorobenzene tricarbonylchromium was also investigated, but *d.e.* was moderate (20%) (Chaari et al., 1991).

2.1.5.2 Williams method

Example 1: This heterocycle, with two asymmetric centres, was easily formed from the commercially available optically active 2-amino-1,2-diphenylethanol and ethyl bromoacetate, followed by Boc protection of the amine moiety (Williams and Im, 1988; Solas et al., 1996). As above, alkylation took place at low temperatures with a very high diastereoselectivity (*d.e.* > 99%). The subsequent smooth cleavage of the heterocycle allowed recovery of the enantiomerically pure amino acid (Fig. 9).

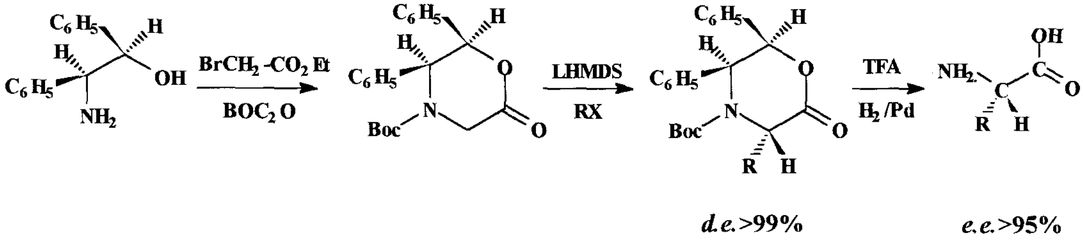


Fig. 9

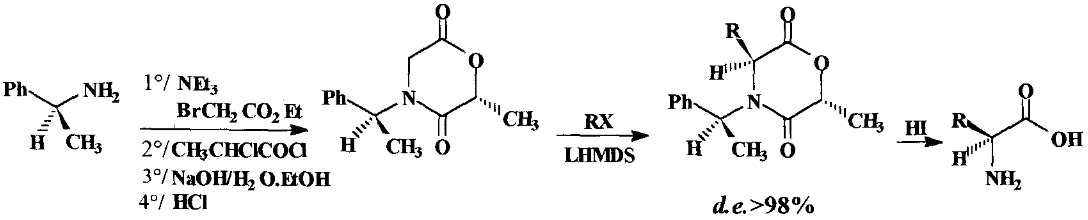


Fig. 10

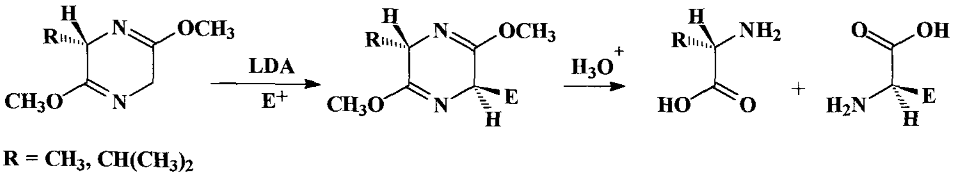


Fig. 11

Example 2: Recently (Fig. 10), the action of ethyl bromoacetate on the cheap commercially available optically active 2-phenyl-ethylamine, Schotten-Baumann reaction with chloropropionyl chloride and subsequent treatment with NaOH/H_2O, EtOH followed by 1N HCl, has been reported to afford the enantiomerically pure 6-methyl-4-substituted-morpholine-2,5-dione. Alkylation of the corresponding enolate at −78°C gave the *trans* product in good yield and with diastereoisomeric excesses greater than 98%. Debenzylation and heterocycle cleavage was carried out in one step in refluxing 57% HI (Porzi and Sandri, 1996).

2.1.5.3 Bis-lactim ether (Schöllkopf method)

Many examples of this method are mentioned in the literature, alkylation taking place at −78°C with a high stereoselectivity (>95%) and in high yield, the incoming group entering at the opposite face to the alkyl group of the chiral auxiliary moiety (Schöllkopf et al., 1979 and 1981). The only drawbacks result from the somewhat harsher hydrolysis conditions and the final separation step of two amino acids (Fig. 11).

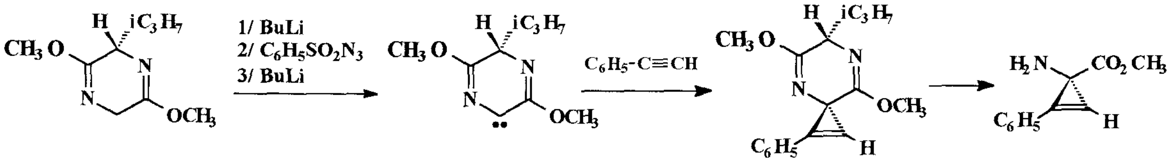


Fig. 12

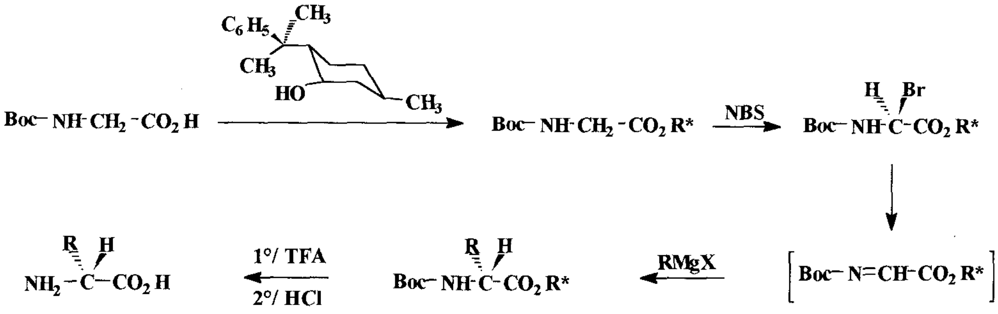


Fig. 13

Remark: Most of the methods previously noted are used for the preparation of α-disubstituted glycines from α-amino acids.

2.2 Addition to an electrophilic glycine carbene

The addition at −78°C of some aryl acetylenes to an electrophilic carbene, generated from a chiral lithio-bislactim ether, gave only the corresponding *anti*-isomers (Schöllkopf et al., 1988) (Fig. 12).

2.3 Nucleophilic addition reactions

Although the first work appeared in 1970 (Fiaud and Kagan, 1970), there are only very few publications in this field. These concern addition of organometallics or enamines to glycine derivatives possessing an activated double bond *e.g.* of the imine or acrylic type.

Example 1: Acid function derived as chiral ester. As early as 1970 Fiaud and Kagan (Fiaud and Kagan, 1970, 1971) prepared optically active amino acids by addition of CH_3MgI to various glyoxylic imine menthyl esters, but in modest chemical yields and with 46–67% optical purities.

More recently, treatment of 8-phenylmenthyl N-Boc-bromoglycinate with a variety of Grignard reagents at −30°C gave the corresponding 2-alkylglycinates in 51–84% yield and with 51–98% stereoselectivity (Hamon et al., 1992). The ester hydrolysis was carried out without racemisation with a HCl/TFA solution (Fig. 13). It was assumed that the imine, resulting from

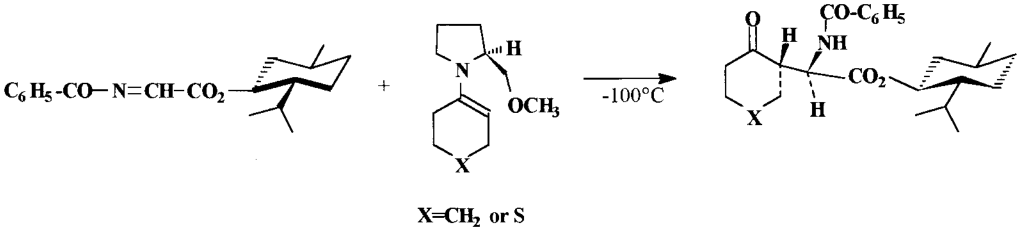


Fig. 14

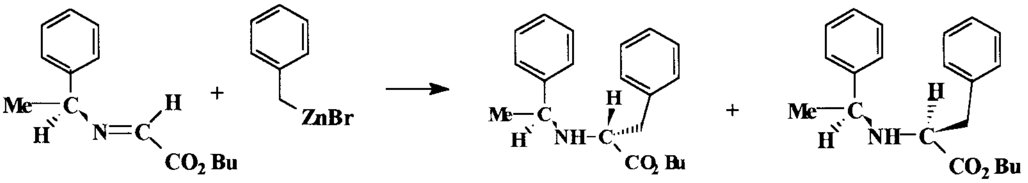


Fig. 15

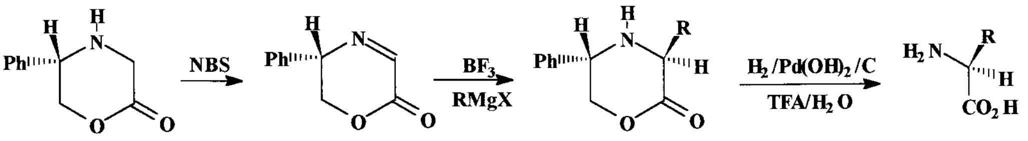


Fig. 16

dehydrobromination of the bromo ester, was the intermediate adding the Grignard reagent.

Example 2: The asymmetric enamine addition to a similar chiral imine at −100°C simultaneously afforded two asymmetric centres, the *anti*-adducts being mainly provided but with modest enantiomeric excesses (27–67%). When a chiral enamine was used (double induction), the enantiomeric excesses increased to as much as 98% (Fig. 14). Unfortunately, the conversion of the adducts to the corresponding amino acids was not described (Kober et al., 1985).

Example 3: The addition of benzyl zinc bromide to a chiral imine of glyoxylic acid *ter*-butyl ester at −78°C afforded a mixture of two isomers, *S*,*R* and *S*,*S* in the ratio 74/26. The chiral benzylic moiety was easily cleaved by hydrogenolysis (Yamamoto et al., 1985 and 1988) (Fig. 15).

Example 4: Both acid and amine functions chirally derived as heterocycle.

Recently, Grignard reagents were added at −30°C to the imine double bond of an optically active oxazinone thus affording adducts in yields ranging from 33 to 57%. After hydrogenolysis and hydrolysis, enantiomerically pure amino acids were obtained (Harwood et al., 1997) (Fig. 16).

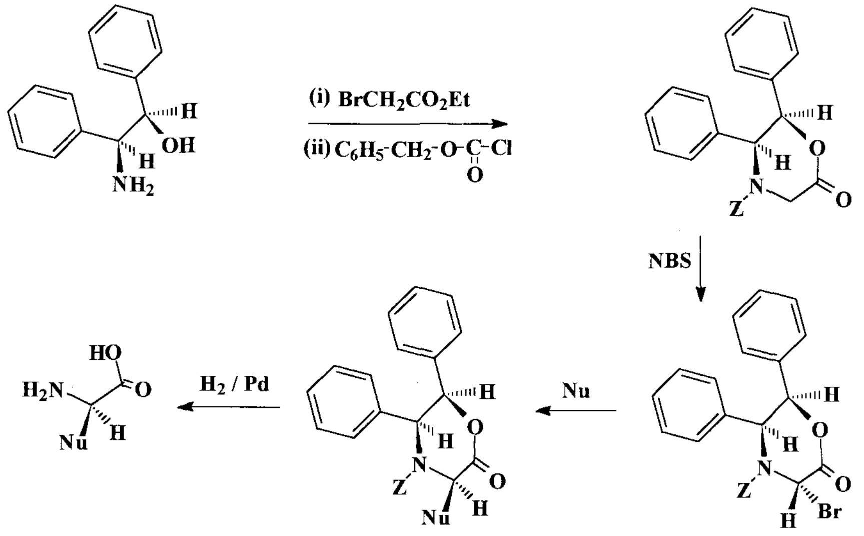


Fig. 17

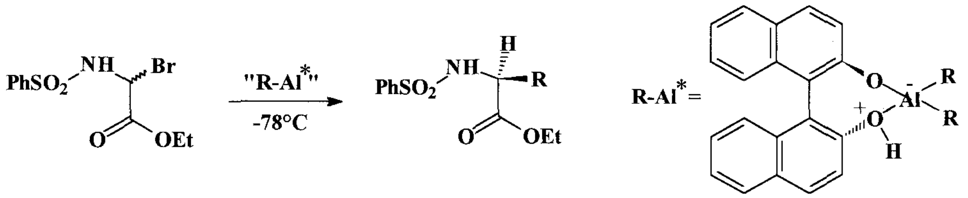


Fig. 18

2.4 Nucleophilic substitution of α-halogeno glycines

Example 1: Chiral derivation of both acid and amine functions as an oxazine ring: bromine was stereoselectively introduced at the least hindered face, opposite to that containing both the aromatic rings. In the subsequent S_N2 reaction, the nucleophile (R'S-, Si-based nucleophiles, malonates,) entered the same face as the aromatic rings (Fig. 17). Thus, it is possible to predict the absolute configuration of the generated amino acid (Williams et al., 1988).

Example 3: Reaction at −78°C of a racemic α-bromoglycinate with chiral alkyl-aluminium reagents modified by binaphthol gave rise to the α-amino acid derivatives in high yields and with enantiomeric excesses up to 62% (Morgan et al., 1996) (Fig. 18).

3 From α-substituted acids, asymmetric amination

3.1 Electrophilic amination

Some suitable NH_2^+ equivalents have been successfully proposed for electrophilic amination, for example, di-*ter*-butyl azodicarboxylate,

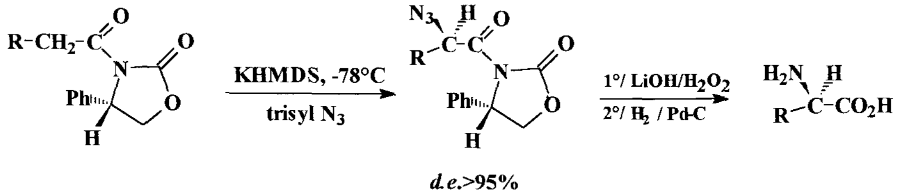


Fig. 19

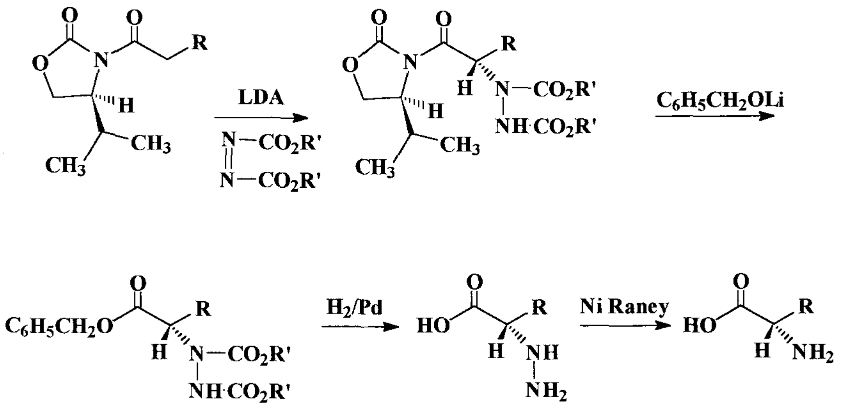


Fig. 20

trisyl azide, 1-chloro-1-nitrosocyclohexane and lithium *ter*-butyl-N-tosyloxycarbamate (Erdik and Ay, 1989).

Example 1: Use of 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide): the starting acid, transformed into a chiral acyloxazolidinone, was successively treated with KHMDS at −78°C followed by trisyl azide. After removal of the chiral auxiliary with $LiOH/H_2O_2$, the azido acid was hydrogenated over Pd/C (Fig. 19) (Evans et al., 1989, 1990a,b; Chen et al., 1992; Beylin et al., 1993; Lundquist and Dix, 1998).

Example 2: The reaction of azodicarboxylate at −78°C with chirally derived carboxamide or ester enolate, afforded adducts in excellent yields and with *e.e.* ranged from 50 to 95% depending on the azodicarboxylate used (Evans et al., 1986; Gennari et al., 1986; Trimble and Vederas, 1986) (Fig. 20).

Example 3: 1-Chloro-1-nitrosocyclohexane, associated with bornane [10,2]sultam as a chiral auxiliary, was used by Oppolzer as the electrophilic source of nitrogen. The reaction took place at −78°C in *ca.* 60% overall yield and with *d.e.* higher than 99% (Oppolzer and Tamura, 1990) (Fig. 21).

Example 4: Lithium *t*-butyl-N-tosyloxycarbamate (LiBTOC) has been found to be a $^+$NHBoc synthon (Genêt et al., 1991) capable of achieving an electrophilic amination of chiral amide cuprate at −78°C in 51–77% yield and with *d.e.* higher than 99% (Zheng et al., 1997) (Fig. 22).

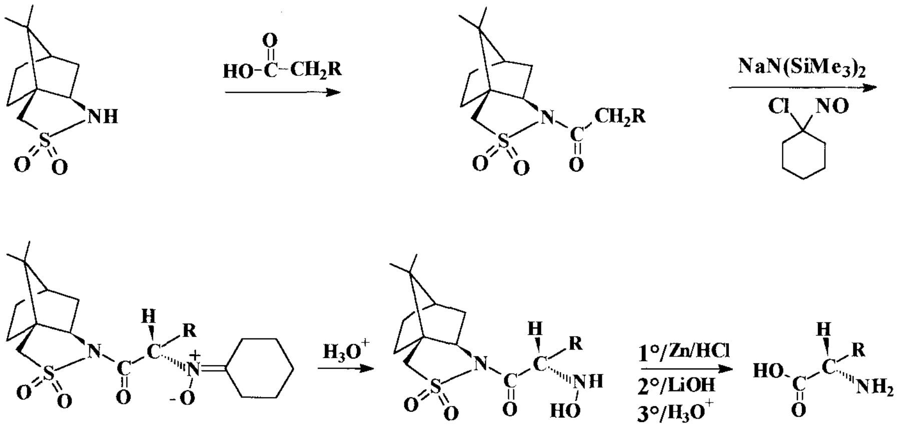


Fig. 21

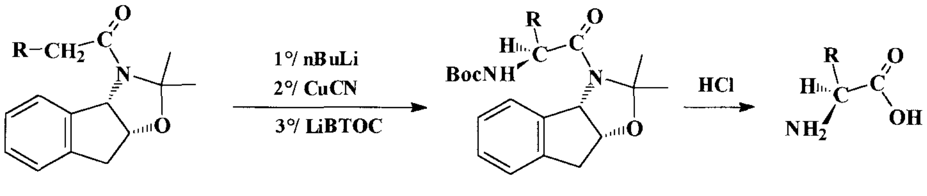


Fig. 22

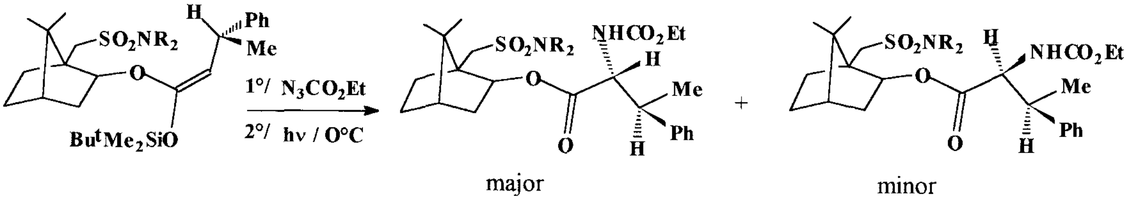


Fig. 23

Another NH_2^+ equivalent, N-Boc-3-(4-cyanophenyl)oxaziridine, has also been used for the preparation of α-amino or α-hydrazino-acid derivatives (Vidal et al., 1993)

Example 5: Amination reaction of silyl ketene acetal derivatives of (*R*)-3-phenylbutanoic acid with (ethoxycarbonyl)nitrene, generated by photolysis of N_3CO_2Et, was achieved with or without optically active ester moiety, to obtain derivatives of α-amino acids with two stereogenic centres (Fig. 23). The diastereoselectivity (up to 88:12) seems to be affected more by the chirality present in the ester moiety than by the resident chirality at the β-carbon (Fioravanti et al., 1994).

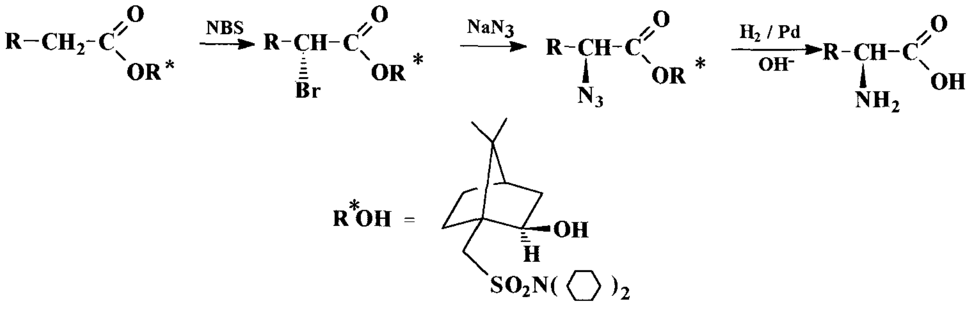


Fig. 24

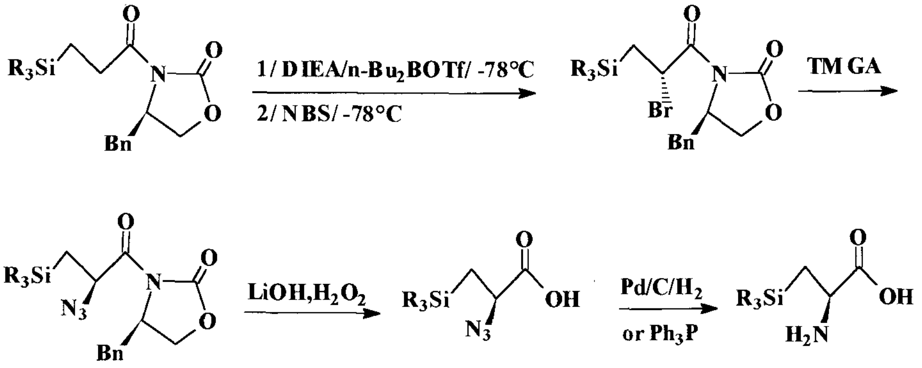


Fig. 25

3.2 Nucleophilic amination

3.2.1 Amine equivalent substitution

The chirally derived starting compounds are carboxylic acid derivatives bearing a leaving group on the chiral α-position. The leaving group may be halogen, epoxide or the triflic group. The suitable NH_2^- equivalent may be N_3Na, azide exchange resin, tetramethylguanidinium azide (N_3TMG), the phthalimide sodium or potassium salt, or a secondary amine.

Example 1: The S_N2-type halide substitution by N_3Na as nucleophile was achieved at room temperature in 72–87% overall yield and with 93–98% enantiomeric excess, followed by concomitant liberation of both carboxylic acid and amino group thereby regenerating the auxiliary alcohol, (Oppolzer et al., 1986; Ward et al., 1995) (Fig. 24).

Example 2: Optically pure (trimethylsilyl)alanine has been obtained from 3-(trimethylsilyl)propionic acid using 4-benzyl-2-oxazolidinone as chiral auxiliary. The corresponding bromide was subjected to an S_N2 azide displacement reaction with TMGA, giving a single diastereoisomer (Xiang et al., 1995; Walkup et al., 1995) (Fig. 25).

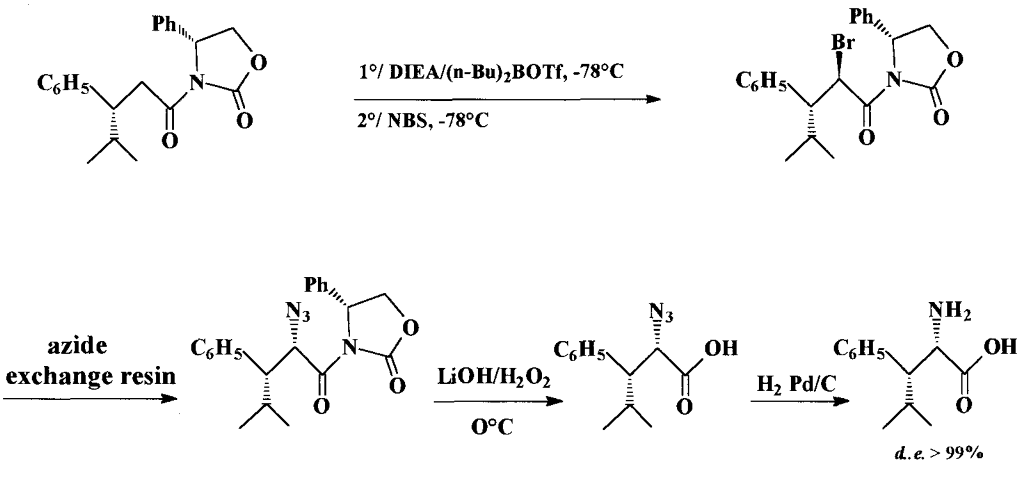


Fig. 26

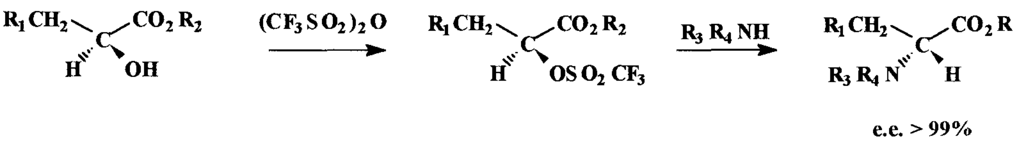


Fig. 27

Example 3: Azide was prepared by displacement of the bromo group with azide exchange resin *via* an S_N2 mechanism, the chiral auxiliary being removed by hydrolysis and the subsequent hydrogenolysis of the α-azide compound giving the corresponding optically pure α-amino acid (Qian et al., 1995; Liao and Hruby, 1996) (Fig. 26).

Example 4: Optically active α-hydroxy acids activated as triflate, underwent S_N2 displacement with an amine in high yield without detectable racemization and without notable elimination (Effenberger et al., 1983) (Fig. 27).

Bomine substitution of α-bromoamides derived from bornane-10,2-sultam with the soft, quite hindered dibenzylamine giving a single diastereoisomer was also described (Ward et al., 1995).

Example 5: An interesting case of dynamic kinetic resolution was described with potassium phthalimide as NH_2^- equivalent (Kubo et al., 1996). The reaction was achieved at room temperature and the major diastereoisomer was obtained with 76–94% *d.e.* depending upon the solvent used (DMSO, DMF, HMPA or NMP) (Fig. 28).

Example 6: Recently Mitsunobu's replacement of the hydroxy group of an optically active α-hydroxy acid derivative by amine was described. *e.e.* was generally excellent (95–99%) except when R contained an aromatic ring (0–60%) (Decicco and Grover, 1997) (Fig. 29).

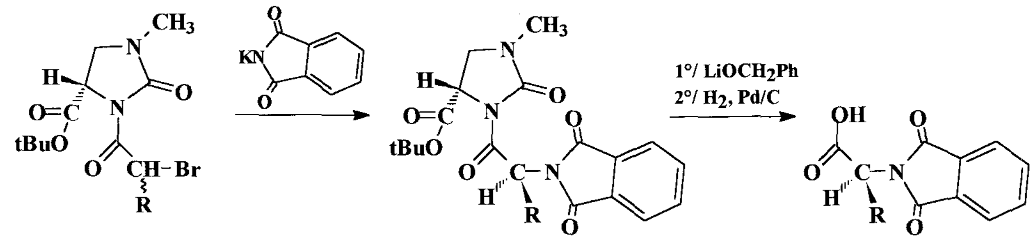


Fig. 28

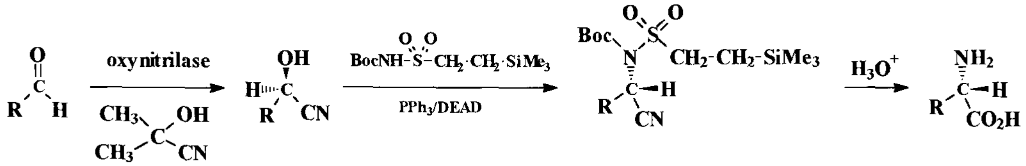


Fig. 29

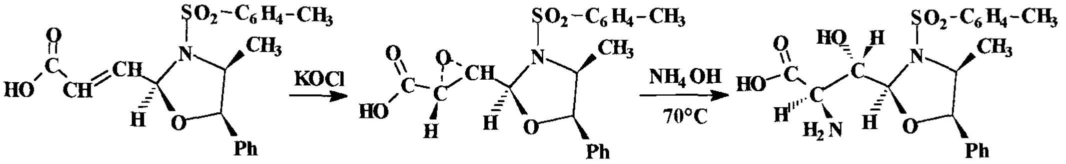


Fig. 30

Remark: Another possibility of OH replacement by an amine, not yet tried to our knowledge, might result from mesylation followed by S_N2 displacement by hydroxylamine, following a very recent work on the synthesis of chiral isoxazolines (Farr, 1998), and their subsequent reduction (Oppolzer and Tamura, 1990).

3.2.2 Epoxide opening

The opening of optically active epoxides by warming at 70°C in ammonia solution gives the corresponding *anti* α-amino β-hydroxy acid as a single isomer in quantitative yield (Cardani et al., 1988) (Fig. 30).

4 From amines, by asymmetric carboxylation

The few examples so far published in the literature concern both enantioselective and diastereoselective electrophilic α-carboxylations of amines.

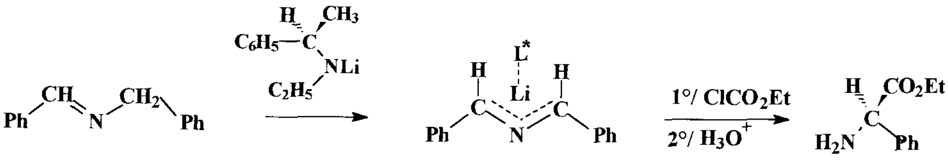


Fig. 31

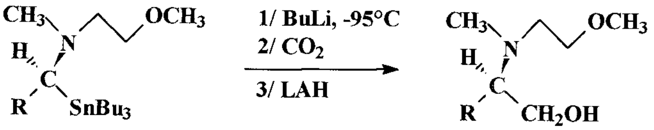


Fig. 32

Example 1: The early work (Duhamel et al., 1978) involved the treatment of the lithium salt of the benzylic Schiff base of benzylamine (afforded by action of a chiral amide base) with ethyl chloroformate at low temperature. After the Schiff base hydrolysis, the phenylglycine ethyl ester was formed with moderate *e.e.* (<40%) (Fig. 31).

Example 2: α-Amino organostannanes undergo Sn-Li exchange to form carbanions which react with chloroformate to afford amino esters in 48% yield. Both reactions take place at −78°C. In one case, the reaction was carried out from enantiomerically-enriched amino-stannane, chloroformate being replaced with CO_2. The resulting amino ester was not isolated but reduced in situ to the corresponding β-amino alcohol. This reaction takes place with complete retention of configuration of the asymmetric centre if the intermediate organolithium is generated at low temperature and quickly treated with CO_2 (Burchat et al., 1993) (Fig. 32).

Example 3: N-Boc-phenylglycine asymmetric syntheses involved first the enantioselective deprotonation of N-Boc-methyl-benzylamine at −78°C by the chiral complex s-BuLi / (−)sparteine (prepared directly or by tin-lithium exchange), followed by substitution with CO_2 or methyl chloroformate with retention of the configuration. The (*R*) enantiomer is always favoured with *e.e.* ranging from 29 to 96% (Voyer et al., 1995 and 1997). However this method, like the previous one, seems to be limited to benzylic amines (Schlosser and Limat, 1995; Park and Beak, 1997) (Fig. 33).

Example 4: A more general and interesting asymmetric synthesis was recently applied to (*S*)-methionine synthesis from methylthiopropanal (Jeanjean et al., 1997). The process involved the synthesis of a chirally derived stannane which, after transmetallation with nBuLi at −78°C followed by carboxylation by gaseous CO_2, produced in less than 15 minutes a single diastereoisomer. The chiral auxiliary was easily cleaved according to Birch's reaction (Fig. 34).

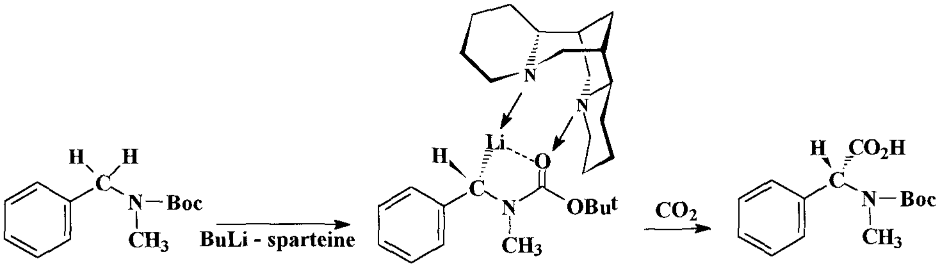


Fig. 33

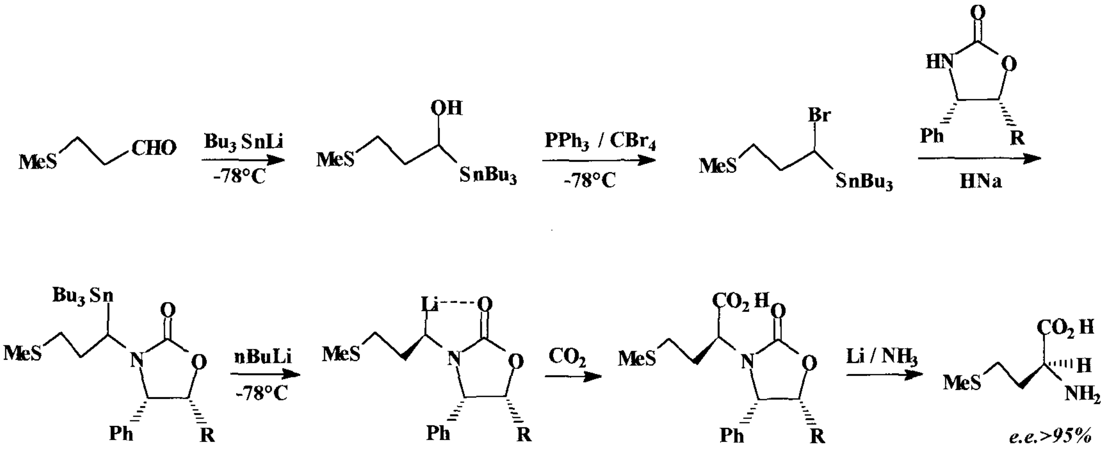


Fig. 34

5 From unsaturated α-amino acids, by asymmetric hydrogen addition

5.1 *From α,β-dehydro-amino acids*

Two possibilities of induction have been reported, either heterogeneous hydrogenation of chirally derived dehydro-amino acids or homogeneous hydrogenation of achiral dehydro-amino acids in the presence of a soluble optically active catalyst. Since both these possibilities have been reviewed (Kreuzfeld, 1996) and widely used, we have not emphasized this methodology. We only report one example of each.

5.1.1 From chirally derived dehydro-amino acids

Example 1: As early as 1968 Vigneron (Vigneron et al., 1968) showed the efficiency of this methodology. They achieved the Raney nickel catalyzed diastereoselective hydrogenation of a dehydro-aspartic acid derivative, both the amine and the α-carboxylic acid functions being included in a chiral

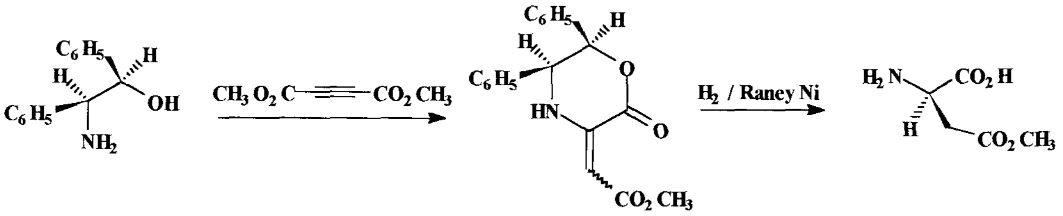


Fig. 35

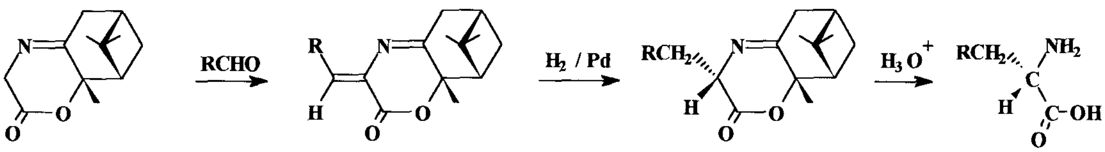


Fig. 36

oxazinone ring. This reaction afforded (*R*)-*β*-methyl aspartate in high yield and with *e.e.* greater than 98%, hydrogen entering the face opposite to the phenyl groups. More recently, similar hydrogenation was achieved by use of phenylglycinol as chiral auxiliary, but with lower *e.e.* (Tamura and Harada, 1980) (Fig. 35).

Example 2: In a similar way, dehydro-amino acids chirally derived with 2-hydroxy-3-pinanone as cyclic imino-esters, were hydrogenated in the presence of Pd/C with >95% diastereofacial discrimination, the hydrogen entering the same face as the gem dimethyl group (Fig. 36). Hydrogenation of the same double bond with L-selectride®, through an enolate intermediate, gave the same results (Cativiela et al., 1992).

5.1.2 Use of soluble optically active catalysts

Many optically active diphosphine ligands of metal catalysts, becoming steadily more efficient, have been reported in the literature and extensively studied. In addition of the ligands reported by Williams (1989) and Kreuzfeld et al. (1996): DIOP (Kagan and Dang, 1972), CHIRAPHOS (Fryzuk and Bosnich, 1977), BINAP (Miyashita et al., 1980), and new derivatives JOSIPHOS (Togni et al., 1994), (2,2)PHANEPHOS (Pye et al., 1997). *etc* . . . , we wish to only mention some recent typical asymmetric hydrogenation studies concerning amino acrylic derivatives.

Example 1: High *e.e.* (96–99%) were obtained by use of electron-rich D-glucose derived phosphinites as ligand in the Rh-catalyzed hydrogenation of dehydroarylalanines at room temperature (RajanBabu et al., 1994) (Fig. 37).

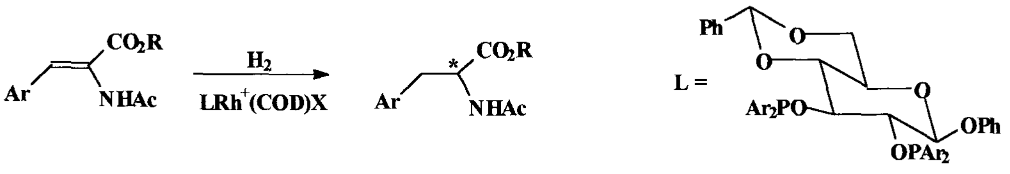


Fig. 37

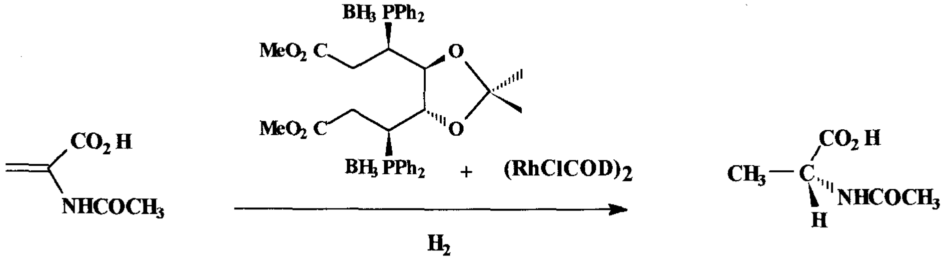


Fig. 38

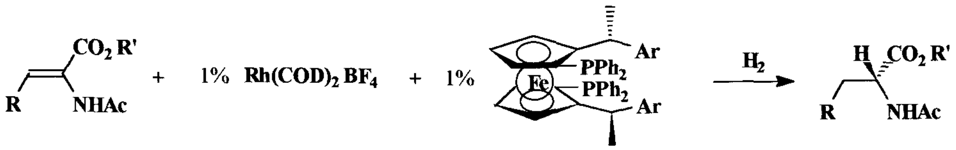


Fig. 39

More recently, a chiral rhodium catalyst based on a bicyclo[3.2.0]heptane was used (Adger et al., 1997), phenylalanine derivatives were obtained with 59–92% enantiomeric excesses.

Example 2: This work involves diastereoselective synthesis and use of diastereoisomeric diphosphine-borane Rh complexes (Pellon et al., 1996). The catalyzed hydrogenation of N-acetyl acrylic acid was achieved at room temperature in 60 minutes in good yield and with 80% *e.e.* (Fig. 38).

Example 3: A new family of chiral C_2-symmetrical ferrocenyl diphosphines (FERRIPHOS) used as ligand in the rhodium-catalyzed hydrogenation of α-acetamidoacrylic acid derivatives gave high enantioselectivities (97.3–98.7%) (Almena Perea et al., 1998) (Fig. 39).

5.2 *From imino-esters*

Reaction of chiral sulfinimine of α-keto triesters with 9-borabicyclo [3.3.1]nonane gave the corresponding saturated ortho-esters in 95% yield and

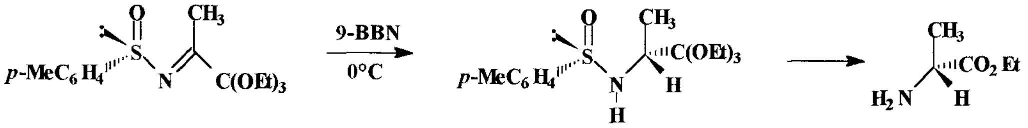


Fig. 40

as a single diastereoisomer. After hydrolysis of the ortho-ester and removal of the N-sulfinyl group, amino acids were obtained in optically pure form (Hua et al., 1995) (Fig. 40).

6 Asymmetric transformation of a racemic amino acid

The principle consists in the transformation of the whole of the racemic amino acid into a single enantiomer, the yield being theoretically 100% unlike the chemical or the enzymatic resolution. It is a very promising method because the asymmetric centre is generated in the last step of the synthesis. Initially, the sp^3 α-carbon of the aminoacid is changed into a prochiral sp^2 carbon by proton extraction. In a second step, a proton is added stereoselectively. This has been achieved in two ways, either through a prochiral enolate which is stereoselectively protonated, or through a prochiral ketene to which an alcohol is stereoselectively added.

6.1 Enantioselective protonation of enolates

Asymmetric protonation of prochiral enolates (Fehr, 1996; Krause et al., 1997), first reported by Duhamel et al. (1978) has been little used to date in the case of amino acids in spite of seeming a promising method. The asymmetric induction may stem from the chiral base used for the enolate formation, or from a chiral derivation of the prochiral enolate, or from a chiral proton source. It may also result from a combination of two auxiliaries.

Example 1: The chiral auxiliary does not belong to the amino acid (enantioselective protonation). In the pioneering work carried out by Duhamel (Duhamel et al., 1978, 1980, 1984, 1986, 1988) the amine functional group of the aminoester was protected as the benzylidenic Schiff base, enolate formation resulting from action of LDA or LHMDS, and the proton source being a homochiral acyl tartaric acid. Enantiomeric excesses were modest, reaching only 62% at −50°C, but they were slighty improved (up to 70%) by use of a chiral lithium N-ethyl 1-methyl-benzylamide as additional chiral source in place of LDA or LHMDS (Fig. 41).

Example 2: The chiral auxiliary belongs to the amino acid (diastereoselective protonation), and it may result from the chiral derivation of either the amine or the carboxylic functional group. All the chiral auxiliaries used for the diastereoselective electrophilic asymmetric alkylation of glycine enolates, which were mentioned previously, can be used.

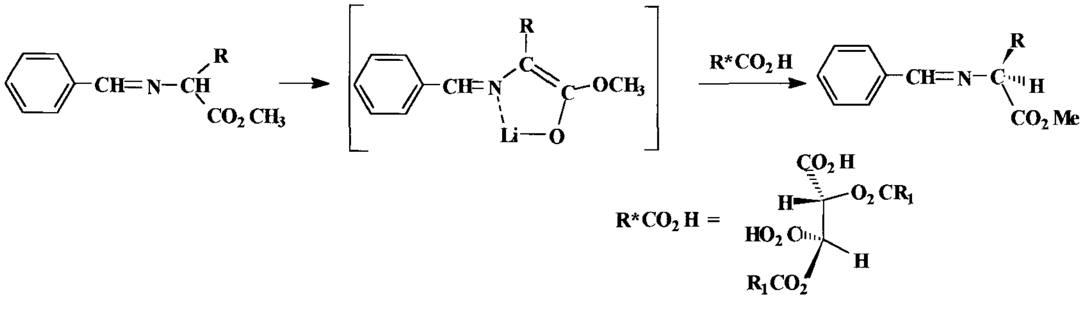


Fig. 41

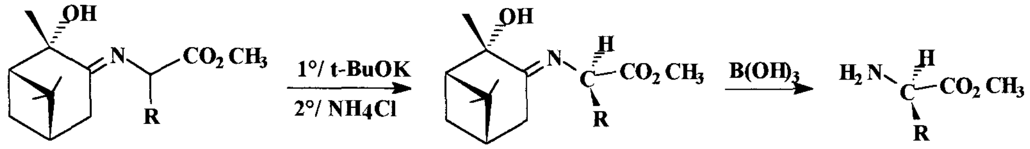
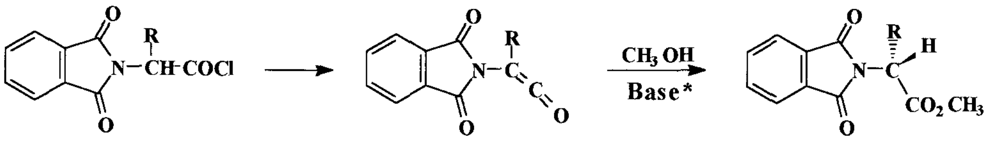


Fig. 42



Base* = brucine or acetyl-quinine

Fig. 43

Very recently, some racemic amino acid methyl esters, chirally derived as Schiff base with (*S*)-2-hydroxy-3-pinanone, were asymmetrically transformed in excellent yield at −78°C to a major diastereoisomer (79–98% *d.e.*), *via* protonation of the corresponding enolates with NH_4Cl (Tabcheh et al., 1998) (Fig. 42).

6.2 Stereoselective addition of an alcohol to an α-amino-ketene

Three possibilities of induction have been investigated.

Example 1: Thirty-five years ago (Pracejus, 1959), it was noted that in the presence of a chiral tertiary amine, addition at room temperature of an achiral alcohol to a prochiral N-diprotected α-amino-ketene, prepared from a racemic amino acid, afforded the corresponding acid ester with very modest diastereomeric excesses (22 and 33.5%) (Winter and Pracejus, 1966) (Fig. 43).

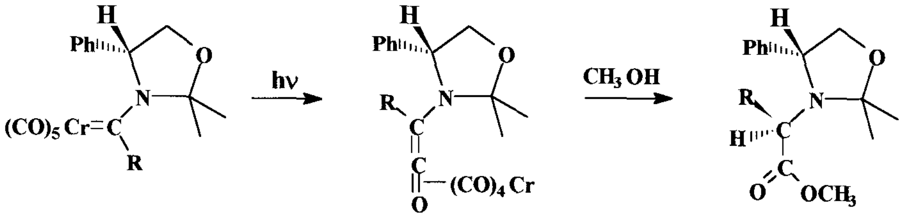


Fig. 44

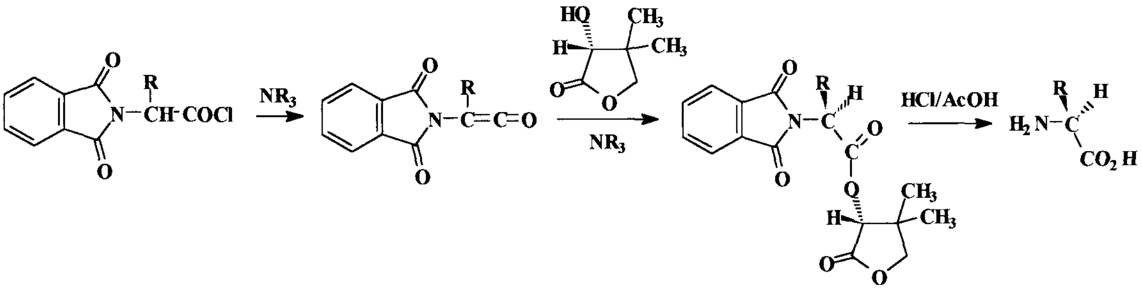


Fig. 45

Example 2: Hegedus (1995) has shown that the stereoselective addition of an achiral alcohol at room temperature to a chirally derived chromium aminoketene, generated by photolysis of the corresponding chromium amino carbene complex, occurs with a high diastereoisomeric excess (>95%). This method suffers from long irradiation times and sometimes gives poor yields of aminocarbene precursors (Fig. 44).

Example 3: Very recently Calmes et al. (1997a,b) showed that addition of (*R*)-pantolactone to a N-diprotected α-amino-ketene affords the corresponding ester with 80–95% stereoselectivity, depending upon the base catalyst. The reaction is easily achieved at room temperature when R is an alkyl group and at −78°C when R is an aryl group. Both the protecting groups are cleaved in the final step by acid hydrolysis (Fig. 45).

7 Asymmetric Strecker reaction

Strecker's synthesis (Strecker, 1850) is a very attractive and general reaction widely used for α-aminoacid synthesis. Initially, Harada (1963) used the chiral 2-phenyl ethylamine, and in this way many optically active aminoacids have been synthesized (Fig. 46). Thanks to the use of other chiral auxiliaries, yields and optically purities have been improved (Patel and Worsley, 1969; Phadtare et al., 1985), as previously reviewed (Williams, 1989; Duthaler, 1994).

Recently, diethylaluminium cyanide was allowed to react stereoselectively with enantiopure sulfinimines. The corresponding diastereomerically en-

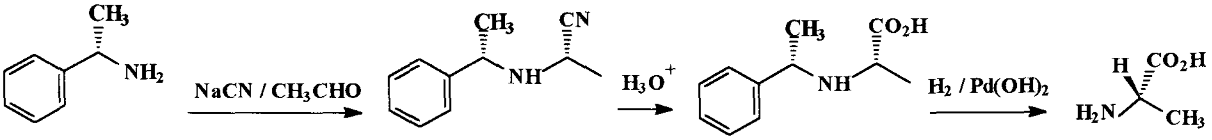


Fig. 46

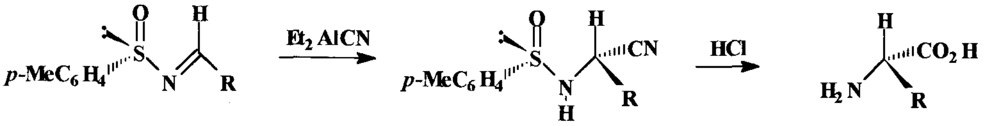


Fig. 47

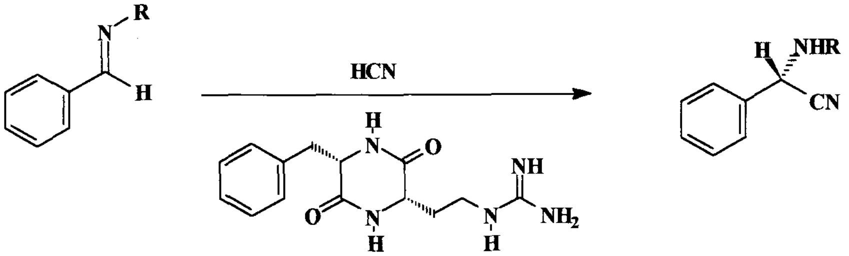


Fig. 48

riched α-aminonitriles were afforded in fair yield and in 20–66% *d.e.* (Davis et al., 1994a). Each diastereoisomer was easily isolated pure after one crystallization of the mixture. Diastereoselectivities were strongly improved (82–94%) by the use of ethyl-(alkoxy)aluminium cyanide [Et(R'O)AlCN] of reduced Lewis acidity (Davis et al., 1996a, 1998) (Fig. 47).

In order to avoid the use of a stoichiometric amount of the chiral auxiliary linked to the amine (*e.g.* amino-sugar derivatives or counterparts, chiral sulfinimines) often of high cost and difficult to recover, it was proposed to achieve the reaction in the presence of a catalytic amount of a chiral auxiliary not linked to any reagent (enantioselective reaction), *e.g.* a chiral base, an enzyme or a peptide. This process has been very recently reviewed (Iyer et al., 1996). Although the mechanism of the Strecker reaction has never been unambiguously proved, it was noted that there is a solvent effect during addition of HCN to an imine. Likewise it has been noted that addition of a base to the reaction mixture gives rise to a rate acceleration. For instance, the chiral base shown in Figure 48 (2 mol % in methanol) catalyzed at −25°C the

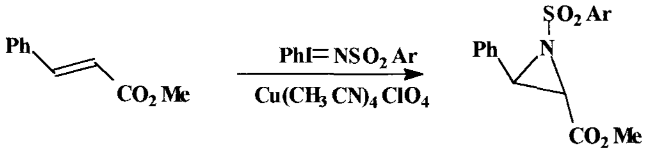


Fig. 49

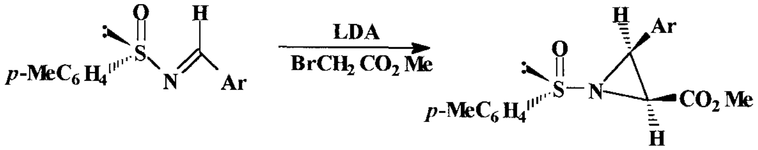


Fig. 50

addition of hydrogen cyanide to N-alkylimines affording (*S*)-α-amino nitriles in 88–98% yield and 75–99% *e.e.* (Iyer et al., 1996).

8 Nucleophilic ring-opening of aziridine-2-carboxylates

The ring opening of aziridine-2-carboxylates with various nucleophiles is a simple way to prepare a large range of unusual aminoacids with a functionalized and/or branched side chain. Preparations of aziridine-2-carboxylates were widely reviewed (Tanner, 1994; Osborn and Sweeney, 1997). While racemic aziridine-2-carboxylates are readily available, enantiomerically pure forms are more difficult to obtain *via* an asymmetric synthesis. They can result from natural sources, such as amino acids, hydroxyacids or carbohydrates, but also from transformations of epoxides, from nitrene addition to acrylate derivatives (Södergren et al., 1997) (Fig. 49) and from the reaction of methyl bromoacetate enolate with chiral sulfinimines (Davis and Fanelli, 1998) (Fig. 50). But most often they result from chemical or enzymatic resolution of racemic mixtures.

The ring opening of aziridine-2-carboxylates may be acid-catalyzed or may result from a nucleophilic attack, but in both cases two possibilities are expected to occur, affording either α- or β-aminoacid derivatives (Legters et al., 1992; Tanner, 1994).

Acid-catalyzed ring-opening (Davis et al., 1994b, 1998; Tanner, 1994): recently a chiral N-sulfinyl aziridine carboxylate was regio- and stereo-selectively opened with 50% aqueous trifluoroacetic acid to give α-methyl-β-phenylserine in 75% yield and 96% *d.e.* (Davis et al., 1996b) (Fig. 51).

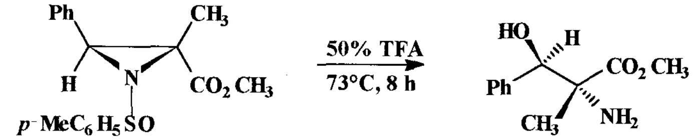


Fig. 51

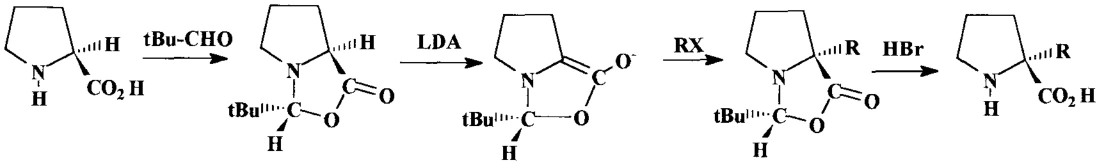


Fig. 52

9 Miscellaneous methods

We only mention some characteristic reactions, particularly some typical α-alkyl α-amino acid syntheses.

9.1 Self-reproduction of chirality (Seebach methodology)

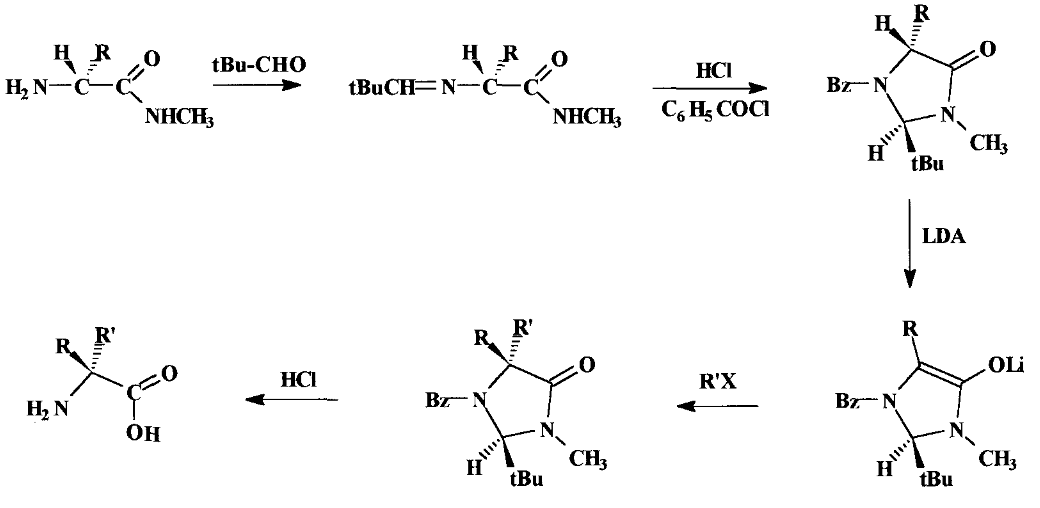
This process allowed the elegant synthesis of optically active α-disubstituted aminoacids from the corresponding α-monosubstituted amino acids. These latter compounds were used as chiral auxiliaries to afford a second asymmetric centre which in turn was used as chiral auxiliary in the alkylation of the enolate to afford chiral α-disubstituted amino acids.

Example 1: The condensation of (S)-proline with pivaldehyde afforded an oxazoline ring as the single diastereoisomer. After deprotonation with LDA at 0°C, alkylation of the corresponding prochiral enolate took place with total retention of the initial configuration (Seebach et al., 1981, 1983, 1996) (Fig. 52).

Example 2: The cyclisation of the pivalyl imine of aminoacid N′-methylamide followed by N-benzoylation led to an *anti*-imidazolidinone as the dominant diastereoisomer. The newly generated chiral centre was used as chiral auxiliary in the subsequent alkylation of the corresponding enolate (Fig. 53). Alkyl derivatives were afforded in good yields and with diastereoselectivities higher than 95% (Aebi et al., 1985; Calderari et al., 1985; Seebach et al., 1985, 1996).

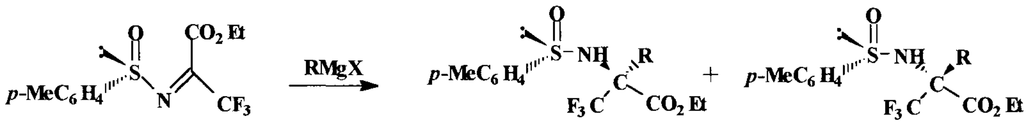
9.2 From imines by reaction with organometallic compounds

Example 1: Reaction of chiral sulfinimines with benzylmagnesium chloride at −78°C provided the corresponding diastereomeric N-sulfinyl amino esters in



d.e.>95%

Fig. 53



$2S,S_S$ $2R,S_S$

Fig. 54

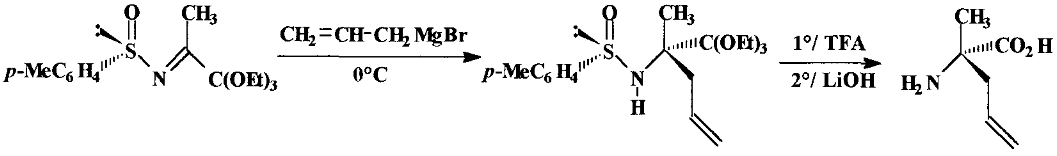


Fig. 55

55–70% yields and moderate diastereoselection ($2S,S_S/2R,S_S$ ratio from 72/28 to 87/13) (Fig. 54). Diastereomerically pure sulfinamides were obtained by flash chromatography (Bravo et al., 1998).

Example 2: Reaction of the chiral sulfinimine of pyruvic acid ortho-ester with allylmagnesium bromide afforded the adduct in 95% yield as a single isomer. The protecting groups were then readily cleaved by hydrolysis (Hua et al., 1995; Davis et al., 1998) (Fig. 55).

Example 3: Optically active α-amino acids (*e.e.* = 48–88%) were prepared in 43–86% yield by sparteine induced asymmetric addition of organolithium

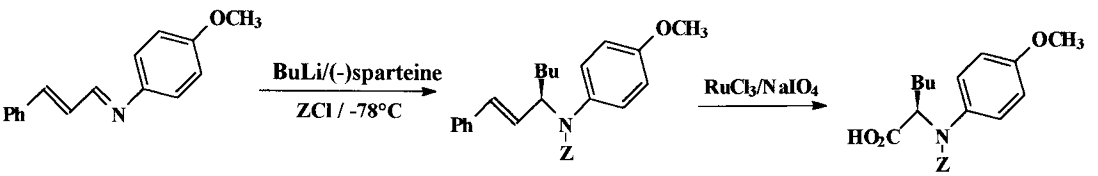


Fig. 56

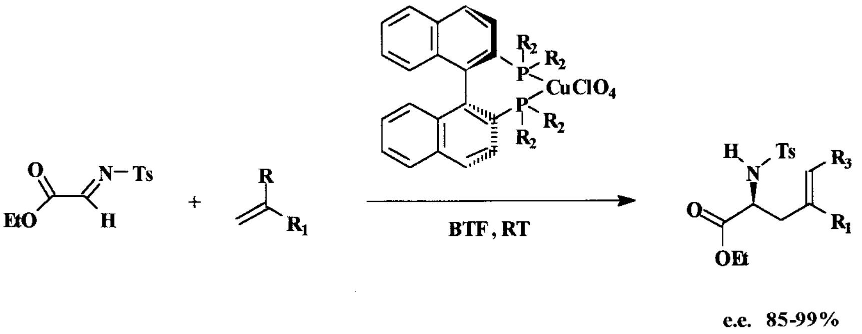


Fig. 57

reagents to α,β-insaturated imines and subsequent oxidation (Gittins and North, 1997) (Fig. 56).

9.3 Ene reaction of α-imino esters

Very recently enantioselective imino ene reaction of α-imino esters with alkenes catalyzed by optically active Lewis acid complex provided α-amino esters of high optical purity (85–99%) and in good yield (85–92%) at room temperature when benzotrifluoride (BTF) was used as solvent (Drury et al., 1998) (Fig. 57).

9.4 From β-keto-esters and Schmidt rearrangement

Some enantiopure hindered C-alkyl glycines were afforded in two steps from chirally derived acetoacetamides: first alkylation of Co(II) complexes of enantiopure acetoacetamides (64% *d.e.*) and then transformation of the acetyl group of the resulting product into an acetylamino group *via* a Schmidt rearrangement in 35% overall yield (Galvez et al., 1996) (Fig. 58).

9.5 Oxidative cleavage of optically active N-protected α-amino alkenes

The treatment of 1,3-diphenylprop-2-enyl acetate with potassium phthalimide in the presence of allylpalladium chloride dimer and a phosphine chiral

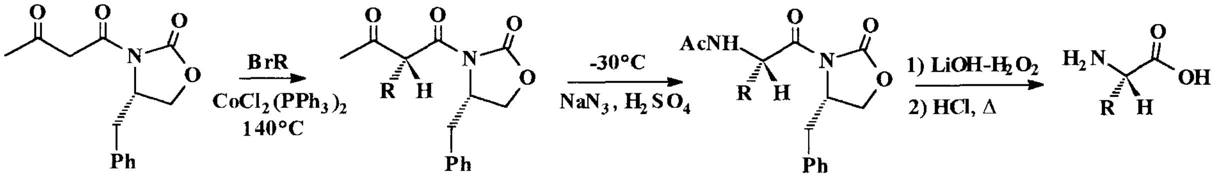


Fig. 58

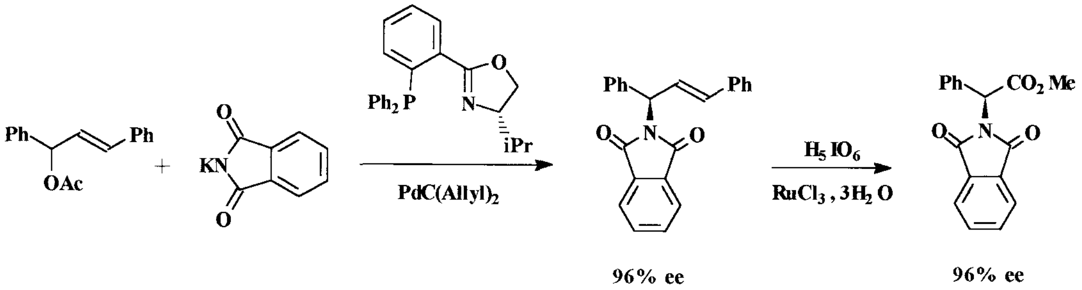


Fig. 59

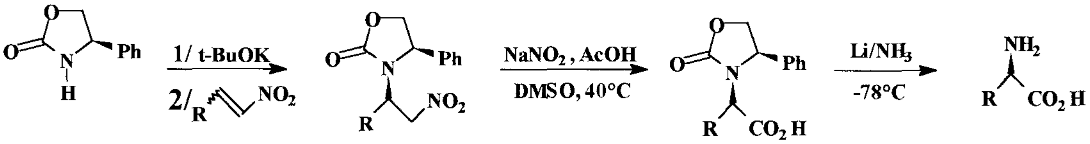


Fig. 60

oxazoline ligand afforded the substitution product with 96% *e.e* and in 65% yield. The subsequent oxydation with periodic acid in the presence of a ruthenium catalyst effected oxidative cleavage of the alkene to (*S*)-phenylglycine derivative in 51% yield with preservation of the enantiomeric purity (Jumnah et al., 1995) (Fig. 59).

9.6 Oxidation of optically pure 3-nitroalkyl-4-phenyl-2-oxazolidinones

They resulted from the completely diastereoselective addition of the potassium salt of (R)- or (S)-4-phenyl-2-oxazolidinones to monosubstituted nitroalkenes. After oxidation, N-substituted amino acids were obtained in 62–99% yield and with 95–96% enantiomeric excess (Sabelle et al., 1998) (Fig. 60).

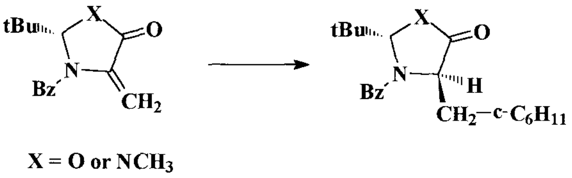


Fig. 61

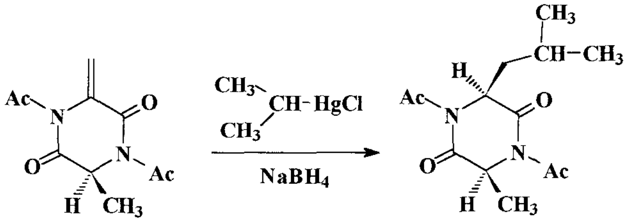


Fig. 62

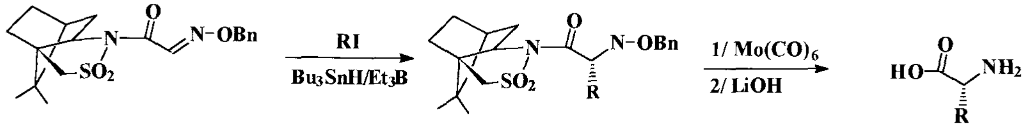


Fig. 63

9.7 Free-radical addition

9.7.1 Addition to dehydro-amino acid derivatives

This area was recently reviewed by Easton (1997).

Example 1: Chiral cyclic dehydro-alanine derivatives were allowed to react with cyclohexylmercury chloride and sodium borohydride to give adducts in at least 60% diastereoisomeric excess (Beckwith and Chai, 1990) (Fig. 61).

Example 2: The addition of alkyl radicals (formed from alkylmercury halides) to optically active methylene piperazinonediones at room temperature gave an unique diastereoisomer in 46–49% yield (Fig. 62).

The *cis* configuration of the adduct was ascertained in the case of R = isopropyl by comparison of the data with those for the authentic compound (Chai and King, 1995).

9.7.2 Stereoselective free radical addition to imines

Example: Enantiomerically pure α-amino acids were synthesized at room temperature and in 25–86% yield with a high degree of stereocontrol (72–96% *d.e.*) by radical addition to Oppolzer's glyoxylic oxime ether camphor sultam derivative (Miyabe et al., 1997) (Fig. 63).

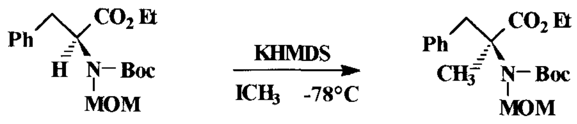


Fig. 64

9.8 Cα alkylation of chiral amino acid derivatives with memory of chirality

Memory of chirality is a phenomenon (Fuji and Kawabata, 1998) in which the chirality of the starting material is preserved in a reactive intermediate for a limited time at low temperature. According to this principle, the optically pure N-Boc N-MOM phenylalanine methyl ester was alkylated with ICH_3 with retention of the starting configuration (Fig. 64). Reaction occured at −78°C in 88% yield and 84% *e.e* with potassium hexamethyldisilazide as a base, without addition of any external chiral source (Kawabata et al., 1996).

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