Tetrahedron: Asymmetry Vol. 3, No. 2, pp. 163-192, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

TETRAHEDRON: ASYMMETRY REPORT NUMBER 7

Recent Developments in the Synthesis of Optically Active α-Arylpropanoic Acids: An Important Class of Non-steroidal Anti-inflammatory Agents#

Harikisan R. Sonawane, Nanjundiah S. Bellur, Jaimala R. Ahuja and Dilip G. Kulkarni*

National Chemical Laboratory, Pune 411 008, INDIA

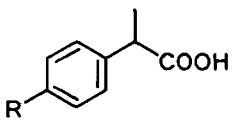
(*Received* 1 *November* 1991)

CONTENTS

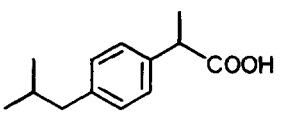
I	Introduction	164
II	Strategies based on asymmetric reactions	165
	1. Methylation of 2-arylacetic acids	165
	2. Hydrogenation of 2-arylpropenoic acids	167
	3. Hydroformylation of styrenes	168
	4. Hydrocarboxylation of olefins	168
	5. Hydrovinylation	171
	6. a Sharpless epoxidation	172
	b Sharpless epoxidation and hydrogenolysis	173
	7. Aryl alkyl coupling reactions	173
	a Alkylation of aromatics	174
	b Grignard coupling reaction	174
	c Cross Grignard coupling	175
	8. a,b Enantioselective protonation	175,176
	9. 1,2-Aryl shift	178
	a Introduction	178
	b Stuctural requirements	178
	c Mechanistic pathway	179
	d,e Rearrangement of chiral α-sulfonyloxy acetals	180,181
	f,g Stereoselective α-bromination of homochiral acetals	181,182
	h Rearrangement of chiral α-halo acetals	184
	i Rearrangement of chiral α-hydroxy acetals	184
	j Use of Ph_3P/CCl_4	185
	k Photochemical method	187
III	Resolution methods	
	10. a Resolution via diastereomeric salt formation	188
	b Kinetic resolution	188
	c,d Enzymatic resolutions	189
IV	Conclusion	189

I INTRODUCTION

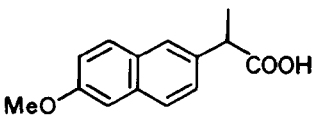
α-Arylpropanoic acids (**I**) have emerged as an important class of non-steroidal anti-inflammatory agents during the past two decades. The therapeutic efficacy of this class of drugs is well demonstrated by the introduction and extensive use of more than a dozen compounds exemplified by Ibuprofen (**1**), Naproxen (**2**), Ketoprofen (**3**) and Flurbiprofen (**4**) to mention just a few. The flood of publications emanating from various research laboratories and the ever increasing number of patents filed by industrial houses in this area bear testimony to the frenetic synthetic efforts.



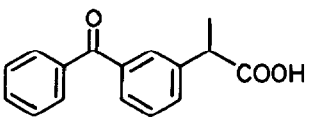
I



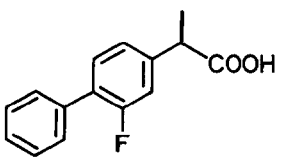
1



2



3

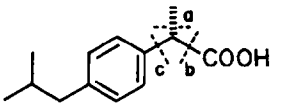


4

However, in recent years the use of enantiomerically pure drugs in chemotherapy is becoming almost mandatory not only to realize enhanced specificity of drug action but to avert the possible toxicity and undesirable load on the metabolism by the other enantiomer. This situation is equally true with α-arylpropanoic acids as evidenced by the known[1] higher activity of the enantiomers of **1** and **2** with the (S)-configuration at the chiral center. This awareness led to great synthetic efforts to obtain non-racemic compounds of this class, particularly during the past five years. Notwithstanding this, the available review articles[2] in this area pertain essentially to the synthesis of the racemic compounds. In this context, time is ripe to present a concise and a critical review of various methodologies developed to obtain chiral compounds of this class so that a cogent picture might emerge. This report is intended to serve this purpose. Attempt is made to include most of the reported literature up to July 1991 in this direction. Among various methods reported so far which include the classical resolutions and enzymatic reactions, this review primarily deals with asymmetric synthesis.

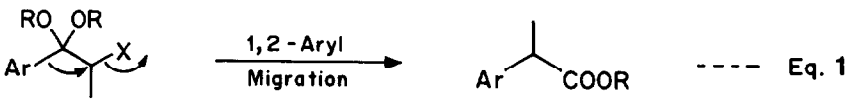
II STRATEGIES BASED ON ASYMMETRIC REACTIONS.

A retrosynthetic analysis of the asymmetric molecule such as **1** as shown in the following figure helps to visualize the asymmetric reactions that can generate the desired chiral center.



1

The mode **a** is suggestive of asymmetric methylation of 2-arylacetic acid while the mode **b** implies an asymmetric hydroformylation/hydrocarboxylation of the appropriate styrene derivative. The last mode necessitates the formation of aryl-alkyl carbon-carbon bond in a stereoselective manner indicating the suitability of an asymmetric aryl alkyl coupling reaction or asymmetric alkylation of appropriate aromatic compounds. Another major class of reactions not included in the above analysis and which, nevertheless, has led to practical methods for the asymmetric synthesis of α acids is the stereospecific 1,2-aryl migration in chiral α-substituted acetals of propiophenones as indicated in eq. 1.



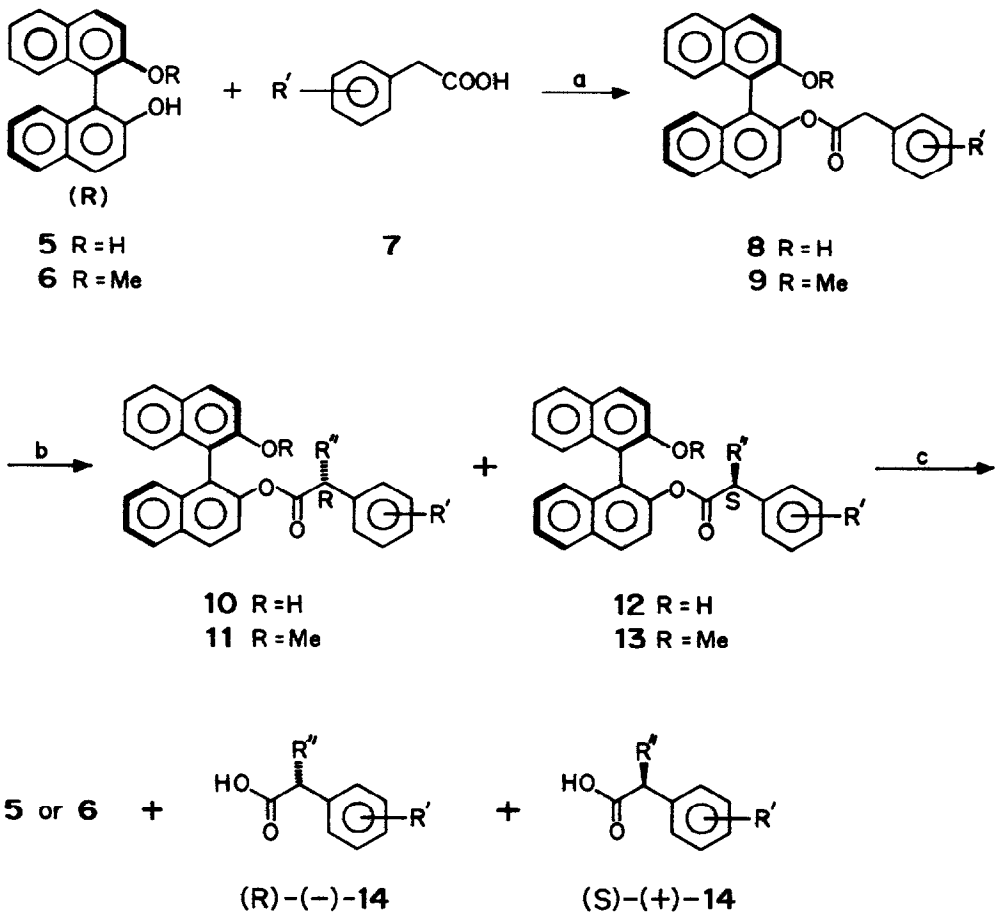
---- Eq. 1

This review essentially deals with the discussion of the merits and demerits of these approaches; nonetheless, the other methods of obtaining chiral α-arylpropanoic acids are included briefly.

1. Methylation of 2-Arylacetic Acids.

The atropisomers of binaphthols are finding extensive application in the preparation of chiral metal complexes which provide an ideal way to multiply chirality.[3] Recent years have witnessed an explosive growth of industrially useful chiral catalysts based on 2,2'-bis(diarylphosphino)-1,1'-binaphthyl (**5**) (BINAP). Synthesis of optically active α-arylpropanoic acids via diastereoselective alkylation of binaphthyl esters of arylacetic acids has been recently reported by Fuji et al.[4] These authors observed a significant diastereoselectivity (92-96%) in the alkylation of the ester **8** containing the free hydroxyl group leading to **10** and **12** while the corresponding methyl ester **9** furnished a 1:1 mixture of the diastereoisomers **11** and **13** (**scheme-1a**). Moreover, a high selectivity in alkylation was noticed with the use of bulkier alkylating agents such as isopropyl and t-butyl iodides. On the contrary, the stereoselectivity in methylation was not impressive (72%).

Scheme-1a

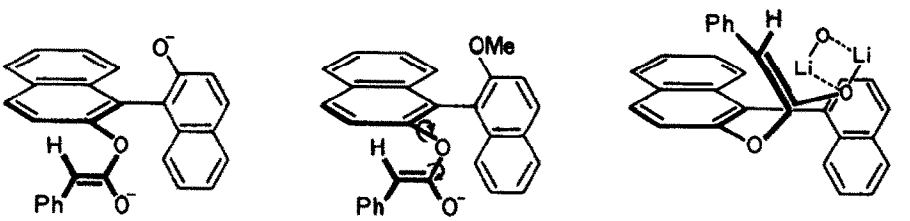


a) $H^{\oplus}$ b) LDA, THF, HMPA, R''-I, -78°C, 4h c) $H^{\oplus}$, H_2O, Recrystallization

The hydroxyl group in **8** appears to be indispensable in realizing high diastereoselectivity. This has been rationalized in terms of the possible conformations of the enolates. Besides this, the known[5] exclusive formation of Z-enolate from the ester on deprotonation by LDA in THF/HMPA has been utilized. It can be seen (**scheme-1b**) that in the conformation (a), two naphthyl rings bisect each other at a torsional angle of about 90° due to the steric factors and the electrostatic repulsion keeps the negatively charged oxygens maximally apart. Thus, the re-face of the nucleophilic carbon is more open for alkylation, when (R)-binaphthol is used as a chiral auxiliary. On the contrary, such a face discrimination is reduced in methylated phenol (b) resulting in reduced diastereoselectivity. In the

absence of HMPA, the diastereoselectivity is rather enhanced and has been attributed to a chelated configuration of the E-enolate wherein the si-face is blocked sterically (conformation c). It is pertinent to note that the (R)-Binaphthyl esters invariably introduced (R)- configuration at the new chiral center and vice-versa.

Scheme-1b: Possible Conformation of Enolates

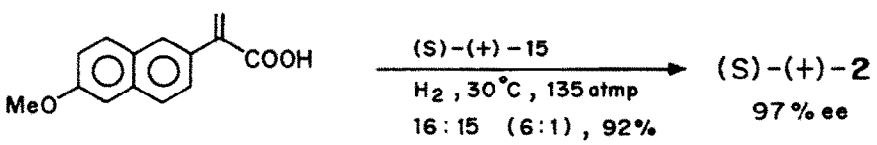


(a) (b) (c)

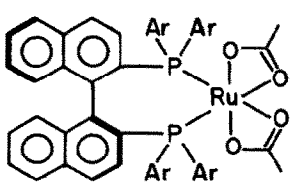
2. Hydrogenation of 2-Arylpropenoic Acids.

Homogeneous hydrogenation of olefins utilizing chiral phosphine rhodium complexes discovered in 1968 has generated a variety of impressive chemistry.[6] This has led to the availability of both natural and unnatural amino acids in greater than 90% ee from Z α-(acylamino)acrylic acids or esters and the methodology has gained practical significance in industry.

Scheme-2



16



(S)-(+)-**15**

While the scope of the rhodium-catalyzed reaction is rather limited, the more recently developed BINAP-ruthenium chemistry has definitely wider utility.[7,8] BINAP-Ru dicarboxylate complexes of the type **15** hydrogenate prochiral α,β or β,Γ- unsaturated carboxylic acids giving rise to optically active saturated acids. In this process, chelate complexes in which the carboxylate and the olefinic double bond co-ordinate to a Ru-metal center are supposed to be the reactive intermediates and the extent of asymmetric induction is known to depend on the substitution pattern and the reaction conditions, particularly, the hydrogen pressure.

Noyori et al[9] have demonstrated the efficacy of the reaction by the synthesis (S)-(+)-**2** in a 92% chemical yield and an enantiomeric purity of 97% (**scheme-2**). Nonetheless, the relatively high pressures (135-150 atm) required for the reaction may present a practical limitation.

3. Hydroformylation of Styrenes.

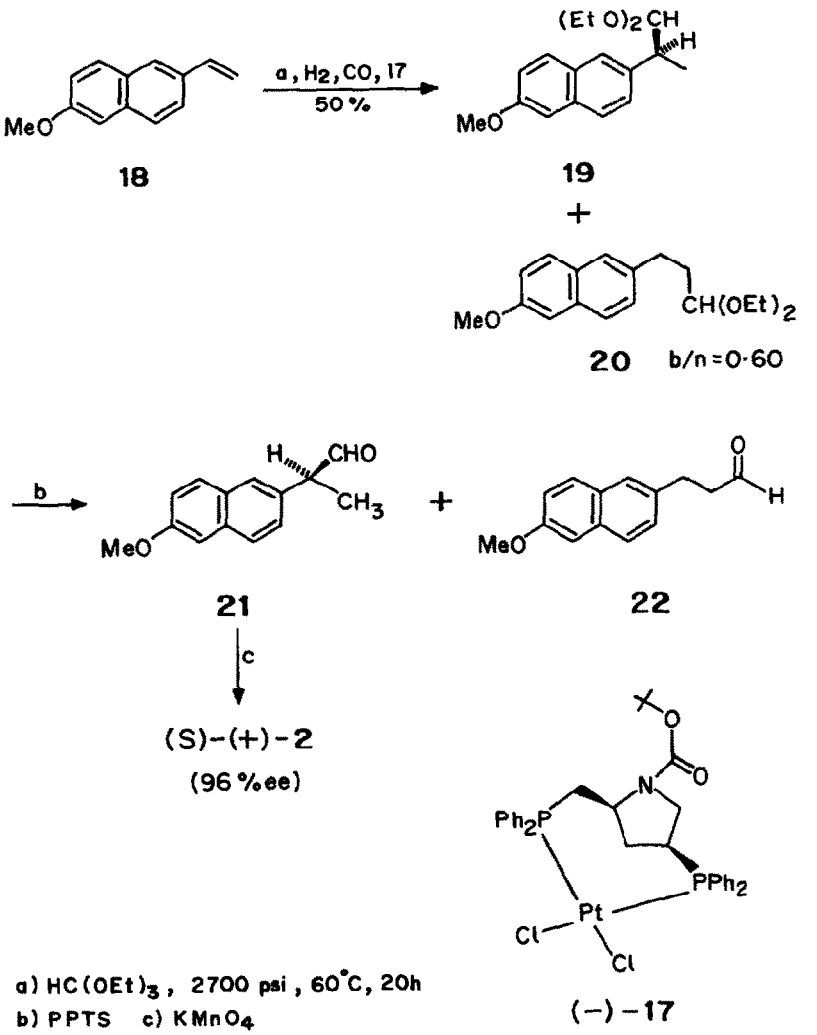
Parinello and Stille[10] have explored the hydroformylation reaction in the synthesis of (S)-(+)-**2** (**scheme-3**). Use of the chiral catalyst viz. $PtCl_2$[(-)-BPPM]$SnCl_2$ [a complex of Pt(II) containing the chiral ligand (2S,4S)-N-(t-butoxycarbonyl)-4-(diphenylphosphino-2-(diphenylphosphino) methyl pyrrolidine i.e. [(-)-BPPM] (**17**) in the presence of $SnCl_2$ enabled them to realize[11,12] a 73% enantiomeric excess of the branched aldehyde with a branched/normal olefin ratio of 0.60. With the use of triethyl orthoformate as a solvent, the ee of the required aldehyde could be enhanced to 96% as the racemization of the aldehyde could be averted due to ketalization. The ketals on hydrolysis with pyridinium p-toluenesulfonate afforded the aldehyde mixture from which **21** was isolated by medium pressure liquid chromatography. Oxidation of **21** with $KMnO_4$ furnished the desired acid (+)-**2**.

4. Hydrocarboxylation of Olefins.

Alper et al[13] studied this reaction employing C_8 to C_{12} olefins incorporating both the terminal and internal double bonds to identify the experimental parameters leading to high regioselectivity to offer branched-chain acids. These authors observed that the sequential addition of reagents and the quantity of water and the concentration of the hydrochloric acid used essentially determine the regioselectivity. for example, when carbon monoxide was bubbled through THF containing water (< 5 mol), 0.1 mol Pd (II), Cu (II) chlorides, HCl, followed by oxygen and the addition of the alkene, very high yields of the branched acids were obtained.

Prompted by these findings, this reaction was extended to the asymmetric syntheses of (+)-**1** and (+)-**2**. Reaction of p-isobutyl styrene (**23**) under the conditions described above in the presence of a chiral catalyst such a d-menthol furnished (S)-(+)-**1** in 94% chemical yield although the optical yield was insignificant[13] (2%). Similarly, the use of the other chiral ligands which included l-menthol, (R)-1,1'-bi2-naphthol, d-diethyl tartarate (DET), (S)-BINAP was not fruitful in realizing significant enantioselectivity. On the other hand, the use of (S)-(+)- and (R)-(-)-[1,1'-binaphthyl-2,2'-diyl hydrogen phosphate] (BNPPA) **24** led to high enantiomeric excess of the product **1** (83-84%) (**scheme-4a**).

Scheme-3

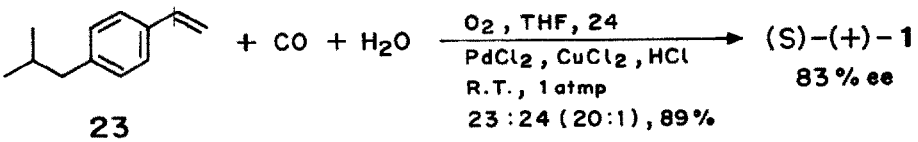


A 20:1 substrate/BNPPA ratio was found to be optimum. This procedure enabled the authors to obtain (S)-(+)-**2** as well (91% ee). It is pertinent to note that the use of (S)-(+)-BNPPA created the new chiral center with the (S)- configuration and vice-versa.

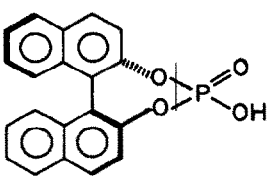
In this context, a comparison of this methodology with previously reported asymmetric reactions becomes useful. While BINAP-Ru(II) catalyzed hydrogenation of 2-(6-methoxy-2-naphthyl)propenoic acid led to higher enantiomeric excess of the (S)- acid, the reaction was to be performed at high pressure of hydrogen. Similarly, although the hydroformylation of the corresponding olefins using Pt(II) complex of (-)-BPPM with $SnCl_2$ afforded

an attractive enantiomeric excess, the regioselectivity was not very significant, as only an unfavourable branched/normal ratio of 0.5 could be realized. Thus, the hydrocarboxylation reaction affording exclusively the branched acids in high yields under mild conditions (room temperature and atmospheric pressure) appears attractive.

Scheme-4a



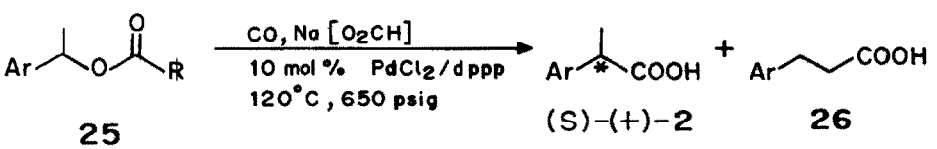
23



(S)-(+)-BNPPA (24)

The most recent attempt in this direction is due to Lee and coworkers[14] who investigated Pd-catalyzed formate mediated hydroxycarboxylation of optically pure 1-aryl ethyl esters (**scheme-4b**). They observed that the esters **25** are carbonylated with Pd(monodentate triaryl phosphine)$_n$ precursors yielding approx. 70% of essentially the required iso-acid in an ee range of 33-82%.

Scheme-4b

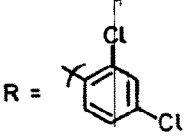


25

(S)-(+)-2 26

96 : 4

Ar = 6-methoxy-2-naphthyl



dppp = 1-bis (diphenyl phosphino) propane

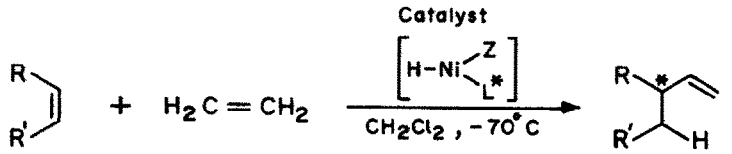
However, the reaction with the ester possessing 2,4-dichlorophenyl moiety furnished the corresponding acid in a high enantiomeric excess (94%). These authors realized that the reaction needed the use of a polar solvent and the efficacy depended on the nature of the ester.

5. Hydrovinylation

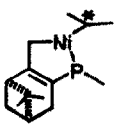
Hydrovinylation reaction discovered by Wilke et al[15] in the late sixties has been a useful reaction in homologation of olefins, In a formal sense, the reaction consists of the addition of the C-H bond of one olefin molecule to the C=C bond of a second (**scheme-5a**). This reaction was extensively investigated in the dimerization of propene leading to 2,3-dimethylbutene. Various catalysts have been developed to achieve asymmetric induction in the C-C bond formation.

The same authors have shown[16,17] the synthetic utility of this reaction in obtaining optically pure **1** (**scheme-5b**). The primary product **28** obtained by the addition of ethylene to p-isobutyl styrene (**23**) on ozonolysis furnished the chiral aldehyde **29** with high asymmetric induction.

Scheme-5a

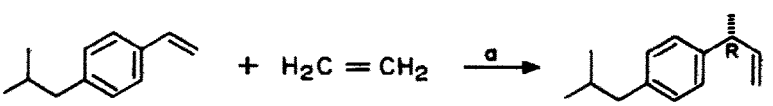


Catalyst = $\eta^3-C_3H_5Ni\cdot L^*\cdot Et_3Al_2Cl_4$

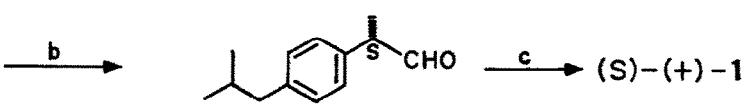
L^* = Chiral Phosphine 

Z = Complexing Anion $Et_3Al_2Cl_4^-$, ClO_4^- , BF_4^- -----

Scheme-5b



23 **27** **28**



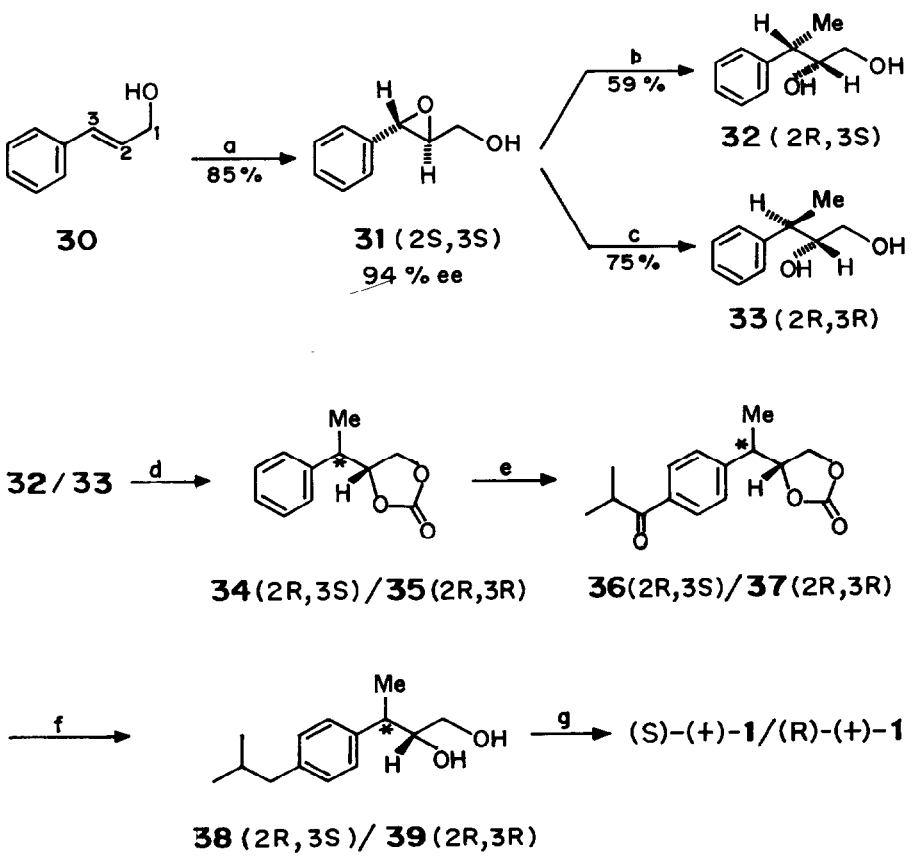
29

a) Catalyst , CH_2Cl_2 , -70°C b) O_3 c) $KMnO_4$

6a. Sharpless Epoxidation

The findings by Katsuki and Sharpless[18] that the combination of $Ti(i\text{-}OPr)_4$/(+)-RR-diethyl tartarate (1:1) promoted enantioselective epoxidation by t-BuOOH of many allylic alcohols turned out to be a major breakthrough in the asymmetric synthesis. Chiral epoxy alcohols are versatile synthetic intermediates in the total synthesis of natural products and drugs. Takano et al[19] have elegantly utilized this reaction in the synthesis of both the enantiomers of **1**. As the **scheme-6a** indicates, the key element in this enantiodivergent synthesis is the enantiospecific epoxidation of trans-cinnamyl alcohol **30** followed by the alkylative opening of the oxirane ring with Me_3Al and the higher order organocuprate $Me_2Cu(CN)Li_2$ with retention and inversion of configuration respectively.

Scheme-6a



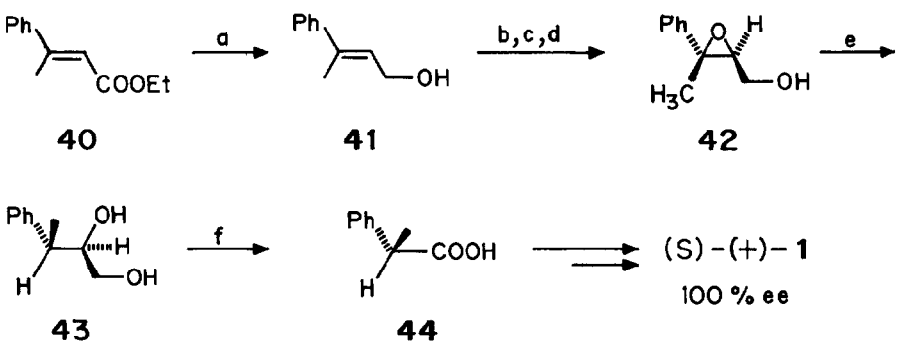
a) $Ti(i\text{-}OPr)_4$, (+)-DET, TBHP, CH_2Cl_2, -20°C, 3Å Molecular Sieves
b) Me_3Al, CH_2Cl_2, -70°C c) $Me_2Cu(CN)Li_2$, Et_2O, -50°C
d) $(EtO)_2CO$, K_2CO_3, 80°C e) $Me_2CHCOCl$, $AlCl_3$, CS_2
f) $NH_2\text{-}NH_2$, H_2O, KOH, $O(CH_2CH_2OH)_2$, ~ 180° C
g) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $MeCN/CCl_4/H_2O$ (2:2:3)

This feature deserves a comment; although the regioselectivity observed can be attributed to the steric factors in the nucleophilic reaction, the differing stereoselectivity displayed by Me_3Al is rather surprising. This reagent, too, is known to result in inversion of configurations in reaction with various other epoxides and the retention observed here is peculiar to the oxirane **31** derived from trans cinnamyl alcohol. Although a convincing rationale is not provided, an intimate ion pair containing the carbonium ion stabilized by the phenyl ring in the solvent cage has been implicated. Friedel-Crafts acylation of the cyclic carbonates **34/35** furnished the enantiomerically pure products **36** and **37** which on routine functional group manipulations led to (S) and (R)-**1**.

6b. Sharpless Epoxidation and Hydrogenolysis.

Another variation in the utilization of the asymmetric epoxidation reaction is its combination with stereospecific hydrogenolysis. Hamon and coworkers[20] subjected the enantiomerically pure levorotatory epoxide **42** obtained from the olefin[21,22] **41** by the Sharpless epoxidation to hydrogenolysis (stereochemical outcome of which was not known until then). The diol[23] **43** on oxidative cleavage afforded (S)-2-phenylpropanoic acid (+)-**44** (**scheme-6b**). The obtention of acid **44** with (S)- configuration in conjunction with the prediction of the stereochemistry of the Sharpless epoxidation established that the hydrogenolysis proceeded with inversion of configuration at the benzylic carbon. These authors demonstrated[20] (+)-2-phenylpropyl acetate could be acylated with isobutyryl chloride without racemization thereby leading to the synthesis of (S)-**1**.

Scheme-**6b**



a) $LiAlH_4$ b) (+)-DET, TBHP, CH_2Cl_2, -20°C c) P-Nitrobenzoic acid
d) Aq. NaOH e) 10% Pd/C, EtOH, NaOH f) RuO_4, $NaIO_4$

7. Aryl Alkyl Coupling Reactions

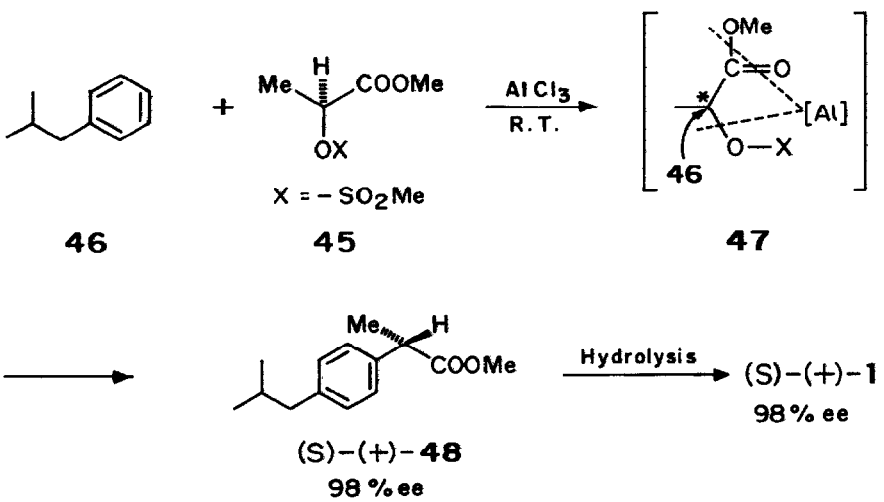
Achieving asymmetric synthesis of α-arylpropanoic acids by the formation of aryl-aliphatic C-C bond obviously involves a highly stereospecific alkylation of substituted benzene with a chiral alkylating agent or a Grignard type of aryl alkyl coupling with a chiral alkyl halide.

7a. Alkylation of Aromatics

Friedel-Crafts alkylation with optically active alkylating agents is generally associated with the problem of racemization due to the acidic conditions of the reaction. Nevertheless, there are examples of highly stereospecific reactions such as the alkylation of benzene with (R)-1,2-epoxy propane and (R)-1,2-epoxy butane leading to 100% ee with inversion of chirality.[24,25] The stereospecificity observed has been rationalized by the cyclic nature of the alkylating agent or by the intermediacy of a cyclic transition state.

Piccolo et al[26] have provided the first example of a Friedel-Crafts alkylation with an acyclic alkylating agent leading to high orders of enantioselectivity. These authors used the lactic acid derivative viz. (S)-2-(mesyloxy)propanoate **45** as chiral alkylating agent in the alkylation of **46** in the presence of anhydrous $AlCl_3$, to obtain (S)-(+)-**1** in excellent optical yield (98% ee) even though the chemical yield was moderate (50%) (**scheme-7a**). The observed high stereospecificity is rationalized by involving the formation of rigid cyclic intermediate of the type **47** involving co-ordination of Al with -COOR and -OX groups of **45**. The chiral carbon is then attacked by the aromatic ring in a nucleophilic manner from the backside of the leaving group resulting in inversion of configuration.

Scheme-7a

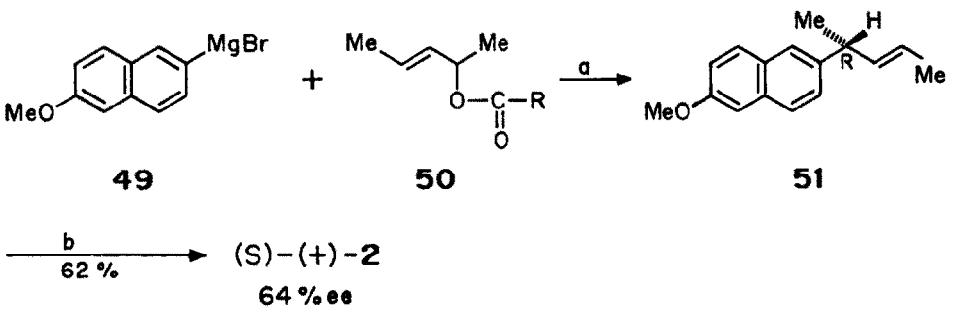


7b. Grignard Coupling Reaction.

Hiyama and Wakasa[27] carried out the reaction of 3-penten-2-yl acetate pivalate and carbonate or methyl ester) with different aryl magnesium bromides in the presence of $NiCl_2$[(S,S)-chiraphos] catalyst and realized high chemical and optical yields in the C-C bond formation. Thus, the reaction of 6-methoxy-2-naphthyl magnesium bromide **49** with 3-penten-2-yl

pivalate **50** using $NiCl_2$[(-)-2S,3S)-2,3-bis(diphenylphosphino)butane] as a catalyst [abbreviated as $NiCl_2$[(S,S)-chiraphos] afforded (R)-4-(6-methoxy-2-naphthyl)-1-butene **51** which on oxidative cleavage of the double bond led to (S)-**2** in 62% chemical yield with 64% ee (**scheme-7b**).

Scheme-**7b**



a) $NiCl_2$ [(SS)-Chiraphos] 0·01 mmol, THF, R.T. b) $NaIO_4$, $KMnO_4$

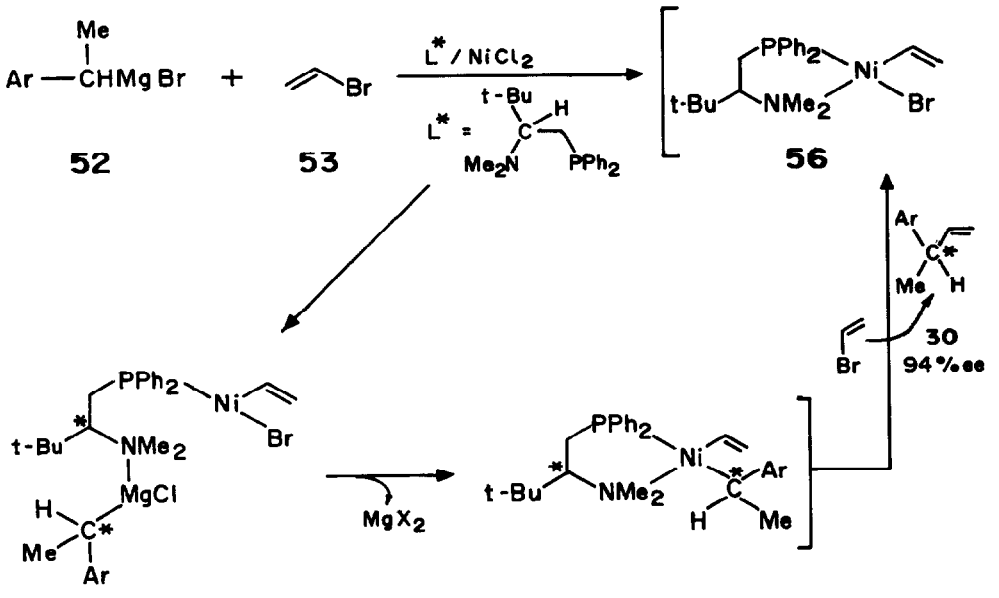
7c. Cross Grignard Coupling

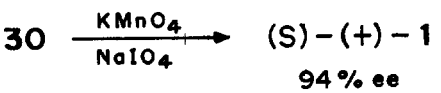
A reaction comparable to that of the racemate separations by the formation of diastereomers leading to optically active products is the catalytic asymmetric Grignard coupling. This method has been utilized by Hayashi et al[28] in synthesizing (S)-(+)-**1**. Chiral (β-aminoalkyl)phosphine (R)-t-Leuphos was used as ligand (L^*) in the nickel catalyzed asymmetric cross coupling of 1-(4-isobutylphenyl)ethyl magnesium bromide **52** with vinyl bromide **53** to furnish 3-(isobutylphenyl)-1-butene **30** with 94% ee. The key intermediate in the reaction is the diastereomeric **54**, which involves the co-ordination of the amino group on the ligand to the Mg atom in the Grignard reagent. This co-ordination is considered to occur selectively with one of the enantiomers of the racemic Grignard reagent **52** and allows it to readily undergo subsequent transmetallaton to **55**.Olefin **30** on oxidative cleavage yielded (S)-(+)-**1** in 62% yield and 94%ee (**scheme-7c**).

8a. Enantioselective Protonation.

Among the various approaches for the asymmetric transformations of a racemic compound into its optically active form, enantioselective protonation of a suitable derivative constitutes an important one. Larson et al[29] have explored the addition of naturally occurring chiral α-hydroxy esters and lactones to the prochiral ketene intermediate derived from the racemic α-arylpropanoic acid and obtained significant diastereoselectivity in the range of 94-99%. They observed that in the chiral reagent a hydroxyl group in close proximity to a hydrogen bonding moiety such as a carbonyl function was a primary requirement to high diastreoselectivity.

Scheme-7c



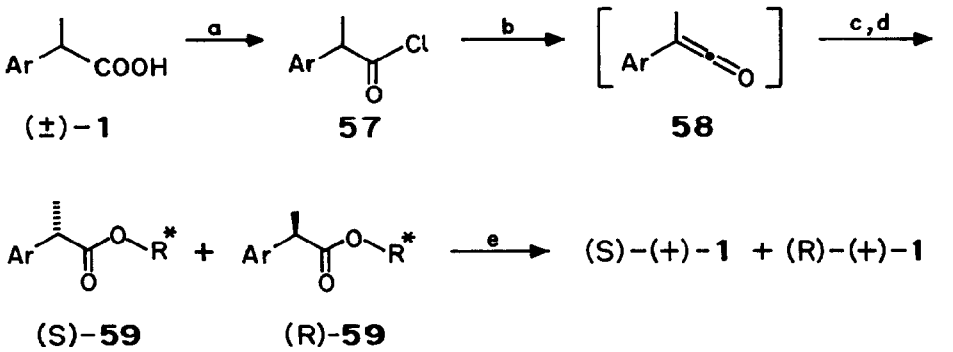


Ar = 4-isobutylphenyl

For example, while a 94.5% ee was realized with use of (S)-ethyl lactate **60** and or isobutyl lactate **62** the use of (R)-pantolactone **63** afforded the (R)-acid **1** almost exclusively (**scheme-8a**).It appears that the use of non-polar solvents enhance the diastereoselectivity. This strategy also led to the asymmetric synthesis of (S)- and (R)- **2** in 80% ee.

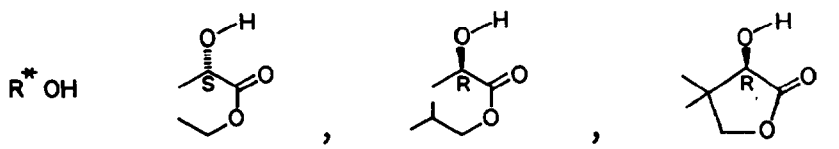
8b. In a similar approach, Dike and coworkers[30] probed asymmetric Michael addition of benzenethiol to α-phenyl acrylates using different optically pure cinchona alkaloids as catalysts. They observed that use of quinine gave an optimum ee of 50%. Among the various alkyl atropates, the isopropyl atropate (**63**) was found to induce maximum optical activity. A noteworthy feature of this strategy is the induction of asymmetry on the carbon β- to the sulfur atom. The primary products, eg **64** on hydrogenolysis under acidic conditions afforded the corresponding acids. Thus, these authors realized (S)-**2** in an enantiomeric excess of 46% (**scheme-8b**).

Scheme-8a

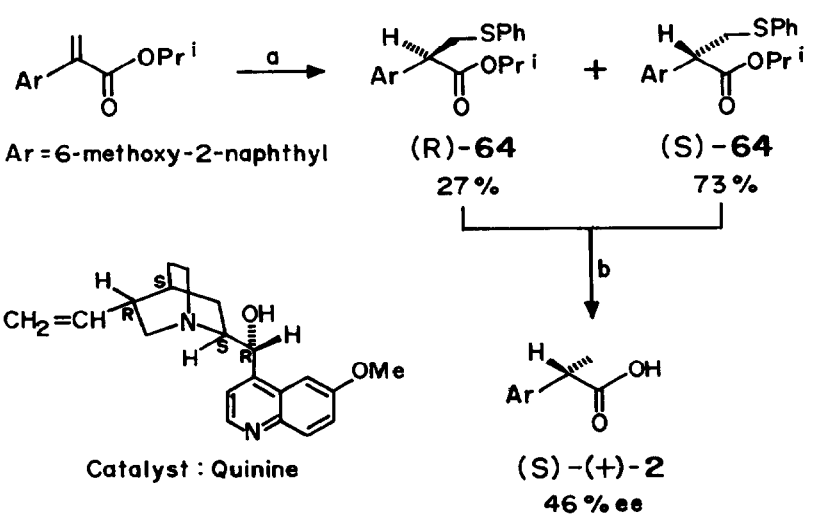


Ar = 4-isobutylphenyl

a) $SOCl_2$, DMF , Toluene , 50°C b) NEt_3 , 25°C c) R^*OH, Toluene, −78°C
d) CH_3COOH, H_2O , 70°C e) CH_3COOH , 2N-HCl , 85°C



Scheme-8b

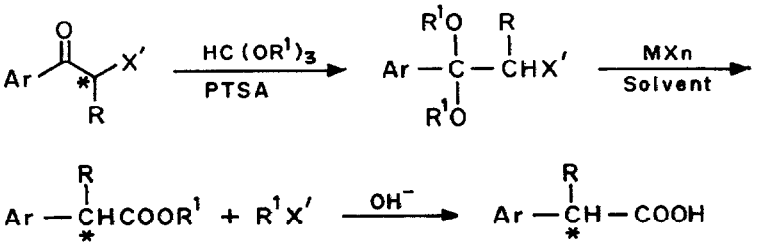


a) PhSH, Catalyst, Toluene, R.T. b) Raney-Nickel, AcOH-HCl

9. 1,2-Aryl Shifts.[2b]

9a. Introduction Although numerous asymmetric reactions have been reported so far for optically active α-arylpropanoic acids, currently the practical method appears to be based on an entirely different strategy viz. stereospecific 1,2-aryl rearrangements.[31,32] The industrial practice of this reactions attests both the simplicity of the reaction and its cost-effectiveness. In this category, most of the methods employed[2b,33] are based on Lewis acid promoted rearrangement of acetals of α-haloalkyl aryl ketones (**scheme-9a**).

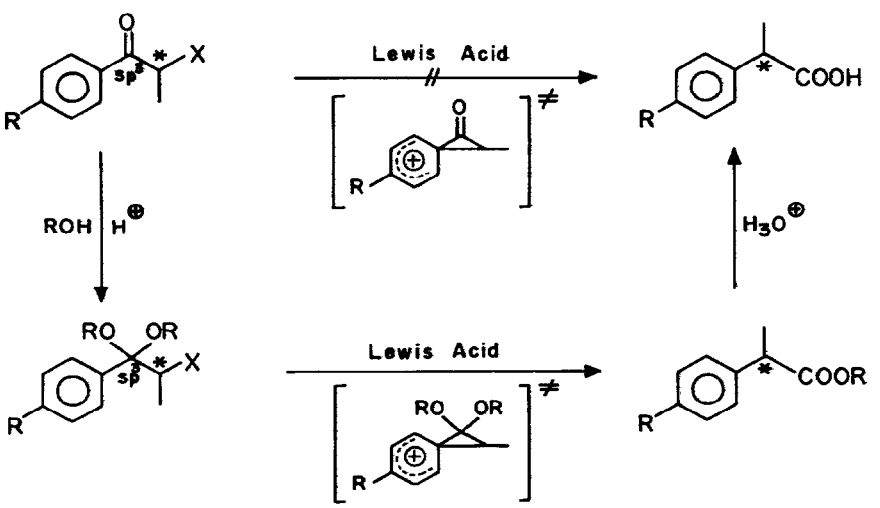
Scheme-9a



MXn – $ZnBr_2$, Silver salts etc.

9b. Structural Requirements As this rearrangement is known to involve a cyclopropyl-like transition state[2b,34] (**scheme-9b**) in its mechanistic pathway, the sp^2 nature of the carbonyl carbon deters the attainment of such a state, if a ketone were to be used. This feature is attributed to the non-occurrence of the acid-catalyzed rearrangement in α-haloalkyl aryl ketones.

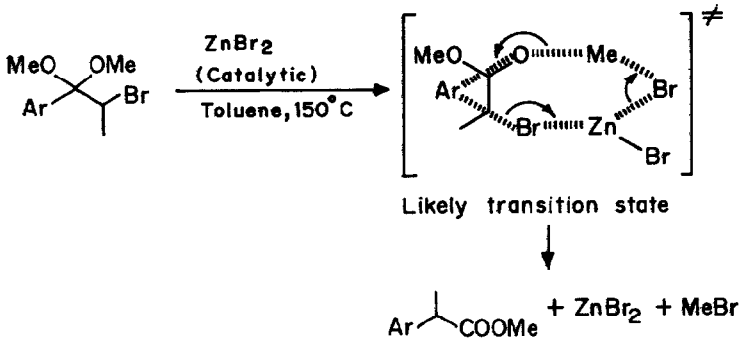
Scheme-9b



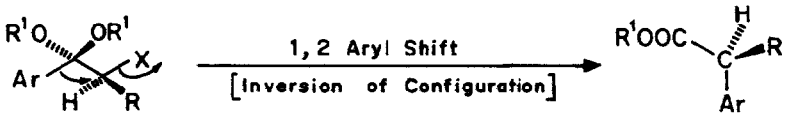
On the contrary, the corresponding acetals, owing to their sp^3 geometry favoured the rearrangement and resulted in practical yields of the α-arylpropanoic acids. Lewis acids have been invariably employed in activating the carbon-halogen bond.

9c. Mechanistic Pathway The feasible mechanistic pathway for the formation of products has been depicted in **scheme-9c**. As the hard acids such as $AlCl_3$ or $BF_3{:}OEt_2$ are known to co-ordinate with the oxygen atoms, these catalysts caused dekatalization. Investigations on the mechanism of the reaction proved that the role of border line soft acids such as $ZnBr_2$ parallels that of silver salts in promoting the 1,2-aryl shifts. It is apparent from the scheme that the transition state shown leads to the α-arylpropanoate, regenerating $ZnBr_2$, indicating thereby the catalytic requirement of the Lewis acid.

Scheme-9c



The most fascinating and useful aspect of this rearrangement from the point of asymmetric synthesis is its stereospecific nature. It is worth mentioning that the 1,2-rearrangements are known to proceed with a total inversion of configuration at the migration terminus, consistent with an S_N2 mechanism (**eq. 2**). This facet provided the impetus to develop methodologies for the asymmetric synthesis of α-arylpropanoic acids. Thus, differently α-substituted chiral propiophenone derivatives were checked for their suitability for efficient migration. Obviously, this situation necessitated the synthesis of optically pure α-substituted acetals as the starting materials. The reported methods for the asymmetric synthesis of these chiral substrates and their rearrangement to **1** and **2** have been shown below.

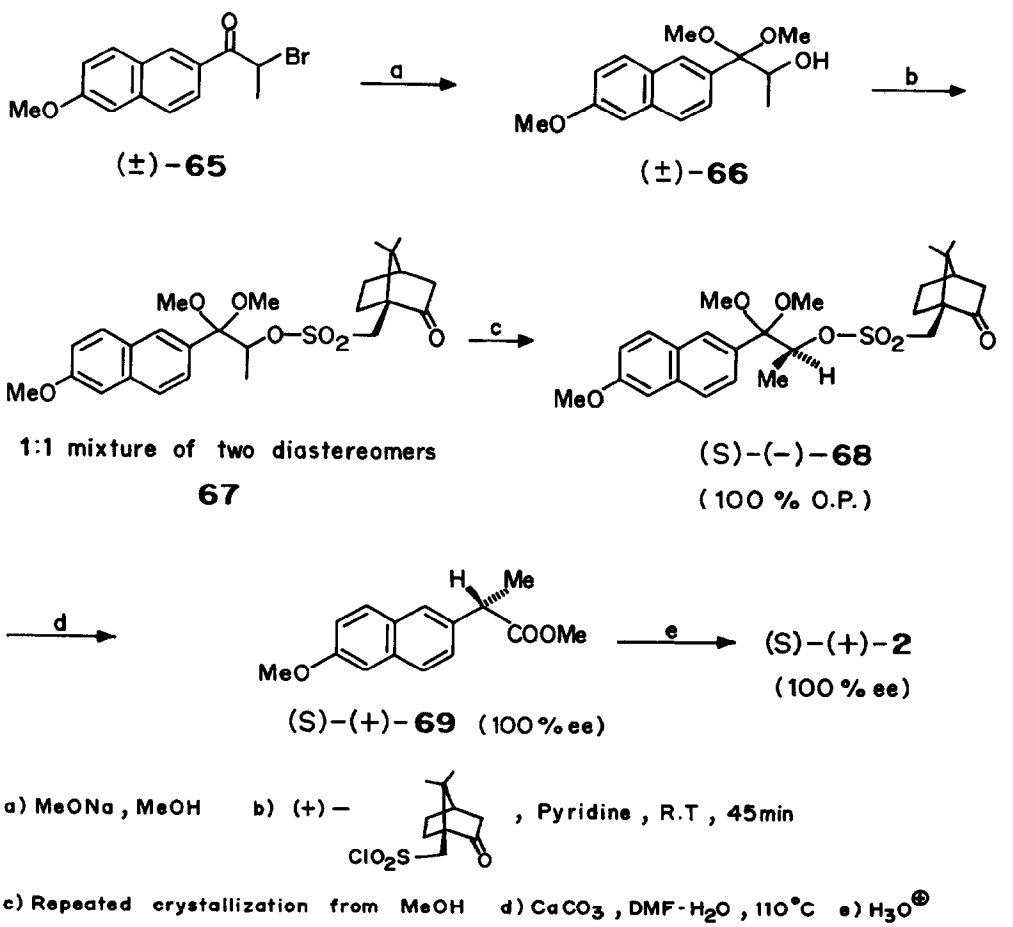


Eq. 2

9d. Rearrangement of chiral α-Sulfonyloxy acetals.

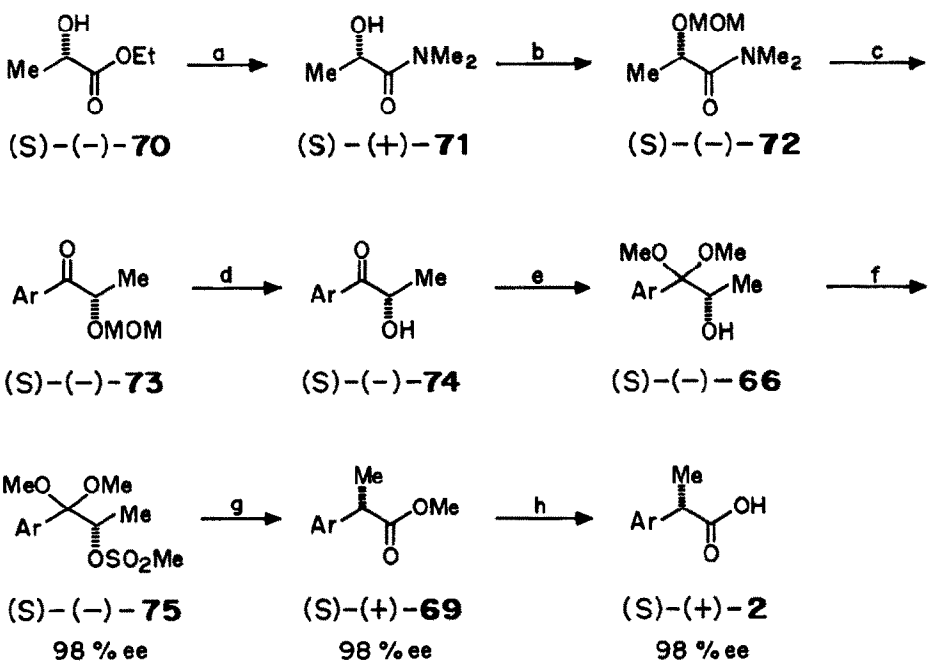
The earliest attempt in this direction is due to Tuchihashi et al[35] who synthesized optically active (S)-(+)-**2** utilizing the stereospecific 1,2-rearrangement in the corresponding 1-aryl-2-sulfonyloxy-1-alkanone acetals (**scheme-9d**). The chiral acetals were obtained by the separation of the diastereoisomers **67** resulting from the reaction of the racemic acetal **66** and the optically pure 1-10-camphorsulfonyl chloride. The total transformation of (S)-(-)-**68** into (S)-(+)-**69** confirmed the stereospecificity of the rearrangement. The significant feature of this synthesis is the transfer of chirality of the C-O bond in (+)-**68** into that of the product and the dual role of the optically active camphorsulfonyl chloride which served as a resolving agent and as an efficient leaving group as well.

Scheme-9d



9e. In an alternative approach[36] (**scheme-9e**) these authors have prepared (S)-1-(6-methoxy-2-naphthyl)-2-sulfonyloxy-1-alkanone acetal (-)-**75** from natural (S)-(-)-ethyl lactate **70** by the use of a Grignard reaction instead of the classical resolution of (±)-**66** with 1-10-camphorsulfonyloxy chloride. The acetal **75** on rearrangement under hydrolytic conditions in the presence of a base afforded methyl(S)-2-(6-methoxy-2-naphthyl)propanoate **69** which was hydrolyzed to (S)-(+)-**2**. It should be noted that during the transformation of (S)-(-)-**74** to (S)-(-)-**66**, a little racemization occurred and some dimeric products were also obtained. Obtention of 98% ee was possible with extensive crystallization.

Scheme-9e



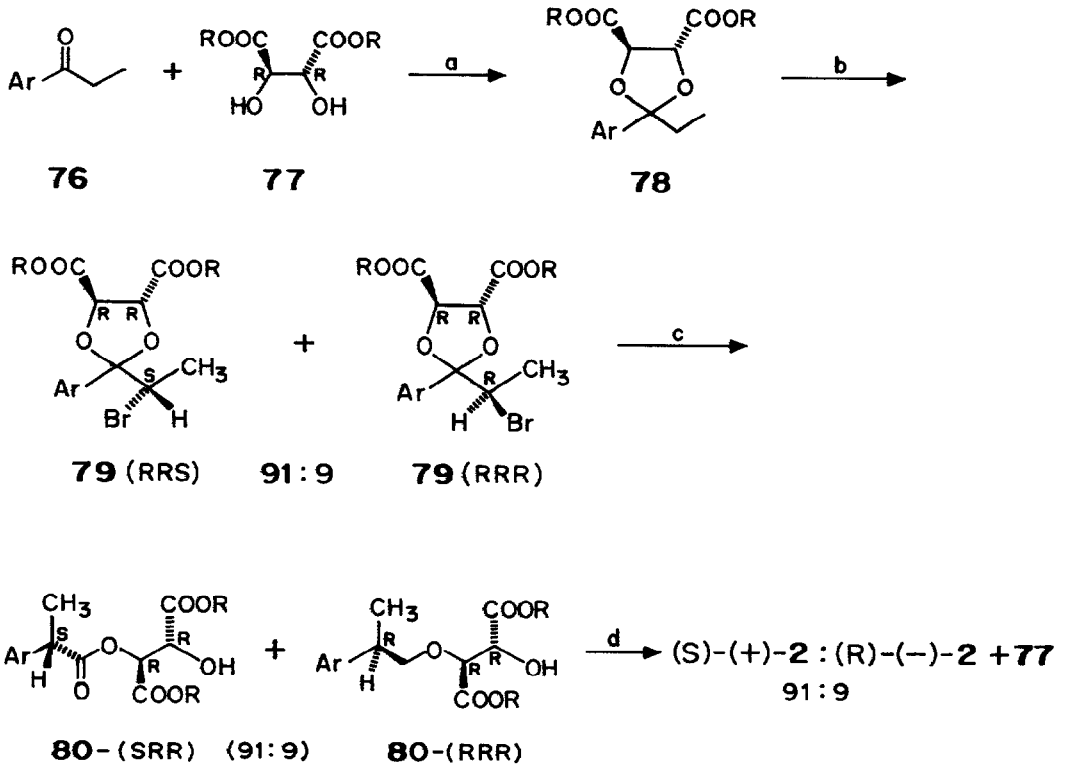
Ar = 6-methoxy-2-naphthyl

a) Anhydrous Me_2NH in pressure bottle, 70°C, 60h b) NaH, THF, $Cl-CH_2-O-CH_3$
c) ArMgX, THF d) 1M HCl in EtOH e) MeOH, $HC(OMe)_3$, $MeSO_3H$, 50°C, 1hr
f) Pyridine, MSCl g) Pyrex pressure bottle, NaOAc, $MeOH-H_2O$ (7:3 v/v), 100°C, 18h
h) Dil. HCl, Repeated crystallization

9f. Stereoselective α-bromination of homochiral acetals

As an alternate procedure for the synthesis of enantiomerically pure acetals with a chiral α-center Castaldi et al[37] developed a method for stereoselective α-bromination (**scheme-9f**). It was found that the homochiral acetal **78** could be effectively brominated with the use of bromine in

Scheme-9f



Ar = 6-methoxy-2-naphthyl

a) $H^{\oplus}$ b) HBr (Cat.), Br_2, 15°C, CCl_4 c) $AgBF_4$ (1·5 Equivalent), CH_2Cl_2, 15°C, H_2O
d) Conc. HCl, 85°C, H_2O

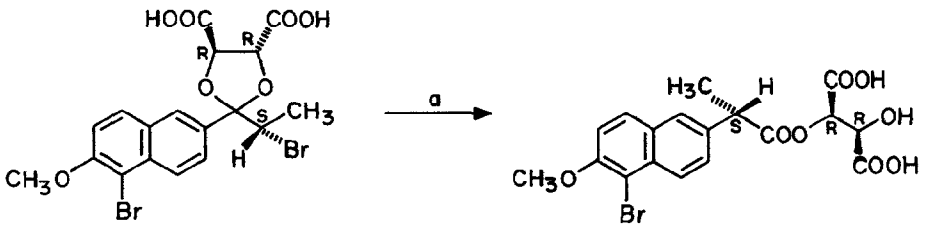
the presence of catalytic quantity of HBr, in the absence of which the reaction showed an induction period.

A high diastereoselectivity of 91:9 could be realized in the bromination. The chiral bromo derivative **79** on silver assisted rearrangement furnished the optically active ester **80** in a corresponding diastereoselectivity (**scheme-9f**). A notable feature of this strategy is that the chiral auxiliary **77** could be recovered for reuse.

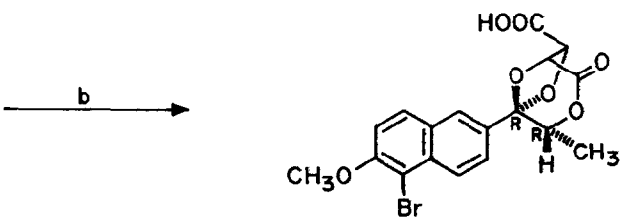
9g. It is evident that owing to the stereospecificity of the rearrangement, the final enantioselectivity of the products reflected the diastereomeric composition of the α-bromo acetals. In an attempt to improvise, these authors developed a scheme[38] equivalent to kinetic resolution (**scheme-9g**). They observed that the α-bromo carboxylic acids **81a** and **81b** in the presence of their monosalts at pH 4-6 displayed a differential

reactivity towards rearrangement and intramolecular nucleophilic displacement leading to the corresponding lactones **83a,b**. The required optically pure esters could be chromatographically separated from the lactones. The major lactone **83b** arising from the minor α-bromodiacid **81b** could be transformed by alkaline hydrolysis to the corresponding α-hydroxy acetal **84** which could be utilized for further rearrangement to the (S)-acid. Thus, this modification not only led to higher enantiomeric excess of the product but constituted a stereoconvergent method for the synthesis of both the enantiomers of **2**.

Scheme-9g



81a-(RRS) **82a** (SRR) major (80%)



83a - (RR) minor

82a-(SRR) $\xrightarrow{c,d}$ (S)-(+)-**2**

81b-(RRR) $\xrightarrow{a}$ **82b** (RRR) + **83b** (RS) $\xrightarrow{b}$ **82b** (RRR) $\xrightarrow{c,d}$ (R)-(-)-**2**

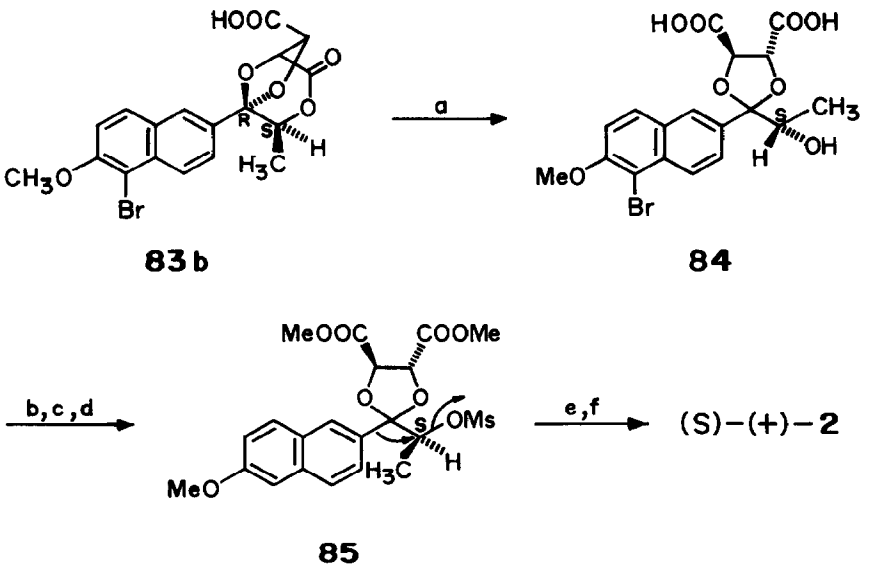
minor major

81a + **81b** $\longrightarrow$ (S)-(+)-**2** + (R)-(-)-**2**

96 : 4 99 : 1

a) KH_2PO_4, NaOH, pH 5·2-4·6, 90°C b) SiO_2 Chromatography
c) MeOH, $H^{\oplus}$ d) H_2, 10% Pd/c

Scheme - 9g (contd.)



83b 84 85

a) aq. NaOH b) MeOH, $H^{\oplus}$ c) H_2, Pd/C d) MsCl, Et_3N e) MeOH-H_2O f) $H_3O^{\oplus}$

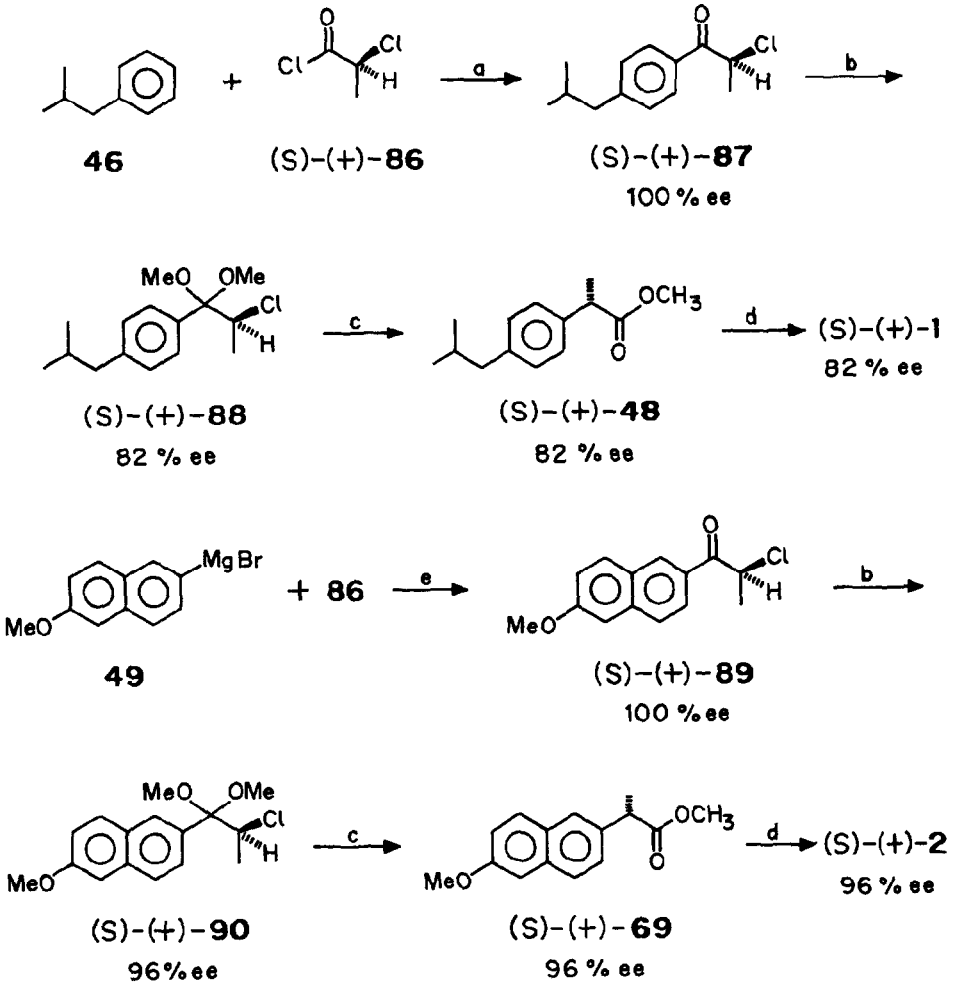
9h. Rearrangement of Chiral α-Haloacetals.

Piccolo et al[39] prepared optically active **1** and **2** by $ZnCl_2$-catalyzed rearrangement of the corresponding optically pure α-chloro- acetals (**scheme-9h**). However, these authors obtained chiral α-haloketones **87** by acylation of isobutylbenzene (**46**) with optically pure α-chloropropionyl chloride (**86**). The chirality of the latter was derived from (S)-alanine. On the other hand the corresponding optically active chloro ketone **89** required for **2** was prepared by a Grignard coupling reaction.

9i. Rearrangement of chiral α-hydroxy acetals.

A similar strategy was adopted by Yamauchi et al.[40] They acylated isobutylbenzene with enantiomerically pure acyl chloride (S)-(-)-**94** obtained from (S)-(+)-lactic acid **91** in five steps. The effectiveness of the mesyl group as a leaving group enabled a facile conversion of (S)-(-)-**95** to the α-hydroxy acetal (R)-(-)-**96**. On treatment with SO_2Cl_2 in the presence of pyridine, the acetal (R)-(-)-**96** with 74% ee rearranged via **97** to (R)-(-)-**48** involving a completely stereospecific 1,2-aryl migration with inversion of configuration. Mild acid hydrolysis of (R)-(-)-**48** afforded (R)-(-)-**1** with 74% ee (**scheme-9i**).

Scheme 9h



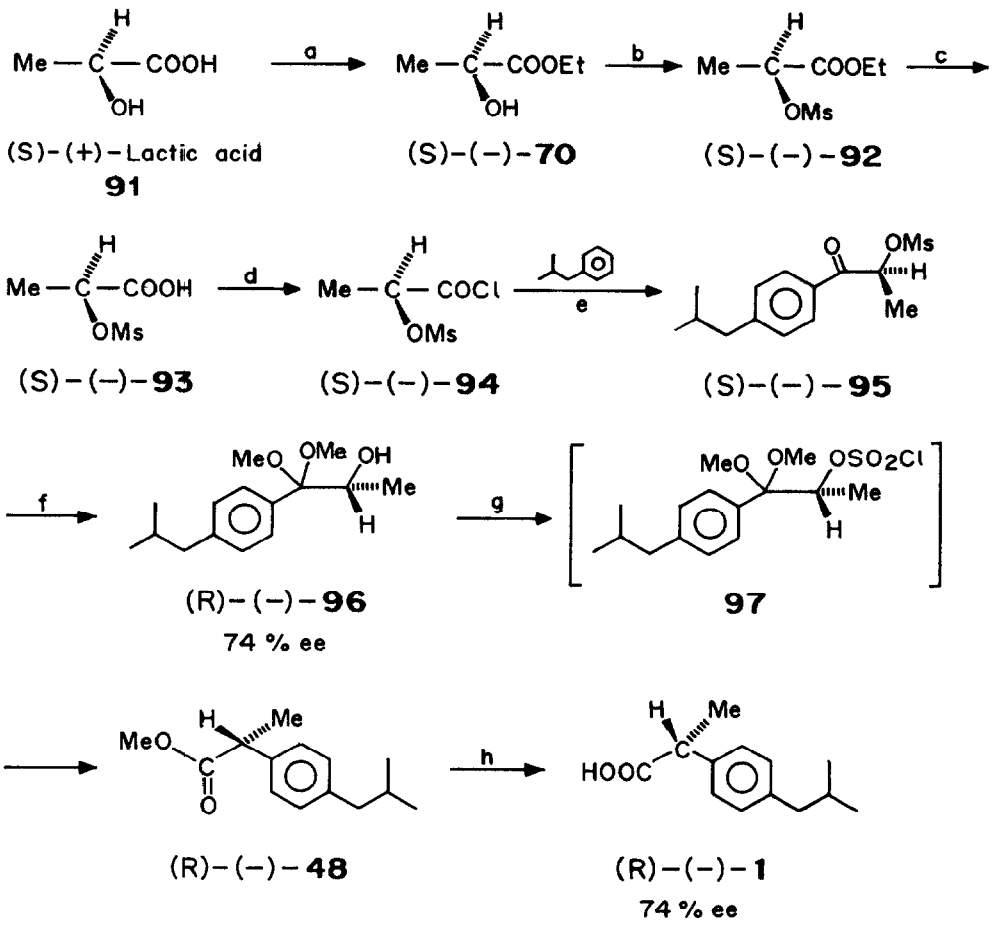
a) $AlCl_3$, CH_2Cl_2 , 0-5°C, Crystallization b) $HC(OMe)_3$, Methanol, H_2SO_4

c) $ZnCl_2$, Toluene , Δ , Crystallisation d) Conc. HCl , Δ e) THF , -40°C

9j. Use of Ph_3P/CCl_4

It is interesting to note that the well-known Arbuzov reaction generally employed for the transformation of aliphatic alcohols into the corresponding halides has been utilized by us as a key reaction for the synthesis of both racemic[41] and optically active[42] α-arylpropanoic acids. Substituted 2-hydroxy-propiophenone dimethyl acetals, when subjected to the conditions of the Arbuzov reaction (Ph_3P/CCl_4), furnished the corresponding methyl-2-arylpropanoates in varied yields. Significantly high yields were realized in case of (±)-**96** and (±)-**66** leading to (±)-**48** and (±)-**61**

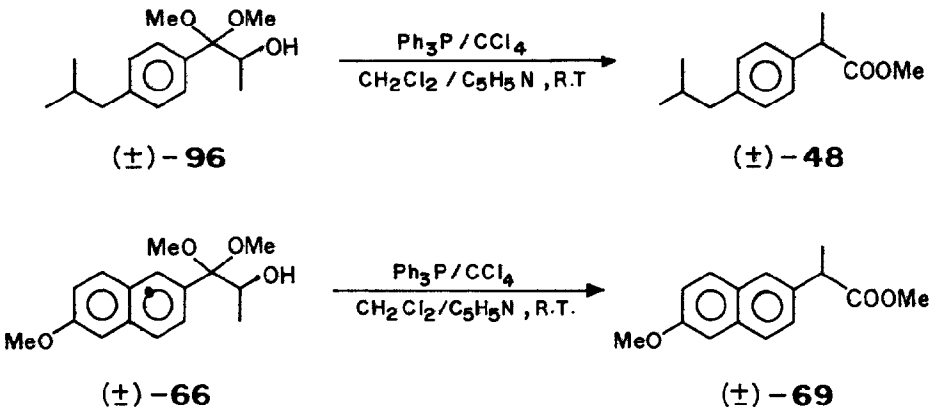
Scheme-9i



(**scheme-9j**). A pronounced substituent effect was observed in the rearrangement in that the electron-releasing alkyl groups promoted the reaction while the withdrawing ones were not conducive.

The S_N2 mechanistic nature supposed to be involved in this reaction prompted us to utilize this reaction in the asymmetric synthesis of **1** and **2**. Thus, the optically active 2-hydroxy acetals (S)-**96** (82% ee) and (S)-**66** (70% ee) under the conditions described above furnished the corresponding esters (R)-(-)-**48** and (R)-(-)-**69** without any significant loss of optical purity, indicating the occurrence of a stereospecific rearrange-

Scheme-9j

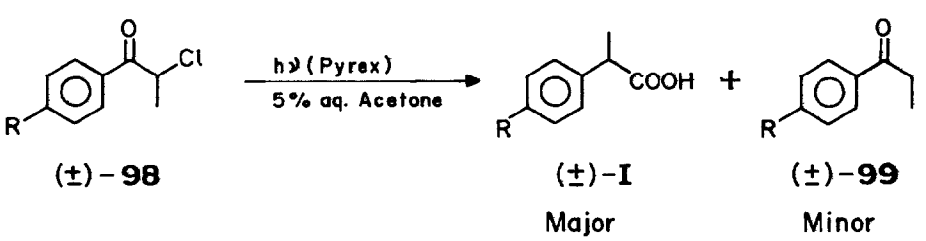


ment. Significantly this reaction represents one of the very few examples of asymmetric processes employing Ph_3P/CCl_4.

9k. Photochemical Method

It may be recalled that Lewis acid promoted rearrangement of 2-substituted propiophenone dimethyl acetals constitutes a practical method. Masking of the carbonyl group as an acetal was necessitated to obviate the geometric constraint posed by the sp^2 carbonyl carbon in the attainment of spirocyclopropyl transition state implicated in the rearrangement. In this context, we envisaged that an analogous change in the excited carbonyl carbon would promote the reaction and indeed found it to be the case.[43] Irradiation of 2-chloro-propiophenones (±)-**98** readily afforded the corresponding α-arylpropanoic acids (±)-I in attractive yields (40-80%) (**scheme-9k**), along with minor amounts of the reduction products (±)-**99**. A significant substituent effect in the formation of products was noticed.

Scheme-9k



Prompted by these findings, this photoreaction was explored for its potential in the asymmetric synthesis of **1** and **2**. Irradiation of optically pure (+)-**98** furnished the corresponding optically active 2-arylpropanoic acids in good yields.[44] Thus (S)-(+)-**98** (R = iBu) on photolysis at 300 nm in aq. acetone afforded (S)-(+)-**1** in 74% chemical and 40% optical yield. Both the efficiency of the reaction and the magnitude of optical induction appeared to be substituent dependent. This transformation constitutes the first example of this class in the synthesis of α-arylpropanoic acids.

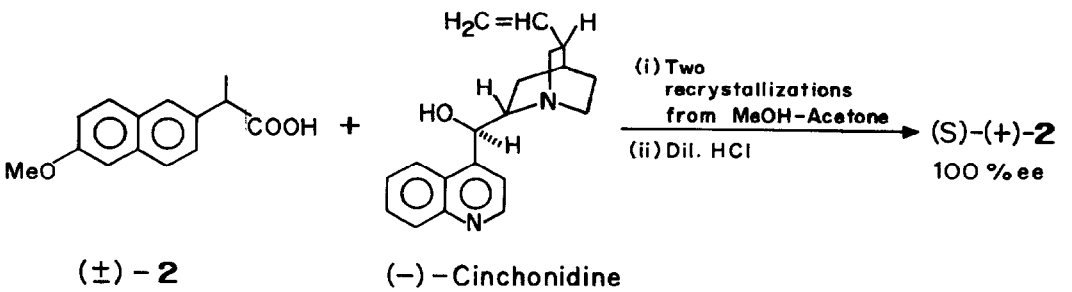
III RESOLUTION METHODS

The classical approach of obtaining enantiomerically pure compounds by resolution of the racemate is still in vogue. Nevertheless, with the development of efficient methodologies for the asymmetric synthesis and due to the loss involved of the undesirable enantiomer and the chiral resolving agents, this technique is receding to the background. Notwithstanding this there are isolated attempts to obtain (S)-**2** by resolution.

10a. Resolution via diastereomeric salt formation

Harrison et al[45] utilized (-)-cinchonidine to realize the desired (S)-(+)-**2** in an optically pure form (**scheme-10a**). Repeated crystallization of the diastereomeric mixture furnished the less soluble diastereomer of the (S)-(+)-acid which on treatment with HCl yielded the desired (S)-enantiomer.

Scheme - 10a

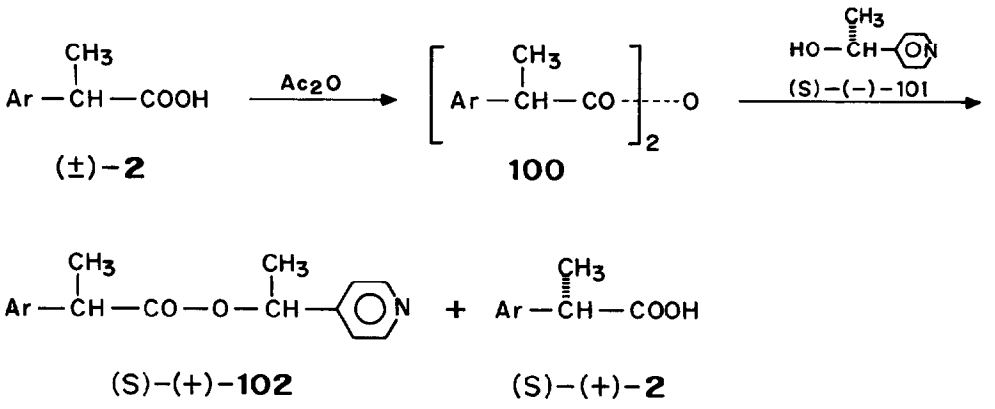


(±) - 2 (-) - Cinchonidine

10b. Kinetic Resolution.

Franck and Ruchardt[46] achieved a moderate enantiomeric excess of 50-54% in their stereospecific synthesis of (+)-**2** utilizing kinetic resolution (**scheme-10b**). The reaction of the anhydride **100** derived from the racemic acid with optically active 1-(4-pyridyl)ethanol **101** afforded the required (S)-acid and the pyridyl ester **102** with a high diastereoselectivity, the hydrolysis of which gave the (S)-acid. This result has been attributed to the differential reactivity of the diastereoisomers of the anhydride.

Scheme - 10b

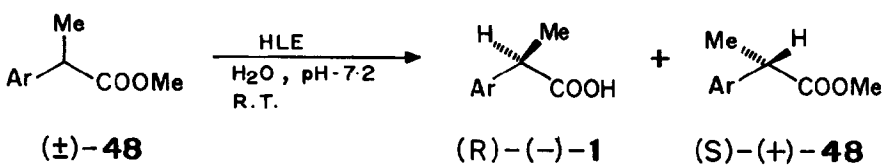


Ar = 6-methoxy-2-naphthyl

10c. Enzymatic Resolutions.

The stereospecificity of enzymatic reactions has been advantageously employed in the synthesis of both the enantiomers of **2**. The enzyme Horse liver esterase (HLE), used as its inexpensive and commercial acetone powder, catalyzed the selective hydrolysis of the ester **48** to afford the acid (R)-**1** and unreacted ester (S)-(+)-**48** which are readily separable.[47] The latter is then hydrolyzed to the acid (S)-(+)-**1** (**scheme-10c**).

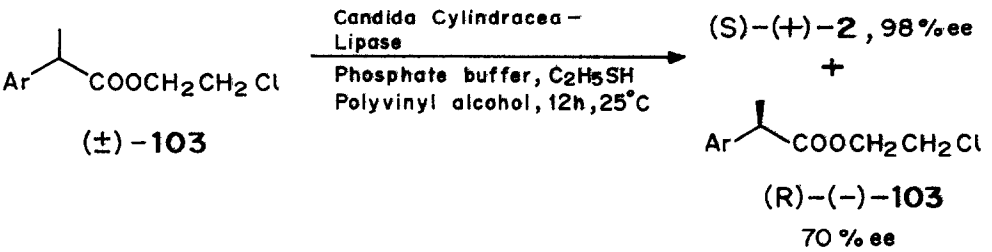
Scheme - 10c



Ar = 4-isobutylphenyl

10d. An analogous preferential hydrolysis of the racemic ester (±)-**103** of **2** with enzyme Lipase of Candida Cylindracea furnished the enantiomerically pure (S)-(+)-**2** along with the unreacted ester[48] (R)-(-)-**103** (**scheme-10d**).

Scheme-10d



Ar = 6-methoxy-2-naphthyl

IV CONCLUSION

This review summarizes the various known methods for obtaining chiral α-arylpropanoic acids, particularly ibuprofen and naproxen. Of the different strategies, Lewis acid-promoted stereospecific 1,2-aryl migration in suitably α-substituted chiral propiophenone acetals appears to be the commercial method of choice. With the current trend of chiral catalyst gaining importance in stereoselective C-C bond forming reactions, development of such catalysts for hydrovinylation, hydroformylation and hydrocarboxylation reactions potentially suitable for realizing chiral α-arylpropanoic acids becomes relevant. We believe that this review would not only be beneficial to active researchers in this area in terms of providing a concise account of the current state of the art but also evince further interest to develop newer and efficient strategies for this important class of anti-inflammatory agents.

Acknowledgements: The authors would like to thank Mr. P. A. Bhujang and Mr. M. H. Maidargi for their technical assistance in preparation of the manuscript. Two of us (J.R.A. and D.G.K) would like to thank the C.S.I.R. (India) for fellowships.

REFERENCES

NCL communication number 5286

1. Shen, T.Y. Angew.Chem.,Int.Ed.Engl., **1972**, 6, 460.
2. a) Rieu, J.P.; Boucherle, A.; Cousse, H.; Mouzin, G. Tetrahedron, **1986**, 42, 4095. b) Giordano, C.; Castaldi, G.; Uggeri, F. Angew.Chem., Int.Ed. Engl., **1984**, 23, 413. c) Georgiev, V. Survey of Drug Research in Immunologic Diseases Vol. 6, Non Condensed Aromatic Derivatives Part V, Karger, Basel, **1985**.
3. Noyori, R.; Takaya, H. Acc.Chem.Res., **1991**, 23, 345.
4. Fuji, K.; Node, M.; Tanaka, F.; Hosoi, S. Tetrahedron Lett. **1989**, 30, 2825.

5. a) Ireland, R.E.; Willard, A.K. Tetrahedron Lett, **1975**, 3975. b)Ireland, R.E.; Mueller, R.H.; Willard, A.K. J.Am.Chem.Soc., **1976**, 98, 2868.
6. a) Horner, L.; Siegel, H.; Buthe, H. Angew.Chem.,Int.Ed.Engl. **1968**, 7, 942. b) Knowles, W.S.; Sabacky, M.J. J.Chem.Soc.,Chem.Commun., **1968**, 1445.
7. Noyori, R. Chimia, **1988**, 42, 215.
8. Noyori, R. Chem.Soc.Rev. **1989**, 18, 187.
9. Noyori, R.; Nagai, K.; Kitamura, M. J.Org.Chem, **1987**, 52, 3176.
10. Stille, J.K.; Parrinello, G. J.Am.Chem.Soc., **1987**, 109, 7122.
11. Stille, J.K.; Parinello,G. J.Mol.Cat., **1983**, 21, 203.
12. a) Baker, G.L.; Fritschel, S.; Stille, J.K. J.Org.Chem., **1981**, 46, 2954. b) Ojima, I., Kogure, T.; Yoda, N. J.Org.Chem., **1980**, 45, 4728. c) Achiwa, K. J.Am.Chem.Soc., **1976**, 98, 8265.
13. Alper, H.; Nathalie, H. J.Am.Chem.Soc., **1990**, 112, 2803.
14. Baird, J.M.; Kern, J.R.; Lee, G.R.; Morgans, D.J.; Sparacino, M.L. J.Org.Chem., **1991**,56, 1928.
15. a) Wilke, G.; Bogdanovic, B.; Hardt, P.; Heimbach, P.; Keim, W.; Kroner, M.; Oberkirch, W.; Tanaka, K.; Steinrucke, E.; Walter, D.; Zimmerman, H. Angew.Chem.,Int.Ed.Engl., **1966**, 5, 151. b) Bogdanovic, B.; Wilke, G. Brennstoff Chem. **1968**, 49, 323.
16. Kwiotek, B.; Mollbach, A.; Monkiewicz, J.; Wilke, G. unpublished results.
17. Wilke, G., in "Organometallics in Organic Synthesis 2", Helmut, W.; Gerhard, E., (Eds), Springer-Verlag, New York, Chapter I, pp 1-21.
18. Katsuki, T.; Sharpless, K.B. J.Am.Chem.Soc., **1980**, 102, 5974.
19. Takano, S.; Yanase, M.; Ogasawara, K. Heterocylces, **1989**, 29, 1849.
20. Coghlan, D.R.; Hamon, P.G.; Massy-Westropp, R.A.; Slobedman, D. Tetrahedron: Asymmetry, **1990**, 1, 299.
21. Lipkin, D.; Stewart, T.D. J.Am.Chem.Soc, **1939**, 61, 3295.
22. Bussas, R.; Munsterer, H.; Kreze, G. J.Org.Chem., **1983**, 48, 2828.
23. Gao, Y.; Hanson, R.M.; Klunder, J.M.; So, S.Y.; Masamune, H.; Sharpless, K.B. J.Am.Chem.Soc, **1987**, 109, 5765.
24. Nakajima, T.; Suga, S.; Sugita, T.; Ichikawa, K. Tetrahedron, **1969**, 25, 1807.
25. Nakajima,T.; Nakamoto, Y.; Suga,S. Bull.Chem.Soc.Jpn., **1975**, 48, 960.
26. a) Piccolo, O.; Spreafico, F.; Visentin, G. J.Org.Chem, **1985**, 50, 3946. b) Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. J.Org.Chem., **1991**, 56, 183.
27. Hiyama, T.; Wakasa, N. Tetrahedron Lett., **1985**, 26, 3259.
28. Hayashi, T.; Kawamura, N.; Ito, Y. J.Am.Chem.Soc., **1987**, 109, 7876.
29. Larsen, R.D.; Corley, E.G.; Davis, P.; Reider, P.J.; Grabowski, E.J.J. J.Am.Chem.SocS., **1989**, 111, 7650.
30. Kumar, A.; Salunke, R.V.; Rane, R.A.; Dike, S.Y. J.Chem.Soc.,Chem. Commun., **1991**, 485.
31. See : Saunders, M.; Chandrasekhar, J.; Schleyer, P.V.R., in "Rearrangements in Ground and Excited States," Academic Press, **1980**, 1.
32. Shubin, V.G., in Topics in Current Chemistry, Springer-Verlag, **1984** 116/117, pp 267.

33. Castaldi, G.; Belli, A.; Uggeri, F.; Giordano, C. J.Org.Chem., **1983**, 48, 4658.
34. Giordano, C.; Castaldi, G.; Casagrande, F.; Belli, A. J.Chem.Soc., Perkin Trans 1, **1982**, 2575.
35. Tsuchihashi, G. Tetrahedron Lett., **1982**, 23, 5427.
36. Tsuchihashi, G.; Ori, A.; Honda, Y. Bull.Chem.Soc. Jpn., **1987**, 60, 1027.
37. Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. J.Org.Chem., **1987**, 52, 3018.
38. Giordano, C.; Castaldi, G.; Cavicchioli, S.; Villa, M. Tetrahedron, **1989**, 45, 4243.
39. Piccolo, O.; Spreafico, F.; Visentin, G. J.Org.Chem, **1987**, 52, 10.
40. Yamauchi, T., Hattori, K.; Nakao, K.; Tamaki, K. Bull.Chem.Soc. Jpn., **1987**, 60, 4015.
41. Sonawane, H.R.; Nanjundiah, B.S.; Kulkarni, D.G.; Ahuja,J.R. Tetrahedron, **1988**, 44, 7319.
42. Sonawane, H.R.; Nanjundiah, B.S.; Kulkarni, D.G.; Ahuja,J.R. Tetrahedron: Asymmetry, **1991**, 2, 251.
43. Sonawane, H.R.; Kulkarni, D.G.; Ayyangar, N.R. Tetrahedron Lett., **1990**, 31, 7495.
44. Sonawane, H.R.; Nanjundiah, B.S.; Kulkarni, D.G. unpublished results.
45. Harrison, I.T.; Lewis, B.; Nelson, P.; Rooks, W.; Ruzkowki, R.; Tomolonis, A.; Fried, J.H. J.Med.Chem., **1970**, 13, 203.
46. Frank, A.; Ruchardt, C. Chemistry Lett., **1984**, 1431.
47. Bloch, R.; Girard, C.; Ahmar, M. Tetrahedron Lett., **1989**, 30, 7053.
48. Guo, Q.M.; Chen, C.S.; Sih, C.J. Tetrahedron Lett., **1986**, 27, 1763.