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Induced pi-facial discrimination in the alkylation of chiral derivatives of glycine.

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INDUCED π-FACIAL DISCRIMINATION IN THE ALKYLATION OF CHIRAL DERIVATIVES OF GLYCINE

by

Scott O. Peters

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ABSTRACT

Induced π-Facial Discrimination in the Alkylations of Chiral Derivatives of Glycine

Part A: The alkylation *trans* 2-arylcyclohexyl hippurates with a series of electrophiles was examined. The reaction stereoselectivity varied from 46 to 81% depending on the steric and electronic nature of the electrophile when (Ar = phenyl). Higher stereoselectivity was observed when reacting electrophiles of increasing π-character. When the chiral auxiliary contained a naphthyl group the stereoselectivity was > 80% for every electrophile used.

Part B: The alkylation of the *trans* 2-phenylcyclohexylamide of methyl glycinate with a series of electrophiles was examined. Incorporation of the chiral auxiliary on the amino terminus of the amino acid appears to induce good stereoselectivity only when the electrophiles contain a point of unsaturation. The reaction stereoselectivity ranged from 21 to 80% depending on the electronic nature of the electrophiles. It is proposed that a π-stacking interaction between the aromatic group on the auxiliary and the unsaturated electrophiles was responsible for the high stereochemical excess observed.

For Kayla

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ABBREVIATIONS

$CDCl_3$	Chloroform-d
de	Diastereomeric Excess
DMF	Dimethyl Formamide
DMSO	Dimethyl Sulfoxide
ee	Enantiomeric Excess
Et_3N	Triethylamine
EtOAc	Ethyl Acetate
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High Pressure Liquid Chromatography
HSAB	Hard Soft Acid Base
LDA	Lithium Diisopropylamine
LHMDS	Lithium Hexamethyldisilazane
NMR	Nuclear Magnetic Resonance
$SOCl_2$	Thionyl Chloride
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TsOH	Toluenesulfonic Acid

INTRODUCTION

Asymmetric induction

The creation of a new chiral centre in a molecule is a reaction that has great significance to organic chemistry. In the absence of an asymmetric environment, this type of reaction produces two mirror image molecules-enantiomers of the product. Although identical in most physical and chemical properties, biological systems (i.e. enzymes) can recognize the difference between these, sometimes with very dangerous consequences. The best known example of this is the Thaliomide scandal of the early 1960's.[1] Racemic Thalidomide was marketed as an analgesic for pregnant woman. However it was soon found out that the (S)-enantiomer is teratogenic and causes severe birth defects. Pharmaceutical industry regulations regarding enantiopurity have become much more stringent as a result. Therefore, the development of synthetic methods that allow the production of one enantiomer has become a critical part of organic chemistry. In order to direct the excess formation of one enantiomer over the other, an element of asymmetry must be introduced. In the case of the direct formation of enantiomers, this element must be introduced as a catalyst or reagent.[2]

This requirement does not apply to the formation of diastereomers, which have two (or more) chiral centres. The creation of diastereomers frequently begins with a molecule which already has one or more chiral centres in place and thus a source of asymmetry already exists and in such cases no additional element is required. Diastereomers are totally different molecules that have different physical and chemical

properties and because of this they are easily separable. The efficiency of an asymmetric reaction is best described in terms of either enantiomeric excess (ee) or diastereomeric excess (de). These measures of stereoselectivity are actually a measure of the ratio of the amount of one enantiomer(or diastereomer) over the other. Formally the ee or de is determined by subtracting the amount of the minor product from the amount of the major product, dividing by the sum of the amounts of both products and multiplying by one hundred. Enantiopure compounds may be obtained by resolution, and by the use of chiral reagents, catalysts, or chiral auxiliaries.

Resolution

A racemic mixture may be separated into its two enantiomers by the process of resolution.[3] This can be accomplished by reacting the mixture of enantiomers with a pure enantiomer, often called the resolving agent. A mixture of diastereomers results, and these are readily separated from one another usually by fractional crystallization or

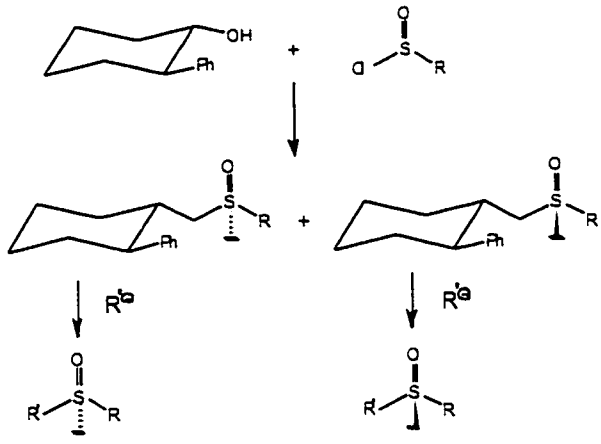


Figure 1. Resolution of a sulfoxide using a chiral auxiliary

chromatography. Another kind of resolution called kinetic resolution utilizes the different reaction rates of the two enantiomers with the resolving agent. This provides the reacted material, which is rich in one enantiomer and the unreacted material, which is rich in the other. The resolving agent is then cleaved from the reacted material to yield the pure enantiomer. As an example, *trans*-2-phenylcyclohexanol can be used as a resolving agent for sulfoxides.[4] (Figure 1)

Chiral Catalysts and Reagents

Chiral catalysts and reagents function in much the same was as kinetic resolution.[5] When the reactant comes into contact with a chiral catalyst or reagent it is in a chiral environment. This induces asymmetry that will be reflected in the relative energies of the transition states, and this energy difference allows for the preferential formation of one enantiomer over another. Enzymes, chiral Lewis acids and chiral crown ethers are often used as catalysts and organometallic reagents, rendered chiral by coordination of a chiral ligand, can be used as chiral reagents .

Chiral auxiliaries

A chiral auxiliary is a temporary appendage which exerts an asymmetric influence on an achiral substrate. The creation of the new stereocenter is governed by many different variables which ultimately allow the hindrance or partial hindrance of one face of the reacting centre allowing the preferential formation of one diastereomer over the other. This hindrance causes a difference in transition state energy that allows the excess

formation of one product. The diastereomeric excess (de) can be converted to the desired enantiomeric excess (ee) by cleavage of the chiral auxiliary. This type of stereocontrol is an active and expanding area of interest to many research groups as they uncover new and practical methods for the control of absolute stereochemistry and as such is the main focus of this paper.

Controlling Stereoselectivity Using Chiral Auxiliaries

Selection of the chiral auxiliary

To be useful as a chiral auxiliary, the stereo director must be reusable. Therefore the covalent linkage to the substrate must be a carbon-heteroatom bond, usually either oxygen or nitrogen. This facilitates the addition and removal of the chiral appendage. Mild conditions for the removal are advantageous as this minimizes the risk of racemization of the product. A rigid framework is usually a requirement as well, because this assures that conformational changes in the auxiliary do not reduce the amount of asymmetric induction. Since the cyclohexane skeleton is considered relatively rigid, when compared to straight chain skeletons, many chiral auxiliaries utilize this framework.[6] Another factor to consider in the selection of an appropriate auxiliary, is choosing one whose conformation introduces asymmetry directly at the reaction centre. In general, to be considered useful the chiral auxiliary must be highly selective (de $\geq$ 90%) in a variety of different situations.

Factors Affecting the Asymmetric Induction[7]

When a reagent approaches a substrate it encounters a multitude of repulsive and attractive forces. In a chemical reaction, differences in repulsive forces are usually responsible for any stereochemical bias observed.

Steric effects[7,8]

Steric effects are non-bonded through space repulsions which are responsible for most of the asymmetric induction observed. This repulsive force is caused by the close proximity of the filled orbitals of both the substrate and the incoming reagent. Thus the least hindered face offers the lowest energy transition state, and the reagent will react there preferentially, forming an excess of one product. These forces are dependent on certain aspects of molecular geometry like bond angles and distances. This allows for some predictability of the possible products. For example, the direction of addition to ketones with a chiral ∝-carbon are readily predictable.[9] When it comes to this type of reaction, the most generally accepted rule is that put forth by Felkin and co-workers[10], which relies on transition state calculations. The model states that groups on the chiral carbon are labelled as small, medium, and large, and in order to reduce repulsive orbital interactions, the large group orientates itself perpendicularly to the carbonyl group. Attack of the nucleophile occurs on the opposite face, which is less sterically hindered.(Figure 2)

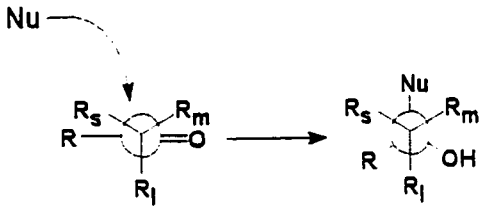


Figure 2. Predicting stereochemistry using Felkin Ahn's rule

Stereoelectronic Effects

Pi-Stacking[11,12]

These charge transfer interactions are stabilizing and are thought to direct attack to one face of a substrate. In order for this to occur, the substrate or chiral auxiliary must contain a point of unsaturation, usually in the form of a phenyl or other large delocalized system. The incoming reagent must also contain a point of unsaturation for a beneficial interaction to take place. First utilized by Corey[13] in 1972, this interaction has gained much popularity in the design of new chiral auxiliaries. It has the ability to lock the substrate in a conformation that would be otherwise unfavourable allowing a high degree of stereoselection. However, the exact nature of the pi-stacking effect is not yet fully understood and is still being hotly debated. As a result, many studies on the subject have been carried out in recent years, with many groups successfully using the effect to achieve excellent results. One of the first to exploit this was Oppolzer[14] and co-workers who studied existing chiral auxiliaries that had been designed[15] to take advantage of pi-stacking when trying to induce asymmetry during a reaction. Oppolzer used the chiral

auxiliary 8-phenylmenthol in an attempt to control the stereochemistry of intramolecular ene cyclizations. This auxiliary induced excellent control as the cyclized product was produced in a 90% "de".(Figure 3)

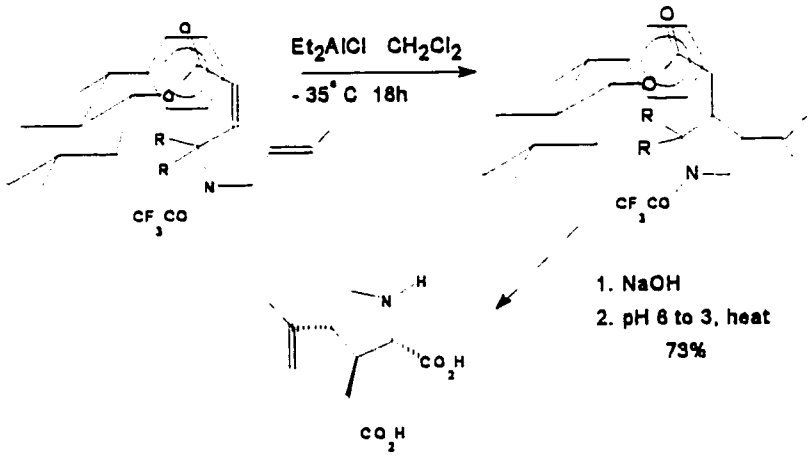
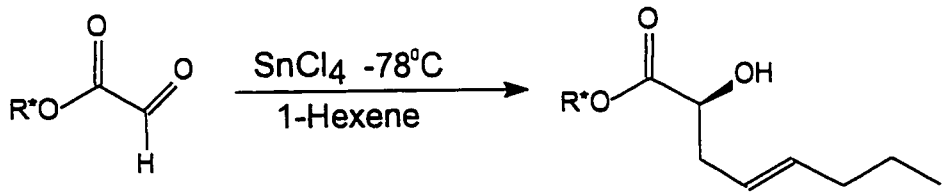


Figure 3. Intramolecular ene cyclization using 8-phenylmenthol as a chiral auxiliary

Whitesell soon expanded work on 8-phenylmenthol to include a wide variety of reactions including glyoxalates and simple alkenes.[16] It was assumed that the beneficial pi-interaction with the phenyl ring on the auxiliary would hold the two carbonyls of the gyloxalate substrate in place, thus effectively blocking one face to the incoming



R = Menthyl (33%de)
R = 8-Ph-menthyl (99%de)

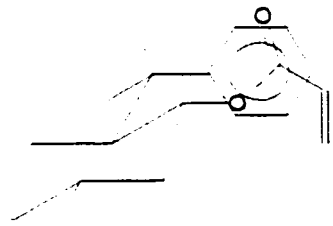


Figure 4. Proposed conformation adopted by 8-phenylmenthol acrylate

nucleophile. They achieved excellent stereochemical bias, often with ≥ 98% "de". Another example of pi-induced facial discrimination was observed using 8-phenylmenthol acrylate in [3+2] additions.[17] As was the case with the glyoxalates, it was thought that the phenyl ring would coordinate the carbonyl and alkene functions in the substrate thereby introducing an element of asymmetry. The cycloaddition was performed by adding methylene cyclopropane with $Ni(COD)_2$ as a catalyst. Although a slightly lower "de" was observed, this versatile and useful cycloaddition reaction proceeded in excellent chemical yield.

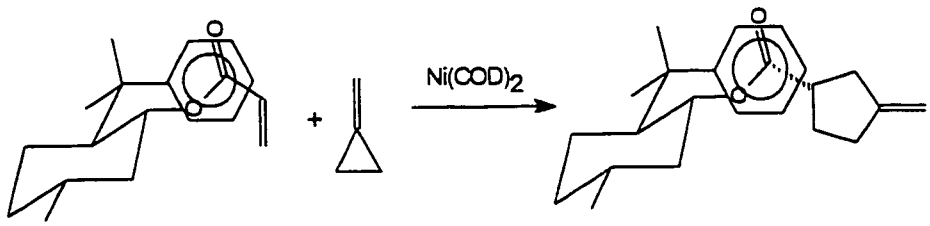


Figure 5. [3+2] cycloaddition of 8-phenylmenthol and methylenecyclopropane

Whitesell and co-workers decided to probe the pi-stacking effect by carrying out similar reactions using menthol (Figure 6) as the auxiliary[18] in order to see if the same

Menthol 8-Phenylmenthol

Figure 6. Menthol and 8-phenylmenthol

stereochemical bias would result when the phenyl group (pi electrons) were not present.[19] They used ene reactions of glyoxalates to probe the effectiveness of various chiral auxiliary features. They found that, in the case of menthol, a "de" of only 33% was obtained, whereas 8-phenylmenthol provided a "de" of > 99%. This did not prove much since replacing a phenyl group with a hydrogen would surely lower any steric effect that was at work. However, the conformation of C (Figure 7) was thought to be unfavourable. Based on steric considerations it was thought that Conformer A would be favoured over B and C. This would mean that the back face of the glyoxalate would be blocked by a methyl group in the transition state. Thus they synthesized a new auxiliary in which a methyl group replaced the phenyl group. The asymmetric induction (59%"de") was not

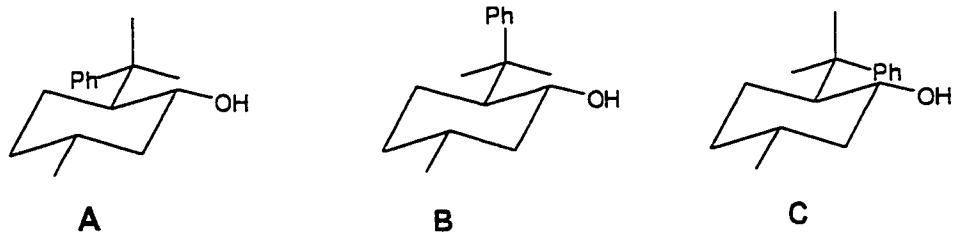
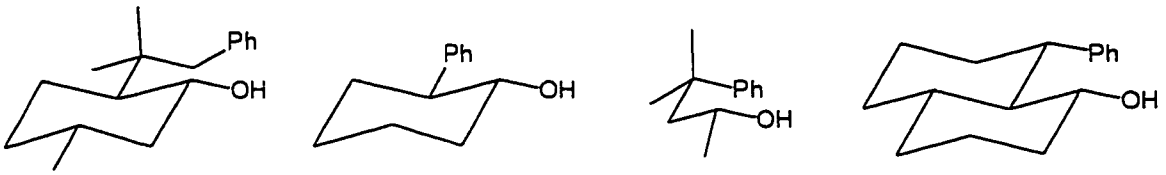


Figure 7. Possible conformations of 8-phenylmenthol

significantly improved over that obtained using menthol and was certainly not comparable to the level observed with 8-phenylmenthol. This proved that conformation C was the one influencing the reactivity at the transition state. It was thought that the pi-pi interaction was responsible for the level of stereochemical discrimination being observed. In order to test this, the phenyl group was replaced with cyclohexyl group which is approximately the same size. The observed "de" for this auxiliary was only ~ 40% and thus it was assumed that the phenyl ring was responsible for the induced stereochemical excess. Whitesell expanded his investigation of this phenomenon by trying to determine if adjusting the pi-electron density in the phenyl ring of the auxiliary would affect the observed "de". In order to change the pi-electron density, they produced auxiliaries which had electron donating and withdrawing groups on the phenyl group of the chiral auxiliary.[20] The groups were fluoro and methoxy respectively. However, while these reactions both showed high stereochemical control > 90% "de", sufficiently pure samples required for this kind of measurement could not be attained. This led Whitesell to experiment with different spatial positioning of the phenyl



77% de 90% de 40% de >98% de

Figure 8. Effects of the spatial positioning of pi-electrons in chiral auxiliaries

moiety. Some of the results were good and some were mediocre, but all showed stereochemical bias that could not be readily explained without the pi-stacking effect. It was also demonstrated that the distance of the pi-electrons from the reaction centre is important. That study led to the use of *trans*-2-phenylcyclohexanol (Figure 8), which has become a popular chiral auxiliary for the study of the pi-stacking phenomenon, as will be demonstrated in the results section of this thesis.

Applying Chiral auxiliary pi-Stacking to other reactions

Enantioselective alkylation[8]

Enantioselective alkylations are powerful carbon-carbon bond forming reactions that have been under investigation for some time. Carbon-carbon bond forming reactions require some kind of activating functionality, most often a carbonyl group. This simple but versatile functional group can act as either an electrophile or as a nucleophile depending on the reaction conditions. The most important types of these reactions involved

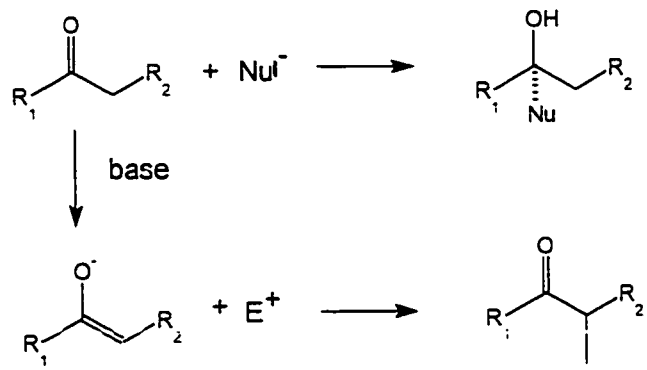


Figure 9. Methods for derivatizing a carbonyl

the formation of enolates because if either R group contains a chiral centre then the faces of the enolate become diastereotopic. Nucleophilic addition to these types of carbonyls (Figure 9), have been widely studied and many rules can now accurately predict the stereochemical outcome of the reaction.[9,10] However the focus of this discussion will be on the enolate and its reaction with electrophiles.

Enolates[5,8,19]

Enolates are generated by the deprotonation of the ∝-carbon by a Bronsted base. The anion formed is delocalized into the pi system of the carbonyl. It is the stability imparted by this resonance distribution of electrons which makes the ∝-carbon acidic. Since the oxygen is the more electronegative element it bears most of the negative charge. The generation of the anion requires careful selection of the appropriate Bronsted base.

The carbanion will only form if the acidity of the carbon is greater than that of the conjugate acid of the base used for deprotonation. Weak bases like alkoxides are not practical for the formation of simple enolates as its conjugate acid (ROH) is too strong and the equilibrium concentrations of the enolate are too small; A stronger organic base like LDA is required. LDA is formed by the addition of n-butyl lithium to diisopropylamine. N-butyllithium is itself a strong base, but it can also act as a nucleophile. Forming LDA circumvents this problem as it is relative bulky and as such tends to be non-nucleophilic.

Regioselective Enolate Formation[5,19]

Complications can arise when dealing with unsymmetrical ketones, because the base has two choices for deprotonation. In order for alkylations of enolates to be synthetically useful, absolute control of enolate regiochemistry must be maintained. The easiest way is to avoid ketones altogether and use esters where there is only one choice. However, it is often desirable to work with ketones, and there are methods to control which enolate forms. To do this experimental conditions of the reaction must be manipulated as the process of enolate formation can be governed by either kinetic or thermodynamic factors.[21]

Kinetic control of enolate formation takes place when production of the product is governed by the relative rates of the two competing proton abstractions. Thermodynamic control is present if the two possible enolates can be equilibrated rapidly, allowing the product composition to reflect the thermodynamic stability of the two enolates. There are

specific types of reaction conditions required in order to establish one type of control. For example, ideal conditions for establishing kinetic control are those in which the deprotonation is, rapid, quantitative, and irreversible.[22] These conditions require a very strong base such as LDA and use of an aprotic solvent. Protic solvents allow equilibration through reversible protonation and deprotonation, and this is not desired as equilibration leads to the thermodynamic enolate. Also the preferred counterion for regiospecific formation of the kinetic enolate is lithium.

Figure 10. Thermodynamic versus kinetic enolate

A general rule has been developed after much study of enolate composition: Kinetic control conditions favour the less substituted enolate whereas at equilibrium, the more substituted enolate is preferred.[5] This is because the stability of carbon-carbon double bonds increases with increasing substitution and the same is true for enolates.

Stereoselectivity of enolate formation[5,19]

As well as there being enolate regioisomers, there can also be enolate

stereoisomers. Most enolates can exist as either the (Z) or (E) stereoisomers. There is a difficulty in applying E-Z nomenclature to enolates. In some cases, changing the metal counter ion can change the stereochemical descriptor from (E) to (Z) and vice-versa. The solution to this problem is to use the method of Evans,[8] wherein the enolate oxygen-metal coordination is always given the highest priority. There are some general trends that are observed here. When ester enolates are deprotonated with LDA , the (E) configuration is preferred, addition of a deaggregating agent such as HMPA or TMEDA promotes equilibration and reverses this preference as the more stable (Z) isomer now predominates.[23] When ketones are enolized , the kinetically preferred enolate is the (E) isomer when sterically demanding bases like LiTMP are used.[24] Less bulky bases like LDA produce mainly the (Z) enolate unless a bulky group is present in the enolate system, in which case the (E) isomer is obtained. In the case of amide enolization, highly selective deprotonation results in formation of the (Z) isomer only.

The above-mentioned trends have been rationalized by a transition state model proposed by Ireland.[25] Ireland stated that the deprotonation process might well be proceeding through one of two pericyclic chairlike transition states. (Figure 11)

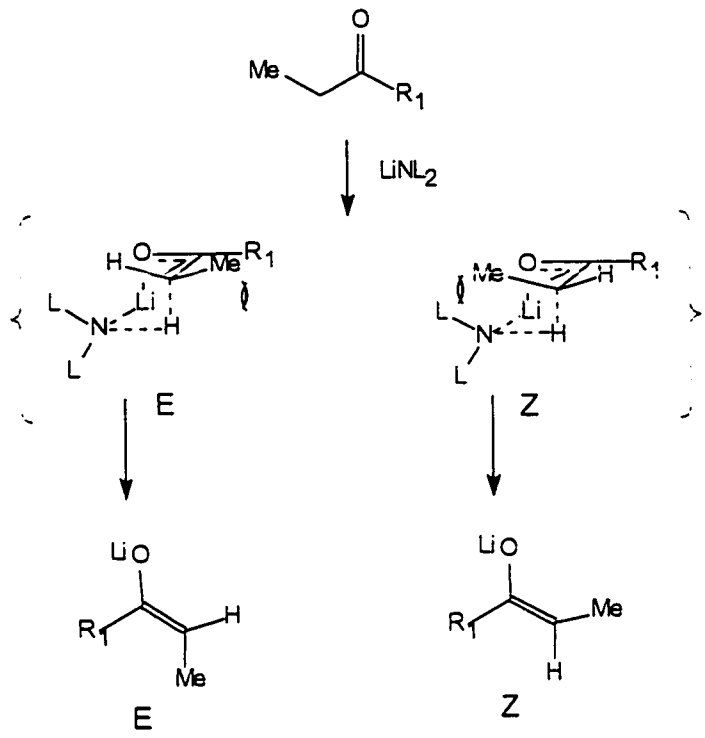


Figure 11. Transition state model rationalizing enolate stereoselection

There are two influencing forces at work here: The R_1-CH_3 allylic strain and the CH_3-L non-bonded repulsion. In general, when R_1 is not sterically demanding, the (E) enolates are formed because the CH_3-L become the dominant force. When R_1 is sterically demanding then the R_1-CH_3 repulsive force dominates and the (Z) enolates are formed.

Alkylation of enolates[5,8,19]

Alkylation of enolates, usually occurs by a S_N2 process, and all subsequent arguments are based on this premise. Other mechanisms (e.g. electron transfer) are less common and do not conform to the models described. The alkylating agent must be

reactive toward nucleophilic displacement. Primary halides and sulfonates, especially allylic and benzylic ones, are the most reactive electrophiles. Secondary halides do not work as well, as elimination becomes a side product, but secondary iodides are reactive enough to be useful. Tertiary electrophiles are of no use at all as they only provide the elimination product. Substrates that have two acidic carbon acids can be deprotonated with two equivalents of base to yield the dianion.[26] The alkylation takes place at the more basic carbon acid, making selective alkylation very convenient.

Factors effecting the alkylation of enolates[5]

Alkylation reactions can be very sensitive to a number of controllable variables. The rate of enolate ion alkylation has been shown to be strongly dependent on the reaction solvent.[27] The best solvents are those that have a high dielectric constant and lack any hydrogen donating centre. These solvents belong to a class called polar aprotic solvents, the best being DMSO and DMF. The drawback to using these solvents is their high boiling points which makes them difficult to remove after completion of the reaction.

The reactivity of enolates that have alkali metal counterions (Li^+, K^+, Na^+) are very sensitive to the state of aggregation. The state of aggregation is influenced by the type of solvent employed. The most reactive type of enolate would be a "bare" one , that is an enolate that is not solvated at all. This ideal cannot be achieved in solution, but it is possible to approach it. In order to induce maximal reactivity, the cation must be strongly

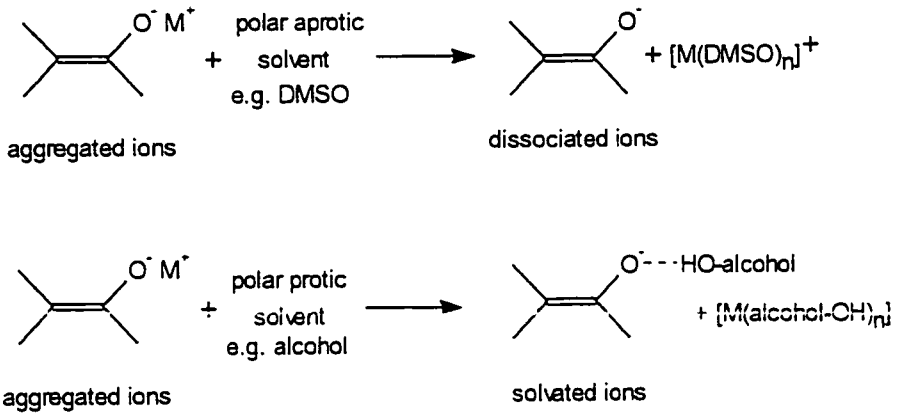


Figure 12. Medium effects on the enolate ion

solvated, leaving the anion exposed. Polar aprotic solvents like the aforementioned ones are good at this because they have a readily available negatively charged moiety and their positive centre is not very accessible.

Many of these solvents are toxic so other alternative solvents are used when possible. One such solvent is THF, which is slightly polar, but is a fairly good cation solvator. However, it does allow some aggregation of enolates often in the form of hexamers.[28] This effect can be partially negated by the use of deaggregating agents in stoichiometric quantities. HMPA, TMEDA and crown ethers are often used for this purpose.

Regioselectivity of enolate alkylation[5,19]

Enolates are ambident nuleophiles[29] as they may attack in more than one way to yield different products. Sometimes mixtures are obtained but, by varying reaction conditions, attack can be directed from one centre. Alkylation may occur at either carbon or oxygen. Since most of the electron density resides on the oxygen atom, one would assume that O-alkylation would dominate. This is not the case as other variables can be controlled in order to make C-alkylation the preferred reaction.

O-alkylation is favoured when a poorly solvated enolate ion is involved. Therefore, polar aprotic solvents like DMF maximize this effect. Solvents of lower dielectric constant like THF, which allow some aggregation of the enolates, favour C-alkylation. Additives like HMPA that deaggregate the enolates will also favour O-alkylation.(Figure 13)

The type of electrophile employed can also affect the C versus O alkylation ratio. Alkyl halides give higher C/O alkylation ratios than alkyl sulfones and sulfates, and alkyl iodides are the most favoured halides for C-alkylation. This can be rationalized as leaving group effects by applying the "hard soft acid base"(HSAB) rules.[30] This rule can be generalized by the statement: Hard likes hard and soft like soft. Of the two nucleophilic sites in an enolate, oxygen is harder than carbon. The HSAB favours nucleophilic

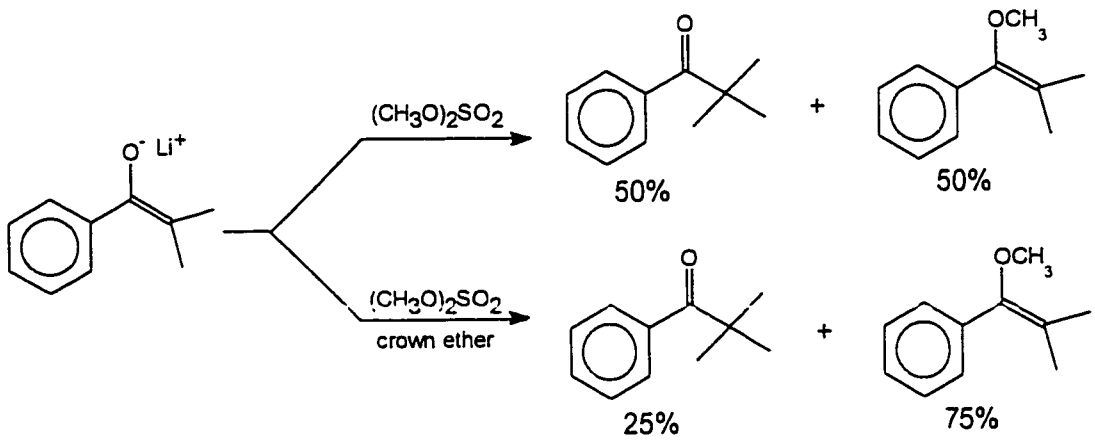


Figure 13. Additive effect on C/O alkylation ratio

substitution of the S_N2 type, so an electrophile like methyl iodide, with a soft leaving group like iodide, will react preferentially with the softer carbon site.[31] Oxygen containing leaving groups are harder and will react with the harder oxygen on the enolate. Even the cation can affect the C/O ratio. Simply changing the counterion from Li^+ to K^+ will favour O over C-alkylation.[32]

Alkylation of chiral enolates[7,8]

These enolates have one (or more) sites of proximal asymmetric centres which render the two faces of the enolate diastereotopic. When the incoming electrophile reacts to form a new chiral centre the products are diastereomers. Performed under kinetic control, the diastereomer that reacts fastest will be the major product. If equilibrium is

established, stereochemical scrambling will occur. When only one new chiral centre is being formed there are only two diasteomeric transition states. These two transition states result from the attack of the electrophile on each of the faces of the enolate. The difference

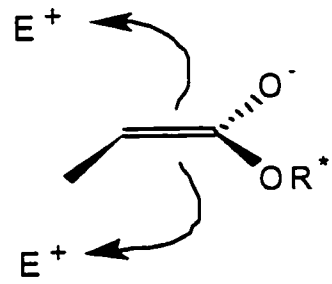


Figure 14. Diastereotopic enolate faces

in activation energies between these two transition states will determine the relative rates of reaction and in so doing the stereochemical composition of the product. If one face is unfavourable for some reason, attack there will require more energy, and the electrophile will attack using the other, lower energy pathway, more often. Several factors can effect the activation energies and thus the preference for one face of the enolate over the other. These factors include conformations of the substrate and reactant, and stereoelectronic and steric interactions in the transition states.[33]

In order to control the stereoselectivity of enolate alkylations, it is necessary to control the activation energies of the two diastereomeric transition states. By maximizing the difference in activation energies, it becomes possible to produce a large diastereomeric

excess (de) in the products. A good way to do this is by using chiral auxiliaries to induce the pi-facial selectivity in the alkylation of enolates. Particular chiral auxiliaries, good at inducing selectivity through electronic (pi-pi) and steric effects in the transition state, have already been discussed. Studies examining the application of these techniques to produce synthetically useful products, like derivatized α-amino acids, are an area of active research.

Asymmetric Alkylation of Derivatized Amino Acids[34]

Amino Acids

Proteins consist of large strings of α-amino acids, called polypeptides. Individual amino acids are linked together by condensing the amino terminus of one amino acid with the C or carboxylic terminus of an another amino acid.[35] Amino acids have a two carbon backbone containing an amine, carboxylic acid and, with the exception of glycine, a side chain at the ∝-position. It is the side chain that conveys unique character on each amino acid - the backbone always stays the same. The point where the side chain joins, is a chiral centre, and in nature only one enantiomer is used. The only amino acid that is achiral is glycine, which is just the unsubstituted backbone. (Figure 15) Glycine is an advantageous

Glycine Chiral Amino Acid

Figure 15. Structure of glycine and a generic α-amino acid

starting point for the synthesis of higher amino acids. Amino acids are zwitterionic and the opposing positive and negative charges cause solubility problems for reactions carried out in the common-aqueous solvents. To avoid this problem the acid is frequently protected as an ester and the amine is protected as an amide. The derivative formed is much easier to work with, and when the synthesis is complete the protecting groups can be removed. Since racemic compounds are of little or no use, the synthesis must have an asymmetric element that will produce an excess of the desired enantiomer. There are many well studied methods on how to functionalize glycine at the ∝-position in an asymmetric fashion.[34] The most common method is to deprotonate glycine at the ∝-position to form an enolate which attacks an electrophile in an S_n2 fashion. As presented previously, a chiral influence is needed to produce an enantiomeric excess, otherwise a racemic mixture will result. Introduction of a chiral auxiliary on the C-terminus of derivatized glycine is currently under study and has shown promising results.[36] Some examples are described in the ensuing pages.

Asymmetric alkylation of Camphor Imine 'Bu glycinates

The asymmetric alkylation of derivatized glycine using chiral auxiliaries is an especially important application of these techniques, as the synthesis of higher amino acids is very important in the development of new drugs. McIntosh and co-workers designed a study to examine this type of reaction using camphor as asymmetric influence.[36] A pi-pi interaction was noticed here as the alkylation of the (R)-camphor imine of t-butyl glycinate, with electrophiles containing a point of unsaturation, led to a larger asymmetric induction than occurred using saturated electrophiles. It was noted that utilizing steric

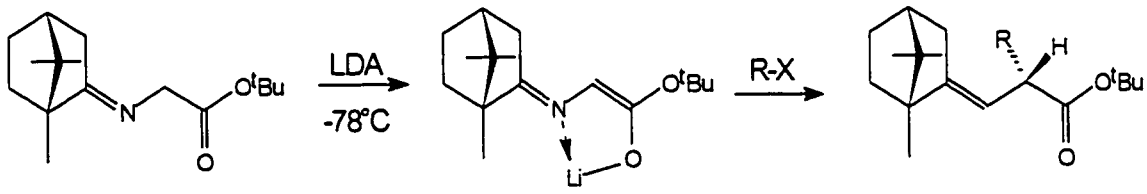


Figure. 16 Reaction model for the alkylation of camphor imines [38]

factors (bulky alkylating agents) would only increase the "de" to a maximum of 50%. However, when the alkylating agent had some kind of pi system the observed "de" was much higher. These results were rationalized by a model[36] wherein the deprotonated camphor imine exists in an internally chelated form. (Figure 16) This allows one face of the enolate to preferentially react with the alkylating agent. It was suggested that the increase in "de" could be attributed to associations between the pi systems of the enolate and the alkylating agent. They showed that an electron rich system in the alkylating agents

(benzyl, p-methyl, 1-naphthyl etc.) gave the best results, whereas systems that contained electron withdrawing groups gave substantially lower values. McIntosh also presented an alternative to the pi-pi theory, which involves a pi-Li complexation. The high selectivities observed when the alkylating agent contains an electron rich centre suggest a possible interaction with a positive lithium centre. Such interactions have been shown to exist in earlier studies.[28,37,39-42] Whether it's pi-Li or pi-pi or a combination of both there is clearly some factor present which causes favourable stereochemical outcomes. The exact nature of this interaction is still being investigated.

Alkylation of Chiral Hippurates[43,44,46]

Menthyl Hippurate[43]

McIntosh and co-workers, redirected their work on alkylation of chiral imine glycinates, to focus on N-acyl derivatives of glycine. Hippuric acid, N-benzoylglycine, was chosen as the substrate. The chirality designed to introduce asymmetry at the

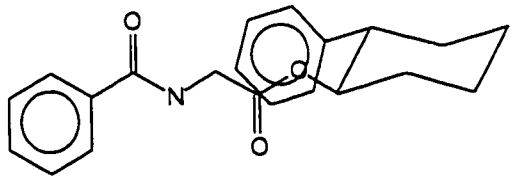


Figure 17. Chiral ester of hippuric acid

newly formed chiral centre can be incorporated in either or both the ester and the N-

benzoyl group. Incorporation of a chiral alcohol in the ester was chosen as this provides the easiest route for addition and removal of the auxiliary. This contrasts with the camphor imine work in that the asymmetry is being introduced from the opposite end of the amino acid. The principle objective, the systematic elucidation of the dependence of the degree of asymmetric induction at the ∝-carbon and nature of the chiral auxiliary, remains unchanged.

It was found that a number of factors influenced the alkylation results. The effect of base and additive was studied in order to maximize chemical and stereochemical yields.[44] It was found that using two equivalents of LDA gave the best result[45] because the N-H is more acidic than the carbon acid. C- alkylation was still observed as the electrophile always reacted with the more basic site first.[26] The use of one equivalent usually resulted in N-alkylation. Incorporation of the additives HMPA and TMEDA appeared to increase the reactivity of the enolate when present in limited amount. Loss of stereochemical selectivity occurred when greater than two equivalents of the additive were used. This result might not be expected considering that more additive usually leads to a more reactive enolate.[27] A possible rationale for this would be that excess additive would disrupt the metallocycle (Figure 18) which allows for more rigid stereocontrol.

When menthol was used as the chiral auxiliary, the highest de observed was 56%. When 8-phenylmenthol was used it produced a much improved "de". This result was consistent with Whitesell's work with these auxiliaries.[20] This pi-pi interaction has still not been fully rationalized, and further study of the effect is required. McIntosh proposed a model which rationalizes the production of the major diastereomer in the alkylation of

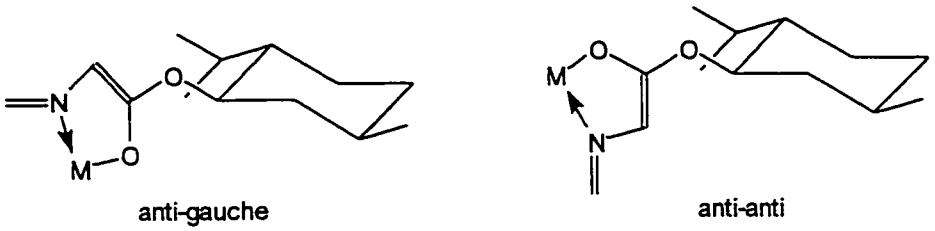


Figure 18. Two possible conformations of enolate metallocycles

menthyl hippurate.(Figure 18) The preferred conformation is anti-gauche as this minimizes the electronic repulsion between the oxygens lone pairs of electrons that is present in the anti-anti conformation. It must be assumed that the O-Li bond is covalent and the metallocycle exists and the cyclohexane ring maintains the all equatorial conformation. If that is the case then the pro-R face is shielded by the isopropyl group of the menthol. Thus, the (S)-diastereomer would be the major product, which is the case in the actual experiment. A phenyl group in the place of the isopropyl gives much better stereochemical induction,[20] however more study is required in order to elucidate this relationship.

Trans-2-phenylcyclohexyl Hippurate[46]

The typical selection criteria for the most suitable chiral auxiliary, usually takes into account the level of induction and the specific enantiomer that would be produced. The conformational mobility associated with chiral ester enolates makes prediction of stereochemical outcome difficult. Since the associations inducing chirality transfer between the auxiliary and the product stereoisomers are very complex, an empirical model which predicts the stereochemical outcome of such alkylations reactions would be a

useful synthetic tool. In order to further our understanding of chirality transfer and the relationship between pi-electron density and stereoselectivity, McIntosh et al. prepared a series of *trans*-2-(p-substituted aryl)cyclohexanol chiral auxiliaries.[46] (Figure 19)

The glycinate ester was prepared easily by combining the auxiliary, *trans*-2-arylcyclohexanol with hippuric acid under azeotropic conditions. The idea was to determine if changing the electron density in the phenyl ring of the auxiliary would have any effect on the stereochemical induction at the remote alkylation centre. The alkylating

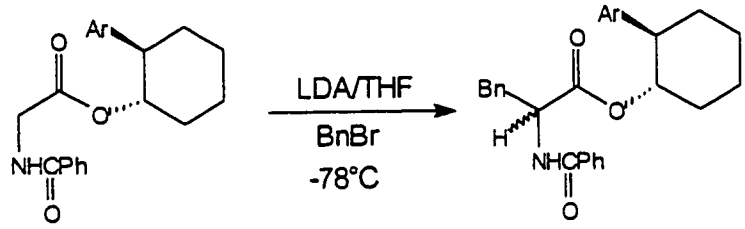


Figure 19. Alkylation of trans-2-arylcyclohexyl hippurates

agent in every case was benzyl bromide, which would afford phenylalanine, once all the appendages were removed. The trials resulted in some high stereoselectivity in the cases of: Ar =, phenyl 80%, p-CF_3-phenyl 84%, 1-napthyl >98%. However there did not appear to be any electronic effect on the "de". If this was the case then the strongly electron-withdrawing CF_3 group should have reduced pi-density in the aromatic ring thereby lowering the "de". Rather, it seemed that only steric effects were at work - Ar = p-^{t}Bu

20% "de". However, the major diastereomer could be predicted by a conformational model which contains the previously discussed enolate metallocycle.[43] (Figure 18)

Current work

Although the results of the alkylation of *trans*-2-cyclohexyl ester were disappointing, it was still considered a useful model for the study of the pi-stacking effect. In the current study the aromatic group on the auxiliary was held constant as either phenyl or 1-napthyl, and electrophiles of differing pi-electron density were examined.

In order to expand our work on the alkylation of chiral glycine analogs, it was decided to examine the influence of the chiral auxiliary's pi directing effects from the amino terminus of the methyl ester of glycine also. (Figure 20) In order to accomplish this a new chiral auxiliary was developed to facilitate the coupling to the amine function of glycine.

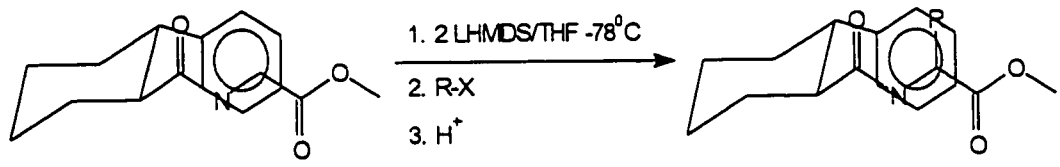


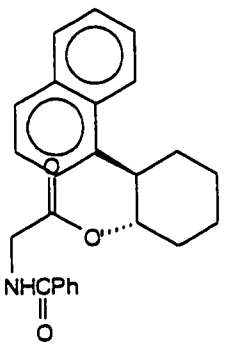
Figure 20. Directing alkylation of glycine analogs from the amino terminus

RESULTS AND DISCUSSION

Part A: Alkylation of *trans* 2-arylcyclohexyl hippurates

In order to elucidate an empirical model for the observed stereochemical bias imposed by chiral auxiliaries bearing aromatic groups, alkylations of *trans* 2-arylcyclohexyl hippurates with electrophiles of differing pi and steric character, were undertaken. The goal was to determine if altering the pi-density of the electrophiles would affect the observed diastereomeric excess "de". The auxiliaries used were *trans*2-

Trans-2-phenylcyclohexyl Hippurate **1**



Trans-2-(1-napthyl)cyclohexyl Hippurate **2**

Figure 21. Chiral esters of hippuric acid

arylcyclohexanols, Ar = 1-naphthyl, phenyl, (Figure 21) which were attached to N-benzoyl glycine via a convenient ester linkage. The preparation of the two esters have been previously reported.[46]

Alkylation of Chiral Esters

The esters were deprotonated by dropwise addition to a solution of 2 equivalents of LDA in THF at -78 °C. The temperature was carefully maintained at -78 °C to ensure kinetic conditions for enolate formation and alkylation were constant. All alkylations were carried out on a 0.74 mmol scale. The solution of the dienolate of *trans*-2-

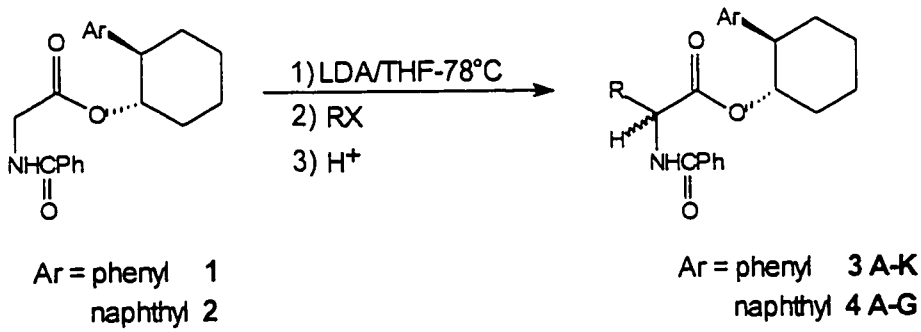


Figure 22. Alkylation of the two esters with various electrophiles

phenylcyclohexyl hippurate was a brilliant yellow whereas that of the dienolate of the naphthyl substrate was an orange-red colour. The mixture was allowed to stir for 90 minutes to ensure complete enolate formation. Then 1.1 equivalents of an appropriate electrophile was added as a solution in approximately 1 mL of THF. The addition was done in a dropwise manner in order to minimize any temperature fluctuations caused by the electrophile-THF solution. The mixture was stirred for an additional 90 minutes. Quenching of the reaction mixture was accomplished by adding 2 mL of 3M HCl at -78 °C. Quenching at low temperature minimizes the risk of the diastereomeric products equilibrating to a ratio other than the one induced by kinetic control. The products were

worked up in standard fashion to yield the crude products which only contained product and unreacted starting material. Products were separated from starting materials by column chromatography using silica gel while carefully avoiding separation of the diastereomers.

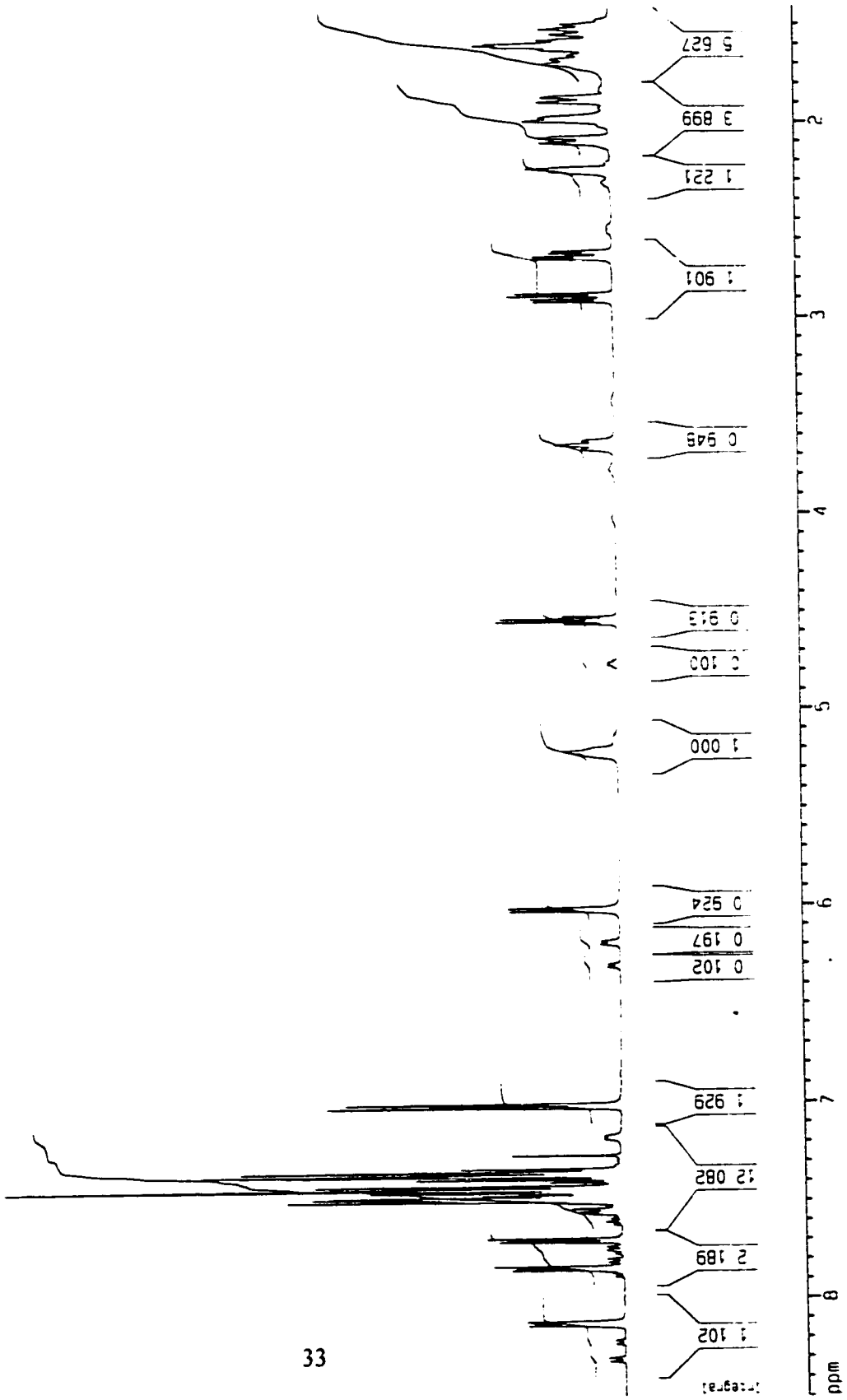
Alkylation of these substrates (esters **1** and **2**) can be a very delicate operation. For example, the failure of the alkylation of ester **1** with benzyl chloride (Table 2, run K) was apparently caused by the increased acidity conferred on the benzyl protons by the chlorine atom as well as its lower leaving group ability. This shifted the reaction preference from substitution to proton abstraction. This effect was also observed in the reaction with methyl bromoacetate, as it did not lead to an acceptable substitution reaction even though it was by far the most reactive electrophile towards S_N2 substitution.[47]

Alkylation with isopropyl iodide under normal alkylation conditions resulted in only a 14% yield. (Table 2, run C) This result could be expected as secondary electrophiles are not as reactive to substitution as primary ones. In order to improve the yield the reaction was run at increased temperature. (Table 2, run C*) The increase in yield was accompanied with the expected decrease in stereoselectivity.

Determination of de from NMR Spectra

Nuclear magnetic resonance (NMR) is a powerful tool for determining the stereochemical outcome of these types of reactions. The traditional method for such determinations has been HPLC. However, it has been determined that the use of this

Figure 23. Example ^{1}H NMR of alkylation product 4G



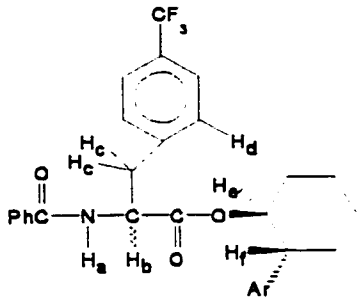


Table 1. NMR assignments for diastereomers of **4G**. Ar = 1-naphthyl.

	Major Diastereomer			Minor Diastereomer		
Proton no.	Shift (ppm)	Mult.	J (Hz)	Shift (ppm)	Mult.	J (Hz)
a	6.01	d	7.3	6.30	d	7.4
b	4.54	dd	6.9, 6.1	4.76	dd	6.9,5.4
c	2.90	½ dABq	14.0, 6.4			
	2.67	½ dABq	14.0, 5.6			
d				6.18	d	7.7
e	5.23	m		5.21	m[a]	
f	3.67	m				

[a] Overlapping.

Table 2 Results of the alkylations of *trans* 2-phenylcyclohexyl hippurate (1)

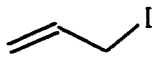
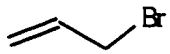
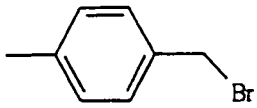
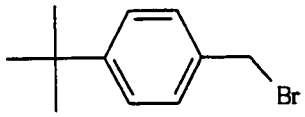
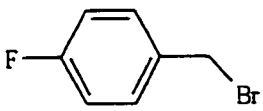
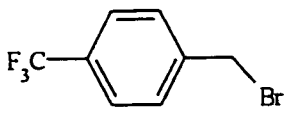
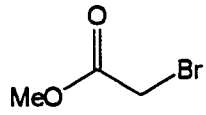
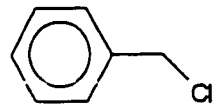
# 3	Electrophile	Yield	de %
A		85	58
B		85	79
C		14	81
C*	 Rx run at elevated temperature.	75	39
D		61	68
E		66	76
F		52	78
G		67	80
H		64	60
I		71	46

Table 2. Continued

J		~60[a]	70[a]
K		0	0

[a]estimated from spectra of crude products, as the product was inseparable from starting material

technique with these products is impractical[46] as separation was difficult under the best conditions. The two protons on the α-carbon of glycine are rendered highly diastereotopic by the 1-naphthyl and phenyl chiral auxiliaries. This effect causes the signals of the two methine diastereomers in the product to be widely separated and distinct (see example spectrum Figure 22). Thus, integration of their intensities yields the ratio of diastereomers produced. The influence of the chiral auxiliary made a number of diastereomeric protons different enough to use them as a measure of stereochemical induction. The most commonly used signals were the methine protons (H_b), the N-H protons (H_a) and the benzylic protons (H_c). In most cases all three measures gave acceptable agreement, but occasionally the N-H integration was inconsistent and in these cases, was not included in the calculation.

Results of the alkylation of *trans* 2-phenylcyclohexyl hippurate

The results for the alkylation of the *trans* 2-phenyl ester are shown in Table 2.

Several trends can be seen immediately. Alkylation of *trans* 2-phenylcyclohexyl hippurates with electrophiles of increasing size seems to increase the de (compare run's A,B, D, E, F). However data exist which indicates that the benzyl group is effectively smaller than methyl or ethyl groups.[48] (A values Me = 1.74, Et = 1.79, benzyl = 1.68) These data, called A values, are a relative measure of size. A values are actually conformational energy values for the interconversion of a particular group, between axial and equatorial positions of a conformationally biased cyclohexane ring. Thus, in the case of alkyl and benzyl groups an increase in conformational energy is related to an increase in size. The de of the benzyl group (80%)[46] being higher than that of the alkyl cases while being smaller in size, suggests the presence of the pi-electron system has a significant and positive effect on the reaction stereoselectivity.

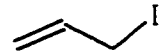
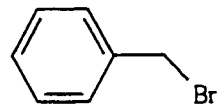
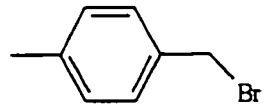
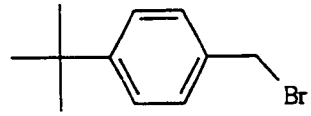
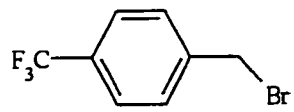
In order to see what effect altering the electron density of the benzyl ring would cause, a series of alkylations was carried out using para-substituted benzyl bromides. (Table 2 runs F,G,H and I) The results of these reactions suggest that higher electron density in the ring leads to a higher degree of induction. Presence of the highly electron withdrawing group clearly lowers the de from 80% in the unsubstituted to 46% with p-trifluoromethyl benzyl bromide.(^{t}Bu > CH_3 ~ H > F > CF_3)

Results of the Alkylations of *Trans* 2-(1-naphthyl)cyclohexyl Hippurate

Results for the alkylations of *trans* 2-(1-naphthyl)cyclohexyl hippurate (**2**) are shown in Table 3. In the alkylation of this ester, no trends are readily visible. However, the results show that in every case the ratio of diastereomers is in excess of 90:10. The only

deviation is the alkylation with methyl iodide. As was the case with ester **1**, the methyl group, lacking any pi-electrons or steric bulk, produced a de of ~ 50% with both esters. It is obvious that the stereochemical induction in this case is a result of a combination of steric and electronic effects. In this case the steric effect seems to be larger as the alteration of the electron density in the aromatic rings of the electrophiles has no effect as it did in the alkylations of ester **1**.

Table 3 Results of the alkylations of *trans* 2-(1-naphthyl)cyclohexyl hippurate (**2**)

# **4**	Electrophile	Yield %	de %
A		75	54
B		70	87
C		70	82
D		70	89
E		66	88
F		63	83
G		65	80

Here, the incorporation of the highly electron withdrawing group in the para position of the benzyl electrophile produces a 80% de. The alkylation of ester **1** with the same group produced a 46% de. This suggests that the steric effects imposed by the naphthyl ring are overriding any pi interaction. The smaller phenyl ring in ester **1** would not have such overriding steric effects, thus the degree of asymmetric induction is more dependant on the interaction between the density of pi-electrons in the electrophile and the pi-electrons in the phenyl ring of the chiral auxiliary. No matter which way the selectivity is introduced, this consistently high level of stereochemical bias introduced makes *trans* 2-(1-naphthyl)cyclohexanol a very useful chiral auxiliary.

Alkylation Stereoselectivity

Favoured Diastereomer

The major diastereomer formed in each alkylation is the same. This was deduced from the fact that the diastereomer with the higher field methine absorption was the major one in every case. In previous work by our group authentic samples of each diastereomer of *trans* 2-phenylcyclohexyl N-benzoyl phenylalanine were synthesized[49]. In that case the pure diastereomer with the (S) configuration at the newly created chiral centre exibited a higher field methine absorption, whereas the diastereomer with the (R) configuration exhibited a lower field methine adsoption that was almost overlapping the carbinol proton adsorption at 4.98 ppm. In the current work the major alkylation diastereomer again had the higher field methine absorption for the newly created chiral centre, and it may be

predicted, but not confirmed, that the major diastereomer formed

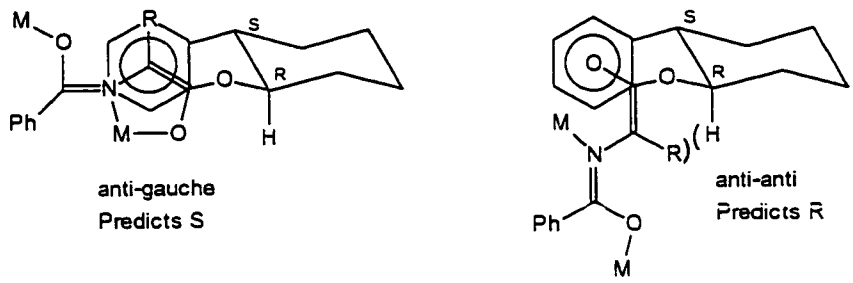


Figure 23. Model for the prediction of alkylation stereochemistry

from the (1R*, 2S*) auxiliary has the (S*) configuration at the newly formed chiral centre. This prediction is further supported by a model[46] that rationalizes the preference for the (S*) configuration through the coordination of an enolate metallacycle with the phenyl ring of ester 1.

Trans 2-Phenylcyclohexanol as a Chiral Influence on Structural Analogs of Glycine

In order to fully explore the influence that pi-electrons exert on reaction centres, a series of structural analogs of glycine were prepared.(Figure 24) These substrates differ from glycine in that their amino terminus is replaced by: methoxy, phenyl or N,N-dimethyl groups. The alkylation of these compounds proved very difficult. Alkylation

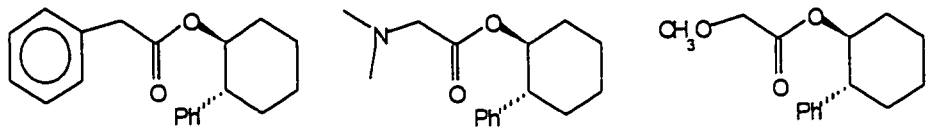


Figure 24. Attempted diastereoselective alkylation of structural analogs of glycine

conditions were the same used for the hippurate series. The chiral ester of methoxy acetic acid was the most closely examined of the three. It failed to alkylate under standard conditions, although reports of the Claisen rearrangement of the allyl ester suggests deprotonation is possible.[50] When the crude reaction mixture was examined it was noticed that a large amount of the free auxiliary present as well as some product of nucleophilic attack of the base LDA on the ester. The alkylation was attempted with the bulkier and more reactive base-^{t} BuLi.The reaction failed once again and a large amount of the free auxiliary was isolated. It was possible deprotonation was not occurring, and this was tested by adding methanol-d_4 instead of the electrophile. No deuterium incorporation was observed in the crude reaction mixture. However, alkylation of the methoxyacetic acid ester of cyclohexanol, resulted in fragmentation of the substrate. Cyclohexanol was isolated and the NMR signal for CH_3O was absent. This suggested that deprotonation was occurring, but fragmentation was taking place instead of the desired substitution.

Alkylation of N,N-dimethyl substrate also failed at the intended site. Alkylation did occur on the nitrogen as the crude spectra showed that the nitrogen was benzylated to

form a quaternary centre, which suggests deprotonation was not occurring. This product could not be isolated as it decomposed during column chromatography. The phenylacetic ester showed some alkylation with benzyl bromide but the product could not be separated from the starting material and this approach was abandoned.

Conclusion

The stereoselectivity introduced by the chiral auxiliaries, *trans* 2-phenylcyclohexanol and *trans* 2-(1-naphthyl)cyclohexanol, seem to stem from a combination of steric and electronic effects. The phenyl auxiliary seems to exibit a dependance between the electron density in the aromatic rings of para-substituted benzyl bromides and the observed de. This effect was not observed in the case of the naphthyl auxiliary, as the the all the electrophiles reacted in high stereochemical excess . It may be concluded that there is an electronic effect in these reactions, however more study is needed in order to fully understand it. Furthermore, the naphthyl group, while not showing the desired electronic effect, can be considered a synthetically useful chiral auxiliary as it produced consistently high stereoselectivity.

Part B: Alkylations of Glycine Derivatives Using a New Chiral Auxiliary: *Trans*-2-Phenylcyclohexanecarboxylic Acid

Synthesis of a new chiral auxiliary

To further explore the benefits of π-unsaturation adjacent to the alkylation site of glycine derivatives, we examined the effect of locating the chiral influence on the amino terminus of glycine. To accomplish this the acid would have to be incorporated directly on the cyclohexane skeleton. As a result we decided to prepare *trans* 2-phenylcyclohexanecarboxylic acid. Both diastereomers of the acid are known, but to the best of our knowledge it has never been used as a chiral auxiliary. The most obvious route to prepare this compound would be Birch reduction of commercially available 2-phenylbenzoic acid. This reaction is reported to afford a mixture of the *cis* isomer of **5**

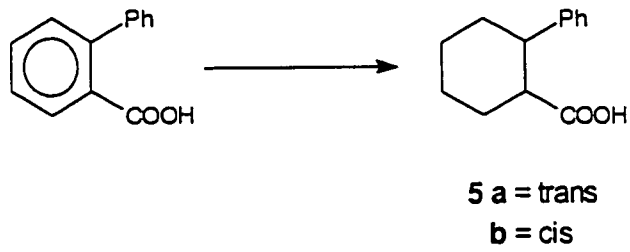


Figure 25. Reduction of 2-phenylbenzoic acid

and some partially reduced material.[51] Epimerization of the methyl ester of **5b** with NaOMe was found to be exceedingly difficult: The result was usually a mixture of the *cis* and *trans* ester as well as some of the *trans* acid **5a** presumably formed by alkyl-oxygen

cleavage. However, reduction of 2-phenylbenzoic acid with Na in pentanol gave **5a** directly.[52]

Coupling of the Auxiliary

The acid chloride was prepared by stirring the *trans* acid **5a** in $SOCl_2$ at room temperature over night and was used without further purification or characterization. Some difficulty was encountered when trying to couple the acid chloride with the hydrochloride of methyl glycinate. The initial approach was to produce the free amine by

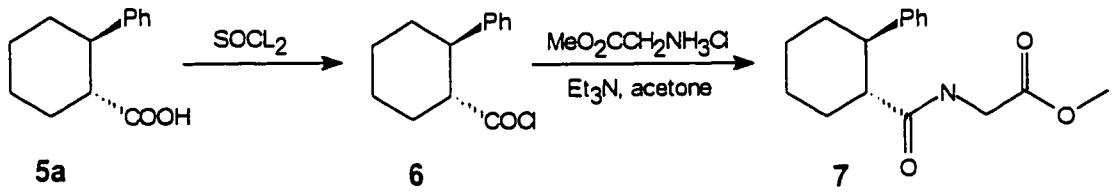


Figure 26. Incorporation of the chiral auxiliary on the amino terminus of methyl glycinate

adding base and then reacting the free amine with the acid chloride. This method failed, however much better results were obtained by adding the glycine hydrochloride to an organic solvent, usually acetone or methylene chloride, to form a slurry. One equivalent of Et_3N was added and the mixture stirred for five minutes. The acid chloride, dissolved in the same solvent was then added to the slurry and the entire mixture was stirred for two hours at room temperature. A standard work-up afforded the *trans* 2-phenyl amide of methyl glycinate **7** in a 55% yield.

Alkylation of the *trans*-2-phenylcyclohexylamide of methyl glycinate

Alkylation of 7 was preformed much in the same manner as the hippurate alkylations. Two equivalents of base were used to form the dienolate at -78 °C. The temperature was carefully maintained to ensure kinetic conditions for enolate formation and alkylation. All alkylations were carried out on a 0.727 mmol scale. The only other

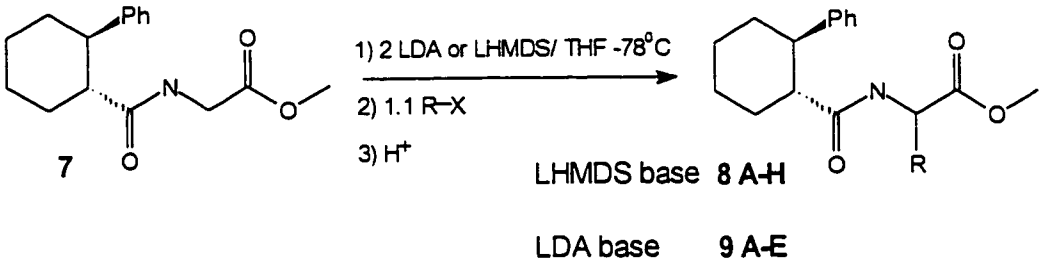


Figure 27. Alkylation of the chiral amide

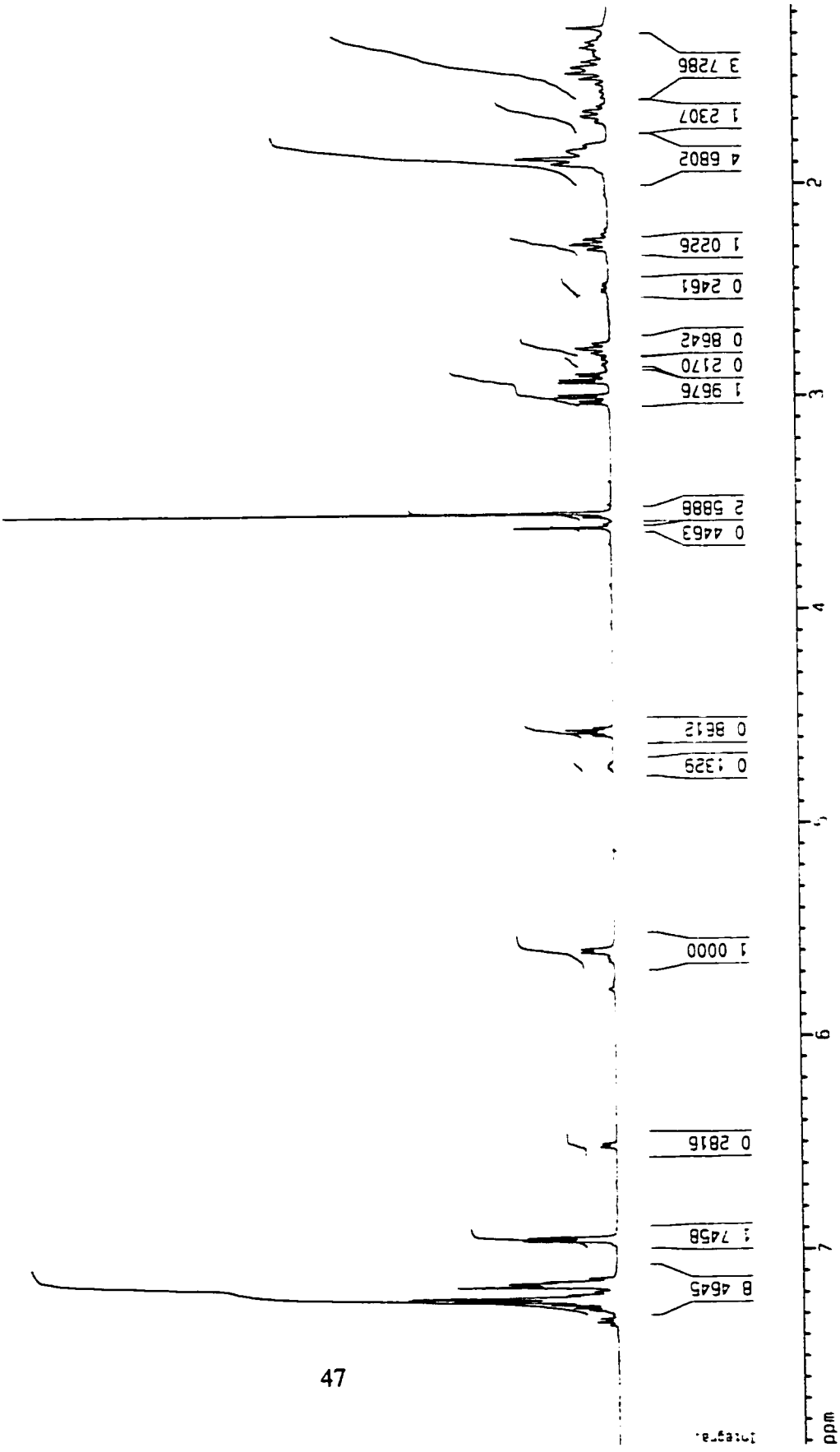
difference from the hippurate alkylations was that in this case the dianion was colourless. The chemical yields for these alkylations were in general lower than those observed in the hippurate series. It should be noted that no attempt to optimize these reactions was attempted due to time limitations.

Determination of the de From NMR spectra

Nuclear magnetic resonance spectra were used to determine the diastereomeric excess directly. The auxiliary on the nitrogen atom induces glycine's two α-protons to be diastereotopic as is evidence by the doublet of ABq observed at 3.75 ppm in the spectrum of **5**. This effect causes separation of NMR signals of the two methine protons in the

product diastereomers into two clearly distinct signals. The intensities of the signals of the two diastereomers relative to each other was used to determine the de in exactly the same manner as with the hippurate alkylations. The only difference was the signals used for de determination and internal checks. The strong influence of the auxiliary made signals for other groups in the product diastereomers clearly different as well. This allows for the de of one reaction to be measured from many signals in the alkylation product (For examples-see Table 4 and Figure 27). Every reaction had different signals associated with it from the electrophile protons. In some cases the two diastereomers could be observed in signals resulting from the newly incorporated appendage. In every case the de was determined from integration of the methyl ester signals on the substrate (H_a Table 4). The other signals were integrated as a series of internal checks to confirm the primary measure's accuracy. The methine signals for the two diastereomers were also clearly separated in many of the reactions and their integrations always compared favourably with the methyl ester integrations (H_b Table 4). As was the case for the hippurate alkylation series the major diastereomer formed in every case was the same. This was deduced from the fact that the signal from the major diastereomer for the methyl ester and methine were

Figure 29. Example ^{1}H NMR of alkylation product 8F



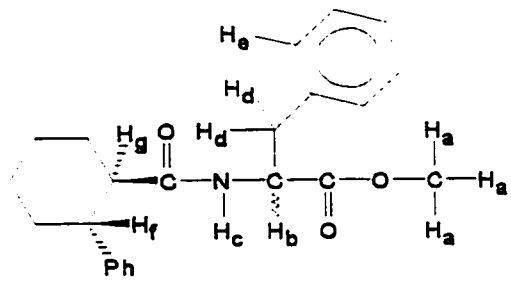


Table 4. NMR assignments for the diastereomers of **8F**

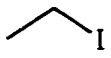
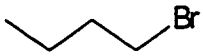
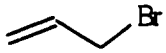
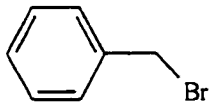
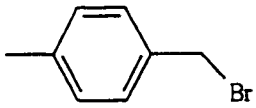
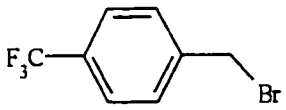
	Major Diastereomer			Minor Diastereomer		
Proton no.	Shift (ppm)	Mult.	J (Hz)	Shift (ppm)	Mult.	J (Hz)
a	3.55	s		3.61	s	
b	4.56	dd	13.1, 5.8	4.73	dd	12.6, 5.8
c	5.59	d	7.2	5.61	d	7.9
d	3.02	½ dABq	13.8, 6.0	2.83	½ dABq	13.7, 4.5
	2.91	½ dABq	13.8, 5.7	2.48	½ dABq	13.7, 5.9
e				6.50	d	6.2
f	2.77	m				
g	2.27	dt	11.5, 3.3	2.23	m[a]	

[a] Overlapping.

always the higher field signals. These results are consistent with the hippurate series. It is interesting to note that with the alkyl and allyl groups in this case, the signals for the N-H are reversed- the minor diastereomer exhibits the higher field signal. When benzyl groups are incorporated the N-H signals are the same as the hippurate series-the major diastereomer exhibits the higher field signal. In most cases the N-H signals were not separated enough to obtain a reliable integration of their intensities.

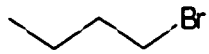
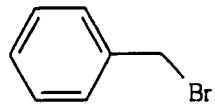
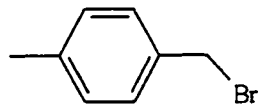
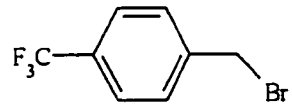
Alkylation Results

Table 5 Results of the alkylation of *trans* 2-phenylcyclohexylamide glycinemethylester (7) using LHMDS as the base

# 8	Electrophile	Yield %	de %
A		70	21
B		63	21
C		38	38
D		0	0
E		58	48
F		65	73
G		55	79
H		50	62

Results for the alkylation of **5** are shown in tables 5 and 6. The series of alkylations was first carried out using LDA as the base. However the chemical yields were so low, it could not be determined how reliable the results were. The series was run again, this time

Table 6 Results of the alkylation of *trans*-2-phenylcyclohexylamide glycine methyl ester (7) using LDA as the base

# 9	Electrophile	Yield %	de %
A		35	45
B		0	-
C		25	74
D		25	80
E		17	56

using lithium hexamethyldisilazane as the base. The resultant chemical yields were much better while the de values remain exactly the same. A few possible explanations for this difference are possible. Some evidence for the attack of LDA on the methyl ester portion of the substrate has been observed. A large doublet in the cyclohexyl region of crude NMR spectra, indicative of the diisopropylamine, has been observed. Subsequent pumping of the crude sample failed to remove this peak suggesting that the diisopropylamine had acted as a nucleophile and attacked the methyl ester carbonyl. It was thought that a LHMDS would not be as nucleophilic. This base did increase the yields dramatically,

however room for improvement still exists. Another possibility is that the carbon acid is not as acidic as with the hippurates and the aggregation state of the LDA does not allow it to be reactive enough for deprotonation to occur. The bulkier LHMDS could be less aggregated and more reactive. A possible way to improve the chemical yields, even in the LHMDS trials, would be to incorporate a bulkier ester into the substrate like ^{t}butyl. In any case the choice of base has been clearly shown not to affect the stereochemical outcome of the reaction.

Alkylations of the *trans* 2-phenylcyclohexylamide of methyl glycinate appear to show a dependence of the stereochemical result on the presence of π-electrons. The results from Table 5 show that alkyl groups have a very low de (21-38%). Adding one point of saturation in the from of an allyl group increases the de (44%). Going from allyl to benzyl dramatically increases the de (73%). As was noted previously, conformational energy A values suggest that the benzyl group is effectively smaller than methyl or ethyl groups. Therefore the dramatic increase in de is not a steric effect: It is due to the favourable interaction between the aromatic group on the auxiliary and the aromatic group on the electrophile. In fact, steric bulk seems to be a shortcoming , as the yield decreases going from methyl to ethyl and then a bigger decrease with the propyl group; butyl bromide failed using either base. This suggests that the π-interaction actually coordinates the electrophile in such a manner as to increase the yield . It also appears that the degree of stereochemical induction is related to the electron density in the aromatic ring of the auxiliary as was the case with *trans* 2-phenylcyclohexyl hippurate. Increasing the electron density by adding a methyl group in the para position increases the de, while incorporation

of a strongly electron withdrawing trifluoromethyl group in the same position decreases the de (See Table 5 and 6). These results are promising but preliminary; a more comprehensive series of alkylations is required to fully elicit the observed relationship

Conclusion

The stereoselectivity induced by the chiral auxiliary, *trans* 2-phenylcyclohexanecarboxylic acid, is clearly an electronic effect. Increasing steric bulk does increase the selectivity in a minor way, but also decreases the chemical yield in a major way. The results also suggest that unsaturation helps to guide the electrophile to the reaction. The stereochemical outcome was also altered by adjusting the electron density of the benzyl electrophiles. This new auxiliary exhibits a clearly defined stereochemical induction that can be altered by the addition or removal of a particular group. This has potential uses in many other reactions, as clearly predictable stereochemical induction is essential in any asymmetric synthesis.

Experimental

Nuclear magnetic resonance spectra for ^{1}H NMR were obtained at 300 or 500 MHz on either a Bruker DPX300 or DRX500 models. ^{13}C NMR spectra were obtained at either 75 or 125 MHz on the above mentioned models. Chemical shifts are reported in ppm and the solvent used was $CDCl_3$ unless otherwise stated. Infared spectroscopy was carried out on a Bomem Michelson model 100, as either thin film or potassium bromide pellets. IR peaks are listed in wavenumbers (cm^{-1}). Mass spectra were run on a Kratos Profile mass spectrometer in electron impact mode. Melting points were obtained on a Fisher-Johns melting point apparatus. Column chromatography was performed using 60 (70-230) mesh silica gel.

Tetrahydrofuran was purified and dried by distillation from a potassium metal/benzophenone still. Diisopropylamine and hexamethyldisilazane were distilled from calcium hydride under a nitrogen atmosphere. All other solvents and chemicals were used "as is" from the supplier.

The term " standard work-up" refers to the extraction of the crude reaction mixture with either diethyl ether or chloroform three times, followed by drying of the combined organic layers over magnesium sulfate. The $MgSO_4$ was removed by filtration, and the solvent evaporated under reduced pressure to afford the crude product.

Preparation of (±) *trans*-2-aryl cyclohexanols[53]

(±) *trans*-2-(1-naphthyl)cyclohexanol

This compound was prepared using a previously published method[53], and is

representative of all alcohols prepared in this manner. To a solution of 20 g (96.6 mmol) 1-bromonaphthalene and 200 mL of anhydrous THF was added 2.35 g (96.6 mmol) of magnesium turnings. The solution was stirred until heat stopped being evolved from the dark brown solution and then cooled to -20 °C. Approximately 0.6 g of copper(I) chloride catalyst was added and the reaction was stirred for 5 minutes. Cyclohexene oxide 9.78 mL (96.6 mmol) was added dropwise over 5 minutes at 0 °C . This solution was stirred for 2 hours at 0 °C and then was warmed to room temperature. The reaction mixture was quenched with a saturated $(NH_4)_2SO_4$ solution which caused the solution to turn a brilliant blue. Excess diethyl ether was added and the aqueous phase was extracted until it was no longer blue. The combined organic fractions were washed with aqueous $(NH_4)_2SO_4$ and sodium chloride. After the standard work up the product was recrystallized from EtOAc\hexanes and yielded 13.12 g (60%) of powdery white crystals; m.p. 131-132 °C (Lit.[53] 129-130 °C); ^{1}HMR: 8.23 (d, 1H, J = 8.4), 7.89 (d, 1H, J = 8.6), 7.75 (m, 1H), 7.52 (m, 4H), 3.98 (br s, 1H), 3.42 (br s, 1H), 2.24 (m, 1H), 1.95 (m, 2H), 1.80 (m, 1H), 1.69 (m, 1H), 1.6-1.4 (m, 4H); ^{13}C NMR: 139.68, 134.29, 132.80, 129.06, 127.17, 126.13, 125.82, 125.75, 123.39, 122.88, 74.32, 46.78, 34.91, 34.05, 26.54, 25.28.

(±) *trans*-2-phenylcyclohexanol

Yield 70% (from pentane)

m.p. 69-71 °C (Lit.[53] 70-72 °C); ^{1}H NMR: 7.35-7.32 (m, 5H),

3.69 (dt, 1H, J = 4.3,10.1), 2.43 (m, 1H), 2.13 (m, 1H), 1.87 (m, 2H), 1.76 (m, 1H), 1.54-1.33 (m, 5H); ^{13}C NMR: 143.49, 128.91, 128.08, 126.97, 74.55, 53.39, 34.63, 33.50, 26.24, 25.24.

Preparation of *trans*-2-arylcyclohexyl hippurates[49]

(±) *trans*-2-phenylcyclohexyl hippurate

This compound was prepared by a previously published method,[46] and is representative of all other hippurates formed in this manner. *Trans*-2-phenylcyclohexanol (2 g, 11.3 mmol), 2.44 g (13.6 mmol) of hippuric acid, and 0.216 g (1.13 mmol) of p-TsOH•H_2O were combined in a 100 mL round bottomed flask. Approx. 40 mL of toluene was added and the mixture was refluxed for 4 h with a Dean Stark trap. The reaction was cooled, and then quenched with 5 mL (2.26 mmol) of 0.5M $NaHCO_3$. After 5 min. of stirring, 20 mL of EtOAc was added and the layers separated. The aqueous phase was extracted 3x with EtOAc and the combined organic layers were washed with brine. After a standard work up the crude product was recrystallized from 3:1 hexanes/EtOAc to yield 2.75 g (73%) of white crystals;

m.p.107-109 °C ; ^{1}H NMR: 7.71 (m, 2H), 7.48 (m, 1H), 7.41 (m, 2H), 7.26 (m,2H), 7.19 (m, 3H), 6.41 (br s, 1H), 5.05 (dt, 1H, J = 4.4,10.6),

4.09 (dd ½ ABq, 1H, J = 18.5,5.18), 3.78 (dd ½ABq, 1H, J = 18.5,4.4), 2.70 (m, 1H), 2.18 (m, 1H), 1.98-1.80 (m, 3H), 1.62-1.39 (m, 4H); ^{13}C NMR: 169.45, 167.31, 142.83,

133.98, 131.88, 128.73, 128.62, 127.66, 127.12, 126.88, 78.04, 49.87, 42.01, 33.66, 32.42, 25.87, 24.91; IR 3219, 1746, 1649, 1536, 1200, 756, 699.

(±) *trans*-2- (1-naphthyl)cyclohexyl hippurate

Yield 75 % (from hexanes/EtOAc)

m.p.138-140 °C ; ^{1}H NMR: 8.15 (d, 1H, J = 8.4), 7.82 (d, 1H, J = 8), 7.68 (d, 1H, J = 7.6), 7.57 (d, 2H, J = 7.8), 7.44 (m, 5H), 7.32 (m, 2H), 6.24 (s, 1H), 5.29 (dt, 1H, J = 3.9,10.5), 3.91 (½dABq, 1H, J = 18.4,5.4) , 3.66 (m, 1H), 3.42 (½dABq, 1H, J = 18.4, 4.5), 2.27 (m,1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.66-1.51 (m, 4H); ^{13}C NMR: 169.23, 167.07, 138.91, 133.95, 133.79, 132.05, 131.56, 128.96, 128.46, 127.01, 126.95, 125.87, 125.65, 125.47, 123.04, 122.81, 77.83, 43.39, 41.62, 33.78, 32.64, 26.05, 24.85; IR: 3310, 1743, 1600, 1488, 1198, 797, 778.

General procedure for the alkylation of *trans*-2-arylcyclohexyl hippurates

Under a nitrogen atmosphere, 208 μL (1.482 mmol) of diisopropylamine was dissolved in 3 mL of anhydrous THF. The mixture was then cooled to 0 °C in an ice bath. 2.5M n-butyllithium, 600 μL (1.482 mmol), was added and the mixture stirred for 1 h. The solution was cooled to -78 °C in a dry ice/acetone bath and then 0.25 g (0.741 mmol) of *trans*-2-arylcyclohexyl hippurate dissolved in 4 mL of dry THF was added. The yellow dianion gradually darkened to an orange colour as more was produced over a 1 ½ hour period. At this point 1.1equiv., (0.815 mmol) of the alkylating agent was added

either neat or dissolved in 1 mL of THF. The reaction was stirred for an additional 1 ½ hours. All alkylations were quenched at -78 °C with approx. 2 mL of 3M HCl. A standard work up yielded the crude product.

All alkylations were separated from their respective starting materials by column chromatography on silica gel using different combinations of Pet.ether/EtOAc.

^{1}H NMR peaks for alkylation products.

bold=major diastereomer *Italicized=minor diastereomer*

Alkylation with methyl iodide **3A**

yield 85% de 58%

7.70 (m, 2H), 7.44 (m, 3H), 7.2 (m, 5H), 6.58 *(d, 1H, J = 6.7)*, **6.47 (d, 1H, J = 6.45),**

5.05 (m, 1H), 4.52 (m, 1H), 2.72 (m, 1H), 2.16-1.38 (m,8H), **1.29 (d, 3H, J = 7),**

0.87 (d, 3H, J = 7.1)

Alkylation with ethyl iodide **3B**

yield 85% de 79%

7.71 (d, 2H, J = 7.6), 7.5-7.43 (m, 3H), 7.17 (m, 5H), *6.59 (d, 1H, J = 7.1)*,

6.45 (d, 1H, J = 7), 5.05 (m,1H), *4.6 (dd, 1H, J = 7.5,5.5)*,

4.51 (dd, 1H, J = 7.2,5.7), 2.72 (m, 1H), 2.17 (s, 1H), 1.97-1.38 (m,10H),

0.74 (t, 3H, J = 7.4), *0.35 (t, 3H, J = 7.4)*

Alkylation with isopropyl iodide **3C**

yield 14% de 81%

7.71 (d, 2H, J = 7.2), 7.45 (m, 3H), 7.18 (m, 5H), *6.44 (d, 1H, J = 8.5),*

6.31 (d, 1H, J = 8.3), 5.02 (m, 1H), *4.59 (dd, 1H, J = 8.7, 4.1),*

4.51 (dd, 1H, J = 8.6, 4.6), 2.69, (m, 1H), 2.18-1.26 (m, 9H), **0.81 (d, 3H, J = 6.9),**

0.74 (d, 3H, J = 6.9), *0.67 (d, 3H, J = 6.9), 0.32 (d, 3H, J = 6.9)*

Alkylation with isopropyl iodide **3C*** (reaction was run at -20 °C)

yield 75% de 39%

7.71 (d, 2H, J = 7.3), 7.45 (m, 3H), 7.18 (m, 5H), *6.45 (d, 1H, J = 8.6),*

6.32 (d, 1H, J = 8.2), 5.02 (m, 1H), *4.59 (dd, 1H, J = 8.7, 4.1),*

4.51 (dd, 1H, J = 8.5, 4.6), 2.70 (m, 1H), 2.17-1.26 (m, 9H), **0.81 (d, 3H, J = 6.9),**

0.74 (d, 3H, J = 6.9), *0.67 (d, 3H, J = 6.9), 0.33 (d, 3H, J = 6.9)*

Alkylation with allyl iodide **3D**

yield 61% de 68%

7.7 (d, 2H, J = 7.3), 7.51 (m, 3H), 7.26 (m, 5H), *6.48 (d, 1H, J = 7.8),*

6.40 (d, 1H, J = 7.3), 5.43 (m, 1H), 5.03 (m, 3H), *4.67 (dd, 1H, J = 7.8, 5.4),*

4.61 (dd, 1H, J = 7.5, 5.3), 2.70 (m, 1H), 2.48 (m, 2H), 2.17-1.37 (m, 8H)

Alkylation with allyl bromide **3E**

yield 66% de 76%

7.69 (d, 2H, J = 7.4), 7.48 (m, 3H), 7.22 (m, 5H), *6.51 (d, 1H, J = 7.4),*

6.43 (d, 1H, J = 7), 5.42 (m, 1H), 5.03 (m, 3H), *4.68 (dd, 1H, J = 7.4, 5.7),*

4.61 (dd, 1H, J = 7.1, 5.3), 2.7 (m, 1H), 2.49 (m, 2H), 2.16 (m, 1H),

1.94-1.78 (m, 3H), 1.6-1.27 (m, 5H)

Alkylation with p-t-butylbenzylbromide **3G**

yield 67% de 80%

7.63 (d, 2H, J = 7.4), 7.42-6.93 (m, 12H), *6.49 (d, 1H, J = 8),* **6.36 (d, 1H, J = 7.3),**

5.03 (m, 1H), *4.91 (dd, 1H, J = 7.5),* **4.76 (dd, 1H, J = 6.3, 6.0),**

3.08 (½ dABq, 1H, J = 14, 6.5), 3.04 (½ dABq, 1H, J = 14, 5.1), 2.71 (m, 1H),

2.14-1.45 (m, 8H), 1.33 (s, 9H)

Alkylation with p-methylbenzylbromide **3F**

yield 52% de 78%

7.63 (d, 2H, J = 7.4), 7.42 (m, 3H), 7.34 (m,2H), 7.23 (m, 3H), 7.05 (d, 2H, J = 7.8),

6.96 (d, 2H, J = 7.9), 6.34 (m, 1H), 5.01 (m, 1H), *4.89 (dd, 1H, J = 7.8, 5.3),*

4.73 (dd, 1H, J = 6.2, 6.0), 3.11 (½ dABq, 1H, J = 14.0, 6.3),

2.99 (½ dABq, 1H, J = 14.0, 5.0), *2.88 (½ dABq, 1H, J = 14, 6.3),* 2.71 (m, 1H),

2.58 (½ ABq, 1H, J = 14, 5.1), 2.32 (s, 3H), 1.95-1.29 (m, 8H)

Alkylation with p-fluorobenzylbromide **3H**

yield 64% de 60%

7.61 (d, 2H, J = 7.5), 7.52-6.73 (m, 12H), 6.3 (m, 1H), 4.98 (m, 1H),

4.89 (dd, 1H, J = 12.2, 5.1), **4.71 (dd, 1H, J = 11.7, 6.4),**

3.1 (½ dABq, 1H, J = 14, 6.3), 3.01 (½ dABq, 1H, J = 13.9, 4.6),

2.95 (½ dABq, 1H, J = 14, 5.6), 2.67 (m, 1H), *2.61 (½ dABq, 1H, J = 14, 4.4),*

2.14-1.27 (m, 8H)

Alkylation with p-trifluorobenzylbromide **3I**

yield 71% de 46%

7.61 (d, 2H, J = 7.2), 7.5-7.1 (m, 12H), 6.45 (d, 1H, J = 7.9), *6.37 (d, 1H, J = 7.2),*

6.3 (d, 1H, J = 6.9), 4.93 (m, 1H), **4.75 (dd, 1H, J = 11.6, 6.6),**

3.18 (½ dABq, 1H, J = 13.8, 6.5), 3.11 (½ dABq, 1H, J = 13.8, 4.6),

3.04 (½ dABq, 1H, J = 13.8, 5.7), 2.66 (m, 1H), 2.13-1.26 (m, 8H)

Alkylation with methyl bromoacetate **3J**

(Inseparable from starting material-values are estimated).

Yield ~70% de ~60%

6.51 (br s, 1H), 5.03 (m, 1H), *4.82 (m, 1H),* **4.72 (ABq, 1H, J = 7.5, 3.7),** 3.64 (s, 3H)

Alkylation with methyl iodide **4A**

(Product and starting material were inseparable, and as a result of the de being taken from the crude mixture, only the diagnostic peaks are reported below)

yield 75% de 54%

6.51 (d, 1H, J = 7.2), **6.22 (d, 1H, J = 7.0),** *4.41 (m, 1H),* **4.31 (m, 1H),**

1.03 (d, 3H, J = 7.1), *0.48 (d, 3H, J = 7.1)*

Alkylation with ethyl iodide **4B**

yield 60% de 87%

8.15 (m, 1H), 7.88 (m, 1H), 7.69 (m, 1H), 7.58 (d, 2H, J = 7.2), 7.42 (m, 7H),

6.44 (d, 1H, J = 7.5), **6.16 (d, 1H, J = 7.4),** 5.26 (m, 1H), *4.45 (dd, 1H, J = 7.5, 5.5),*

4.34 (dd, 1H, J = 7.5, 5.5), 3.67 (m, 1H), 2.27 (m, 1H), 1.97 (m, 3H),

1.63-1.27 (m, 5H), **0.52 (t, 3H, J = 7.4),** *0.04 (t, 3H, J = 7.5)*

Alkylation with allyl iodide **4C**

yield 70% de 82%

8.14 (d, 1H, J = 8.3), 7.85 (m, 1H), 7.72 (d, 1H, J = 7.8), 7.59 (m, 2H), 7.45 (m, 7H),

6.36 (d, 1H, J = 7.7), **6.09 (d, 1H, J = 7.6),** 5.24 (m, 1H), 5.10 (m, 1H), 4.81 (m, 2H),

4.52 (m, 1H), **4.44 (dd, 1H, J = 5.5, 5.4),** 3.67 (m, 1H), 2.29 (m, 2H), 2.07 (m, 4H),

1.85-1.27 (m, 4H)

Alkylation with benzyl bromide **4D**

yield 70% de 89%

8.05 (m, 1H), 7.70 (m, 2H), 7.32 (m, 12H), 6.84 (m, 2H), 6.13 (m, 1H),

5.93 (d, 1H, J = 7.3), 5.12 (m, 1H), *4.65 (dd, 1H, J = 7.7, 5.5),*

4.42 (dd, 1H, J = 7.2, 6.1), 3.56 (m, 1H), **2.78 (½ dABq, 1H, J = 14.0, 6.0),**

2.47 (½ dABq, 1H, J = 14.0, 6.0), 2.02-1.19 (m, 8H)

Alkylation with p-methylbenzylbromide **4E**

yield 66% de 88%

8.14 (m, 1H), 7.79 (m, 2H), 7.43 (m, 9H), 7.01 (d, 2H, J = 7.8), 6.81 (d, 2H, J = 7.8),

6.21 (d, 1H, J = 7.7), 6.11 (d, 1H, J = 7.5), **6.02 (d, 1H, J = 7.3),** 5.22 (m, 1H),

4.71 (dd, 1H, J = 7.7, 5.5), **4.50 (dd, 1H, J = 7.1),** 3.67 (m, 1H),

2.83 (½ dABq, 1H, J = 14.0, 5.9), 2.52 (½ ABq, 1H, J = 14.0, 5.9), 2.3 (s, 3H),

2.32 (m, 1H), 1.98 (m, 3H), 1.66-1.29 (m, 4H)

Alkylation with p-trifluorobenzylbromide **4G**

yield 65% de 80%

8.15 (m, 1H), 7.79 (m, 2H), 7.4 (m, 11H), 7.01 (d, 2H, J = 8), *6.3 (d, 1H, J = 7.4),*

6.18 (d, 1H, J = 7.7), **6.01 (d, 1H, J = 7.3),** 5.22 (m, 1H), *4.76 (dd, 1H, J = 6.9, 5.4),*

4.54 (dd, 1H, J = 6.9, 6.1), 3.67 (m, 1H), **2.90 (½ dABq, 1H, J = 14, 6.4),**

2.67 (½ dABq, 1H, J = 14, 5.6), 2.24 (m, 1H), 1.97 (m, 3H), 1.65-1.27 (m, 4H)

Alkylation with p-t-butylbenzylbromide **4F**

yield 63% de 83%

8.16 (m, 1H), 7.86 (m, 1H), 7.72 (m, 1H), 7.51-7.26 (m, 11H), 6.89 (d, 2H, J = 8.1),

6.23 (m, 2H), **6.01 (d, 1H, J = 7.4),** 5.24 (m, 1H), *4.73 (dd, 1H, J = 7.5),*

4.52 (dd, 1H, J = 7.2, 6.1), 3.67 (m, 1H), **2.83 (½ dABq, 1H, J = 14.0, 6.1),**

2.55 (½ dABq, 1H, J = 14.0, 6.0), 2.26 (m, 1H), 1.89 (m, 3H), 1.63-1.52 (m, 4H),

1.31 (s, 9H)

Preparation of (±) *trans*-2-phenylcyclohexanecarboxylic acid[52]

Gradually sodium metal 15.6 g (0.68 mol) was added in small pieces to a boiling solution of 5 g (25.2 mmol) o-phenylbenzoic acid in 200 mL of n-pentanol. This was done with and without a nitrogen atmosphere in different runs. The addition took approx. 3 h as the dissolving metal reacted violently with the boiling amyl alcohol. As the last gram of Na was added the solution became very viscous and cloudy with a yellow tinge. The reaction mixture was allowed to cool and the amyl alcohol was partially evaporated at reduced pressure (boiling water bath) to produce a wet yellow solid. The solid was dissolved in approx. 150 mL of water, and the alkaline solution was neutralized with 60 mL of conc. HCl. This produced a two phase mixture and the top phase was a brilliant

yellow. Diethyl ether, 100 mL, was added and the layers were separated, followed by a standard work up to yield a viscous yellow liquid. The residual amyl alcohol was evaporated under vacuum to produce a yellow white solid, which was recrystallized from ligroin and cyclohexane to afford 3.31 g (64%) of white crystals;

m.p. 103-104 °C ; ^{1}H NMR: 7.25 (m, 2H), 7.19 (m, 3H), 2.74 (dt, 1H, J = 11.4,3.6), 2.58 (dt, 1H, J = 11.6,3.4), 2.07 (m, 1H), 1.86 (m, 3H), 1.57 (dABq, 1H, J = 12.6, 3.2), 1.49-1.26 (m, 3H); ^{13}C NMR: 181.63, 144.62, 128.54, 127.55, 127.38, 126.59, 109.75, 49.96, 46.14, 34.43, 30.47, 26.31, 25.44; IR 3200-2600br, 1703, 1599, 1491, 1445, 1419, 757, 699.

Preparation of (±) *trans*-2-phenylcyclohexylamide methylglycinate

Trans-2-phenylcyclohexanecarboxylic acid (1 g) was dissolved in an excess of thionyl chloride, and stirred under nitrogen overnight. The excess $SOCl_2$ was removed under vacuum to yield the crude acid chloride.To a suspension of glycine methyl ester hydrochloride in 10 mL of acetone was added 280 μL (2.0 mmol) of Et_3N. The acid chloride (0.47 g, 2.0 mmol) was added to the glycine methylester solution and stirred for 2 h. The reaction mixture was poured into ice water and worked up in a standard fashion. The crude product was recrystallized from hexanes/EtOAc to produce 0.305 g (55%) of white crystals.

m.p. 132-133 °C ; ^{1}H NMR: 7.2 (m, 5H), 5.51 (br s, 1H), 3.91

(½ dABq, 1H, J = 18.5, 5.6), 3.64 (s, 3H), 3.56 (½ dABq, 1H, J = 18.5, 4.3), 2.79 (dt, 1H, J = 11.5,3.4), 2.31 (dt, 1H, J = 11.5, 3.5), 1.99-1.83 (m, 4H), 1.71 (dABq, 1H, J = 13, 3.4), 1.58 (m, 3H); ^{13}C NMR: 174.98, 170.43, 144.97, 128.62, 127.58, 127.35, 109.77, 52.54, 52.35, 46.73, 41.09, 34.09, 30.36, 26.28, 25.61; IR: 3326, 1753, 1643, 1545, 1498, 1435, 1418, 1365, 1206, 986, 754, 703.

Anal. Calcd. ($C_{16}H_{20}NO_3$) C; 70.05, H; 7.35, N; 5.1. Found: C; 69.57, H; 7.61, N; 4.90

General procedure for the alkylation of (±)*trans*-2-phenylcyclohexylamide methylglycinate

Under a nitrogen atmosphere, diisopropylamine (191 μL, 1.45 mmol) or hexamethyldisilazane (307 μL, 1.45 mmol) was dissolved in 3 mL anhydrous THF, cooled to 0 °C and 582 μL (1.45 mmol) of n-butyllithium was added. The mixture was stirred for 1 h, cooled to -78 °C and 0.2 g (0.727 mmol) of the N-substituted methyl glycinate dissolved in 3 mL of dry THF was added. The reaction was stirred for 90 minutes and then 0.799 mmol of the appropriate electrophile was added. After stirring for an additional 90 minutes the reaction was quenched at -78 °C with approx. 2 mL of 3 M HCl and worked up in a standard fashion. Separation of product from starting material was performed by column chromatography using 3:1 pet.ether/EtOAc solvent system.

^{1}H NMR signals for alkylation products

Bold=major diastereomer *Italicized=minor diastereomer*

Alkylation with methyl iodide **8A** (LHMDS as the base)

yield 70 % de 21%

7.23 (m, 5H), **5.69 (d, 1H, J = 6.6),** *5.49 (d, 1H, J = 7.5),* 4.29 (m, 1H), *3.64 (s, 3H),*

3.56 (s, 3H), 2.75 (m, 1H), 2.30 (dt, 1H, J = 11.6, 3.5), 1.85 (m, 4H), 1.53-1.25 (m, 4H),

1.17 (d, 3H, J = 7.1), *0.78 (d, 3H, J = 7.1)*

Alkylation with ethyl iodide **8B** (LHMDS as the base)

Yield 63 % de 21%

7.20 (m, 5H), **5.64 (d, 1H, J = 7.3),** *5.58 (d, 1H, J = 7.9), 4.36 (dd, 1H, J = 13.8, 5.9),*

4.28 (dd, 1H, J = 13.4, 6.2), *3.66 (s, 3H),* **3.57 (s, 3H),** 2.76 (m, 1H), 2.35 (m, 1H),

1.91-1.67 (m, 5H), 1.53-1.21 (m, 5H), **0.66 (t, 3H, J = 7.5),** *0.28 (t, 3H, J = 7.5)*

Alkylation with propyl iodide **8C** (LHMDS as the base)

Yield 55 % de 44 %

7.26-7.14 (m, 5H), **5.58(d, 1H, J = 7.6),** *5.51 (d, 1H, J = 7.5),* 4.35 (m, 1H),

3.66 (s, 3H), **3.57 (s, 3H),** 2.76 (m, 1H), 2.35(dt, 1H, J = 11.5, 3.4), 1.98-1.85 (m, 4H),

1.69 (m, 1H), 1.61 (m, 4H), 1.50-1.26 (m, 3H), *0.91 (t, 3H, J = 7.4),*

0.78 (t, 3H, J = 7.2)

Alkylation with allyl bromide **9A** (LDA as the base)

yield 35% de 45%

7.21 (m, 5H), **5.64 (d, 1H, J = 7.0),** *5.57 (d, 1H, J = 7.5),* 5.45 (m, 1H), 5.0 (m, 2H),

4.43 (dd, 1H, J = 13.3, 5.5), **4.38 (dd, 1H, J = 13.1, 5.8),** *3.65 (s, 3H),* **3.57 (s, 3H),**

2.77 (m, 1H), 2.48-2.29 (m, 3H), 1.88 (m, 4H), 1.69-1.25 (m, 4H)

Alkylation with allyl bromide **8E** (LHMDS as the base)

Yield 40% de 44%

7.23 (m, 5H), **5.65 (d, 1H, J = 7.1),** *5.58 (d, 1H, J = 7.5),* 5.45 (m, 1H), 5.0 (m, 2H),

4.43 (dd, 1H, J = 13.3, 5.5), **4.38 (dd, 1H, J = 13.1, 5.8),** *3.65 (s, 3H),* **3.57 (s, 3H),**

2.77 (m, 1H), 2.42-2.29 (m, 3H), 1.98-1.82 (m, 4H), 1.68 (m, 1H), 1.51-1.26 (m, 3H)

Alkylation with benzylbromide **9C** (LDA as the base)

yield 25% de 74%

7.16 (m, 8H), 6.94 (m, 2H), *6.5 (d, 1H, J = 6.3), 5.60 (d, 1H, J = 7.9),*

5.55 (d, 1H, J = 7.2), *4.73 (dd, 1H, J = 12.6, 5.8),* **4.56 (dd, 1H, J = 13.1, 5.8),**

3.61 (s, 3H), **3.54 (s, 3H), 3.01 (½ dABq, 1H, J = 13.8, 6.0),**

2.91 (½ dABq, 1H, J = 13.8, 5.6), *2.82 (½ dABq 1H, J = 13.7, 4.5),* 2.77 (m, 1H),

2.48 (½ dABq, 1H, J = 13.7, 7.6), 2.27 (dt, 1H, J = 11.6, 3.3), 1.85 (m, 4H),

1.68 (m, 1H), 1.51-1.26 (m, 3H)

Alkylation with benzylbromide **8F** (LHMDS as the base)

yield 65% de 73%

7.26-7.14 (m, 8H), 6.94 (m, 2H), *6.5 (d, 1H, J = 6.2), 5.61 (d, 1H, J = 7.9),*

5.59 (d, 1H, J = 7.2), *4.73 (dd, 1H, J = 12.6, 5.8),* **4.56 (dd, 1H, J = 13.1, 5.8),**

3.61 (s, 3H), **3.55 (s, 3H), 3.02 (½ dABq, 1H, J = 13.8, 6.0),**

2.91 (½ dABq, 1H, J = 13.8, 5.7), *2.83 (½ dABq, 1H, J = 13.7 , 4.5),* 2.77 (m, 1H),

2.48 (½ dABq, 13.7, 5.9), 2.27 (dt, 1H, J = 11.5, 3.3), 1.85 (m, 4H), 1.69 (m, 1H),

1.65-1.26 (m, 3H)

Alkylation with p-trifluoromethylbenzylbromide **9E** (LDA as the base)

Yield 17% de 56%

7.46 (d, 2H, J = 7.9), 7.36-7.13 (m, 5H), 7.02 (d, 2H, J = 7.9), *6.54 (d, 2H, J = 7.9),*

5.62 (d, 1H, J = 7.5), **5.55 (d, 1H, J = 6.8),** *4.76 (dd, 1H, J = 12.6, 5.4),*

4.55 (dd, 1H, J = 12.6, 5.9), *3.63 (s, 3H),* **3.58 (s, 3H),**

3.08 (½ dABq, 1H, J = 13.8, 5.9), 2.95 (½ dABq, 1H, J = 13.8, 5.5), 2.75 (m, 1H),

2.60 (½ dABq, 1H, J = 13.8, 5.6), 2.29 (m, 1H), 1.87 (m, 4H), 1.68-1.22 (m, 4H)

Alkylation with p-trifluoromethylbenzylbromide **8H** (LHMDS as the base)

yield 50% de 62%

7.46 (d, 2H, J = 7.9), 7.37-7.13 (m, 6H), 7.03 (d, 2H, J = 7.9), *6.54 (d, 2H, J = 7.9),*

5.63 (d, 1H, J = 7.5), **5.56 (d, 1H, J = 6.8),** *4.76 (dd, 1H, J = 12.6,5.5),*

4.55 (dd, 1H, J = 12.6, 6.0), *3.63 (s, 3H),* **3.58 (s, 3H),**

3.08 (½ dABq, 1H, J = 13.8, 6.0), 2.95 (½ dABq, 1H, J = 13.8, 5.6), 2.74 (m, 1H),

2.6 (½ dABq, 1H, J = 13.5, 5.6), 2.29 (m, 1H), 1.86 (m, 4H), 1.51-1.26 (m, 4H)

Alkylation with p-methylbenzylbromide **9D** (LDA as the base)

yield 25% de 80%

7.34-7.12 (m, 6H), 7.03 (d, 2H, J = 7.8), 6.81 (d, 2H, J = 7.9), *6.38 (d, 2H, J = 7.9),*

5.55 (m, 1H), *4.69 (dd, 1H, J = 12.8, 5.6),* **4.53 (dd, 1H, J = 12.9, 5.7),** *3.61 (s, 3H),*

3.54 (s, 3H), 2.95 (½ dABq, 1H, J = 13.8, 5.9), 2.87 (½ dABq, 1H, J = 13.8, 5.4),

2.77 (m, 1H), 2.29 (s, 3H), 1.92-1.26 (m, 8H)

Alkylation with p-methylbenzylbromide **8G** (LHMDS as the base)

Yield 55% de 79%

7.23 (m, 5H), 7.03 (d, 2H, J = 7.5), 6.82 (d, 2H, J = 7.7), *6.83 (d, 2H, J = 7.6),*

5.55 (m, 1H), *4.70 (dd, 1H, J = 12.6, 5.4),* **4.53 (dd, 1H, J = 12.4, 5.9),** *3.62 (s, 3H),*

3.54 (s, 3H), 2.95 (½ dABq, 1H, J = 13.8, 5.9), 2.87 (½ dABq, 1H, J = 13.8, 5.3),

2.77 (m, 1H), 2.29 (s, 3H), 1.88 (m, 4H), 1.69 (m, 1H), 1.67-1.26 (m, 3H)

Preparation of *trans*-2-phenylcyclohexyl phenylacetate

Trans-2-phenylcyclohexanol (2 g, 11.3 mmol), 1.86 g (13.6 mmol) of phenyl acetic acid, and 0.22 g (1.13 mmol) of pTsOH·H_2O were mixed. Approximately 40 mL of toluene was added and the mixture was refluxed under a Dean-Stark trap for 5 h. The reaction mixture was allowed to cool and 5 mL of saturated sodium bicarbonate solution was added. The aqueous phase was extracted with EtOAc and $CHCl_3$, and the combined organic phases were washed with brine. Standard work-up afforded the crude product. Recrystallization from 3:1 Hexanes/EtOAc yielded white crystals in 80% yield.

m.p. 42-43 °C ; ^{1}H NMR: 7.2 (m, 8H), 6.91 (m, 2H), 5.05 (dt, 1H, J = 10.6,4.3), 3.36 (s, 2H), 2.68 (m, 1H), 2.16 (m, 1H), 1.85 (m, 3H), 1.60-1.38 (m, 4H); ^{13}C NMR: 171.03, 143.21, 134.3, 129.14, 128.53, 128.5, 127.73, 126.83, 126.58, 76.63, 49.94, 41.64, 34.11, 32.44, 25.98, 24.92; IR: 1731, 1603, 1495, 1452, 1256, 1157, 1124, 1018, 755, 724, 699.

Anal. Calcd. ($C_{20}H_{22}O_2$) C; 81.6, H; 7.53. Found: C; 82.03 , H; 7.60

Preparation of *trans*-2-phenylcyclohexyl methoxyacetate

Trans-2-phenylcyclohexanol (3.2 g, 18.2 mmol), 1.96 g (21.7 mmol) of methoxyacetic acid, and 0.345 g (1.82 mmol) of pTsOH·H_2O were mixed. Approximately 40 mL of toluene was added and the mixture was refluxed under a Dean-Stark for four hours. The reaction was cooled and about 5 mL of sat. sodium bicarbonate solution was added to quench the reaction. Standard work-up afforded the crude product as a yellowish

(95%) oil that was used without further purification.

^{1}H NMR: 7.27-7.15 (m, 5H), 5.1 (dt, 1H, J = 10.6, 4.4), 3.77 (1/2ABq, 1H, J = 16.2), 3.65 (1/2ABq, 1H, J = 16.2), 3.12 (s, 3H), 2.68 (dt, 1H, J = 12.3, 3.7), 2.14 (m, 1H), 1.86 (m, 3H), 1.59-1.37 (m, 4H); ^{13}C NMR: 169.73, 142.99, 128.47, 127.67, 126.66, 76.69, 69.77, 59.06, 49.98, 33.96, 32.44, 25.90, 24.90; IR: 1749, 1449, 1193, 1124, 757, 700. *Anal.* Calcd. ($C_{15}H_{20}O_3$) C; 72.55, H; 8.12. Found: C; 71.24 , H; 8.03

Preparation of *trans*-2-phenylcyclohexyl N,N-dimethylglycinate

Trans-2-phenylcyclohexanol (2 g, 11.3 mmol), was in 30 mL of anhydrous THF and 4A molecular sieves were added (To adsorb the ethoxide as its produced in order to push the equilibrium to the right).The solution was cooled to 0 °C and added 4.54 mL (11.3 mmol) of 2.5 M n-butyllithium. The reaction was allowed to stir for 2 hours. N,N-dimethylglycine ethyl ester (1.5 g, 11.3 mmol) dissolved in 5 mL of THF, was added slowly using a syringe pump. The reaction was warmed to room temperature and stirred for 36 hours. A standard work-up afforded the crude product as a yellow oil (65%).

^{1}H NMR: 7.23-7.11 (m, 5H), 5.07 (dt, 1H, J = 10.6, 4.4), 2.89 (1/2ABq, 1H, J = 16.1), 2.78 (1/2ABq, 1H, J = 16.1), 2.66 (dt, 1H, J = 12.2, 3.7), 2.01 (s, 6H), 1.92-1.74 (m, 3H), 1.54-1.33 (m, 5H); ^{13}C NMR: 169.83, 143.09, 128.34, 127.61, 126.47, 76.13, 60.51, 49.89, 44.87, 34.03, 32.38, 25.84, 24.83; IR: 1730, 1630, 1494, 1449, 1192, 756, 699. *Anal.* Calcd. ($C_{16}H_{23}NO_2$) C; 73.52, H; 8.87, N; 5.36. Found: C; 73.70 , H; 8.81, N; 5.39

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