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Enantioselective Synthesis of β-Amino Acids

Iodobenzene Diacetate and Related Hypervalent Iodine Reagents in the Synthesis of Heterocyclic Compounds

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Aldrichimica Acta

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About Our Cover:

This vibrant summer scene entitled **A Bend in the Epte River, Near Giverny** (oil on canvas, 61 x 81 cm) was painted by Claude Monet in 1888. It is an astonishingly fresh and vivid portrayal of poplar trees, in full flower, along the edge of the Epte. The effect of strong sunlight through dense foliage is brilliantly rendered by a web of sharp diagonal brushstrokes animating the upper canvas with an almost endless variety of touch and color.

Giverny, where Monet lived from 1888 until his death in 1926, is a small village at the confluence of the Seine and Epte Rivers, 60 kilometers northwest of Paris. It was at his home in this village that Monet created his famous water garden which provided him with many motifs towards the end of his career.

The painting is in the William L. Elkins Collection of the Philadelphia Museum of Art.

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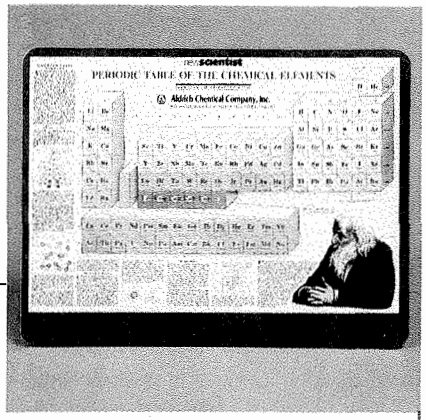
The first ACD database with available chemical listings provided by Sigma-Aldrich will be released in 1994. Semi-annual updating will follow.

Lab Notes



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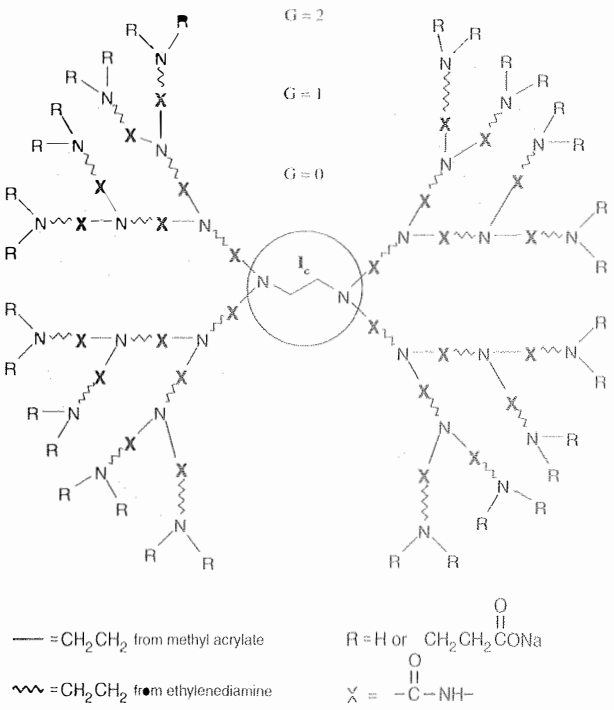
Dear Acta Reader:

The structural formula on page 101 of our previous issue (*Aldrichimica Acta* **1993**, 26(4)) representing integral generations (i.e. G = 0,1,2,...) of Starburst™ (PAMAM) dendrimers is incorrect. The formula works only for G = 0 (i.e, N = 1). A more accurate representation of the PAMAM dendrimers is indicated below.



The initiator core (I_c) is ethylenediamine, thus its multiplicity and molecular weight are N_c = 4 and M_c = 60.10, respectively. The branching multiplicity, N_b, is 2, and the repeat unit molecular weight, M_{RU}, equals 114.15.

Using these parameters and the mathematical formulas described on page 95 of the previous issue, one can calculate for a given generation, G, its molecular weight, number of repeat units, number of terminal groups and number of substituents on the periphery. Note that integral generations G = 0,1,2,... end in $-NH_2$ groups and half-integral generations G = 0.5, 1.5, 2.5,... end in $-N(CH_2CH_2CONa)_2$ groups.

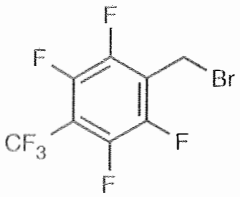
Please accept our apology for any confusion our error may have caused.

The Editorial Staff

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



Professor Roger W. Giese of the Department of Pharmaceutical Sciences at Northeastern University suggested that we make TTBB, a new electrophoric derivatization reagent analogous to pentafluorobenzylbromide(PFBB). Both TTBB and PFBB are used to enhance the detectability of substances such as DNA nucleobases, phenols, indole-amine metabolites, etc. by gas chromatography-electron-capture negative ion mass spectrometry (GC-ECNI-MS). TTBB can be used along with, or as a substitute for, PFBB to help control test interferences and confirm results.

Naturally we made this useful analytical tool.

Saha, M.; Saha, J.; Giese, R.W. *J. Chromatogr.* **1993**, *641*, 400 and references cited therein.

It was no bother at all, just simply a pleasure to be able to help.

Enantioselective Synthesis of β-Amino Acids

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Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apdo. Postal 14-740, 07000 México, D.F. México

INTRODUCTION

As a result of the wide spectrum of applications of α-amino acids, a great deal of attention has been paid to the development of new methodologies for the preparation of both natural and unnatural α-amino acids in optically pure form.[1-4]

β-Amino acids, although less abundant than their α analogues, are also present in peptides,[5] and in free form they show interesting pharmacological effects.[6] Furthermore, β-amino acids are synthetic precursors of β-lactams,[7] which are potentially biologically active and of current interest.[8] In this respect, several methods for the synthesis of racemic β-amino acids have been developed,[9] but only recently has the preparation of enantiomerically pure compounds emerged as an important and challenging synthetic endeavor.[10]

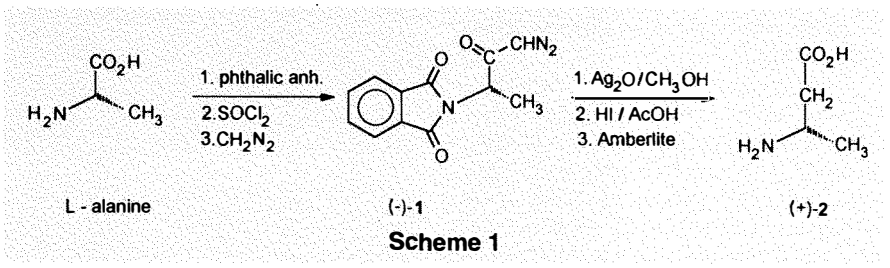
From left to right, Jaime Escalante, Dr. Eusebio Juaristi, and Delia Quintana

MAIN METHODS FOR THE PREPARATION OF ENANTIOMERICALLY ENRICHED β–AMINO ACIDS

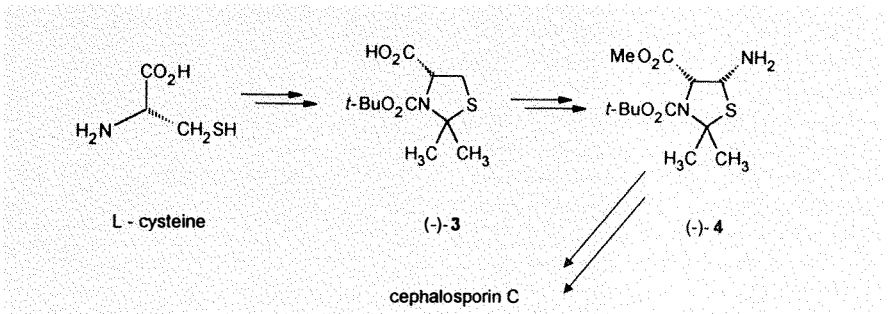
The procedures developed thus far for the enantioselective synthesis of β-amino acids can be tentatively separated into seven categories, as detailed below.

A. THE "CHIRAL POOL"

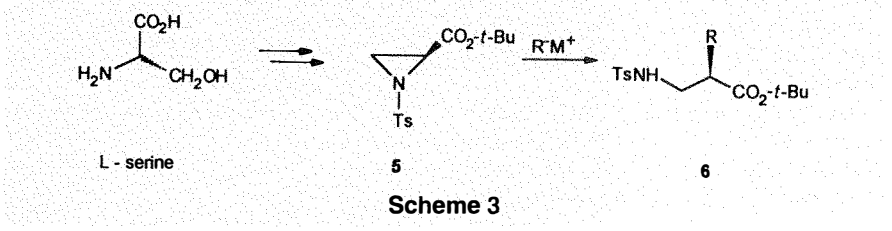
The "chiral pool"[11] refers to the utilization of inexpensive, readily available natural products as substrates to be converted into enantiomerically pure β-amino acids via conventional organic synthesis. According to this strategy, Balenovic and coworkers[12] described in 1952 the application of the Arndt-Eistert reaction to (-)-1-diazo-3-phthalimidobutan-2-one (**1**), prepared from L-alanine, to give (+)-β-aminobutyric acid (**2**, **Scheme 1**). Also relevant is the conversion of L-(+)-cysteine into L-(-)-2,2-dimethylthiazolidine-4-carboxylic acid (**3**), which reacted with dimethyl azodicarboxylate to give (following further manipulation) the *cis*-β-amino ester **4**, a key precur-



Scheme 1



Scheme 2



Scheme 3

sor in Woodward's total synthesis of cephalosporin C (**Scheme 2**).[13]

More recently, Baldwin et al.[14] reported the stereoselective ring opening of aziridine-2-carboxylate esters **5**, derived from L-serine, to afford β-amino acid precursors **6** in 20-55% yield (**Scheme 3**). Along similar lines, an efficient method for the synthesis of chiral β-amino acids starting from (*S*)-asparagine was described by Gmeiner (**Scheme 4**).[15] Furthermore, access to enantiomerically pure β-amino acids from optically active 1-arylethylamines was recently described by Bringmann and Geuder.[16] This interesting approach (**Scheme 5**) is based on a regiospecific cleavage performed by Birch reduction and subsequent ozonolysis. Finally, a multistep procedure has been recently proposed for the conversion of leucine, norleucine, and phenylalanine into optically active α,β-disubstituted β-amino acids.[17]

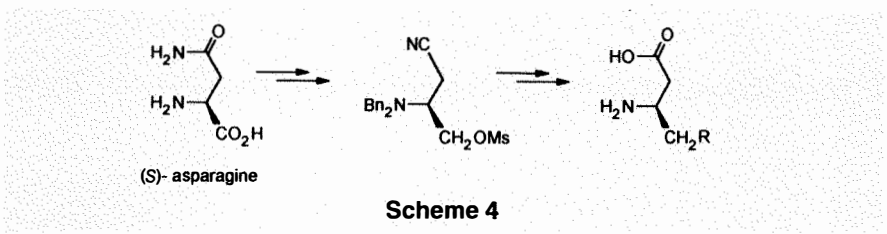
B. ASYMMETRIC ADDITION OF AMINES TO α,β-UNSATURATED ESTERS AND NITRILES

In 1965 Terentev and co-workers reported the first example of an enantioselective addition of a chiral amine to crotonic acid;[18] nevertheless, the enantiomeric ratios obtained were quite low (**Scheme 6a**). Similarly disappointing were the studies of Furukawa et al.[19] on the corresponding conjugated nitriles (**Scheme 6b**).

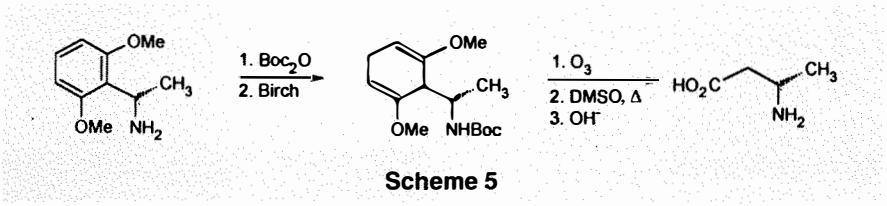
Much better results were attained by Hawkins and co-workers[20] with the C_2 symmetric chiral secondary amine **7**. Initially, treatment of (±)-**7** with methyl crotonate gave amino ester (±)-**8** as a 78:22 mixture of diastereomers in 68% yield (**Scheme 7a**). More useful Michael additions of the lithium amide (*S*)-**7**-Li occurred with very good diastereoselectivity to afford (*R*)-**8** as a 98:2 mixture of diastereomers in 81% yield (**Scheme 7b**).

Recently, Davies and Ichihara[21] described the synthetic usefulness of secondary amines **9**, **10**, and **11** as additional "chiral ammonia" synthons (**Scheme 8**).[22] For example, Michael addition of the lithium amide derived from (*R*)-*N*-(α-methylbenzyl)benzylamine (**9**) to benzyl (*E*)-crotonate was highly stereoselective (d.r. = 97.5:2.5) giving, after debenzylation, enantiomerically pure (*R*)-β-aminobutanoic acid (**Scheme 8a**).[21] A similar addition to methyl (*E*)-(*p*-benzyloxy)cinnamate was completely stereoselective leading to enantiomerically pure (*S*)-β-tyrosine (**Scheme 8b**).[21]

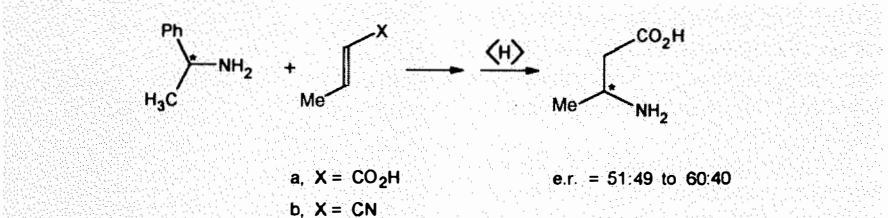
In a further elegant application, the antifungal antibiotic (-)-(1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid (cispentacin, **12**) was prepared via the highly stereoselective



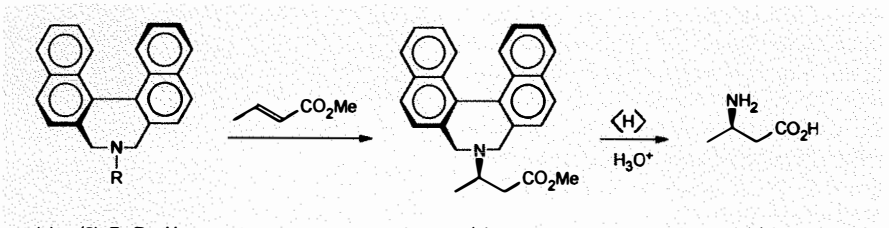
Scheme 4



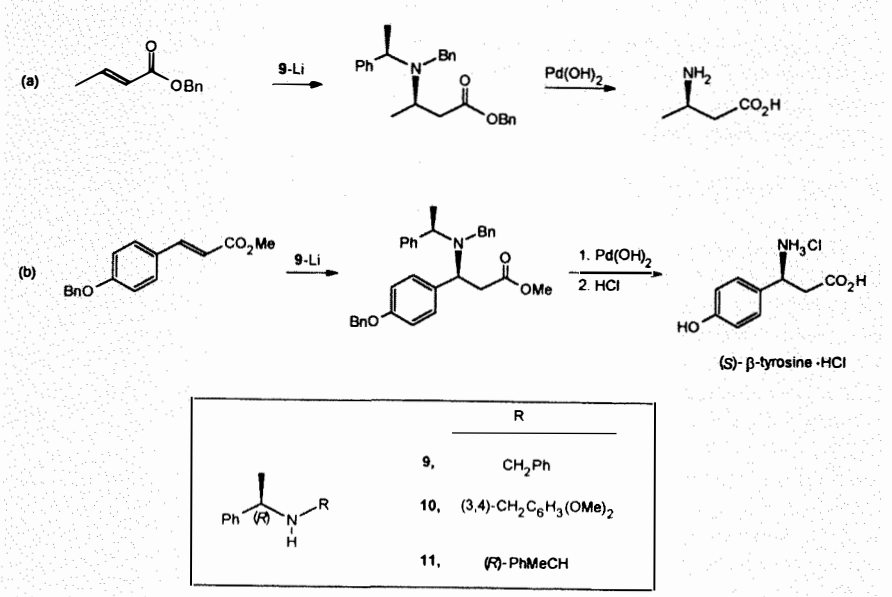
Scheme 5



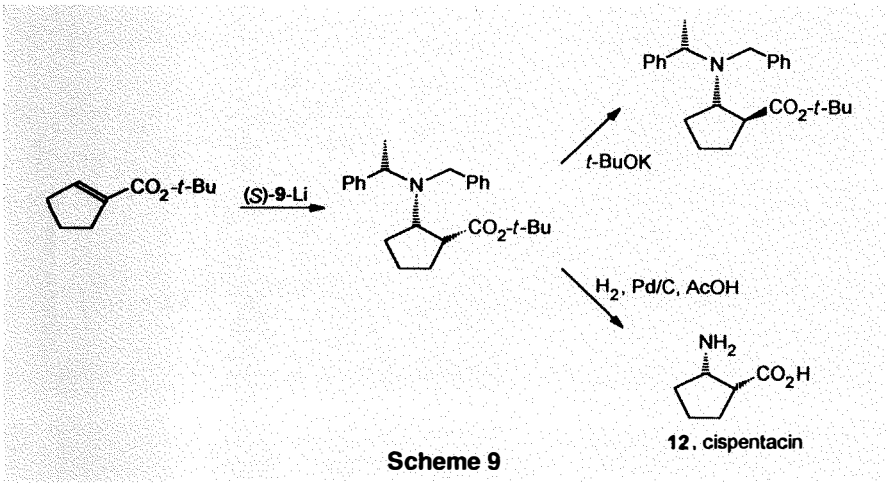
Scheme 6



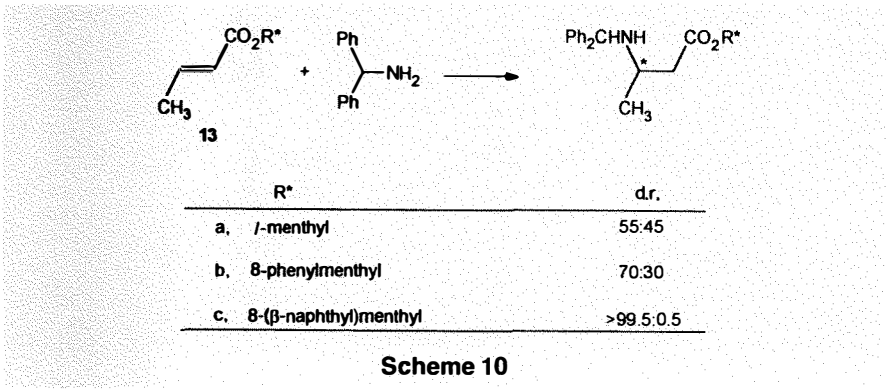
Scheme 7



Scheme 8



Scheme 9



R*	d.r.
a, *l*-menthyl	55:45
b, 8-phenylmenthyl	70:30
c, 8-(β-naphthyl)menthyl	>99.5:0.5

Scheme 10

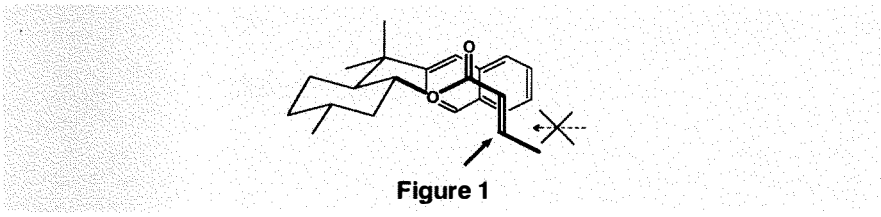
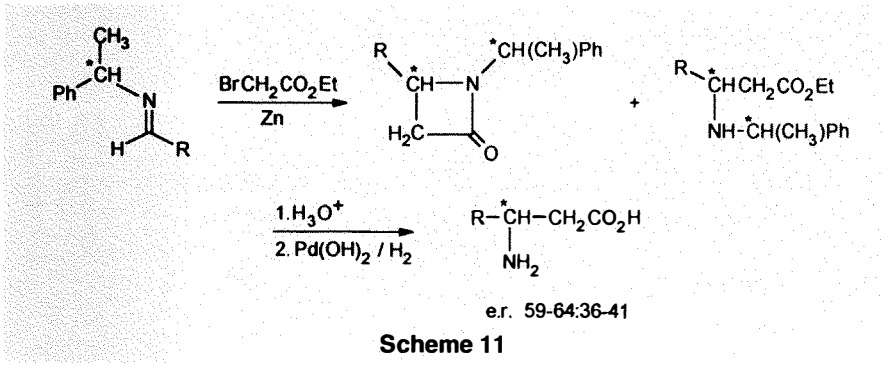
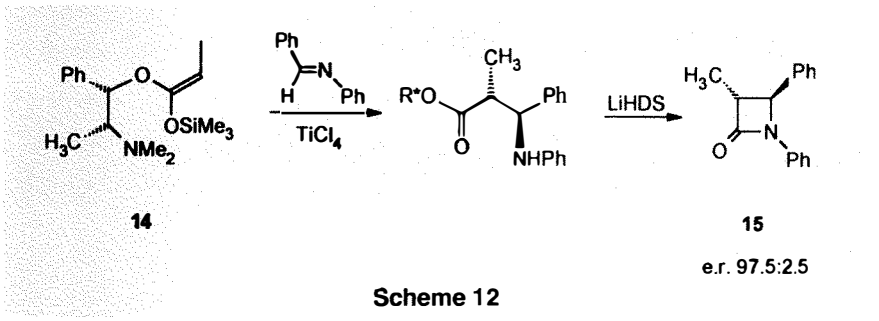


Figure 1



e.r. 59-64:36-41

Scheme 11



14 **15**

e.r. 97.5:2.5

Scheme 12

conjugate addition reaction of lithium (*S*)-(α-methylbenzyl)benzylamide [(S)-**9**-Li] to *tert*-butyl 1-cyclopentene-1-carboxylate (**Scheme 9**).[23] This method should also provide an efficient enantioselective synthesis of *trans*-**12** by base-catalyzed isomerization at C(1) (**Scheme 9**).[23]

d'Angelo and co-workers[24] achieved very high stereocontrol in the conjugate addition of amines to chiral α,β-ethylenic esters **13** (**Scheme 10**) using high pressure as an activating condition to produce excellent chemical yields. The incorporation of appropriate chiral inductors in **13** allowed very high stereocontrol at the newly created stereogenic center. Indeed, *l*-menthyl crotonate was found to give poor diastereomeric ratios (**Scheme 10a**), 8-phenylmenthyl crotonate afforded moderately good d.r.'s (**Scheme 10b**), and analogues in which the phenyl ring is substituted in the *para* position by bulky groups gave excellent stereoselectivities, with essentially complete diastereofacial control in the case of 8-(β-naphthyl)menthyl crotonate (**Scheme 10c**).[24a] The authors suggest a "π-stacking" model,[25] in which the aryl group of the inductor shields one face of the olefin (**Figure 1**), to interpret the stereochemical outcome of the reaction.

In a conceptually related system, Perlmutter and Tabone[26] observed modest to excellent diastereoselectivities in the conjugate addition of benzylamine to chiral 2-hydroxyalkylpropenoates. Also relevant in this context are the interesting variants developed by Murahashi et al.[27] and by Barnisch and co-workers,[28] who have developed efficient syntheses of naturally occurring alkaloids [(+)-sedridine, and (+)-hygroline][27] as well as (*S*)-tyrosine derivatives.[28]

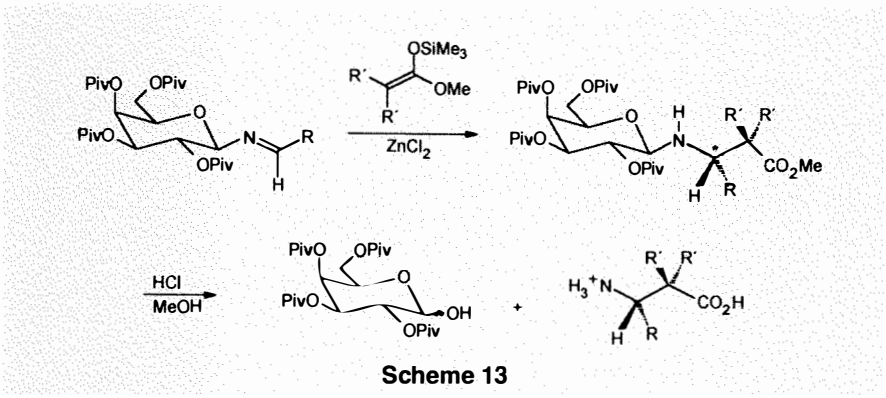
C. ADDITION OF *C*-NUCLEOPHILES TO CHIRAL IMINES

Pioneering efforts in this direction were first reported by Furukawa and collaborators in 1978.[29] These researchers carried out the asymmetric addition of Reformatsky reagents to Schiff bases prepared from aldehydes and (*R*)-(+)- and (*S*)-(-)-α-methylbenzylamine (**Scheme 11**). When the Schiff bases having (*R*)-amino chiral adjuvant were used in the reaction, (*S*)-β-amino acids were formed, albeit in low enantiomer ratios. (59-64:36-41).

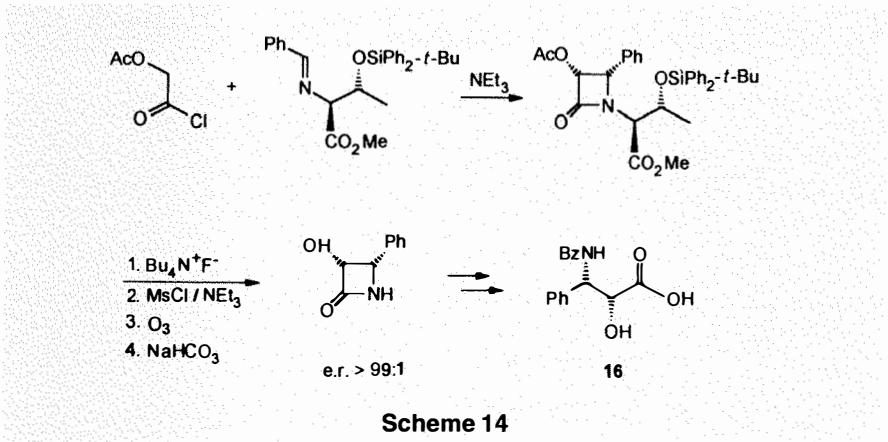
Dramatic improvements in the enantioselectivity of this methodology were reported by several groups a decade later. For example, Gennari and co-workers[30] reported in 1987 that the $TiCl_4$-mediated addition of the chiral silyl ketene acetal **14** to benzylideneaniline proceeds with high stereoselectivity to give, after cyclization, *trans*-β-lactam **15** in good yield and excellent e.r. (97.5:2.5)

(**Scheme 12**). More recently, Kunz and Schazenbach[31,32] described the asymmetric synthesis of *N*-unsubstituted β-amino acids via the diastereoselective Mannich reaction of Schiff bases of 2',3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine. One advantage of this method is the recovery of the chiral auxiliary group (**Scheme 13**). In this regard, Farina et al.[33] incorporated derivatives of L-threonine as chiral adjuvants in the starting imine. This methodology allowed for the preparation of the α-hydroxy-β-amino acid **16** present in taxol (**Scheme 14**).[34]

In a brilliant development, Corey reported in 1991 the first asymmetric synthesis of chiral β-amino acid thioesters from *achiral* imines and esters using the chiral organoboron reagent **17** (**Scheme 15**).[35] Indeed, the reaction of (*S,S*)-diazaborolidine **17** with (*S*)-*tert*-butyl thiopropionate produces the (*Z*)-enolate **18**, which reacts with the *N*-benzyl or *N*-allyl imines of a variety of aldehydes with high diastereo- and enantioselectivity to form mainly the β-amino thioesters **19** (**Scheme 15**).



Scheme 13



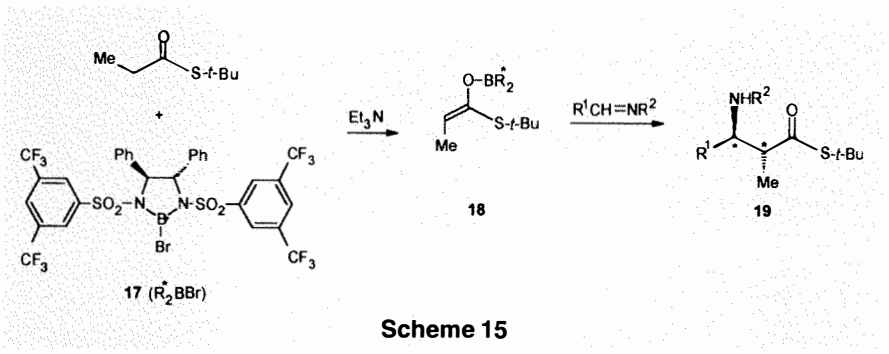
Scheme 14

D. ENANTIOSELECTIVE HYDROGENATION OF PROCHIRAL 3-AMINO-ACRYLIC ACID DERIVATIVES

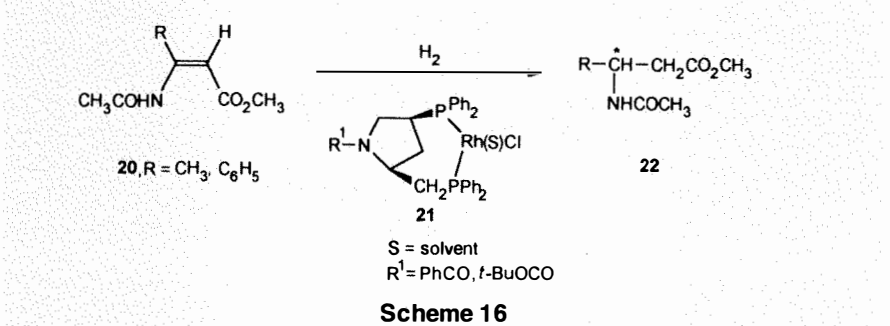
In pioneering studies, Achiwa and Soga[36] carried out the catalytic asymmetric hydrogenation of β-(acetylamino)acrylic acid derivatives **20,** using bisphosphines **21** as the chiral ligands, to give the optically active protected β-amino esters **22** (**Scheme 16**). Unfortunately, these reactions had only modest success, affording the desired products in low enantiomeric purities (e.r. = 51:49 to 78:22).[36]

Dramatic improvements in the efficiency and understanding of this approach were achieved by the Noyori group,[37] who demonstrated that BINAP-Ru(II) metal complexes [BINAP = 2,2'-bis(diarylphosphino)-1,1'-binaphthyl] serve as excellent catalysts for enantioselective hydrogenation of β-substituted (*E*)-β-(acylamino)acrylic acids (**Scheme 17**). Interestingly, the (*Z*) double bond isomers (which possess an intramolecular hydrogen bond between amide and ester groups) are more reactive but are hydrogenated with poor enantioselectivity.[37] BINAP-Rh(I) complexes afford only moderate stereoselectivity with the opposite sense of enantioinduction.[37]

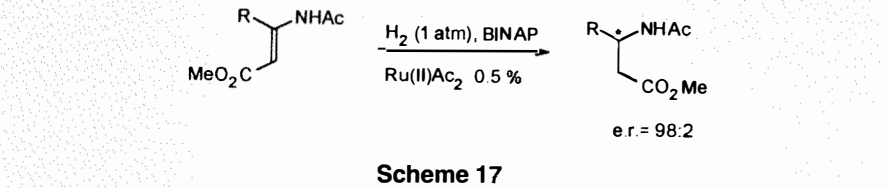
Because the enantioselective hydrogenation of prochiral 3-aminoacrylic acid derivatives under the influence of a chiral catalyst may offer the most efficient route for large scale preparation of enantiopure β-amino acids, it is not dangerous to predict that many more developments will appear in time.



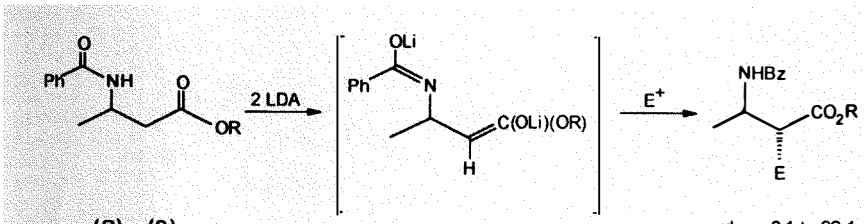
Scheme 15



Scheme 16



Scheme 17



Scheme 18

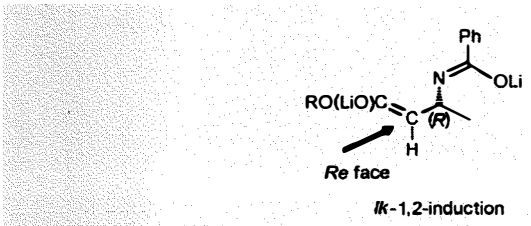
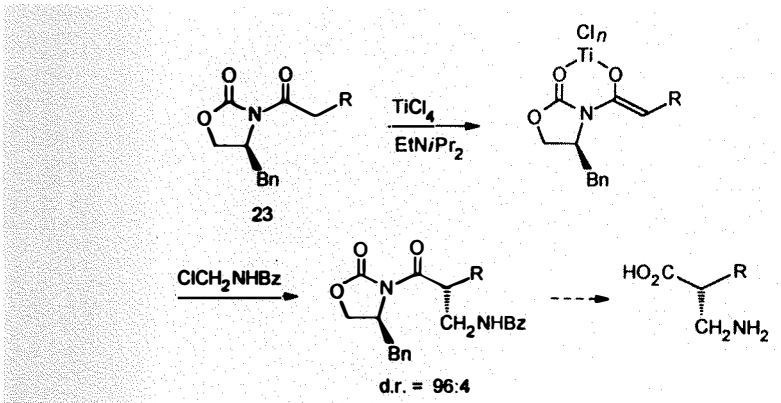
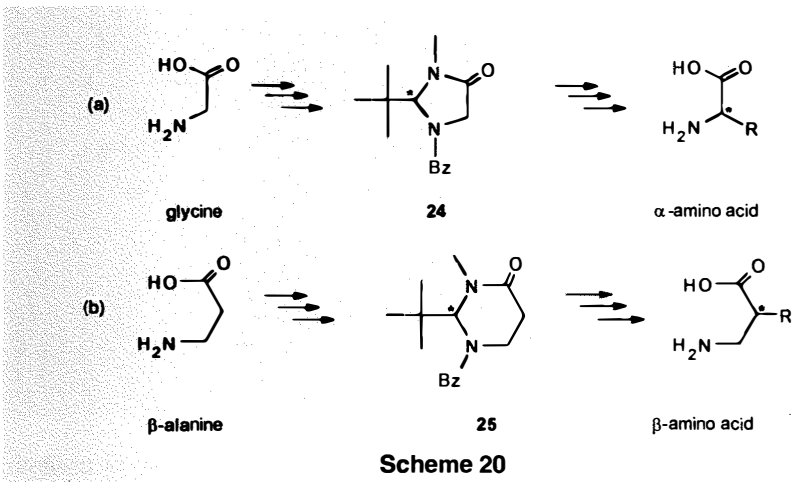


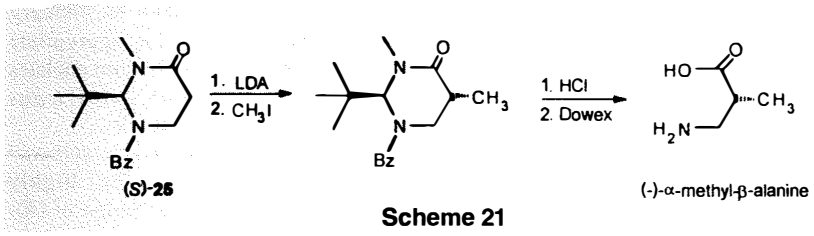
Figure 2



Scheme 19



Scheme 20



Scheme 21

E. STEREOSELECTIVE ALKYLATION OF β-AMINO ESTER α-ENOLATES

N-Acyl-β-amino acid derivatives have been doubly deprotonated and then α-alkylated with moderate to excellent selectivity.[38] Enantiomerically pure 3-aminobutanoic acid derivatives were prepared by Seebach and Estermann[39] via dilithiated methyl- or ethyl-*N*-benzoyl-3-aminobutanoates (**Scheme 18**). The selectivity with which these reactions took place was usually very high, affording the product that originates from addition of the electrophile (E+) to the enolate with relative *like*[40] topicity (**Figure 2**).

In another interesting application of oxazolidines of type **23**, Evans and co-workers[41] recently described the diastereoselective reaction of titanium enolates with a variety of electrophiles, including *N*-chloromethylbenzamide, which allows efficient amidoalkylation (**Scheme 19**).

Encouraged by the enormous potential of nonracemic derivatives of glycine as precursors of optically active α-amino acids,[3,4] Juaristi et al.[42] decided to explore the usefulness of chiral β-alanine enolates as starting materials for the preparation of (*R*)- or (*S*)-α-substituted-β-amino acids. In particular, in view of the successful development of the imidazolidinone **24** for the preparation of (*R*)- or (*S*)-α-amino acids[43] (**Scheme 20a**), it was considered that tetrahydropyrimidinone **25** might serve as an effective reagent for the synthesis of chiral β-amino acids[42] (**Scheme 20b**). Alkylation of enolates **25**-Li with alkyl halides RX at -75 °C took place with high diastereoselectivity (ds = 86-97%) from the side opposite the *tert*-butyl group, to afford the *trans* products.[44] The hydrolysis of the resulting adducts proceeded with 6*N* hydrochloric acid to afford the desired α-substituted β-amino acids in good yields.[42]

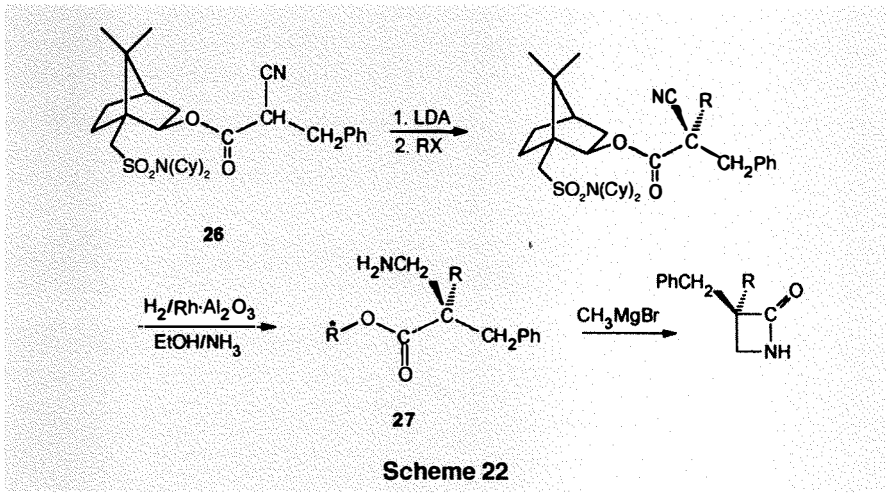
The above results paved the road for the development of a new asymmetric synthesis of β-amino acids. Indeed, enantiomerically pure pyrimidinone (*S*)-**25** has been prepared and used for the preparation of a variety of enantiopure α-substituted-β-amino acids, for example, (-)-α-methyl-β-alanine (**Scheme 21**).[45]

Very recently, Cativiela and co-workers[46] described the diastereoselective alkylation of the enolate of isobomyl derivative **26**. This alkylation took place with very good yield and selectivity. The products were subsequently reduced to β-amino esters **27** which were then cyclized to β-lactams (**Scheme 22**).

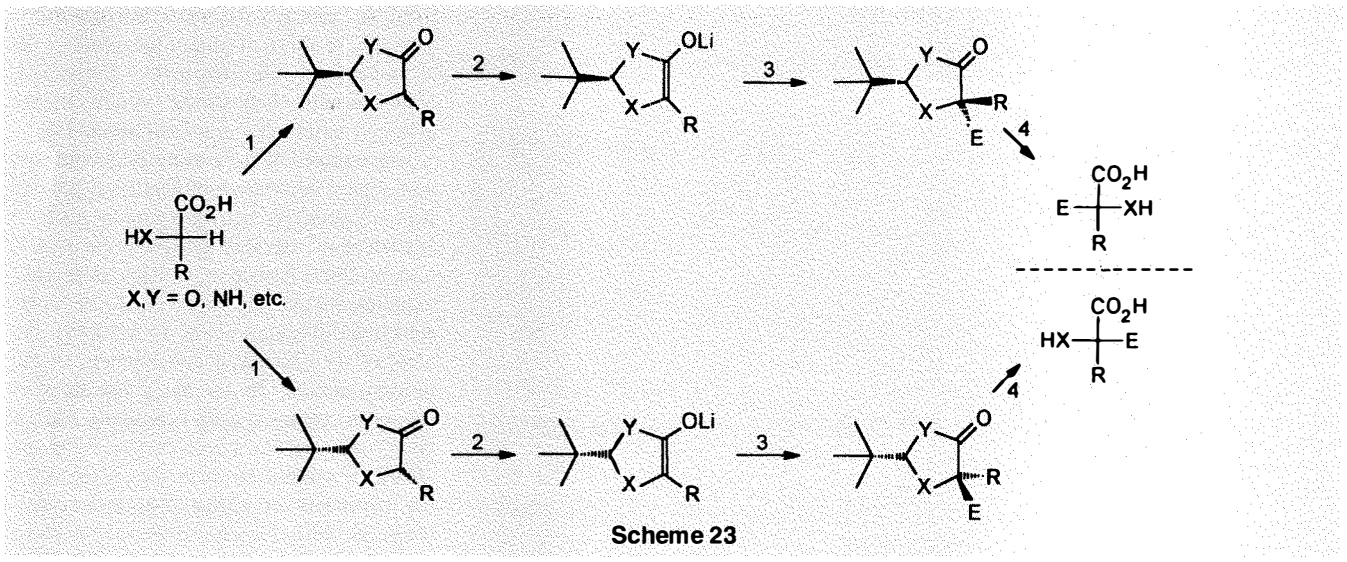
Finally, in a sophisticated and elegant development, Jacobi and Zheng have utilized the Nicholas reaction for the synthesis of enantiomerically pure β-amino acids.[47]

F. SELF-REGENERATION OF STEREOGENIC CENTERS

Over a decade ago, Seebach and co-workers carried out transformations in which α-hydroxy and α-amino acids were α-alkylated without racemization and without employing a chiral auxiliary reagent.[48] To this end, the starting acid was first converted to one of two possible diastereomeric cyclic acetals with pivalaldehyde so that a *temporary* auxiliary stereogenic center was created. Then, an enolate was generated by deprotonation with base: *the original center of stereogenicity is destroyed* (converted to a trigonal center). In the third step, the reaction of the enolate with an electrophile, the



Scheme 22

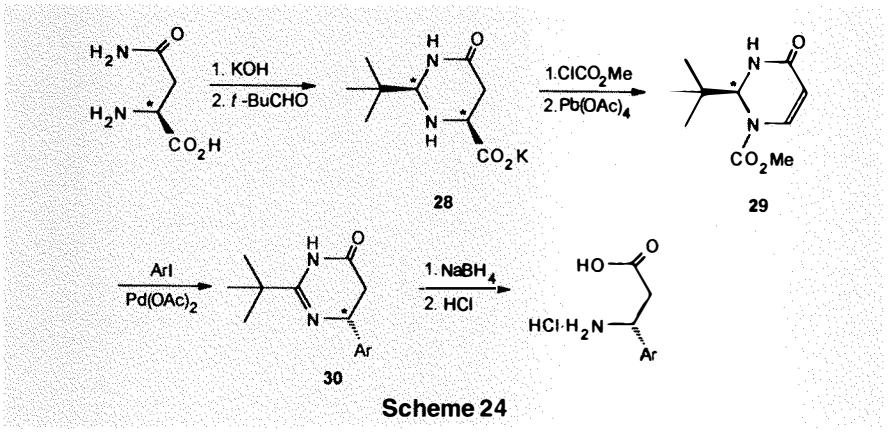


Scheme 23

bulky substituent on the acetal center induces the *stereoselective regeneration* of the original center of chirality. Finally, the temporary stereogenic acetal center is removed, affording the new α-branched carboxylic acid (**Scheme 23**).

Mindful of the above seminal work, Konopelski et al.[49] developed a methodology in which the acetalization of the potassium salt of (*S*)-asparagine formed pyrimidinone carboxylate **28** diastereoselectively. Carbomethoxy derivatization of the secondary amine group followed by oxidative decarboxylation gave unsaturated heterocycle **29**. Although the original stereogenic center is converted to a trigonal center, the bulky *tert*-butyl group on the acetal carbon induced the stereoselective formal conjugate addition of aryl iodides in the presence of catalytic amounts of $Pd(OAc)_2$ to afford derivatives **30**. Treatment of **30** with $NaBH_4$ followed by hydrolysis gave the desired enantiomerically pure β-amino acid hydrochlorides (**Scheme 24**).

Contemporaneously with the above developments, Juaristi et al.[42,50,51] prepared

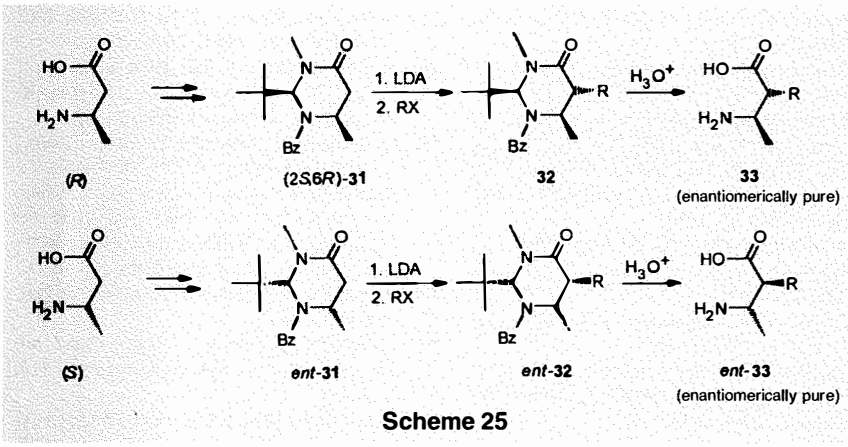


Scheme 24

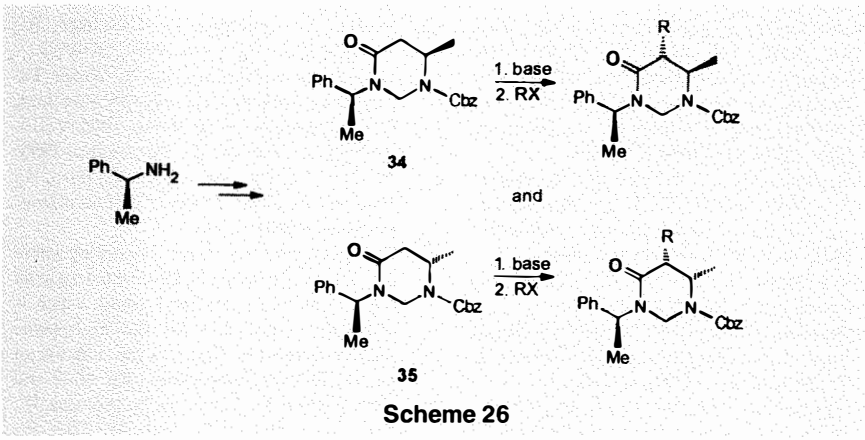
enantiomerically pure perhydropyrimidin-4-ones **31** and *ent*-**31** from (*R*)- and (*S*)-3-aminobutanoic acids. These heterocycles were alkylated with formation of a single diastereoisomer (**32** and *ent*-**32**). Hydrolysis of these 5,6-dialkylperhydropyrimidin-4-ones led to the important α,β-disubstituted β-amino acids **33** (**Scheme 25**).[50]

Closely related heterocycles were also exploited by Cardillo et al.[52] in their program directed towards the synthesis of α-substituted-β-amino acids. Compounds **34** and **35** were synthesized by means of mercury cyclofunctionalization of the appropriate aminal. The corresponding lithium enolates were then alkylated with good *trans* stereoselectivity (**Scheme 26**).[52b]

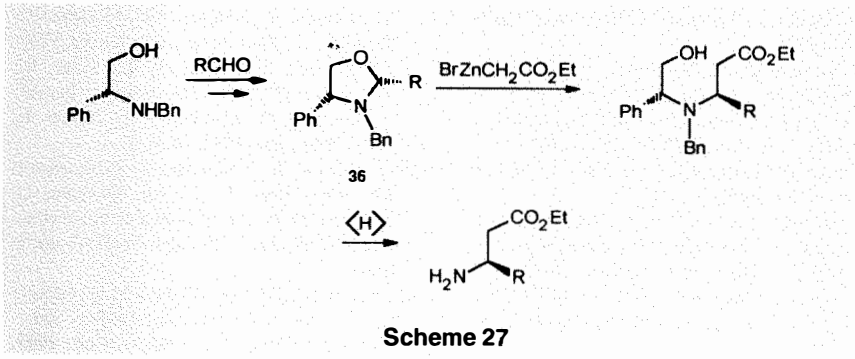
In this context, Pedrosa and co-workers[53] have recently reported the highly diastereoselective *N,O*-acetalization of (*R*)-



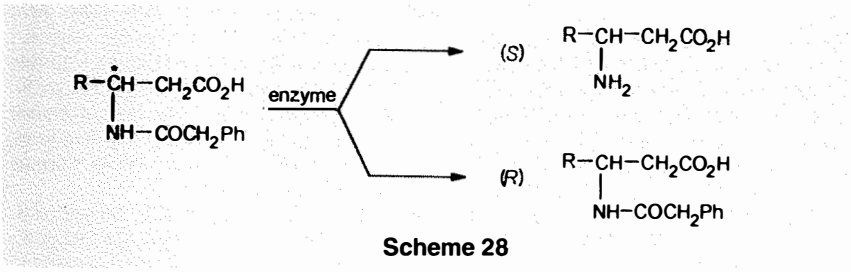
Scheme 25



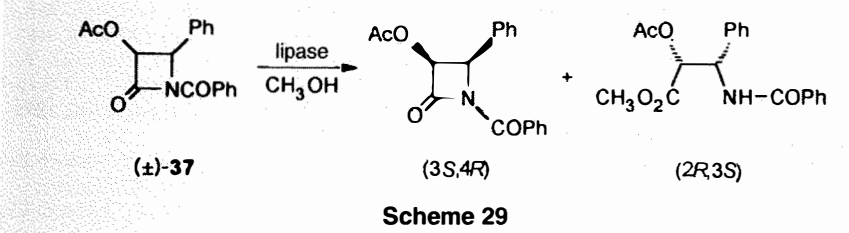
Scheme 26



Scheme 27



Scheme 28



Scheme 29

or (*S*)-*N*-benzylphenylglycinol with aldehydes. The resulting chiral oxazolidines **36** reacted with the Reformatsky reagent derived from ethyl bromoacetate, leading to β-amino carboxylates in good diastereomeric ratios (80:20 to 96:4) (**Scheme 27**).

G. ENZYMATIC METHODS

Recently, enantiomerically pure β-amino acids have been prepared by routes involving the enzymatic resolution of racemates.[34h,54-55] For example, fifty percent conversion of racemic *N*-phenylacetylderivatives of β-amino acids with penicillin acylase allowed for the separation of the (*S*)-amino acid from the (*R*)-*N*-protected derivative (**Scheme 28**).[55]

On the other hand, lipase-catalyzed cleavage of racemic β-lactams (±)-**37** yielded derivatives of (2*R*,3*S*)-phenylisoserine in high enantiomeric purity (**Scheme 29**).[34h]

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Iodobenzene Diacetate and Related Hypervalent Iodine Reagents in the Synthesis of Heterocyclic Compounds

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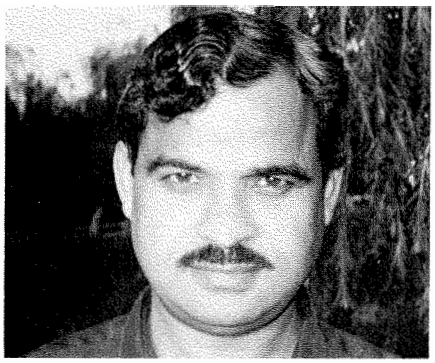
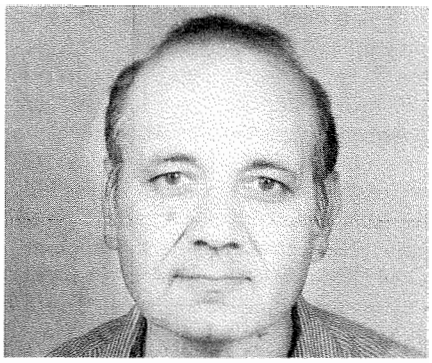


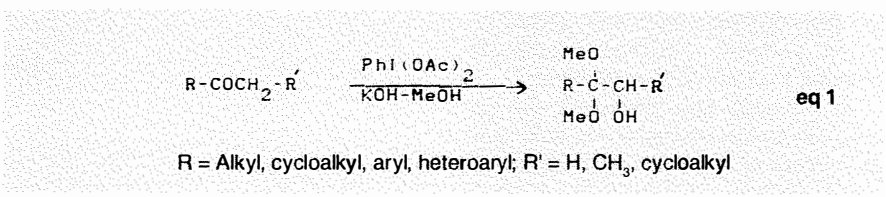


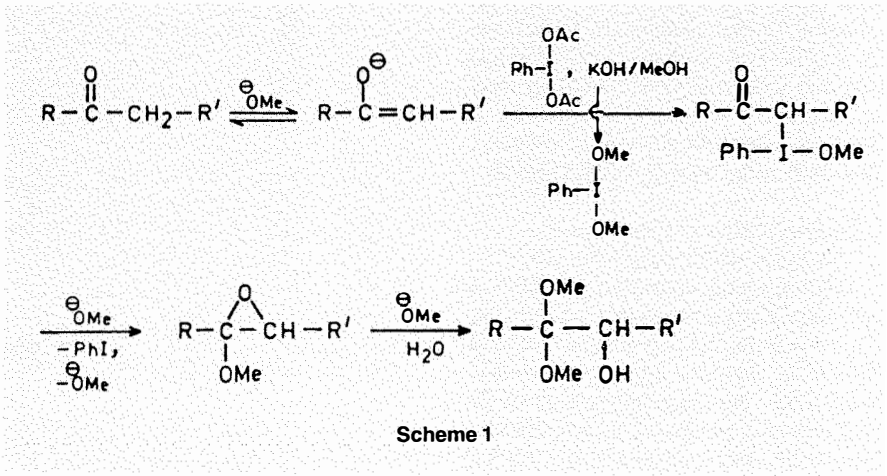
1. INTRODUCTION

In recent years there has been a considerable interest in the use of organohypervalent iodine reagents in organic synthesis.[1-11] Most of these reactions of I(III) reagents involve oxidation. A particularly noteworthy example being the hypervalent iodine oxidation of enolizable ketones to give various α-functionalized ketones which are, in turn, useful precursors for the synthesis of a wide variety of heterocyclic compounds. Such an approach has distinct advantages over conventional methods.

In addition to α-functionalization of ketones, several I(III) mediated syntheses of a number of heterocyclic compounds have also been recently developed. Some of these syntheses are of general applicability. In view of the rapid development in this area, an effort has been made in this article to review recent developments, particularly those involving applications of iodobenzene diacetate (IBD) as well as some related hypervalent iodine reagents.

For the sake of brevity, the subject matter covered in this article has been divided into three major parts (2.1, 2.2, and 2.3). Part 2.1 deals with the applications of IBD in methanolic KOH, whereas part 2.2 highlights the utility of iodonium ylides/salts which, are in turn obtained from IBD and related I(III) reagents. The last part (2.3) outlines syntheses of various heterocyclic compounds using miscellaneous reagents and conditions.





Scheme 1

2.1 SYNTHESIS OF HETEROCYCLES USING IBD IN METHANOLIC KOH (IBD-KOH/MEOH)

Hypervalent iodine oxidation of enolizable ketones using IBD-KOH/MeOH provides an efficient method of preparation for α-hydroxydimethylacetals (eq 1). The reaction proceeds through the pathway outlined in **Scheme 1**.[12]

The reaction becomes especially important in building "O"-containing heterocyclic systems when intramolecular participation by a suitably placed hydroxyl group occurs. These results are presented in this section.

2.1.1. COUMARAN-3-ONES

2,2-Disubstituted-coumaran-3-ones, aurones, and isoaurones[13]

When *o*-hydroxyacetophenones **1** are oxidized with IBD-KOH/MeOH (condition i), formation of 2,2-disubstituted-coumaran-3-ones **2** occurs by a novel route. The conversion **1** ► **2** proceeds via intermediate **4**, induced by intramolecular participation of *o*-hydroxy group (**3** ► **4**) as shown in **Scheme 2**.

Such an approach for obtaining **2** has been successfully employed for the synthesis of aurones **6** and isoaurones **7** starting from **2d** (**Scheme 3**).

It should be mentioned that a similar reaction yielding coumaran-3-one **8** without substitution at the 2-position involves the oxidation of silyl enol ether **9** with iodosobenzene, boron trifluoride etherate, and water (condition ii)(**Scheme 4**).[14]

2-Aroylcoumaran-3-ones (11)[15]

The oxidation of α-aroyl-*o*-hydroxyacetophenones **10** with IBD provides a useful extension of the reaction outlined in **Scheme 2** for obtaining 2-aroylcoumaran-3-ones **11**. A noticeable feature of the reaction is the observation that β-diketones **10** do not yield ylides **12**, a fact

well established in the literature for other β-dicarbonyl compounds (e.g., malonates, **Scheme 5**).

2.1.2 BENZO-4*H*-PYRAN-4-ONES AND DERIVATIVES

Cis- and *trans*- 3-hydroxyflavanones and 2-furyl analogues[16-19]

On treatment with IBD-KOH/MeOH, *o*-hydroxychalcones **13**/flavanones[16-18] and 2-furyl analogues[19] give *cis*-3-hydroxyflavanone dimethylacetals and the corresponding 2-furyl analogues **14**. This reaction is regio- as well as stereospecific. Acid hydrolysis of these acetals under controlled conditions (aq. AcOH) completes a novel method of synthesizing *cis*-3-hydroxyflavanones **15** which are not readily available following conventional procedures. Replacement of AcOH with concentrated HCl in acetone results in the formation of corresponding *trans* isomers **16** (**Scheme 6**).

A mechanistic rationale for the observed *cis*-stereochemistry based on the general reaction pathway outlined previously (**Scheme 1**) is described in (**Scheme 7**).

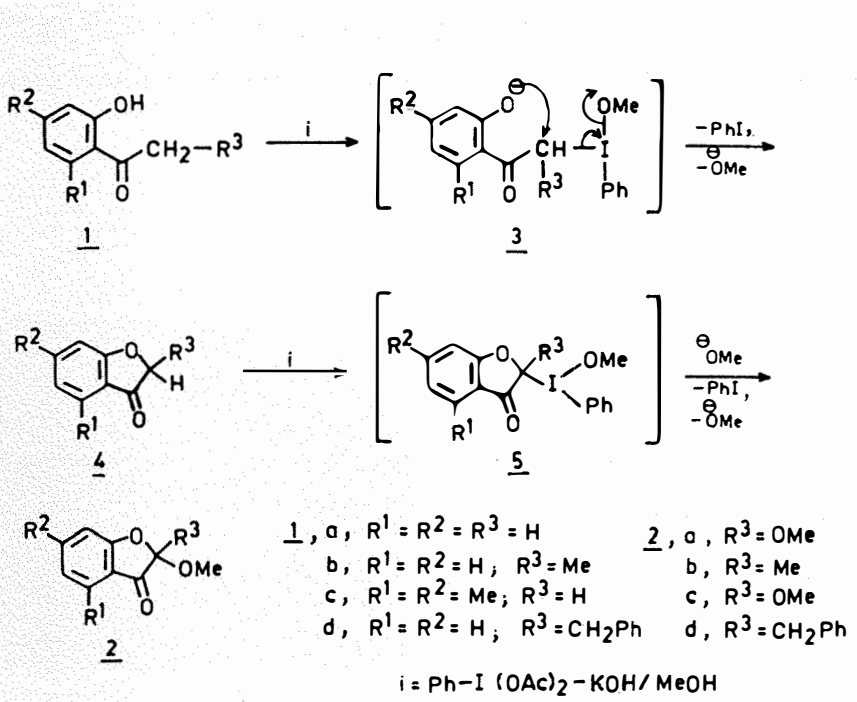
As is evident from **Scheme 6**, this approach to hydroxyflavanones is quite general and can be applied to chromanones, 2-furylchromanones, and a variety of substituted flavanones. However, a noticeable exception to this reaction is 7-methoxyflavanone/*o*-hydroxychalcone (**17**) which on oxidation with IBD-KOH/MeOH at room temperature produces a mixture of 7-methoxyflavone (**18**) and normal dimethylacetal (**14**) in the ratio of 3:1 (**Scheme 8**).

C_3-Hydroxylation of Chromones/ Flavones and β-Naphthoflavone[20,21]

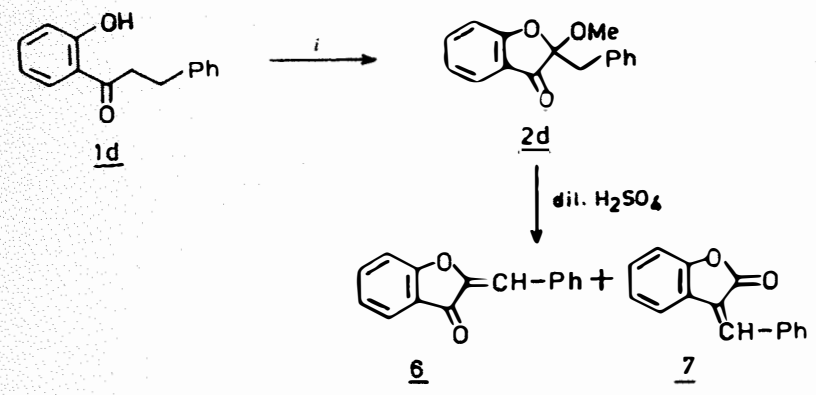
An interesting application of IBD in methanolic KOH involves the C_3-hydroxylation of α,β-unsaturated ketones, namely chromones, flavones **19**, and α-naphthoflavones **22**. The reaction proceeds via the formation of 2-methoxy-3-hydroxychromanones or flavanone dimethylacetals **20** and **23** which on acid hydrolysis undergo loss of three molecules of methanol to yield C_3-hydroxylated products (**21** and **24**) (**Scheme 9**).

2.1.3. STEROIDAL SPIRO-OXETAN-3-ONES[22]

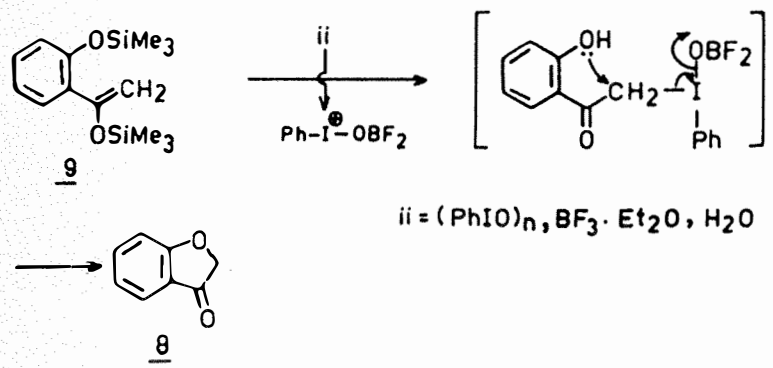
Oxidation of 17β-acetyl-17α-hydroxysteroids **25** with IBD-KOH/MeOH at 20°C gives steroidal spiro-oxetan-3-ones **27**. This is an interesting example of intramolecular participation wherein the C-17 α-hydroxyl group acts as an intramolecular nucleophile (**25** ⟶ **27**) and competes favorably with intermolecular attack by methoxide (**26** ⟶ **27**, **Scheme 10**).



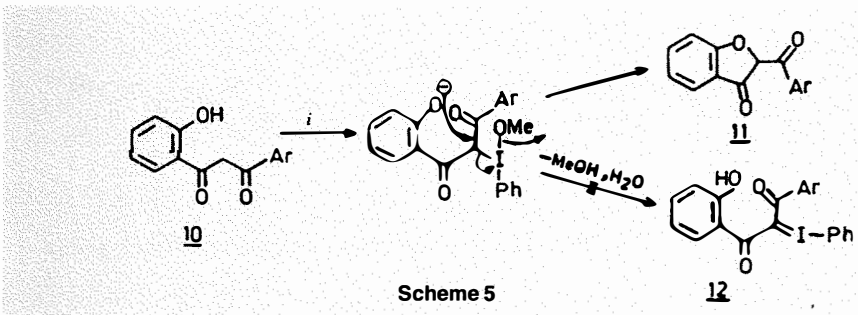
Scheme 2



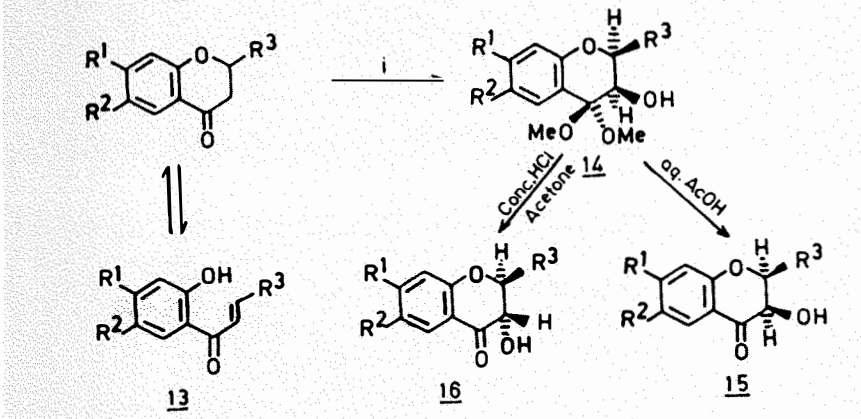
Scheme 3



Scheme 4



Scheme 5

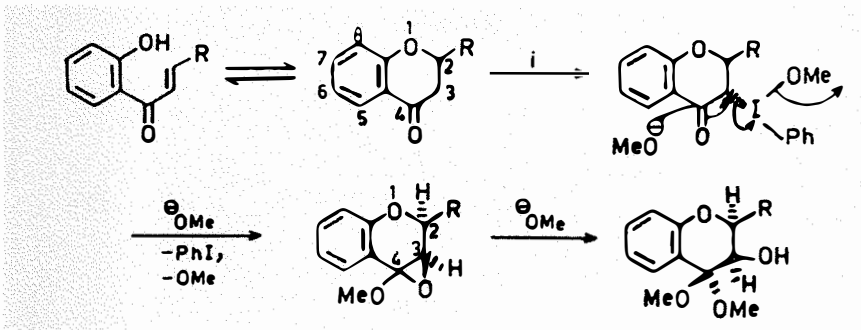


$R^1 = R^2 = R^3 = H$

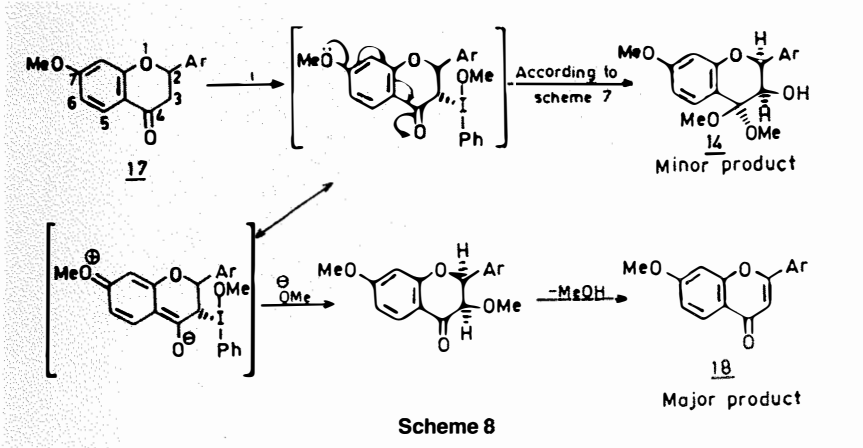
$R^1 = R^2 = H$; R^3 = Ph, substituted phenyl, 2-furyl

R^1 = H, CH_3; R^2 = Cl

Scheme 6



Scheme 7



Scheme 8

2.2. IODONIUM YLIDES/SALTS FORMATION AND PHOTOCHEMICAL CONVERSION TO HETEROCYCLES

As already mentioned, most of the reactions of organohypervalent iodine reagents are oxidations wherein hypervalent iodine compounds are reduced to iodoarenes. In contrast, there are certain other classes of compounds (e.g., β-dicarbonyls) which, on reaction with I(III) reagents, form iodonium ylides and salts. These ylides/salts contain tervalent iodine (eq 2). Of the various methods available for the synthesis of iodonium ylides/salts, the procedures making the use of iodoarene dicarboxylates or iodoso compounds are most widely used. Two important types of iodonium ylides/salts, having general applicability for the synthesis of heterocyclic systems, are generated from β-dicarbonyl compounds (eq 3)[23] and phenols[24-27] having at least one electron accepting group in the *para* position and one free *ortho* position (eq 4). The first step in this reaction is the formation of an iodonium salt which subsequently loses a molecule of water or acid under the influence of heat or in the presence of base to give the stable iodonium ylide. The ylides indicated in equations 2-5 are especially useful in the synthesis of heterocycles.

2.2.1. OXATHIOLE-2-THIONES AND RELATED COMPOUNDS

A common and general property of iodonium ylides **29, 31,** and **35** is their photochemical conversion to oxathiole-2-thiones **36-38** in the presence of CS_2 (**Scheme 11**).[28,29]

In the presence of phenyl isothiocyante or compounds containing a styrene double bond, ylides **31** and **35** undergo photochemical conversion to 2-phenyliminooxathioles **39** and **40** or dihydrofurans/dihydrobenzofurans **41/42**, respectively (**Scheme 12**).[28-30] It is important to mention that phenyliodonium ylide **29** (R=OMe), accessible from dimethyl malonate and I(III) reagents, on reaction with various alkenes in the presence of a Lewis acid (e.g., BF_3•Et_2O) leads to 5,5-disubstituted-3-carbomethoxy-γ-lactones.[31]

Many other interesting reactions of **31** based on the photochemical approach are also reported in the literature. For example, photolysis of **31** in the presence of CH_3CN and PhNCO provides 2-methyl-4-oxo-4,5,6,7-tetrahydro-6,6-dimethylbenzoxazole (**43a**)[28] and *N*-phenyl-4-oxo-4,5,6,7-tetrahydro-6,6-dimethylbenzoxazol-2-one (**43b**),[31] respectively (**Scheme 13**).

2.2.2. BENZOFURANS

A similar approach has been applied for obtaining benzofurans of type **44**. The reaction involves irradiation of 2,4-dinitro-6-phenyliodonium phenolate in the presence of alkynes (**Scheme 14**).[32]

2.2.3. DIBENZOFURANS

A simple procedure for preparing dibenzofurans **46** involves use of iodonium phenolates. The reaction proceeds via irradiation of 2-iodo-substituted diphenyl ethers **45** which in turn are prepared by the thermal rearrangement of iodonium phenolates **33** (**Scheme 15**).[33]

It is interesting to note that suitably substituted 2,4-dihydroxyacetophenones **47** have also been converted to *o*-iododiphenyl ethers **48** by using IBD-KOH/MeOH[34a] (**Scheme 16**). The *o*-hydroxyacetylaryl moiety present in these ketones remains intact under the reaction conditions. This moiety is very useful for obtaining several heterocyclic systems.[34b] Mallik and Mallik[35] have also employed a similar approach on various flavonoids.

2.2.4. 2*H*-CHROMENE DERIVATIVES[36]

A convenient route to the synthesis of 2*H*-chromene derivatives **51** is provided by intramolecular cyclization of iodonium salts of type **50**. The required iodonium salts are obtained by the oxidation of vinyltrimethylsilanes **49** with iodosobenzene and $Et_3O{\bullet}BF_4$ (**Scheme 17**).

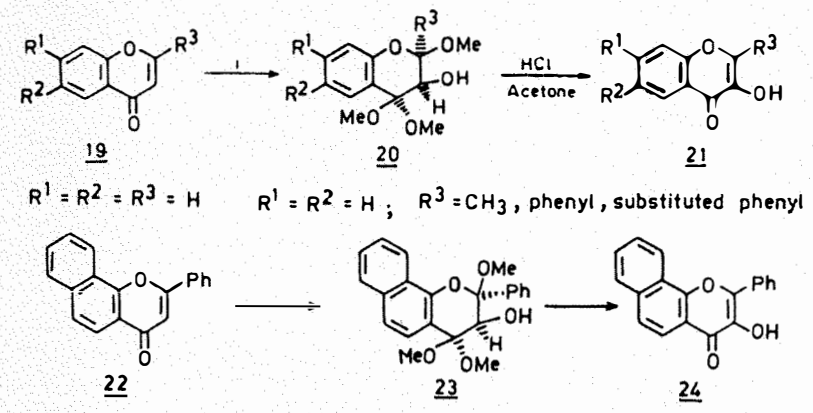
2.3. MISCELLANEOUS REACTIONS

The work described in parts 2.1 and 2.2 provides general routes for the synthesis of a wide variety of heterocyclic compounds. In addition there are some specific reactions which result in the formation of heterocycles. This part of our article delineates the synthesis of various heterocyclic compounds using miscellaneous reagents and conditions. Since general trends are not observed in these syntheses, only selected examples are described. The reactions have been subdivided into two groups depending upon the hetero atom present in the system (N or O).

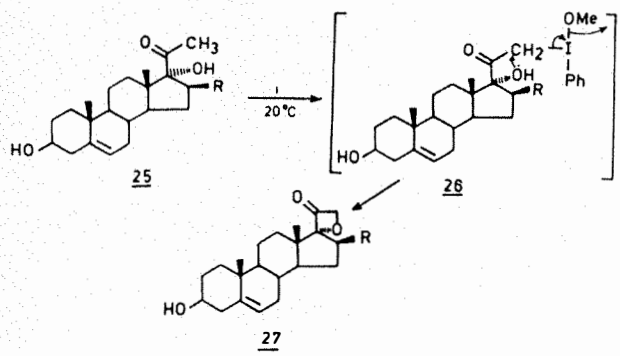
2.3.1. OXYGEN-CONTAINING HETEROCYCLIC COMPOUNDS

3-Aroyl-5-aryl-2-hydroxyfurans[37]

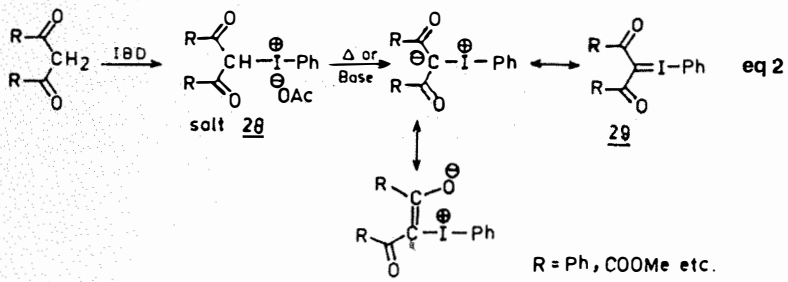
On treatment with IBD in aqueous acetic acid, 4-aryl-2,4-dioxobutanoic acids **52** undergo oxidative coupling. The coupled product **53** then cyclizes to 3-aroyl-5-aryl-2-hydroxyfurans **54** following the loss of CO_2 and H_2O (**Scheme 18**).

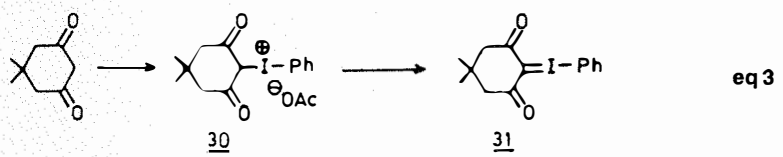


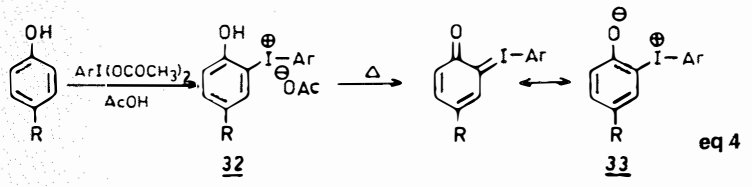
Scheme 9

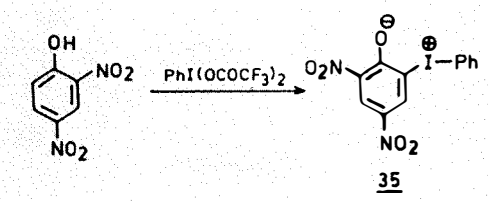


Scheme 10

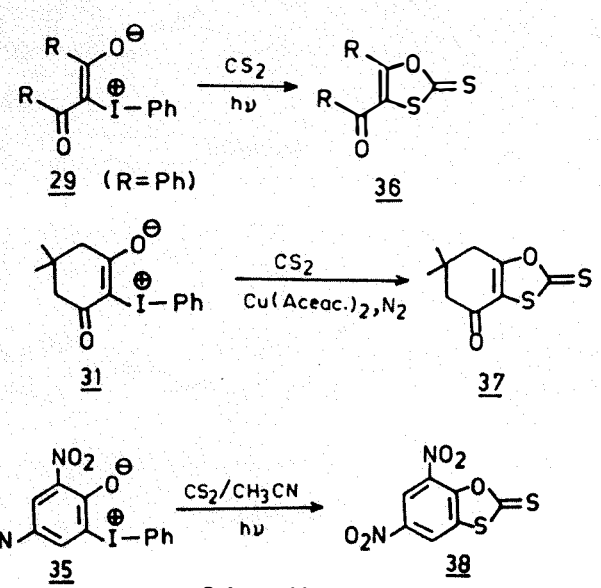




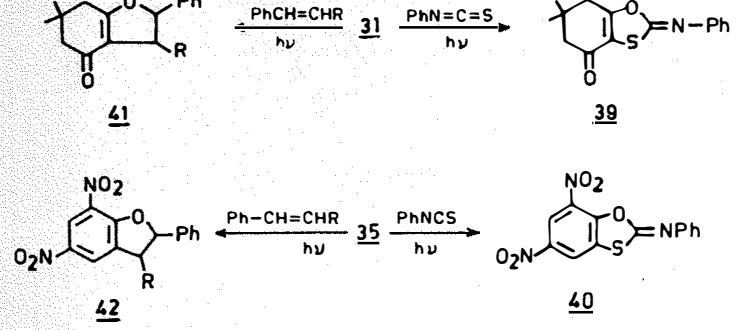




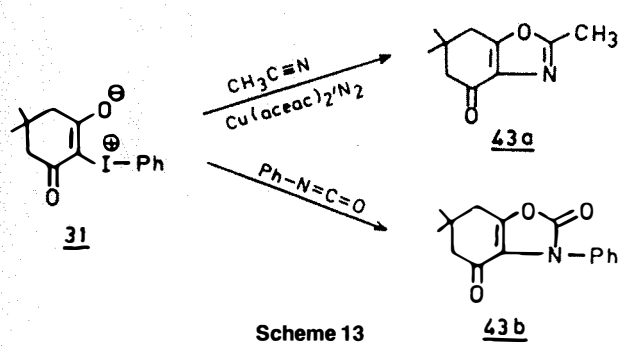
eq 5



Scheme 11



Scheme 12



Scheme 13

Pyrones [38]

Oxidation of tetraketones **55** with IBD leads to the formation of pyrones **57**. This reaction possibly occurs via cyclic ene-hemiacetal forms **56** (**Scheme 19**).[38]

In contrast, the reaction of tetraketones **55** with lead tetraacetate (LTA) yields the isomeric pyrones **58**. This observation provides an example wherein the two reagents (LTA and IBD) show a basic difference, despite the general presumption that these reagents behave in a similar manner.

2.3.2. NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

Diazepines [39-41]

Primary amines are oxidized by iodoarene dicarboxylates to azo compounds under mild conditions.[42] However, suitably substituted amines **59** cyclize under the influence of IBD to diazepines **60** (**Scheme 20**).[39-41]

Benzofuroxans and related compounds

Oxidation of *o*-nitroaniline with IBD in benzene offers a unique route to benzofuroxan (**61**, **Scheme 21**).[42c] This oxidative cyclization is common to anilines having an ortho substituent capable of forming a heterocyclic ring.[43-45]

Furoxans, isoxazoles, and pyrazole dioxides

Dioximes are known to generate a variety of "N"-heterocyclic compounds when oxidized with $PhI(OCOCF_3)_2$ (iodobenzene bistrifluoroacetate; IBTFA). Benzil dioxime **63**, for example, is converted into the corresponding furoxan **64**.[46]

However, these reactions are of limited use. Oxidation of β-dioximes **65** with IBTFA gives rise to a mixture of isoxazoles **66** and 4-oxo-4*H*-pyrazole-di-*N*-oxides **67**[47,48] whereas *trans*-2-unsaturated 1,4-dioximes under similar conditions form a mixture of 3*a*,6*a*-dihydroisoxazolo[5,4-*d*]isoxazoles **69** and pyridazine 1,2-dioxides **70** (**Scheme 22**).[49]

Reticuline to salutaridine and related conversions

An important example of intramolecular oxidative coupling involving IBD is the conversion of reticuline (**71**) to salutaridine (**72**) (**Scheme 23**).[50] Similarly, other aryl analogues undergo this aryl-aryl coupling.[51]

2-Piperidinones, 2-pyrrolidinones, and indol-2(3*H*)-ones[52]

In the presence of IBTFA α-methylthio amides undergo a Pummerer-type rearrangement leading to the formation of nitrogen-containing heterocycles such as *N*-methyl-5-methylene-3-methylthio-2-piperidinone (**74a**, from **73**), *N*-methyl-3-methylthio-pyridin-2(3*H*)-one (**74b**, from **73**), *N*-methyl-

3-methylthio-4-vinyl-2-pyrrolidinone (**76**, from **75**), and 3-methylthio-*N*-phenylindol-2(3*H*)-one (**78**, from **77**) (**Scheme 24**).[52]

As shown in **Scheme 25** for methylthio amide **77**, the reaction with IBTFA is presumed to proceed through the intermediate **81** by elimination of trifluoroacetic acid. Initial attack on the sulfur atom of **77** followed by elimination of trifluoroacetate and iodobenzene leads to sulfonium salt **80** which then undergoes intramolecular cyclization to form **81**.[52]

Azaanthraquinone-spirodienones[50]

On hypervalent iodine oxidation with IBTFA in CF_3CH_2OH, *O*-silylated phenols **82** yield spiroheterocyclic compounds such as azaanthraquinone-spirodienones **83**. The reaction occurs via intramolecular carbon-carbon bond formation as shown in **Scheme 26**. The reaction of *O*-methyl ether of type **84** with IBTFA under the same conditions takes a different course yielding a mixture of the expected product **83** (R=H) and products resulting from a dienone-phenol rearrangement (**85** and **86**, **Scheme 27**).[50]

Bridgehead heterocycles[53]

In a recent report, it has been shown that the reaction of arenecarbaldehyde benzothiazol-2-yl-hydrazones (**87**) with IBD in acetic acid and sulfuric acid yield 1,2,4-triazolo[3,4-*b*]-benzothiaoles **88** exclusively (**Scheme 28**).[53]

3. CONCLUSION

A perusal of the reactions described so far makes it abundantly clear that hypervalent iodine reagents are gaining significance in the syntheses of numerous heterocyclic compounds. However, no systematic studies have thus far been directed to unfold the full potential of these new reactions and the relationship between structure and reactivity. Hypervalent iodine mediated reactions may play a significant role in the development of simpler synthetic procedures for the synthesis of compounds having biological importance. It is expected that in the near future hypervalent iodine reagents will assume a much wider role in the chemistry and syntheses of heterocyclic compounds.

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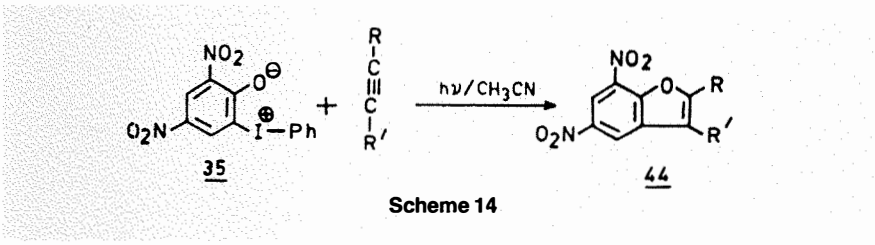
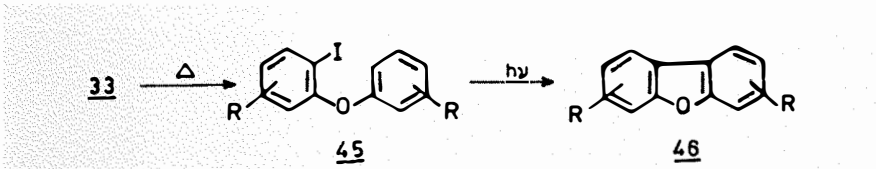
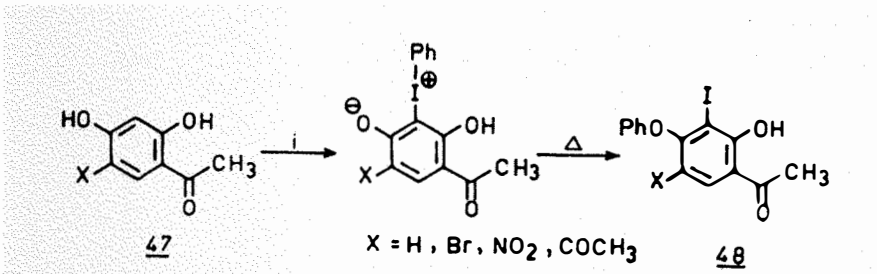


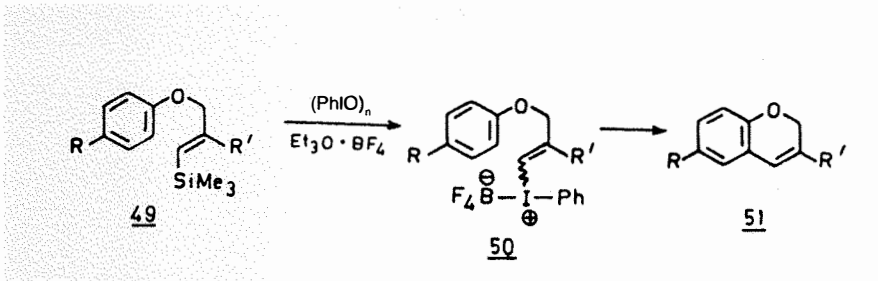
Scheme 14



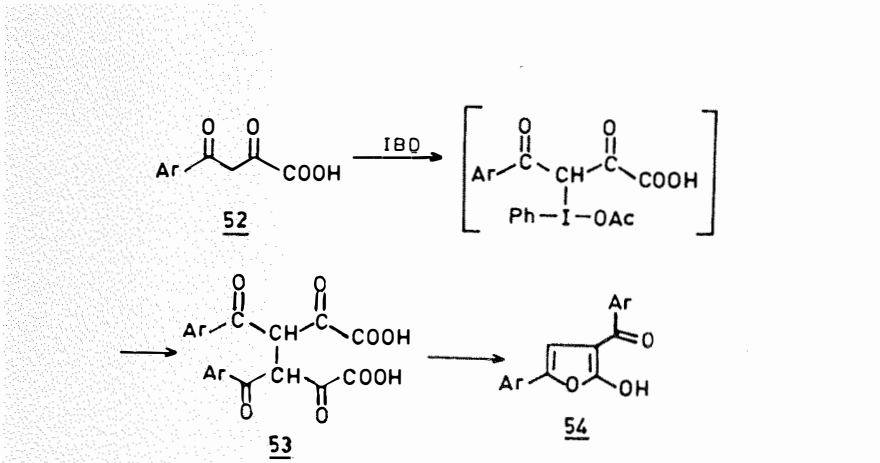
Scheme 15



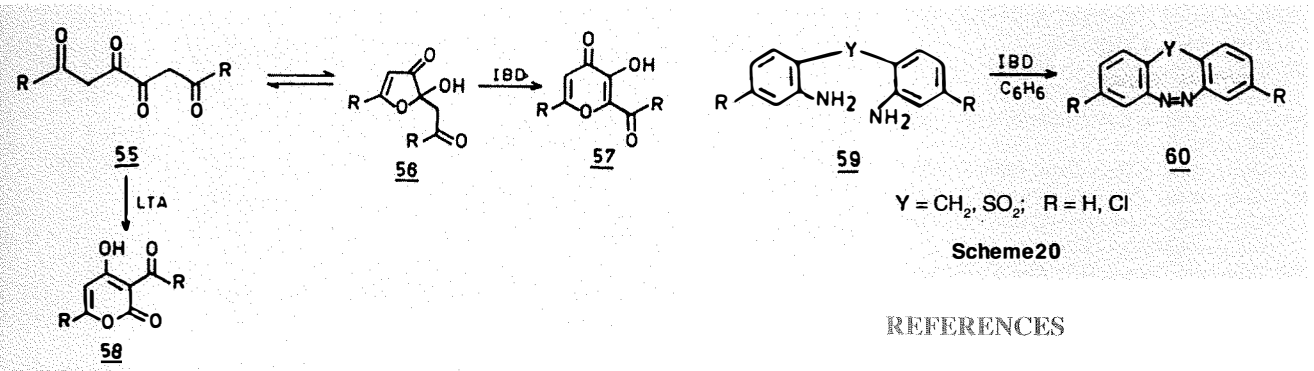
Scheme 16



Scheme 17

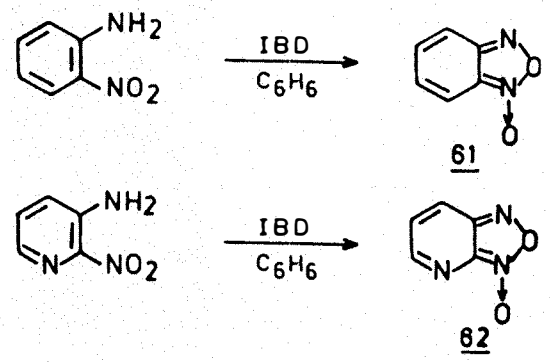


Scheme 18

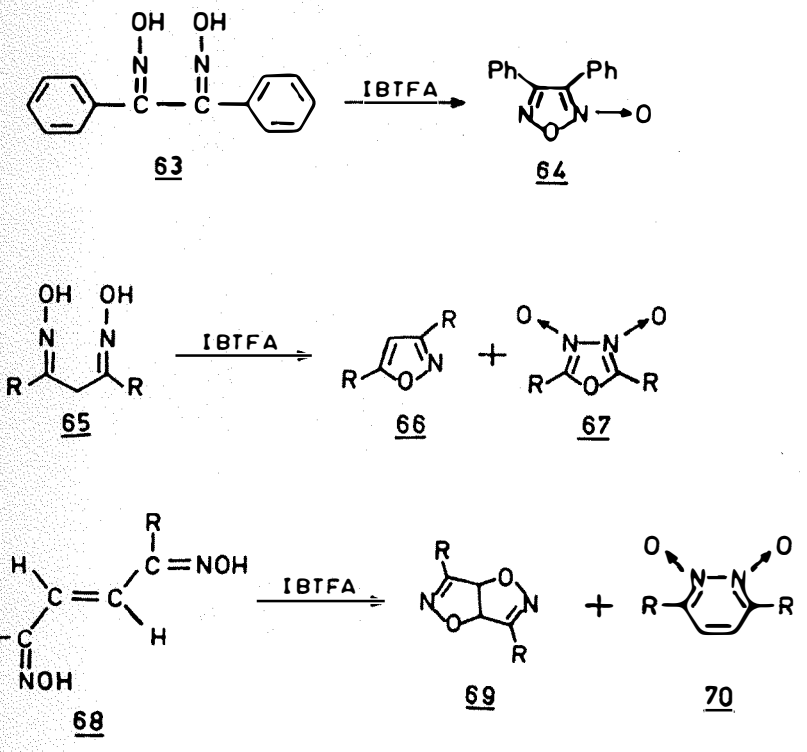


Scheme 19

Scheme 20



Scheme 21



Scheme 22

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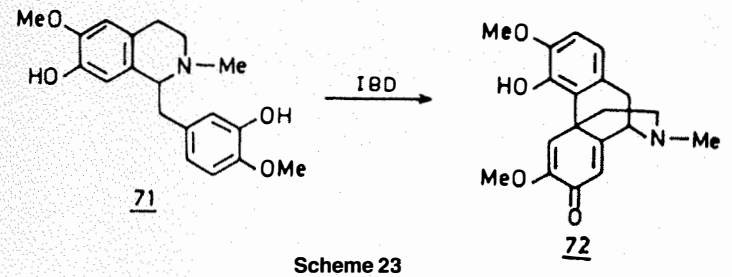
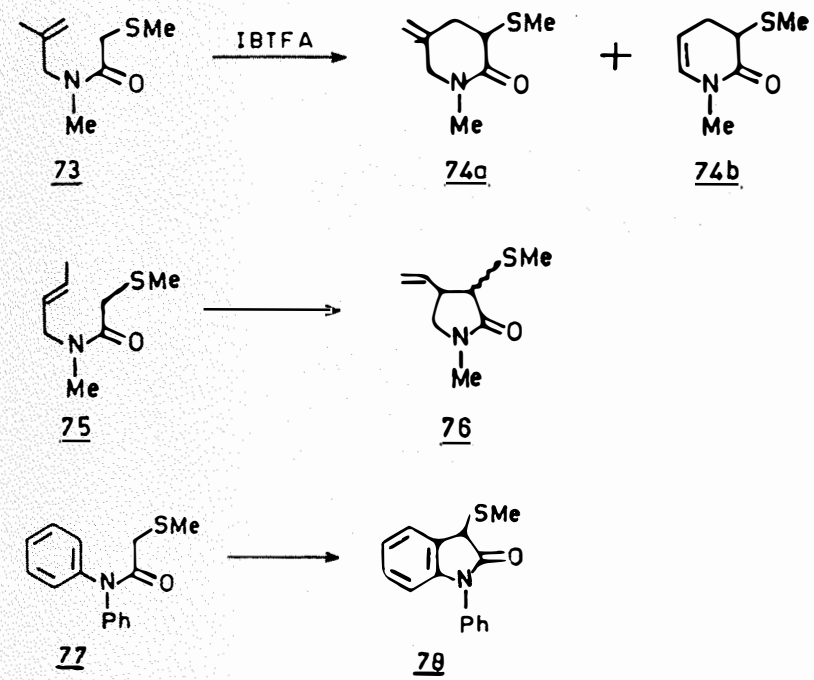
ABOUT THE AUTHORS

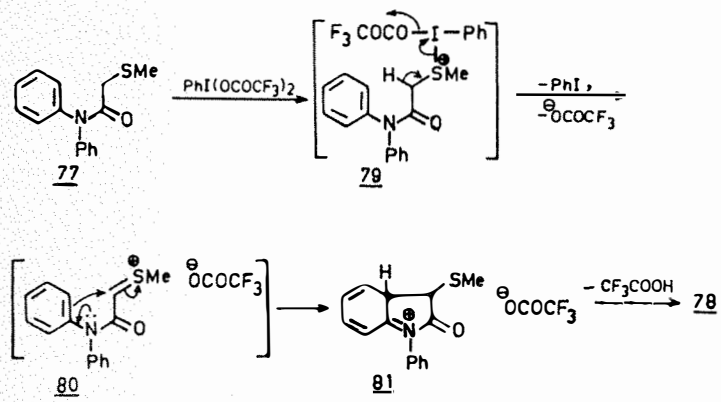
Dr. Om Prakash was born in 1950. He received his Ph.D. from the University of Roorkee, India, in 1976 under the supervision of Professor V.K. Mahesh. After about one year of post-doctoral work with Professor S.P. Singh at Kurukshetra University on the "Synthesis of Heterocyclic Compounds of Potential Medicinal Interest", he joined the faculty as a lecturer in Meerut College in 1977. In 1979, he joined the faculty of Kurukshetra University. He went to the



Scheme 23



Scheme 24



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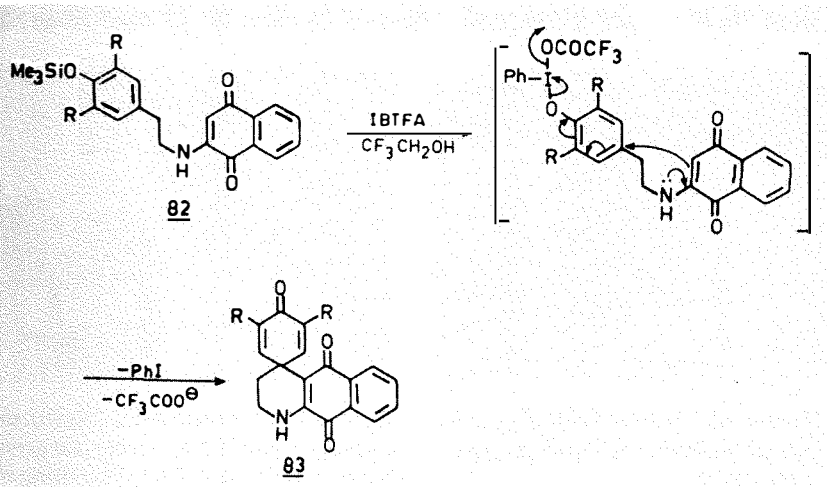
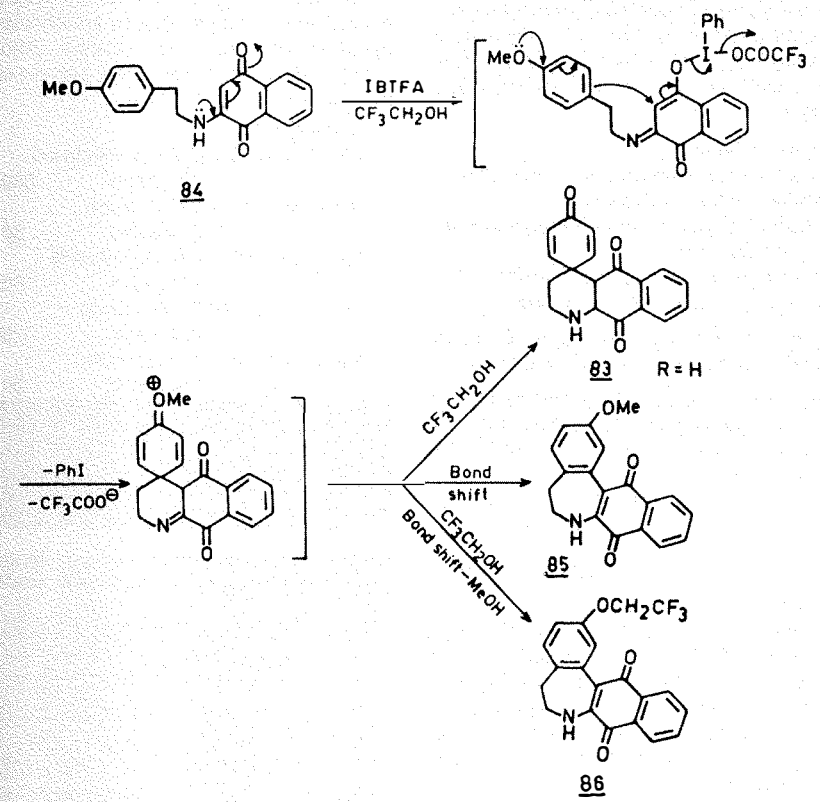
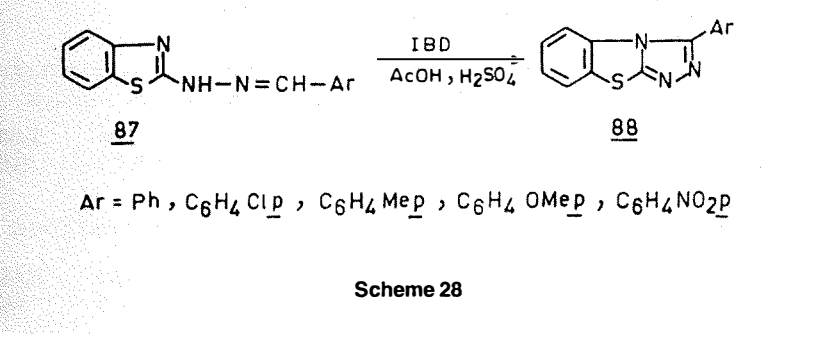


Scheme 26



Scheme 27



Scheme 28

University of Illinois-Chicago in 1983 and worked there as a post-doctoral research associate with Professor Robert M. Moriarty on the "Synthesis of Acetylcholinesterase Reactivators." During his stay at the University of Illinois-Chicago (1983-1986), he also explored the utility of hypervalent iodine reagents in organic synthesis. As a result of his efforts, applications of hypervalent oxidation reactions gained a wider acceptance. He also developed novel applications of many new reagents. In 1986, he came back to Kurukshetra University as a faculty member and then again visited Professor Moriarty's laboratory in Chicago in 1988-89. At present, Dr. Prakash is Associate Professor at Kurukshetra University and his research group consisting of M. Phil, Ph.D. and post-doctoral workers, is working on the applications of newer reagents in organic synthesis and synthesis of heterocyclic compounds.

Professor S.P. Singh received the M.Sc. degree from the University of Lucknow in 1961 and was awarded the Patel Vishwa Shanti Gold Medal for academic distinction. He received his Ph.D. degree from the same institution with a thesis on chemical investigation of Indian medicinal plants under the supervision of Professor A.B. Sen. Following a position as lecturer in Chemistry at Kurukshetra, he joined the University of Illinois-Chicago Circle (UICC, now UIC) to do post-doctoral work (1968-70) with Professor J. Kagan. It was a highly creative period which saw the initiation of mechanistic studies on the chemical and photochemical reactions of glycidic acids and their esters. He visited the United States again as a senior Fulbright Scholar (1979-80) and worked in the newly emerged area of phototoxicity of natural and non-natural substances, the work he is still continuing. He was selected as professor in 1985 and served as chairman of the Department of Chemistry, Kurukshetra University during 1989-92. In between, he was invited as a visiting Research Professor (1989) by UIC where he interacted with Professor Robert M. Moriarty, who is a leading researcher in the development of hypervalent iodine reagents. Later, as an Indo-Spanish Cultural Exchange Fellow, he spent some time with Professor J. Elguero (CSIC, Madrid) and coauthored several research papers dealing with NMR spectral studies of pyrazoles. He visited the UK in 1993 as INSA-Royal Society Fellow and gave seminar lectures at many British Universities. His current research interests center around the structural re-investigation of the products, particularly focusing on those obtained by the reaction of heterocyclic hydrazines with 1,3-diketones, an investigation of their conformation using NMR spectral techniques, synthesis of phototoxic molecules and application of new reagents in organic synthesis.

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About Our Cover:

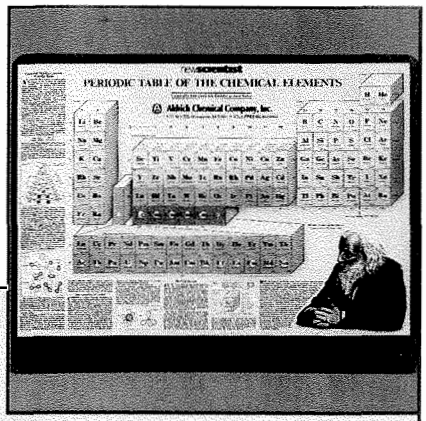
This masterpiece entitled **The Account-Keeper** (oil on canvas, 66.3 x 53.6 cm) was painted by Nicholaes Maes in 1656.

A pupil of Rembrandt, Maes' reputation stands on his genre paintings of domestic scenes with women and children. A similar interior is found in a painting in the Lichtenstein collection, although our painting features a map of the world and a sculpted bust. These lend a scholarly, even humanist, air to the subject, an old woman dozing over ledgers.

It is from Rembrandt that Maes takes the warm color scheme and soft light, which are very much different from Vermeer and his followers. If the appurtenances remind one of Vermeer (lighting from left, maps, etc.), the soft forms and broader paint handling deny it. Several other paintings have the subject matter of a dozing, elderly woman over books, notably works in the Worcester Art Museum and in the Musées Royaux des Beaux-Arts, Brussels.

The painting is in the collection of The Saint Louis Art Museum.

Lab Notes



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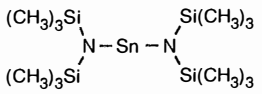

Dr. Eric Roskamp of Northwestern University recently suggested that we offer this interesting, thermally stable, diamagnetic[1] tin(II) amide. $Sn[N(TMS)_2]_2$ reacts with primary aldehydes to give *trans-N,N*-bis(TMS)enamines.[2] Addition of amines to $Sn[N(TMS)_2]_2$ generates in situ unsymmetrical tin(II) amides which, when treated with aldehydes/ketones,[2,3] carboxylic acids[4]/esters,[5,6] and β-amino esters,[7,8] affords *N,N*-dialkylenamines, amides, or β-lactams, respectively.

Naturally, we made this reagent.

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It was no bother at all, just a pleasure to be able to help.

Benzotriazole-Stabilized Carbanions: Generation, Reactivity, and Synthetic Utility

Alan R. Katritzky, Zhijun Yang, and Darren J. Cundy*
Center for Heterocyclic Compounds
Department of Chemistry, University of Florida
Gainesville, FL 32611-7200, USA

ABSTRACT:

Benzotriazole-activated methane systems readily undergo lithiation and reactions with electrophiles to afford the corresponding adducts which, upon acidic hydrolysis or methanolysis, give the corresponding α-functionalized aldehydes, ketones, carboxylic acids, and dimethyl acetals. Thus, such benzotriazole-stabilized methyl anions function as novel formyl-, acyl-, β-aminoacyl-, carboxyl-, and methylal-anion equivalents.

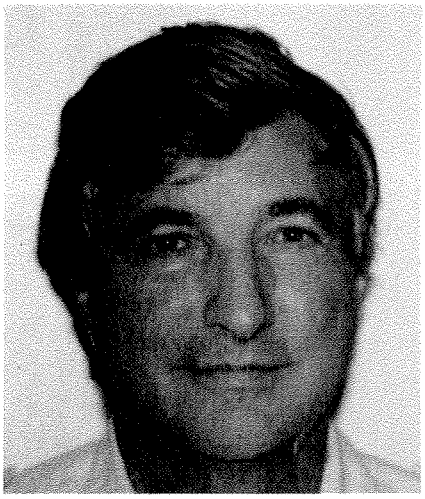
1. INTRODUCTION

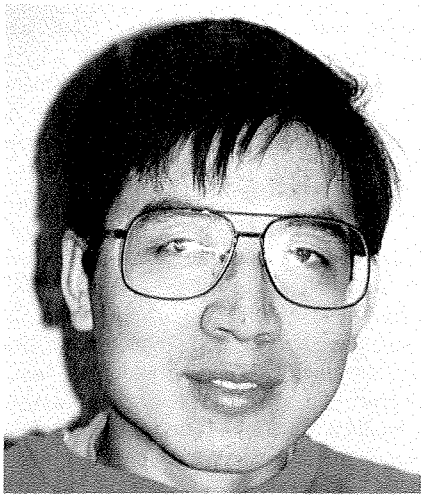
The chemistry of benzotriazole has been an area of intensive investigation in our group for the past few years. Much of the work has involved the benzotriazole-mediated transformations of structurally simpler and readily available organic species into more complex and more highly functionalized molecules. These transformations have been achieved mainly via the introduction and subsequent nucleophilic displacement of a benzotriazolyl group, and have been reviewed on several occasions.[1,2]

Benzotriazole has also demonstrated the ability to act as an activating group towards α-proton loss. This property, together with the well-established leaving ability of the benzotriazolate anion, greatly extends the applications of benzotriazole in organic synthesis. This account will systematically discuss the generation, reactivity, and synthetic utility of α-benzotriazolyl carbanions, and will focus on benzotriazole-stabilized methyl anion systems as functionalized anion synthon equivalents utilized for the synthesis of aldehydes, ketones, carboxylic acids, ethers, dimethyl acetals, and carbocycles.

2. BIS(BENZOTRIAZOL-1-YL)-(*p*-TOLYL)METHYL ANION AS AN ARYLACYL ANION EQUIVALENT

To be an acyl anion equivalent, a compound must satisfy at least two criteria (which apply equally for formyl and carboxyl anion equivalents):

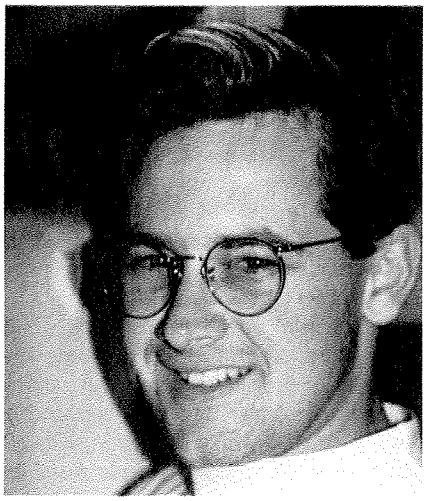


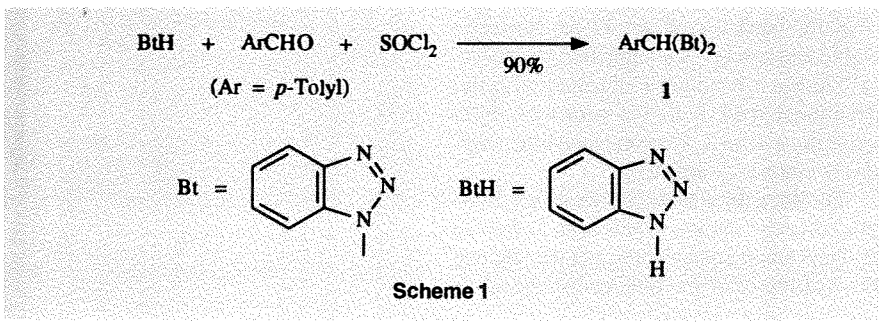


1. It must possess, at the required carbon position, an acidic proton which can be abstracted to provide an anion. The ease of abstraction will depend largely on the activating ability of the groups attached to this carbon.

2. The intermediate products from the subsequent reaction of the anion with electrophiles must be readily hydrolyzed. The facility for this will be determined mainly by the leaving ability as well as electron donating ability (for stabilizing the intermediate cations) of the same activating groups mentioned above.

In addition to these two requirements, other factors should be considered when evaluating the usefulness of a compound as a potential anion synthon equivalent. Among them are: availability, stability, and toxicity; generality of the reaction of the intermediate anion with electrophiles; and the reaction conditions needed for unmasking the protected functionality.





Scheme 1

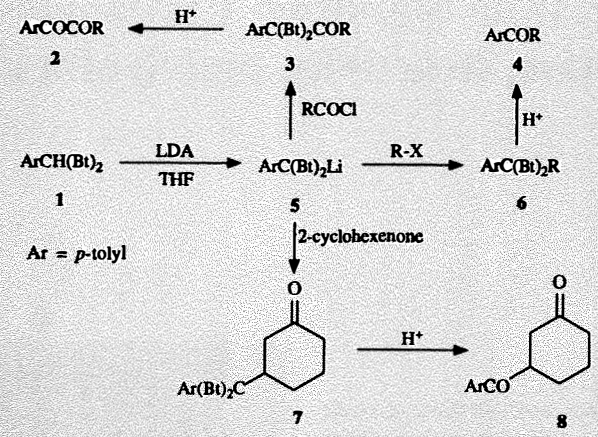
Over the past two decades, sulfur (in divalent or in oxidized form) activated methane systems have been the dominant functionalized anion equivalents.[3,4] However, many of these systems suffer a common drawback in that the cleavage of carbon-sulfur bonds generally requires promotion by toxic, heavy metal salts, most commonly mercury(II). Although other systems, such as phosphorus-,[5,6] silicon-,[7,8] and nitrogen-activated methanes[9-11] have also been reported, we are aware of no example (outside our work) where a methane system is activated solely by heterocycles and acts as a formyl or acyl anion equivalent.

Bis(benzotriazol-1-yl)(*p*-tolyl)methane (**1**) is prepared by a one-pot reaction of benzotriazole with *p*-tolualdehyde and thionyl chloride in 90% yield[12] (**Scheme 1**). Treatment of **1** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C affords the corresponding carbanion **5** which reacts with a variety of electrophiles[12] (**Scheme 2**). With alkyl and allyl halides, the corresponding alkylated products **6** are usually obtained in good to excellent yields (**Table 1**). The low yield obtained with *s*-butyl bromide is presumably a result of the steric hindrance experienced by this electrophile. Reaction of **5** with acyl chlorides yields the corresponding carbonyl compounds **3**, while addition to 2-cyclohexenone gives exclusively the Michael product **7** in 78% yield.

Hydrolysis of adducts **3**, **6**, and **7** is carried out in tetrahydrofuran in the presence of sulfuric acid at 50°C and affords the corresponding aryl ketones **2**, **4**, and **8** respectively in nearly quantitative yields (**Table 1**).

Direct treatment of anion **5** with aldehydes under similar conditions results in complete recovery of the starting material. This is presumably because of the instability of the initial intermediate adducts **9**, which due to steric congestion have a strong tendency to dissociate back into the starting materials. In support of this, the corresponding silyl ethers **11** were obtained in moderate yields when trimethylsilyl chloride was added to the reaction mixture (**Table 2**). Addition of trimethylsilyl chloride to a solution of the anion **5**, followed by treatment of the resulting trimethylsilyl intermediate **10** with aldehydes in the presence of cesium fluoride, also produces compounds **11** in similar yields. The silyl ether derivatives **11** are generally stable and can be easily purified by recrystallization or column chromatography. Treatment of **11** under the same hydrolysis conditions affords the corresponding α-hydroxy ketones (**Table 2**).

The advantage of the bis(benzotriazol-1-yl)arylmethyl anion systems such as **5** as an arylacyl anion equivalent lies in the fact that the hydrolysis of the intermediate products

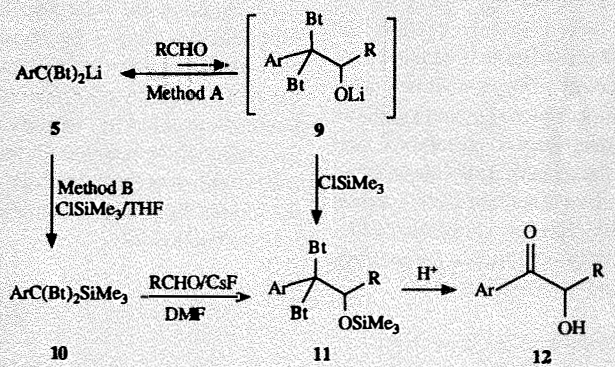


Scheme 2

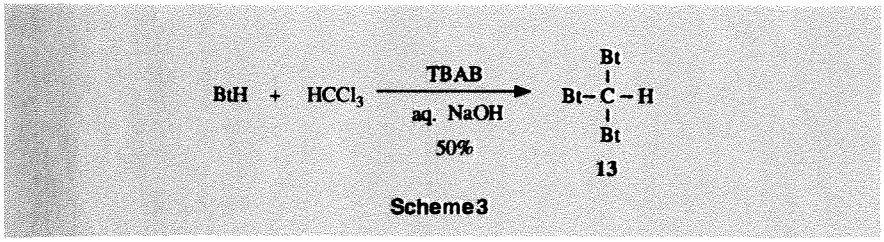
Table 1. Reaction of anion **5** with electrophiles and subsequent hydrolysis of the resulting adducts.

Electrophile	Adduct	Yield (%)	Ketone	Yield (%)
MeI	6a	92	4a	95
i-PrI	6b	52	4b	84
BuBr	6c	78	4c	95
s-BuBr	6d	8	4d	91
Hexyl I	6e	52	4e	96
Hexyl Br	6e	83	4e	-
$PhCH_2Br$	6f	95	4f	93
Allyl Br	6g	84	4g	80
MeCOCl	3a	45	2a	92
PhCOCl	3b	61	2b	88
Cyclohexenone	7	78	8	92

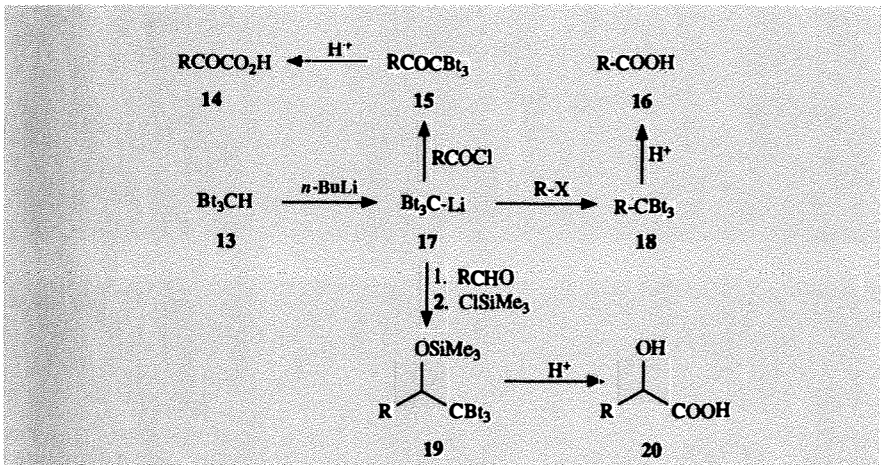
Table 2. Preparation of α-hydroxy aromatic ketones.



R	Adducts	Method	Yield (%)	Ketone	Yield (%)
p-tolyl	11a	A	68	12a	95
		B	76		
phenyl	11b	B	60	12b	95



Scheme 3

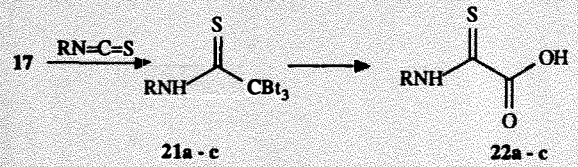


Scheme 4

Table 3. Reaction of 17 with electrophiles and subsequent hydrolysis of the resulting adducts.

Electrophile	Adduct	Yield (%)	Carboxylic acid	Yield (%)
$PhCH_2Br$	18a	92	16a	92
$PhCH{=}CHCH_2Br$	18b	84	16b	73
n-BuI	18c	86	16c	79
PhCOCl	15a	98	14a	81
p-MeC_6H_4COCl	15b	98	14b	83
$PhCHO/ClSiMe_3$	19a	91	20a	78
p-$MeC_6H_4CHO/ClSiMe_3$	19b	94	20b	76

Table 4. Preparation of thio oxamic acids.



21a - c 22a - c

R	Adduct	Yield (%)	thio oxamic acid	Yield (%)
phenyl	21a	90	22a	82
1-naphthyl	21b	89	22b	87
benzyl	21c	80	22c	74

can be effected under mild acidic conditions, thus avoiding the use of toxic, heavy metal reagents needed for sulfur-activated systems. While the yields of the first step are comparable to those reported for other systems, the nearly quantitative yields in the subsequent hydrolysis make our method particularly attractive.

3. TRIS(BENZOTRIAZOL-1-YL)-METHYL ANION AS A $^{-}CO_2H$ EQUIVALENT

Tris(benzotriazol-1-yl)methane (**13**) is prepared by treating benzotriazole with an excess of chloroform in aqueous sodium hydroxide in the presence of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst[13] (**Scheme 3**).

Treatment of **13** with butyllithium in tetrahydrofuran gives the anion **17**, which is subsequently quenched with alkyl halides or acyl chlorides to afford the alkylated **18**, or acylated products **15**, respectively. Similar to the case of the anion **5** described previously, the adducts formed from reaction of the anion **17** with aldehydes require the intermediacy of the trimethylsilyl ether to be synthetically useful (**Scheme 4**). Presumably due to steric effects, **17** fails to react with ketones even under trapping conditions. Hydrolysis of **15**, **18**, and **19** is achieved under similar conditions described previously for the preparation of aromatic ketones[12] and affords the α-functionalized carboxylic acids in good to excellent yields (**Scheme 4** and **Table 3**).

Following a similar protocol, anion **17** reacts with isothiocyanates to afford adducts **21a-c** in excellent yields (**Table 4**). Subsequent hydrolysis gives the corresponding thio oxamic acids **22a-c** which were new compounds and would be otherwise difficult to prepare.

Unlike formyl and acyl anion equivalents which have relied heavily on sulfur-activated systems, the carboxyl anion synthon ($^{-}CO_2H$) has a cheap and convenient source in the cyano anion (^{-}CN). However, the relatively harsh conditions needed for the hydrolysis of the intermediate products can limit its use. Tris(benzotriazol-1-yl)methyl anion provides a useful complement to cyanide in this aspect.

4. (BENZOTRIAZOL-1-YL)-(CARBAZOL-9-YL)METHYL ANIONS AS FORMYL AND ACYL ANION EQUIVALENTS

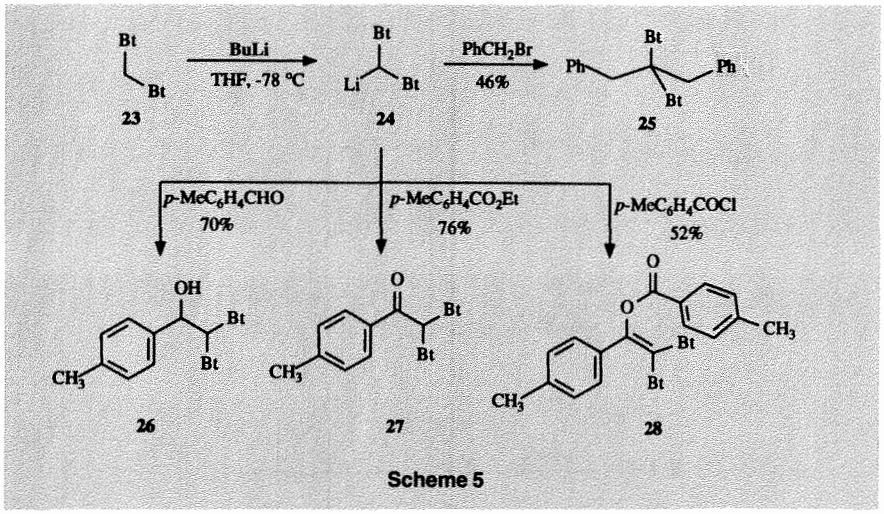
4.1. (Benzotriazol-1-yl)(carbazol-9-yl)-methyl Anion as a Formyl Anion Equivalent

The development of formyl anion equivalents has been an area of intensive investigation over the last two decades due to the diverse usefulness of the formyl

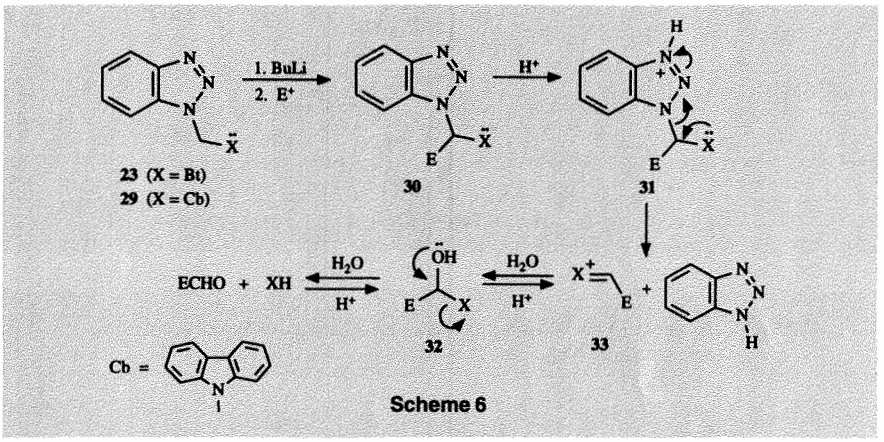
functionality. Although sulfur activated systems, such as 1,3-dithiane, have been the major source of formyl anion equivalents, other systems have also been investigated. A more recent example[14,15] is thiazole which, upon treatment with butyllithium followed by quenching with electrophiles, affords 2-substituted thiazoles. Deprotection is a one-pot operation requiring a sequence of reagents (e.g., methyl iodide, sodium borohydride, and mercury(II) chloride).

The same protocol as used for **13** was applied to bis(benzotriazol-1-yl)methane (**23**) in an attempt to develop a novel formyl anion equivalent. Bis(benzotriazol-1-yl)methyl anion (**24**) is readily generated by treating **23** with butyllithium[16] (**Scheme 5**). Reaction of **24** with benzyl bromide gave mainly the disubstituted product **25**. Ethyl 4-methylbenzoate produced the corresponding carbonyl compound **27**, while 4-methylbenzoyl chloride gave the enol ester **28** in 52% yield, apparently resulting from the further *O*-acylation of the enolate form of **27**. With *p*-tolualdehyde as the electrophile, the corresponding alcohol **26** is obtained in 70% yield (**Scheme 5**).

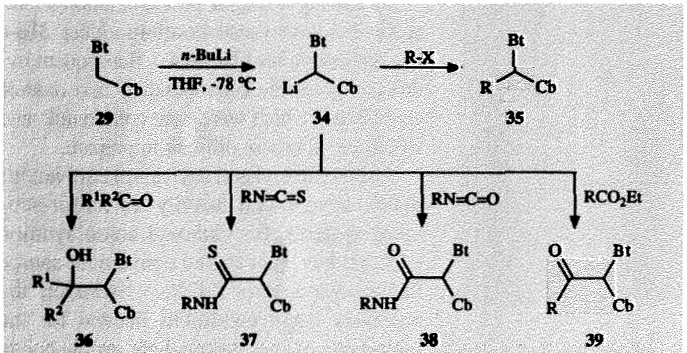
Attempted hydrolysis of **25**, **26**, and **27** was not successful under various acidic conditions, indicating a lack of sufficient electronic assistance from one benzotriazolyl group to allow the departure of the other (protonated benzotriazole) thereby generating imminium ion **33** (**Scheme 6**). Based on



Scheme 5



Scheme 6

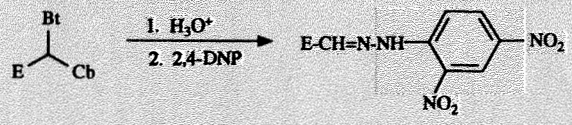


Scheme 7

Table 5. Lithiation of (benzotriazol-1-yl)(carbazol-9-yl)methane and reaction with electrophiles.

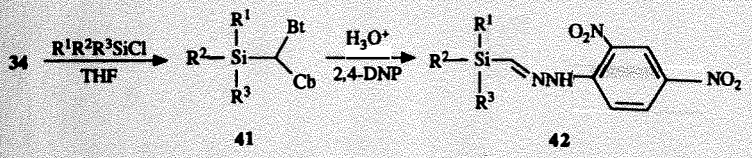
Product	Electrophile	Yield (%)	Product	Electrophile	Yield (%)
35a	$PhCH_2Br$	81	36d	$(C_2H_5)_2CO$	86
35b	$4\text{-}BrC_6H_4CH_2Br$	78	36e	$(CH_2)_5CO$	91
35c	$n\text{-}C_8H_{17}Br$	71	36f	$(CH_2)_4CO$	84
35d	$n\text{-}C_4H_9I$	84	37	PhNCS	78
36a	$4\text{-}MeC_6H_4CHO$	82	38	PhNCO	93
36b	$(CH_3)_2CHCHO$	91	39	$PhCO_2Et$	88
36c	$(CH_3)_3CCHO$	96			

Table 6. Hydrolysis of the adducts **35a-d**, **36a-f**, **37**, and **38**.



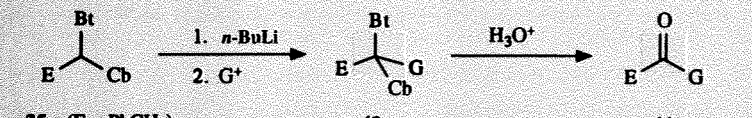
Substrate	E	40	Yield (%)
35a	$PhCH_2$-	a	78
35b	$4\text{-}BrC_6H_4CH_2$-	b	81
35c	$n\text{-}C_8H_{17}$-	c	67
35d	$n\text{-}C_4H_9$-	d	83
36a	$4\text{-}MeC_6H_4CH(OH)$-	e	42
36b	$(CH_3)_2CHCH(OH)$-	f	76
36c	$(CH_3)_3CCH(OH)$-	g	71
36d	$(C_2H_5)_2C(OH)$-	h	73
36e	$(CH_2)_5C(OH)$-	i	71
36f	$(CH_2)_4C(OH)$-	j	61
37	PhNHC(=S)-	k	70
38	PhNHC(=O)-	l	68

Table 7. Preparation of 2,4-dinitrophenylhydrazones of formylsilanes **42**.



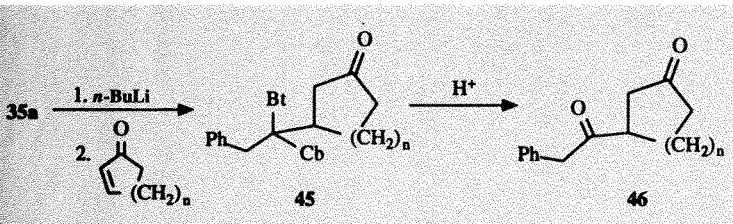
Entry	R^1	R^2	R^3	Yield (%) 41	Yield (%) 42
a	Me	Me	Me	91	48
b	Me	Me	Bu^t	89	81
c	Pr^i	Pr^i	Pr^i	92	79
d	Bu^i	Bu^i	Bu^i	90	84
e	Ph	Ph	Ph	95	58

Table 8. Reaction of substituted (benzotriazol-1-yl)(carbazol-9-yl)methyl anions with electrophiles and subsequent hydrolysis of the resulting adducts.



35a (E = $PhCH_2$)
35d (E = Bu)

Entry	E	G^+	G	Yield (%) 43	Yield (%) 44
a	$PhCH_2$	$PhCH_2Br$	$PhCH_2$	86	63
b	$PhCH_2$	MeI	Me	88	77
c	$PhCH_2$	BuI	Bu	78	82
d	Bu	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$	87	51
e	$PhCH_2$	PhCHO	PhCH(OH)	67	57
f	$PhCH_2$	PhNCO	PhNHC(O)	88	62
g	Bu	MeI	Me	91	86
h	Bu	BuI	Bu	94	89
i	Bu	PhNCO	PhNHC(O)	86	82



45	n	Yield (%)	46	Yield (%)
a	1	76	a	51
b	2	81	b	67

Scheme 8

this rationalization, we selected carbazole as an alternative heterocyclic moiety which, being a better electron donor, was expected to assist in the elimination of benzotriazole without simultaneous deactivation of the methylene group towards deprotonation.

Indeed, (benzotriazol-1-yl)(carbazol-9-yl)methane (**29**) readily undergoes deprotonation with butyllithium and the resulting anion reacts with a wide spectrum of electrophiles to afford the corresponding adducts in good to excellent yields[16,17] (**Scheme 7** and **Table 5**).

Hydrolysis of these adducts is carried out in aqueous tetrahydrofuran in the presence of sulfuric acid, affording the corresponding aldehydes which were isolated as their 2,4-dinitrophenylhydrazones[16] (**Table 6**).

The (benzotriazol-1-yl)(carbazol-9-yl)methane system, the first formyl synthon equivalent developed from a heterocycle-activated methane, is marked by superior reactivity of its anion **34** towards electrophiles and the mild conditions employed in the subsequent hydrolysis of the resulting adducts.

Recently, we have extended this system to the synthesis of formylsilanes which were long regarded as unstable species. Most of the methods for the preparation of acylsilanes are not applicable to the synthesis of formylsilanes due to the instability of the latter. Only four formylsilanes have so far been reported, utilizing three methods for their preparation: (i) a 1,3-dithiane method which afforded a good yield (formyltriisopropylsilane) only when the intermediate was converted into its corresponding dimethyl acetal;[18] (ii) treatment of the corresponding zirconium η^2-sila acyl complex with anhydrous HCl to give formyltris(trimethylsilyl)silane;[19] and (iii) transmetalation of (1,3-dioxolan-2-yl)tributylstannane[20] with butyllithium followed by reaction with *tert*-butyldimethylchlorosilane or trimethylchlorosilane, giving the corresponding intermediates which were then hydrolyzed in the presence of 2,4-dinitrophenylhydrazine to afford the 2,4-dinitrophenylhydrazones of formyl-*tert*-butyldimethylsilane and formyltrimethylsilane, respectively.

Treatment of anion **34** with silyl chlorides gives the corresponding silylated products **41a-e** in excellent yields[21] (**Table 7**). The insensitivity of the reaction to the electronic and/or steric nature of the substituents in the electrophiles is testimony to the generality of this reaction. Hydrolysis of the intermediate products **41a-e** is carried out in dilute sulfuric acid in the presence of 2,4-dinitrophenylhydrazine. In the cases of **41a-d**, the reactions went to completion at room temperature within 24h and afforded the

2,4,-dinitrophenylhydrazones of the corresponding formylsilanes **42a-d**. In the case of **41e**, a higher temperature (50-55°C) was required, presumably because the electron-withdrawing nature of the phenyl group disfavored the formation of the intermediate imminium ion (as was illustrated in **Scheme 6**). The mild hydrolysis conditions avoid the use of toxic reagents and allow a wide range of formylsilanes to be readily accessible.

4.2. Substituted (Benzotriazol-1-yl)-(carbazol-9-yl)methyl Anions as Acyl Anion Equivalents

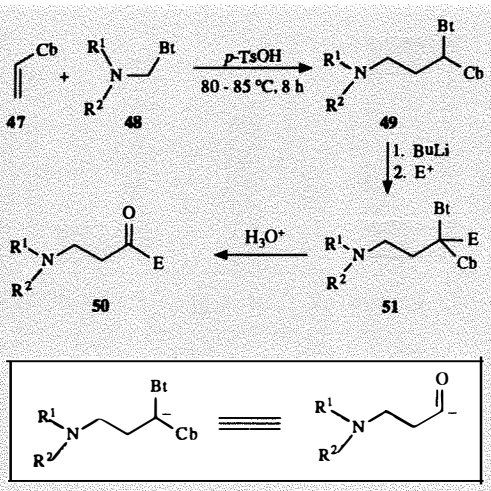
Acyl anion equivalents have been reported previously.[3,22,23] The versatility of (benzotriazol-1-yl)(carbazol-9-yl)methane as a formyl synthon equivalent has naturally prompted us to investigate the possibility of using its substituted derivatives as acyl synthon equivalents.[24] Thus, treatment of 1-(benzotriazol-1-yl)-1-(carbazol-9-yl)-2-phenylethane (**35a**) with butyllithium followed by quenching with electrophiles gives the corresponding disubstituted derivatives **43** (**Table 8**). Subsequent hydrolysis is effected with dilute aqueous hydrochloric acid in tetrahydrofuran (20°C) yielding the corresponding ketones **44**. In a similar way, the butyl derivative **35d** serves as a pentanoyl synthon equivalent.

It is noteworthy that the carbanion of **35a** adds to 2-cyclohexenone and 2-cyclopentenone regiospecifically to give the 1,4 addition compounds **45** which, upon hydrolysis, afford the corresponding 1,4-diketones **46** (**Scheme 8**).

4.3. 3-Dialkylamino-1-(benzotriazol-1-yl)-1-(carbazol-9-yl)propanes as β-Aminoacyl Synthon Equivalents

β-Aminoethyl ketones have been widely used as precursors for the in situ generation of the relatively unstable and reactive vinyl ketones required for Robinson annulation type reactions, e.g., of cyclohexanones[25] or 1,3-diketones[26] for constructing carbocyclic rings in natural products synthesis.[27] Few α-(functionalized alkyl)-β-aminoethyl ketones have been reported in the literature. Most of these have been prepared by the Mannich reaction of simple ketones such as acetone, acetophenone with formaldehyde and amines, and lack other functionality.[28] There has been no report of the synthesis of β-aminoketones via acyl anion equivalents.

Other studies in our laboratory have demonstrated that the benzotriazole adducts of type **48** undergo polar additions to enol ethers[29] and enamines, including *N*-vinylcarbazole, to afford adducts **49**.[30] Employing conditions similar to those described previously,[16,24] **49** undergoes smooth

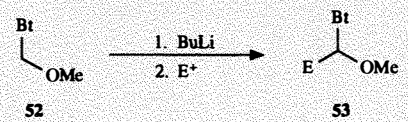


Scheme 9

Table 9. Preparation of adducts **51** and β-aminoketones **50**.

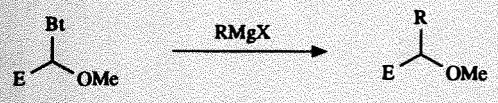
Entry	R^1, R^2	E^+	E	Yield (%) 51	Yield (%) 50
a	-$(CH_2)_2O(CH_2)_2$-	$PhCH_2Br$	$PhCH_2$-	78	92
b	-$(CH_2)_2O(CH_2)_2$-	4-$MeC_6H_4CH_2Br$	4-$MeC_6H_4CH_2$-	74	87
c	-$(CH_2)_2O(CH_2)_2$-	$CH_3(CH_2)_5I$	$CH_3(CH_2)_5$-	86	96
d	-$(CH_2)_2O(CH_2)_2$-	$CH_3(CH_2)_7I$	$CH_3(CH_2)_7$-	82	94
e	-$(CH_2)_2O(CH_2)_2$-	PhCHO/TMSCl	PhCH(OTMS)-	61	89
f	-$(CH_2)_2O(CH_2)_2$-	4-MeC_6H_4CHO/TMSCl	4-$MeC_6H_4CH(OTMS)$-	68	88
g	-$(CH_2)_2O(CH_2)_2$-	*c*-$C_6H_{11}CHO$/TMSCl	*c*-$C_6H_{11}CH(OTMS)$-	57	82
h	-$(CH_2)_4$-	$PhCH_2Br$	$PhCH_2$-	69	84
i	-$(CH_2)_4$-	$CH_3(CH_2)_7I$	$CH_3(CH_2)_7$-	71	91

Table 10. Lithiation of **52** and subsequent reaction with electrophiles.



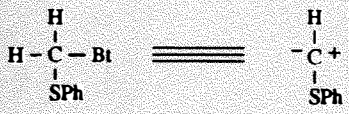
53	Electrophile	E	Yield (%)
a	$PhCH_2Br$	$PhCH_2$-	94
b	$Ph(CH_2)_3Br$	$Ph(CH_2)_3$-	91
c	MeI	Me-	85
d	BuBr	Bu-	80
e	$CH_3(CH_2)_7Br$	$CH_3(CH_2)_7$-	89
f	$CH_3(CH_2)_9Br$	$CH_3(CH_2)_9$-	87
g	Me_3SiCl	Me_3Si-	75
h	CH_3CHO	$CH_3CH(OH)$-	80
i	PhCHO	PhCH(OH)-	53
j	4-MeC_6H_4CHO	4-$MeC_6H_4CH(OH)$-	82
k	Ph_2C=O	$Ph_2C(OH)$-	84
l	$PhCO_2Et$	PhCO-	91
m	4-$MeC_6H_4CO_2Et$	4-MeC_6H_4CO-	92

Table 11. Preparation of methyl ethers.



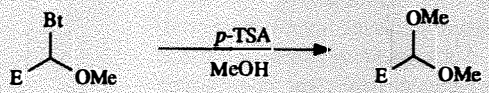
53 54

54	E	RMgX	R	Yield (%)
a	$PhCH_2$	BuMgI	Bu	68
b	C_8H_{17}	BuMgI	Bu	57
c	$C_{10}H_{21}$	BuMgI	Bu	64
d	Bu	$C_8H_{17}MgI$	C_8H_{17}	60
e	$C_{10}H_{21}$	$PhCH_2MgBr$	$PhCH_2$	50



Scheme 10

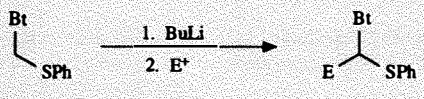
Table 12. Preparation of dimethyl acetals.



53 55

55	E	Yield (%)
a	$PhCH_2$-	88
b	$Ph(CH_2)_3$-	91
c	$CH_3(CH_2)_7$-	83
d	$CH_3(CH_2)_9$-	94
e	4-$MeC_6H_4CH(OH)$-	78
f	$Ph_2C(OH)$-	54
g	PhCO-	86
h	4-MeC_6H_4CO-	88

Table 13. Lithiation of **56** and subsequent reaction with electrophiles.



56 57

57	electrophile	E	Yield (%)
a	MeI	Me	49
b	$PhCH_2Cl$	$PhCH_2$	68
c	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	46
d	p-MeC_6H_4CHO	p-$MeC_6H_4CH(OH)$	44
e	Ph_2CO	$Ph_2C(OH)$-	76
f	PhCN	PhC(=NH)	71

deprotonation with butyllithium to give the corresponding products **51** (**Scheme 9**). Hydrolysis of **51** is readily accomplished at ambient temperature in the presence of dilute hydrochloric acid. Careful control of the pH during workup enables easy removal of carbazole and benzotriazole, affording essentially pure β-aminoketones **50** in excellent yields[31] (**Table 9**).

5. (BENZOTRIAZOL-1-YL)-METHOXYMETHYL ANION: SYNTHESIS OF METHYL ETHERS AND DIMETHYL ACETALS

(Benzotriazol-1-yl)methoxymethane (**52**) is prepared in nearly quantitative yield by treating 1-chloromethylbenzotriazole with sodium methoxide in methanol.[32] The incorporation of the methoxy functionality into the benzotriazole-activated methane system has allowed us to examine the reactivity of the carbanion geminally stabilized by nitrogen and oxygen atoms. Oxygen has been known as a poor α-carbanion stabilizing moiety. In fact, carbanions stabilized solely by alkoxy groups have rarely appeared in the literature. However, (benzotriazol-1-yl)methoxymethane (**52**) undergoes deprotonation with butyllithium smoothly (-78°C, THF, 1h), and the resulting carbanion reacts readily with a variety of electrophiles[32,33] (**Table 10**).

Treatment of adducts **53** with Grignard reagents results in displacement of the benzotriazolyl group and affords the corresponding methyl ethers[33] (**Table 11**). The whole sequence can be thought of as a stepwise insertion of electrophiles (E^+) and nucleophiles (R^-) to give ECH(OMe)R using the synthon $BtCH_2OMe$.

When adducts **53** are treated with methanol in the presence of *p*-toluenesulfonic acid (*p*-TSA), the corresponding dimethyl acetals **55** are obtained in good to excellent yields[32] (**Table 12**). In this way, (benzotriazol-1-yl)methoxymethyl anion functions as a novel methylal anion equivalent [$^-CH(OMe)_2$].

6. (BENZOTRIAZOL-1-YL)-PHENYLTHIOMETHANE AS A 1,1-DIPOLE SYNTHON EQUIVALENT IN AROMATIC ANNULATIONS

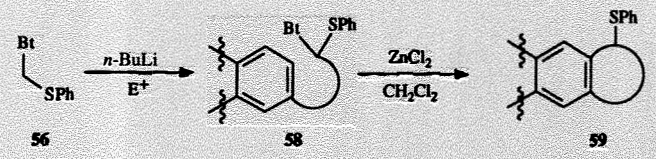
(Benzotriazol-1-yl)phenylthiomethane (**56**) undergoes deprotonation with butyllithium and the resulting carbanion reacts readily with a variety of electrophiles[34] (**Table 13**).

We have demonstrated that the benzotriazolyl group in the compounds BtCH(R)X (where X = NR^1R^2, $NHCOR^3$, or SPh) can be removed under Lewis acid-catalyzed conditions to afford the corresponding carbocations.[35-37] Trapping these cations with electron-rich aromatics or C-H acids in situ produces the corresponding amino-, amido-, or thio-alkylated products in high yields. The convenient reactivity of (benzotriazol-1-yl)phenylthiomethane anion toward electrophiles, together with the facile removal of the benzotriazolyl group to form a carbocation, has initiated an investigation

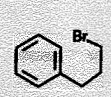
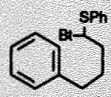
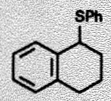
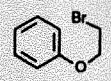
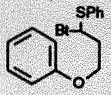
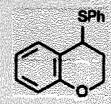
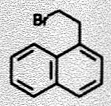
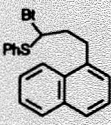
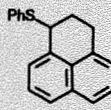
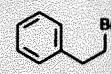
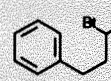
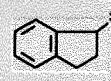
into the participation of this species as a 1,1-dipole synthon equivalent in aromatic annulations[38] (**Scheme 10**).

Treatment of **56** with butyllithium in THF at -78°C for 1 h followed by 1-bromo-3-phenylpropane yields the intermediate product **58a**. Subsequent treatment with zinc chloride in refluxing methylene chloride then affords the cyclization product **59a** in 92% yield (**Table 14**). In a similar manner, the annulation of β-bromophenetole, 2-(1-naphthyl)ethyl bromide, and 2-phenylethyl bromide is accomplished, affording compounds **59b**, **59c**, and **59d** respectively in good yields. The resistance of the phenylthio group to Lewis acid-catalyzed elimination and its subsequent presence in the cyclization products provides further opportunities for synthetic elaboration.

Table 14. (Benzotriazol-1-yl)phenylthiomethane as a 1,1-dipole equivalent.



56 58 59

Electrophile	Alkylated Product		Cyclized Product	
	Structure	Yield (%)	Structure	Yield (%)
	 58a	89	 59a	92
	 58b	84	 59b	87
	 58c	79	 59c	69
	 58d	68	 59d	52

7. SUMMARY

Benzotriazole-activated methane systems undergo deprotonation with organolithiums to afford the corresponding α-carbanions which react with a wide variety of electrophiles. Hydrolysis or methanolysis of the resulting intermediate products under mild acidic conditions leads to the formation of the corresponding α-functionalized aldehydes, ketones, carboxylic acids, and dimethyl acetals. Thus, these benzotriazole-stabilized methyl anions function as novel formyl-, acyl-, β-aminoacyl-, carboxyl-, and methylal-anion equivalents. The high total yields and mild conditions for the liberation of the masked functionalities make them attractive homologation reagents in organic synthesis.

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Diisopinocampheylchloroborane, (DIP-Chloride™), an Excellent Chiral Reducing Reagent for the Synthesis of Secondary Alcohols of High Enantiomeric Purity

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INTRODUCTION

Asymmetric synthesis has received enormous attention over the last two decades.[1] Moreover, the well-documented and publicized case involving thalidomide emphasized the importance of accomplishing the synthesis of enantiomerically pure drugs.[2] New guidelines by the Food and Drug Administration have expressed concern with the enantiomeric purity of any material manufactured either for the promotion of human health or to combat pests.[3] Therefore, all conceivable methods for the production of optically pure chiral materials are being aggressively researched by both academic and industrial laboratories.

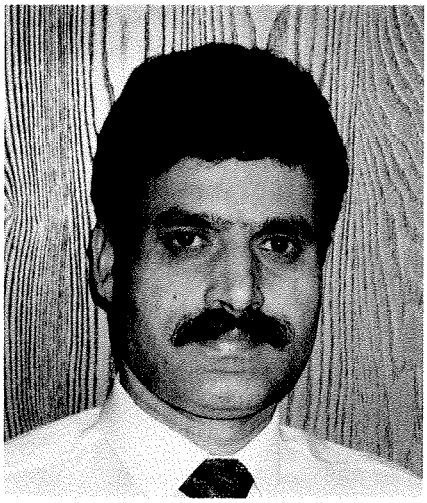
Among the various asymmetric reactions, enantioselective reduction of prochiral ketones has received a great deal of attention.[4] The products, namely optically active secondary alcohols, are components of many naturally occurring compounds, biologically active compounds, and materials such as liquid crystals.[1] They are also important as synthetic intermediates for various functionalities such as halides, amines, esters, ethers, and thiols.[4]

Many different approaches have been utilized to obtain optically active alcohols. However, it is only during the last decade that some good reagents and methodologies for asymmetric reduction have come to prominence. Presently, there are five reagents which are extensively used in asymmetric reduction. These five reagents (**Figure 1**) are: (**1**) diisopinocampheylchloroborane, IPC_2BCl, (DIP-Chloride™); (**2**) *B*-isopinocampheyl-9-borabicyclo-[3.3.1]nonane, (Alpine-Borane™); (**3**) oxazaborolidines; (**4**) aluminum complexes derived from optically active 1,1'-binaphthyl-2,2'-diol, such as BINAL-H; and (**5**) BINAP-Ru complexes.

Brown's DIP-Chloride (**1**),[4a,d] Midland's Alpine-Borane (**2**),[4b] and Noyori's BINAL-H (**4**)[4c] are utilized stoichiometrically, whereas Corey's oxazaborolidines (**3**) and Noyori's BINAP-Ru complexes are utilized catalytically. It is important to mention that no single reagent can be expected to deliver all the desirable properties which one would like in a reducing agent. Nonetheless, efforts are being made to produce a reagent that provides a useful compromise.

Although development of catalytic reagents is usually desirable, stoichiometric reducing agents are preferred if they are: (a) inexpensive, easy to prepare, and commercially available in both enantiomeric forms; (b) able to reduce most classes of ketones with high enantiomeric excess and predictable product configuration; and (c) recyclable with respect to the chiral moiety.

Keeping the above requirements in mind, Brown and his group developed many boron reagents[4d] where α-pinene proved to be a good chiral auxiliary, especially since both enantiomers are commercially available. Among the various boron reagents utilized by Brown's group, DIP-Chloride (**1**) was found to be the reagent of choice. Its continued application in academic and industrial research makes it one of the most popular reagents in asymmetric reduction. The present review discusses in detail the applications of this versatile reagent in asymmetric reduction. Application of DIP-Chloride as an



enolboration reagent for stereoselective aldol condensation and as a reagent for the opening of *meso*-epoxides to form non-racemic halohydrins is also briefly discussed.

Preparation of DIP-Chloride

(-)-DIP-Chloride can be readily prepared from commercially available (+)-α-pinene (92% ee) by hydroboration with borane-

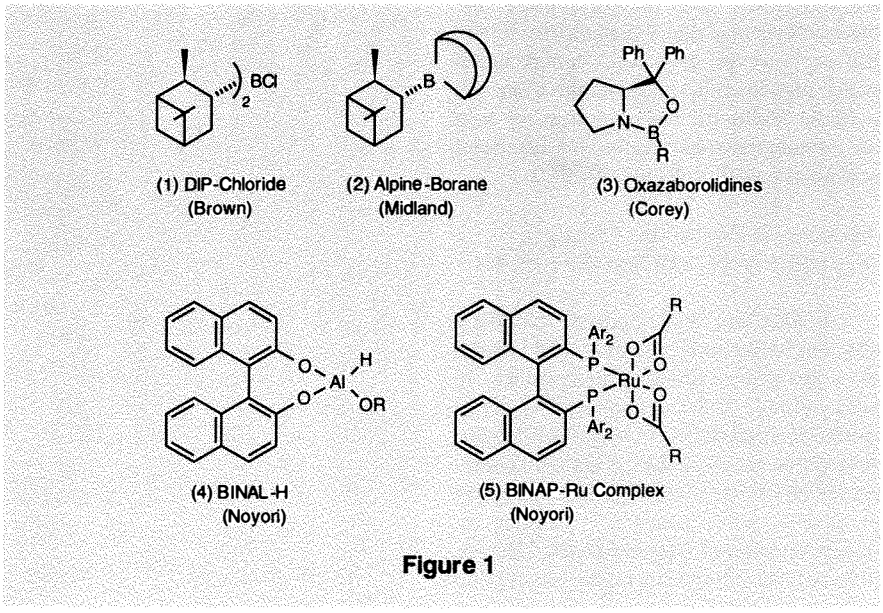
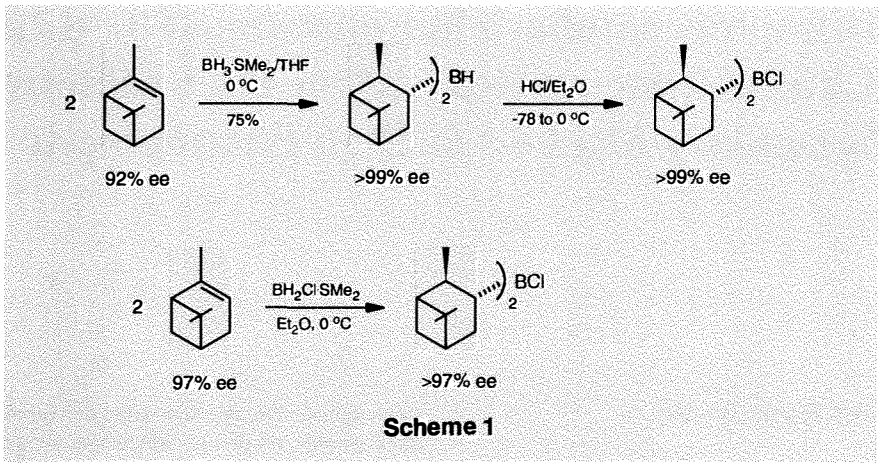


Figure 1

dimethyl sulfide in THF at 0°C. This generates diisopinocampheylborane (IPC_2BH),[5] in greater than 99% ee. During the reaction, the minor isomer is left in the solution and the major isomer, (-)-IPC_2BH, crystallizes out. The crystalline product is treated with dry HCl in diethyl ether. Removal of ether and cooling to 0°C provides solid, crude (-)-DIP-Chloride which may be recrystallized from pentane to produce white, crystalline material[6], with a melting point of 54-56°C (**Scheme 1**). Alternatively, (-)-DIP-Chloride can also be prepared by suspending IPC_2BH in ether at 0°C and bubbling gaseous HCl through the suspension until all of the IPC_2BH dissolves. Removal of ether provides reagent **1** in >98% purity. (+)-DIP-Chloride is prepared similarly from (-)-α-pinene. DIP-Chloride can also be prepared by treating 2 equivalents of α-pinene with monochloroborane-methyl sulfide complex[4d] (**Scheme 1**).



Scheme 1

Table 1. ^{11}B NMR studies of complexation of (-)-DIP-Chloride with one equivalent of tertiary amine in dichloromethane.

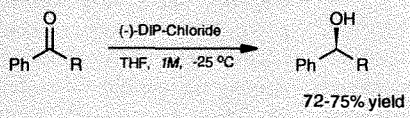
Amine	^{11}B NMR, δ (ppm)	Amine	^{11}B NMR, δ (ppm)
pyridine	13	diethylmethylamine	76
2-picoline	67	dimethylethylamine	76
2,6-lutidine	76	*N*-methylpyrrolidine	76
triethylamine	76		

Note: ^{11}B NMR of DIP-Chloride in CH_2Cl_2 is observed at δ = 76ppm. All ^{11}B values are reported with reference to $BF_3 \cdot OEt_2$.

Table 2. Effect of solvent and temperature on chiral induction during reduction of acetophenone with (-)-DIP-Chloride.

Solvent	Temp., °C	Time, h	% ee
THF	-25	5	97.4
THF	0	3	95.8
ether	-25	5	96.3
CH_2Cl_2	-25	5	95.6
pentane	-25	5	95

DIP-Chloride fumes in air and is sensitive to moisture and oxygen, but can be stored for several years below 25°C under an inert atmosphere. The reagent does not complex with solvents such as ether, and THF.[7] It also does not complex with hindered tertiary amines, such as 2,6-lutidine, triethylamine, diethylmethylamine, dimethylethylamine, and *N*-methylpyrrolidine[7]. It does, however, show weak complexation with 2-picoline and strong complexation with pyridine (**Table 1**). The reagent can be used for asymmetric reduction in both polar and non-polar aprotic solvents (**Table 2**).[4,7]



Scheme 2

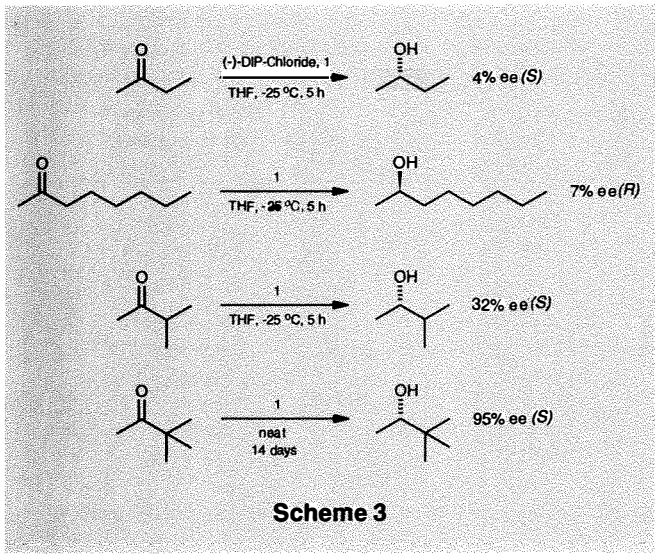
Asymmetric Reduction of Aralkyl, Aliphatic, Cyclic, and Bicyclic Ketones

(-)-DIP-Chloride has proved extremely efficient for the reduction of aralkyl ketones to produce the corresponding alcohols in high yield (72-75%) and high optical purity (>97% ee) (**Scheme 2**).[4d] It has been demonstrated that the reduction of aralkyl ketones proceeds with extraordinary consistency and predictable stereochemistry.[6,7] Testing the reagent on series of substituted aralkyl ketones indicated that substituents on the phenyl ring

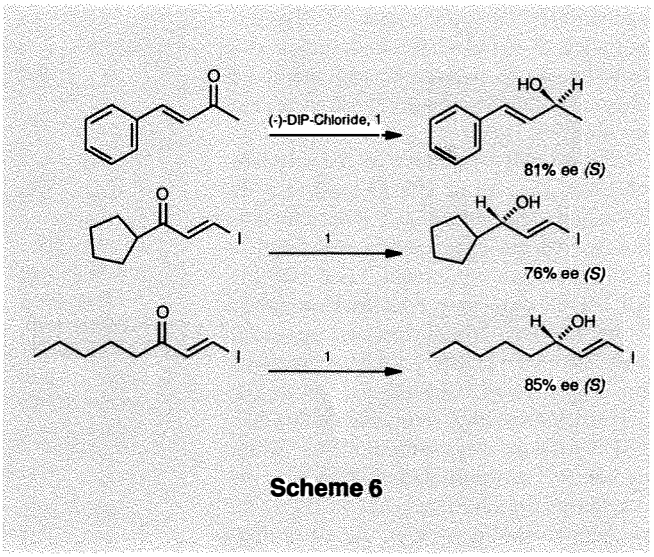
Table 3. Asymmetric reduction of substituted acetophenones with (-)-DIP-Chloride at -25 °C.

Ketone	X-Ph-$COCH_3$; X =	% ee	isomer
1	2-, 3-, or 4-fluoro	95-96	*S*
2	2-, 3-, or 4-chloro	96-98	*S*
3	4-bromo	96	*S*
4	4-iodo	97	*S*
5	2-, 3-, or 4-nitro	94-96	*S*
6	3- or 4-cyano	96-97	*S*
7	2-COOH[a]	25	*R*
8	4-COOH	97	*S*
9	2-COOMe	94	*S*
10	4-COOEt	97	*S*
11	4-$CONR_2$ (R = H or Et)	95	*S*
12	2-, 3-, or 4-Me	94-96	*S*
13	2-OH	81	*R*
14	3-OH	97	*S*
15	4-OH	10	*S*
16	2-OLi[b]	90	*R*
17	4-OLi	90	*S*
18	2-, 3-, or 4-OMe	92-96	*S*
19	2-, 3-, or 4-CF_3	94-96	*S*

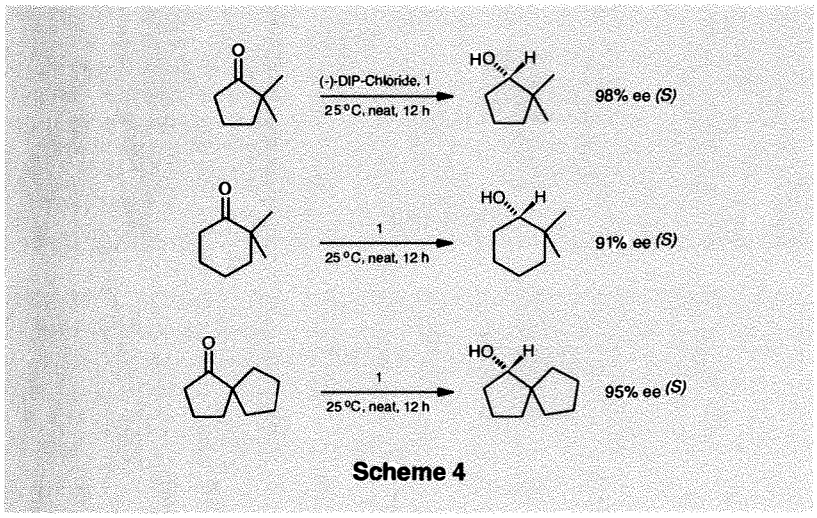
(a) Ketone:reagent, 1:2. (b) Reaction proceeds by initial chelate formation.



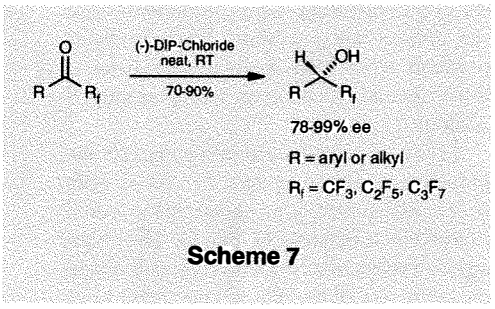
Scheme 3



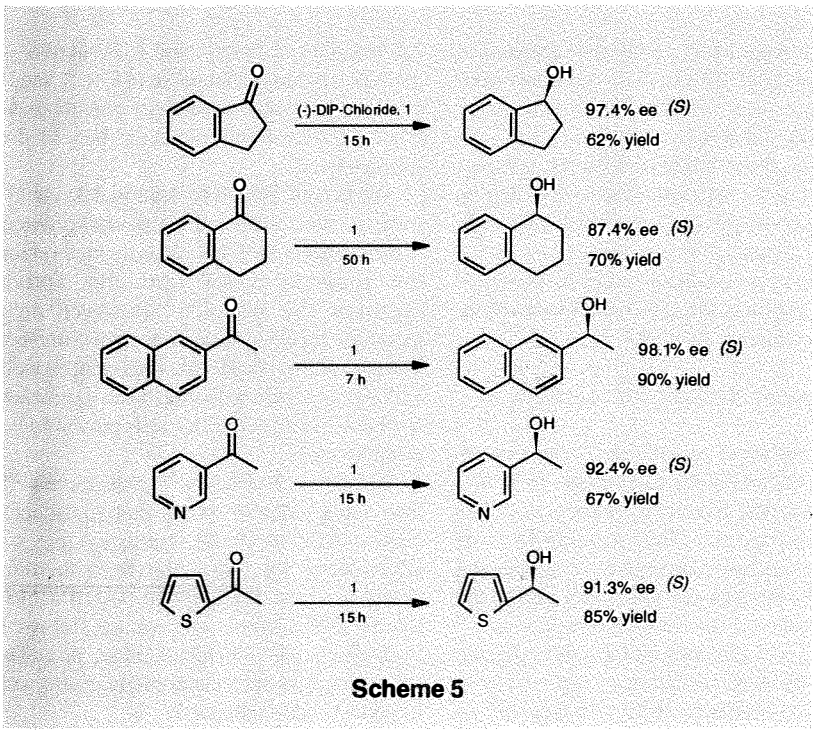
Scheme 6



Scheme 4



Scheme 7



Scheme 5

had little affect on the chiral outcome (**Table 3**).[1g] On the other hand, aliphatic unhindered ketones do not yield good enantioselection with (-)-DIP-Chloride (e.g., 2-butanone, 2-octanone, and 3-methyl-2-butanone are reduced in 4%, 7%, and 32% ee respectively, **Scheme 3**).[6,7] In contrast, hindered ketones have been reduced with high enantioselectivity (e.g., 3,3-dimethyl-2-butanone provides the corresponding alcohol in 95% ee). This aspect is further demonstrated in the reduction of cyclic ketones (**Scheme 4**).[7,8]

Bicyclic ketones, such as 1-indanone, α-tetralone, and 2'-acetonaphthone, are reduced in >97%, 87%, and 98% optical purity, respectively. Substitution of the aromatic group with a heteroaromatic group resulted in a slight decrease in the chiral induction. 3-Acetylpyridine and 2-acetylthiophene are reduced to the corresponding alcohols with 92% and 91% ee, respectively (**Scheme 5**).[7]

Reduction of olefinic ketones with (-)-DIP-Chloride has shown encouraging results (e.g., prostaglandin intermediates such as iodovinyl ketones are reduced in 85% ee, **Scheme 6**).[4d]

Asymmetric Reduction of Trifluoromethyl Ketones

Chiral fluorinated alcohols are potentially of great importance in biological, medicinal, and materials science.[9,10] Optically pure aryl trifluoromethyl alcohols are widely used for chiral stationary phases in liquid chromatography and as chiral solvating

agents in NMR applications.[11,12] The importance of chiral compounds possessing fluorine atoms in organic and medicinal chemistry has been highlighted in several reviews.[9,11]

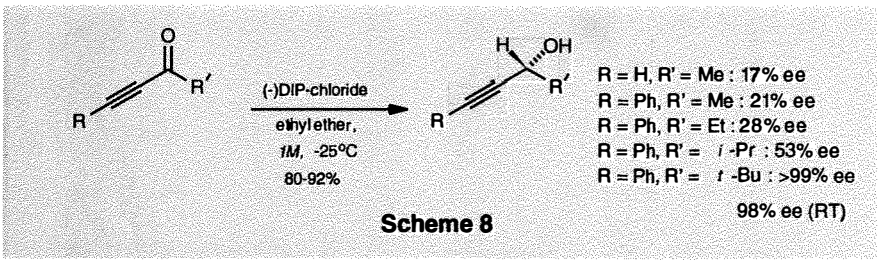
Brown and co-workers have recently demonstrated the use of DIP-Chloride for the reduction of fluoroketones.[13] The reductions are carried out conveniently with high ee without the use of solvent. For example, 1,1,1-trifluoroacetone, 1,1,1-trifluorononan-2-one, and 1,1,1-trifluorodecan-2-one are all reduced in 4-8h in 89% ee, 92% ee, and 91% ee, respectively[13] (**Scheme 7**). Even *sec*-alkyl trifluoromethyl ketones are reduced by DIP-Chloride very efficiently. Thus, cyclohexyl trifluoromethyl ketone is reduced by DIP-Chloride at RT in 12h to the product alcohol in 87% ee. In all of these cases the trifluoromethyl group acts as the enantio-controlling larger group instead of the aryl or alkyl group. This produces products with stereochemistry opposite to those obtained for the corresponding methyl analogs.[14]

Many reagents have been applied for the reduction of fluoroketones.[15-22] It has been observed that there is no pattern in the reduction products obtained (**Table 4**). The inversion in stereochemistry could be ascribed to the steric size of the $-CF_3$ group and/or to its electronic influence. It is surprising to note that Alpine-Borane reduction of trifluoroacetophenone ($PhCOCF_3$) gives the same stereochemistry as for the reduction of acetophenone. The mechanism of reduction for Alpine-Borane and DIP-Chloride is similar, yet they provide the alcohol of opposite configuration. This may indicate that the presence of a chlorine atom in the reagents exerts a significant influence on the stereochemistry of the trifluoromethyl alcohols produced.[13]

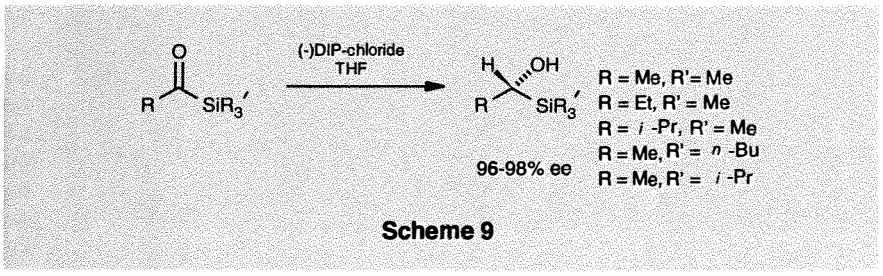
Table 4. Comparison of the stereochemistry of product alcohols from the asymmetric reduction of 2,2,2-trifluoroacetophenone (Ph-CO-CF_3) with several reagents.

Reagent	Reaction conditions	% ee (isomer)	Stereochemistry compared to Ph-CO-Me	Ref.
Mosher's Reagent	THF, 0 °C	50 (*S*)	opposite	15
Nasipuri's Reagent	THF, -78 °C	77 (*S*)	opposite	16
R-BINAL-H	THF, -60 °C	27 (*S*)	same	17
NB-Enantride	THF, -78 °C	50 (*S*)	same	18
K-Glucoride	THF, -78 °C	48 (*S*)	same	19
CBS Cat/BH_3	THF, -78 °C	18 (*R*)	opposite	20
CBS Cat/Catecholborane	THF, -78 °C, 15h	90 (*R*)	opposite	20
Baker's Yeast	H_2O, rt, 2d[a]	44 (*S*)	same	21
Alpine-Borane	neat, rt, 45d[b]	35 (*R*)	same	22[a]
Alpine-Borane	6000 atm, rt, 3d	54 (*R*)	same	22[b]
DIP-Chloride	neat, rt, 24h,	90 (*S*) >99[c]	opposite	13

(a) 80% reaction complete. (b) 90% reaction complete. (c) upon recrystallization in pentane.



Scheme 8



Scheme 9

Asymmetric Reduction of Acetylenic Ketones

(-)-DIP-Chloride reduces unhindered acetylenic ketones such as 3-butyn-2-one or 4-phenyl-3-butyn-2-one in ether (25°C, 1h) to the corresponding alcohol in 17% and 21% ee, respectively. Increasing the bulk of R' to an isopropyl group yields the product alcohol in 53% ee. Finally, increasing the size of R' to the *tert*-butyl group yields the product alcohol in 99% ee (**Scheme 8**).[23] The latter reaction required 6 days for completion under standard conditions (ether, 1*M*, -25°C). However, conducting the reaction at room temperature without solvent results in complete reduction in 8h, providing the product alcohol in 98% ee. Recently, Brown's group has synthesized a variety of new hindered acetylenic ketones and converted them to the corresponding propargylic alcohols in high yields (70-90%) and in essentially optically pure form.[23] Alpine-Borane (**2**), though good for unhindered acetylenic ketones, fails to reduce these hindered ketones, whereas most of the other reducing agents fail to achieve consistency. A modified and operationally simplified workup procedure for the isolation of acetylenic alcohols in high yield should facilitate the scale-up of such asymmetric reduction reactions.[23]

Asymmetric Reduction of Acylsilanes

A number of reports have appeared recently concerning the asymmetric reduction of acylsilanes, producing enantio- enriched hydroxysilanes. The availability of enantiomerically pure α-hydroxysilanes can certainly broaden the scope and extend the applicability of this class of compounds.[24,25] Buynak and co-workers have investigated the asymmetric reduction of acylsilanes to α-hydroxysilanes via the Itsuno reagent[24c] (a 2:1 complex of borane and (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol).[26] A moderate level of enantioselectivity was obtained which increased with the steric bulk of the trialkylsilane.

Panek and Cirillo have explored the asymmetric reduction of α,β-unsaturated acylsilanes via the CBS catalytic method for the preparation of optically active hydroxyallylic silanes.[24a] However, only moderate levels of induction were observed. The use of Noyori's BINAL-H reagent as well as enzymatic reduction with baker's yeast for such reactions have so far also proven to be unsatisfactory.

Recently, Soderquist[24b] and Buynak[24c] have independently shown that acylsilanes can be reduced to the corresponding α-silylalcohol via DIP-Chloride reduction. Addition of the acylsilane to (-)-DIP-Chloride in THF at room temperature, followed by workup with diethanolamine, provides (*R*) alcohols in high enantiomeric excess and in good yields (**Scheme 9**).

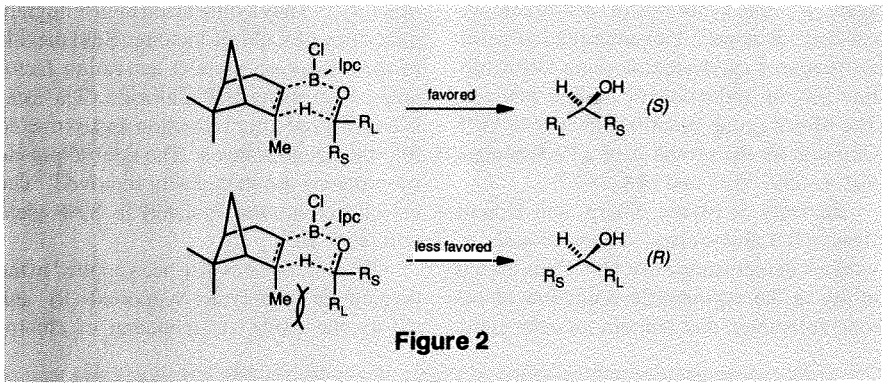


Figure 2

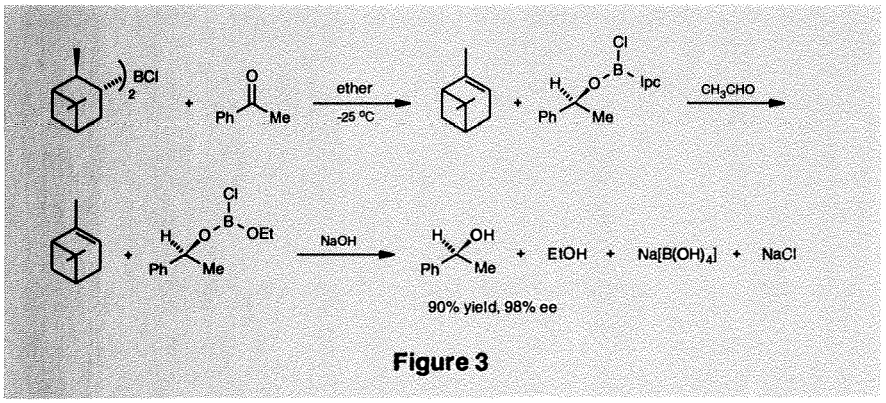
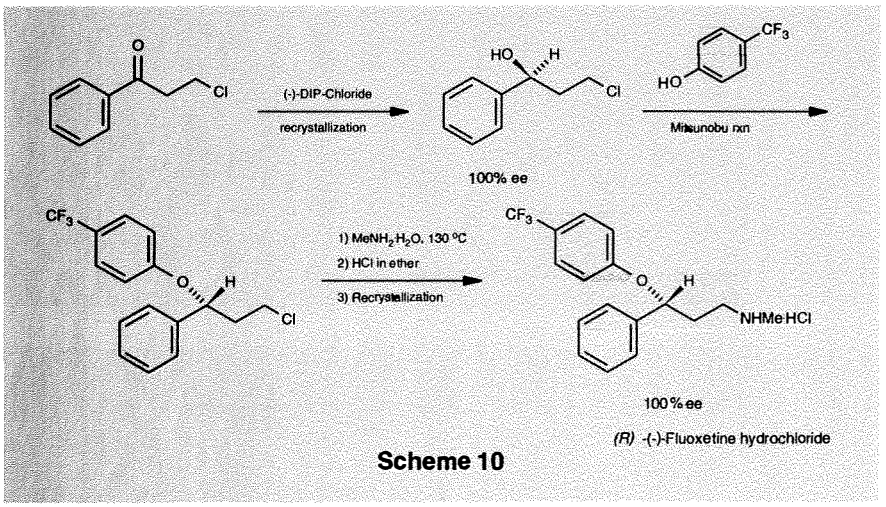
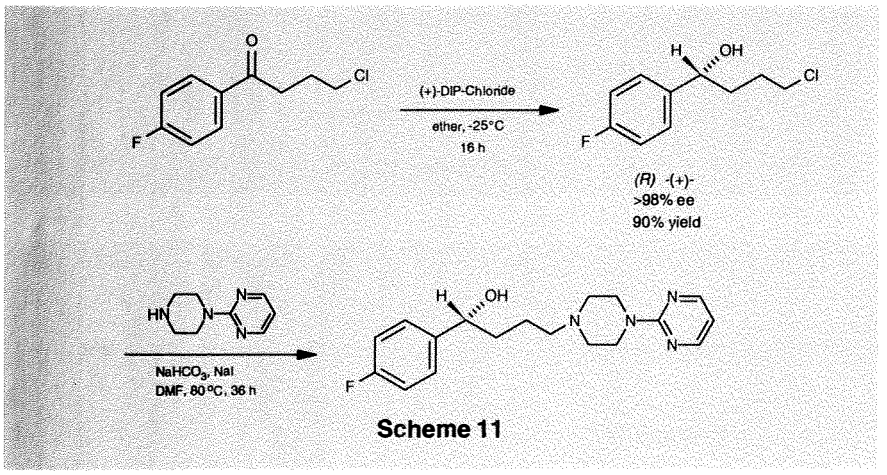


Figure 3



Scheme 10



Scheme 11

Mechanism of Reduction

The mechanism of the reduction of ketones with DIP-Chloride is similar to that proposed by Midland for Alpine-Borane reduction.[4b] Reduction proceeds via a bimolecular, six-membered cyclic, boat-like transition state in which the tertiary hydrogen is transferred to the carbonyl carbon. In the transition state, the smaller alkyl group (R_S) lies in the axial position *syn* facial with the methyl group of pinene, while the bulky alkyl group (R_L) prefers an equatorial position (**Figure 2**). This clearly explains the formation of the *S*-isomer from (-)-DIP-Chloride and *R*-isomer from (+)-DIP-Chloride unless the steric bulk of the carbonyl moiety is changed, as in the case of *tert*-butyl phenyl ketone, or there is a change in priority rule, as in the case of acylsilanes.[4]

Brown has recently developed an improved workup procedure for the isolation of the product alcohol after reduction.[4d,23] This new procedure involves treatment of the reaction mixture (after completion of reduction with DIP-Chloride) with 1 equivalent of acetaldehyde at room temperature. This completely eliminates the second unit of α-pinene from the reagent. The recovered α-pinene can be collected under vacuum and the product is obtained by a simple hydrolysis of the chloroboronate ester, RO(EtO)BCl, with NaOH (**Figure 3**). This convenient procedure avoids formation of the solid diethanolamine complex.[4] This new method is indeed simple and attractive providing product alcohols in good yield, while α-pinene can be readily recovered from the reaction mixture quantitatively.

Applications of DIP-Chloride

DIP-Chloride is an excellent chiral reducing agent for aralkyl ketones containing halogen in the alkyl chain. The corresponding haloalcohols are generally obtained in >90% ee. For example, 3-chloro-1-phenyl-1-propanol, which is initially obtained in 97% ee, can be upgraded to essentially 100% ee by simple crystallization. In turn, 3-chloro-1-phenyl-1-propanol provides access to a highly enantioselective synthesis of antidepressant agents (**Scheme 10**). Brown and co-workers have prepared the series of antidepressant drugs tomoxetine, fluoxetine, and nisoxetine in both enantiomeric forms. These haloalcohols can also be cyclized to oxiranes and 2-substituted tetrahydrofurans of high enantiomeric purity.[27]

The Bristol-Myers-Squibb group recently developed many novel antipsychotic agents bearing the 1-(pyrimidin-2-yl)piperazine (1-PP) pharmacophore and selected the most

successful candidate, α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol (BMS 181100) for clinical evaluation.[28] Unfortunately, the published multistep synthesis of optically pure BMS 181100 is very lengthy and difficult. This procedure involves a chiral resolution using α-methylbenzyl isocyanate, providing ~10% overall yield of the desired product.[28]

The above difficulty has been easily overcome by Ramachandran, Gong, and Brown.[29] They recently described an efficient asymmetric reduction of 4-chloro-4'-fluorobutyrophenone with (+)- or (-)-DIP-Chloride, provides the corresponding (*R*) or (*S*)-alcohol, respectively, in 90% yield and 98% ee. Coupling this with 2-(1-piperazinyl)pyrimidine provides the desired product in 72% yield and >98% ee (**Scheme 11**).[29]

This elegant synthesis utilizing DIP-Chloride can provide both enantiomers of the desired drug in few steps with high chemical and optical yields. Most importantly, the synthesis is quite general. The synthesis of BMS 181100 itself should be straightforward from coupling α-3-chloropropyl-4-fluorobenzenemethanol and 5-fluoro-2-(1-piperazinyl)pyrimidine.[29]

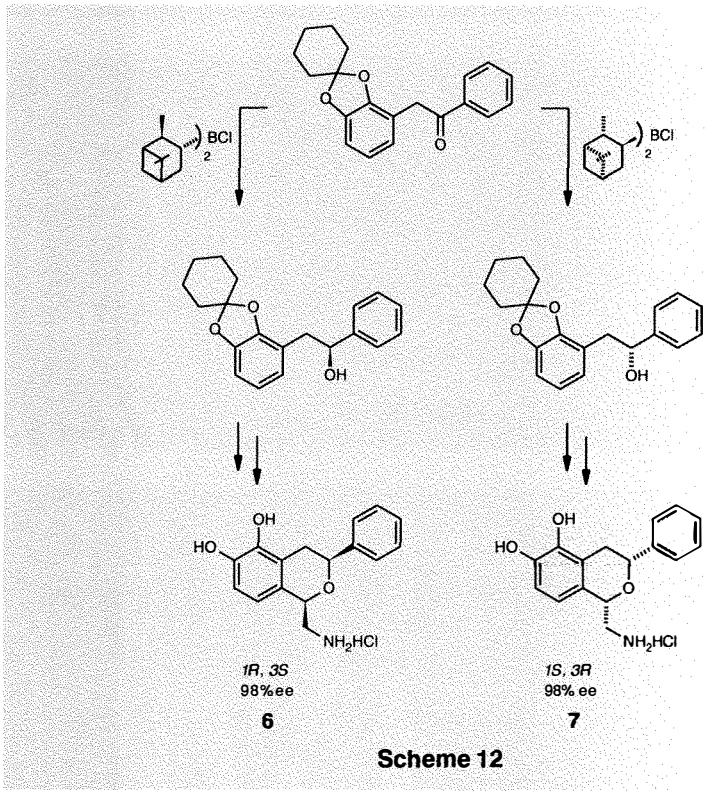
Another representative application of DIP-Chloride is found in the synthesis of (1*R*,3*S*)-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-3-phenyl-1*H*-2-benzopyran (**6**), a potent and selective D1 antagonist, and its enantiomer (**7**) (**Scheme 12**). Pharmacological study of the enantiomers shows that all of the dopaminergic activity resides exclusively in the (1*R*,3*S*) enantiomer.[30]

Dolastatin has been isolated from an Indian Ocean sea hare, *Dolabella auricularia*. It has shown powerful antineoplastic activity and is expected to become a new anticancer agent.[31] Its structural uniqueness as well as its scarce availability in nature has motivated several groups to synthesize this biologically active peptide. (*S*)-Dolaphenine, which represents the C-terminal unit of dolastatin, has been synthesized recently using DIP-Chloride by Shiori and Hamada. They utilized many chiral reducing agents, including Corey's oxazaborolidines. However, only DIP-Chloride provided good isolated yields (80%) of the intermediate for the synthesis of Dolaphenine in 93% ee (**Scheme 13**).[31]

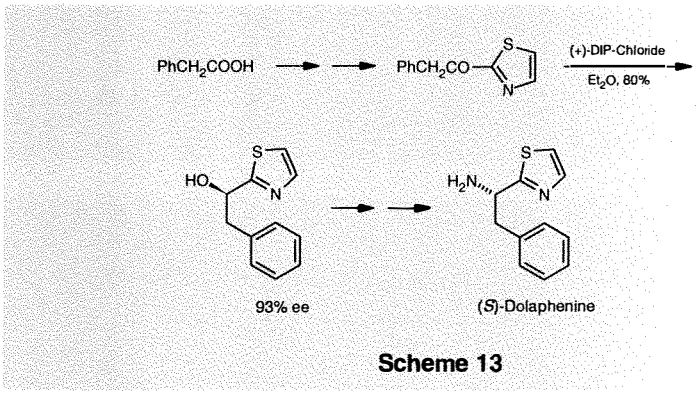
Jean and co-workers synthesized reduced haloperidol using DIP-Chloride.[32] Danishefsky's group also applied this reagent for the synthesis of descarbamoylcalicheamicinone.[33] Yamamura and co-workers prepared aplysiatoxins using DIP-Chloride for the reduction of aralkyl ketone.[34] The Merck group described the use of DIP-Chloride for the synthesis of a PAF-antagonist, L-659, 989[35] and MK-287.[36]

Recently at Merck, Sharp, and Dohme Research Laboratories, Simpson and co-workers demonstrated that DIP-Chloride has utility in the asymmetric reduction of ketone substrates that contain an ester functionality.[37] They synthesized multikilogram quantities of a chiral lactone (**Scheme 14**) in their work on platelet activating factor antagonists using DIP-Chloride. The ester is hydrolyzed after reduction and extracted into the aqueous layer. The neutral pinene by-products are then easily removed. The chiral lactone was isolated in 89% yield with 92% ee[37]

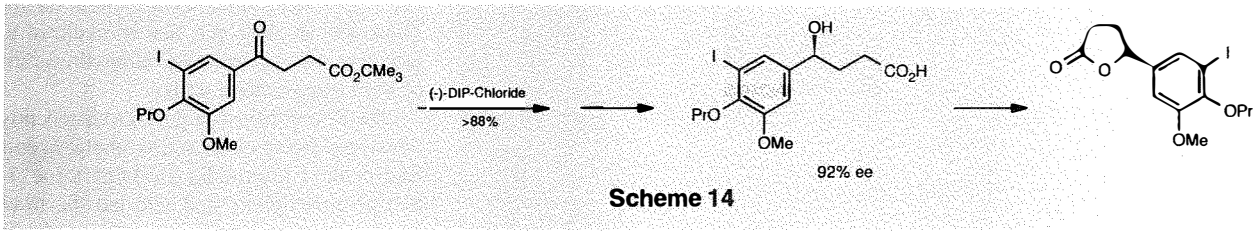
DIP-Chloride has also been applied in the preparation of polymer-supported (*R*)- and (*S*)-styrene oxide via reduction of chloro-



Scheme 12



Scheme 13



Scheme 14

acetylated styrene - 1% divinylbenzene with (-) and (+)-DIP-Chloride respectively.[38]

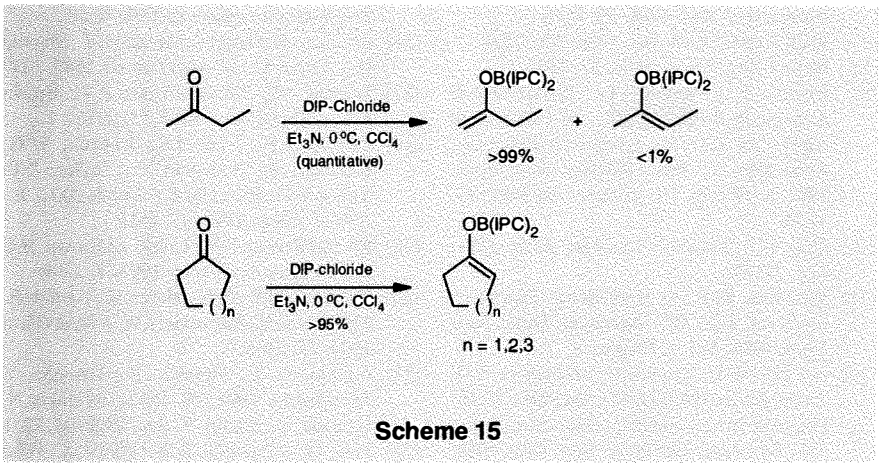
Other applications of DIP-Chloride include the syntheses of *p*-alkoxyphenethanols[39] and (+)-motneine.[40]

Enolboration of Ketones with DIP-Chloride

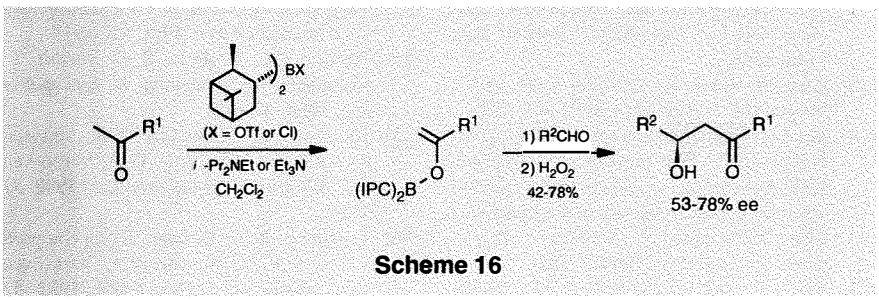
Enolborinates are highly versatile intermediates in organic synthesis.[41] Brown's group has shown that sterically bulky dialkylhaloboranes, in the presence of triethylamine, can enolize various ketones regio- and stereoselectively to generate predominantly [*E*]-enolborinates.[42] It was, therefore, of obvious interest to determine the behavior of DIP-Chloride towards ketones in the presence of tertiary amine. Indeed, it has been observed that reductions of ketones are suppressed in the presence of tertiary amines; enolborations (enolization) predominate completely. Some representative examples of the enolboration of cyclic and acyclic ketones are shown in **Scheme 15**. It is interesting to mention that the regioselective enolboration of 2-butanone with DIP-Chloride is observed exclusively on the methyl side.[42d]

Paterson has applied both IPC_2BOTf as well as DIP-Chloride for the enolboration of methylalkyl ketones for enantioselective aldol condensations[43a] (**Scheme 16**). It has been demonstrated that from ethylalkyl ketones DIP-Chloride provides [*E*]-enolborinates whereas IPC_2BOTf provides predominately [*Z*]-enolborinates.[43b] Surprisingly, it is only the latter transformation which has been found useful for aldol condensations to give good ee's of corresponding *syn* aldol products.[43c] However, both these reagents have been applied by Paterson for the synthesis of optically active dihydropyrones via chiral enolborinates (**Scheme 17**).[43a]

IPC_2BOTf has shown more promising results than DIP-Chloride for asymmetric aldol condensations;[43d] unfortunately, the lack of commercial availability remained a limitation to its wide application. However, it has been shown that commercially available DIP-Chloride can be utilized to generate IPC_2BOTf. This is carried out by treating DIP-Chloride with trifluoromethanesulfonic acid in hexane at 0°C, generating IPC_2BOTf instantaneously (**Scheme 18**). This can then be utilized in situ for enolboration.[43e]



Scheme 15



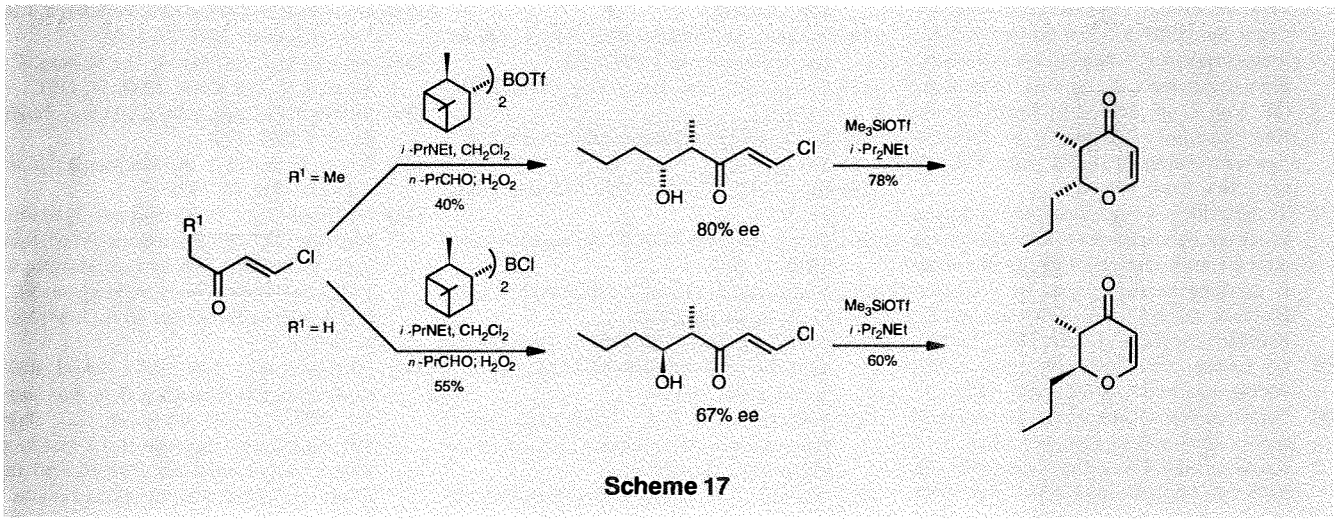
Scheme 16

Enantioselective Opening of *meso*-Epoxides with DIP-X (X = Cl, Br, I)

Dialkylhaloboranes have also been applied for the enantioselective opening of *meso*-epoxides to form halohydrins.[44] The transformation is general, providing highly valuable difunctionalized compounds in good to excellent enantiomeric purity from simple olefins. It has been found that dialkyliodoboranes (DIP-I) provide the best ee's of corresponding halohydrin.

DIP-Chloride as Chiral Catalyst

There is one report where DIP-Chloride has been utilized as a chiral catalyst for the Diels-Alder reaction of 2-methyl-2-propenal and cyclopentadiene, but poor enantioselectivity was observed. Nevertheless, the

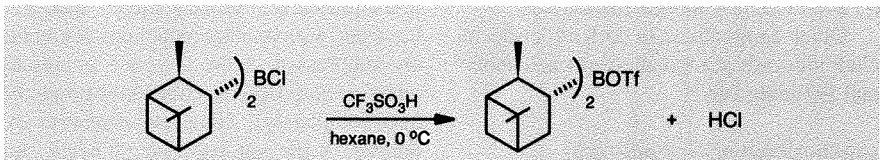


Scheme 17

exo adduct was observed in excess in 90:10 *exo-endo* ratio.[45]

CONCLUSION

DIP-Chloride is a remarkably effective reagent for the asymmetric reduction of a variety of prochiral ketones. Aromatic, heteroaromatic, *tert*-alkyl, hindered acetylenic, trifluoromethyl ketones, as well as aliphatic acylsilanes are smoothly reduced in a highly enantioselective manner with predictable stereochemistry. These alcohols are potentially of considerable importance in organic, biological, pharmaceutical, and materials science. A new, simplified workup recently demonstrated by Brown's group has made isolation of chiral alcohols easy and convenient, and is expected to broaden the utility and scope of this reagent. Moreover, quantitative recovery of the chiral auxiliary, α-pinene, is a bonus which makes this reagent extremely competitive, and even cheaper, than some of the catalytic processes of asymmetric reduction. The ready availability of this boron reagent from a commercial source (Aldrich) in both enantiomeric forms makes DIP-Chloride one of the most attractive and competitive reagents for asymmetric reduction. Furthermore, the application of DIP-Chloride in enolboration reactions to produce chiral aldol products, opening of a *meso*-epoxide to form a chiral halohydrin, and as a chiral catalyst in Diels-Alder reactions are just the beginning of the newer applications of this reagent.



Scheme 18

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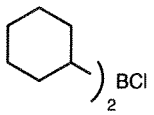
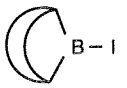
ABOUT THE AUTHOR

Raj K. Dhar was born in Srinagar, India on August 1, 1958. He received his B.Sc. degree in 1979 and M.Sc. degree in 1981 from Jammu University, India. He worked for his Ph.D. with Professor R. Varadarajan (1982-1986) at the Indian Institute of Technology, New Delhi, India, on the oxidation and oxidative rearrangement of sugars (monosaccharides), substituted piperidones, aminopolycarboxylic acids, and monoterpenes by some chromium(VI) complexes. He joined Professor H.C. Brown's group in 1986 as a postdoctoral research associate at the chemistry department of Purdue University. While working with Professor Brown for three and a half years he was involved in the development of new chiral and achiral boron reagents for regio and stereoselective enolboration of various carbonyl compounds for aldol condensation and for the synthesis of optically active *trans* diols. In 1990 he joined Professor P.W. Rabideau's group at Louisiana State University, Baton Rouge, as a research associate with where he carried out silicon mediated organic transformations of various polynuclear aromatic compounds with emphasis on the synthesis of C_{30} hemi-fullerenes and C_{60} Buckminsterfullerene. His research also included silicon mediated regioselective Birch reduction and reductive alkylation of some polynuclear aromatics and their conformational studies. In August 1992 he joined Aldrich Chemical Company, Inc. as a scientist.



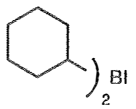
Brown's group has recently demonstrated that dicyclohexylchloroborane/triethylamine serves as an excellent enolboration reagent for ketones, aldehydes, carboxylic acids, anhydrides, thioesters, and β-keto esters.[1,2] The reagent has been successfully utilized for the regio- and stereoselective generation of enolborinates from a variety of alkylethyl ketones. These enolborinates have been applied for the synthesis of aldol products.[1-4]

(1) Brown, H.C.; Dhar , R.K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (2) Idem *ibid.* **1992**, *57*, 2716. (3) Brown, H.C.; Dhar , R.K.; Bakshi, R.K.; Pandiarajan, P.K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. (4) Brown, H.C.; Ganesan, K.; Dhar, R.K. *J. Org. Chem.* **1993**, *58*, 147.



B-Iodo-9-BBN is an excellent reagent for the synthesis of α,β-unsaturated esters by the highly chemoselective reaction of B-I-9-BBN-ethoxyacetylene adduct with aldehydes.[1] This reagent also serves as a stereoselective enolboration reagent for sterically hindered alkylethyl ketones.[2]

(1) Satoh, Y.; Tayano, T.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1989**, *30*, 5153. (2) Brown, H.C.; Ganesan, K.; Dhar, R.K. *J. Org. Chem.* **1993**, *58*, 147.



A smooth, rapid, quantitative enolboration of esters and tertiary amides with control of enolate geometry can be achieved for the first time with dicyclohexyliodoborane.[1,2]

(1) Brown, H.C.; Ganesan, K. *Tetrahedron Lett.* **1992**, *33*, 3421. (2) Ganesan, K.; Brown, H.C. *J. Org. Chem.* scheduled for May 6 issue.

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Aldrichimica Acta

Volume 27, Number 3, 1994 *(Last issue in 1994)*

The Synthetic Potential of the Intramolecular Meta-Photocycloaddition in Arene-Alkene Bichromophoric Systems Containing Oxygen in the Tether

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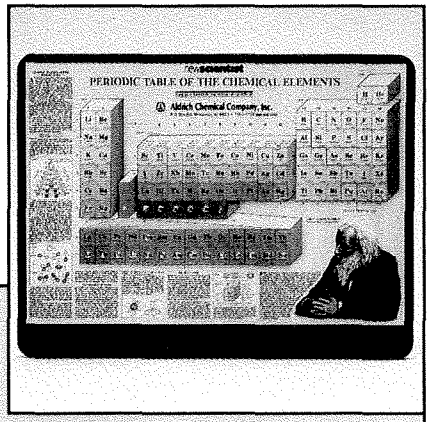
About Our Cover:

This colorful river scene, *Jolly Flatboatmen in Port* (oil on canvas, 117.5 x 175.1cm), was painted by the American artist George Caleb Bingham in 1857 during a stay in Germany. When Bingham arrived in Europe for the first time in 1856, he brought with him the ambition of creating a history painting that would depict an important event in the development of the American West. He also brought along the memory of his well-received paintings of river life dating from the mid-1840s. These works, which had given him national visibility, suggested to him further potential.

After settling with his family in Düsseldorf, Germany, Bingham set to work on *Jolly Flatboatmen in Port*. With more than nineteen figures, it was to be his largest and most complex river painting. Moreover, unlike his earlier paintings of similar subjects, which were set in remote bends of unnamed rivers, this work was to depict a center of commerce, St. Louis. The scene shows a flatboat docked at the wharf, and boatmen amusing themselves with their own homespun entertainment, music, and dancing. The revelry is so lively that another flatboat has pulled alongside to observe it. Bingham borrowed figures from his earlier works for this painting; the tour-de-force dancing figure who holds a red handkerchief had appeared in his best-known river painting, *Jolly Flatboatmen*, 1846.

The painting is in the collection of The Saint Louis Art Museum.

Lab Notes



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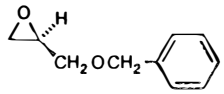
EDITOR'S NOTE

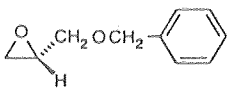
It has come to our attention that there is some confusion concerning the configuration and sign of rotation of our (*R*)-(-)- and (*S*)-(+)-benzyl glycidyl ethers (**36,352-9** and **36,353-7**, respectively).

These products were prepared according to a procedure reported by Bittman[1] and the configuration about the asymmetric center is specified in accordance with a rule change in the CIP convention for glycidol and derivatives.[2] Optical rotations for neat samples have the same sign of rotation as that reported for toluene or benzene solutions.

The correct structures for these products are indicated below. Note that the structures indicated in the 1992-1993 Aldrich Structure Index (**Z23,360-9**) are incorrect and have been revised since its publication.



36,352-9 Benzyl (*R*)-(-)-glycidyl ether



36,353-7 Benzyl (*S*)-(+)-glycidyl ether

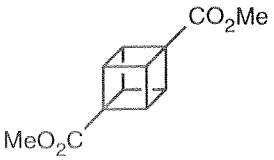
We will be directly notifying customers of these products and apologize for any inconvenience. For more information, please contact our Technical Services Department at 800-231-9327.

(1) Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **1989**, *30*, 2751. (2) Hanson, R.M. *Chem. Rev.* **1991**, *91*, 437 and references cited therein.

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



Professor Philip E. Eaton at The University of Chicago kindly suggested that we offer cubane dimethylester which is a precursor to the parent hydrocarbon, and to a number of functionalized cubane derivatives as well.[1] For example, irradiation in the presence of oxalyl chloride followed by methanolysis leads to tri-, tetra-, and pentacarbomethoxycubanes.[2] Ortho-lithiation of the derived bisamide provides access to 1,2,4,7-tetra-substituted cubanes.[3] Curtius rearrangement leads cleanly to 1,4-diaminocubane which on oxidation with dimethyl dioxirane affords the bisnitro derivative.[4]

(1) Eaton, P.E. *Angew Chem., Int. Ed. Engl.* **1992**, *31*, 1421 and references cited therein. (2) Bashir-Hashemi, A. *ibid.* **1993**, *32*, 612. (3) Eaton, P.E.; Xiong, Y.; Zhou, J.P. *J. Org. Chem.* **1992**, *57*, 4277. (4) Eaton, P.E.; Wicks, E. *ibid.* **1988**, *53*, 5353.

Naturally, we added this interesting cubane derivative to our listings. It was no bother at all, just a pleasure to be able to help.

THE SYNTHETIC POTENTIAL OF THE INTRAMOLECULAR META-PHOTOCYCLOADDITION IN ARENE-ALKENE BICHROMOPHORIC SYSTEMS CONTAINING OXYGEN IN THE TETHER

Denis De Keukeleire
University of Gent
Faculty of Pharmaceutical Sciences
Harelbekestraat 72
B-9000 Gent, Belgium

ABSTRACT

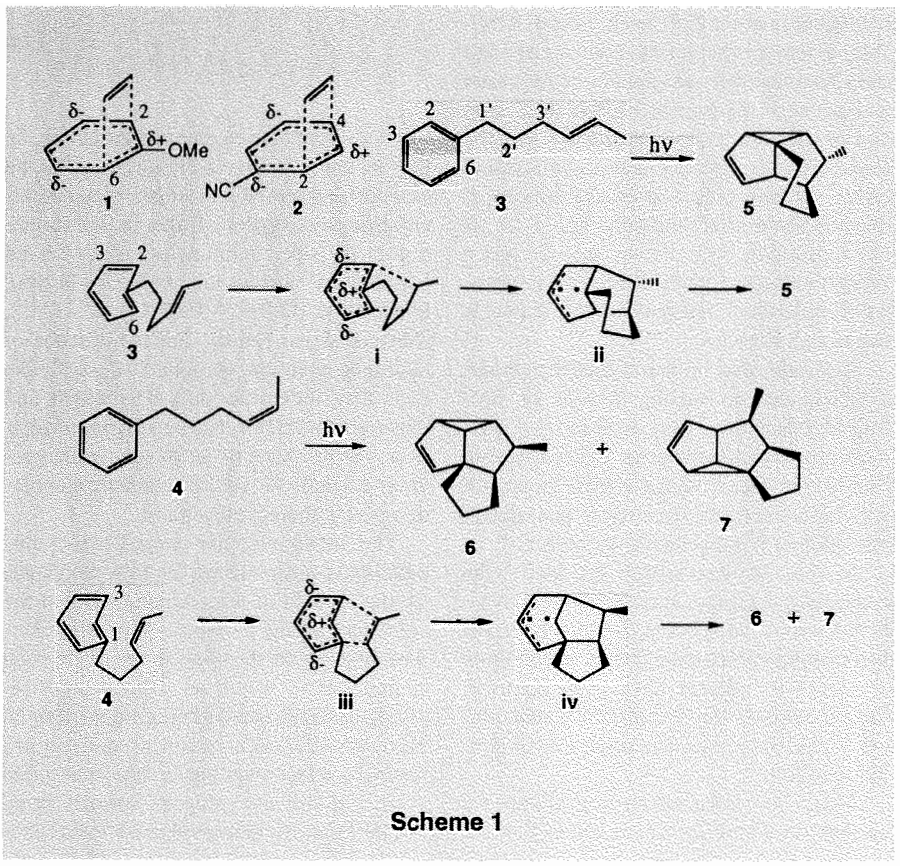
The photochemistry of arene-alkene bichromophoric systems containing oxygen in the tether is reviewed. The emphasis is on the highly selective formation of intramolecular meta-photocycloadducts. Most interesting are (but-3-enyl) phenyl ethers which efficiently lead to 1,6-bridged dihydrosemibullvalene structures. The photoproducts are readily amenable to further transformations, hence various polycarbocyclic skeletons, in particular polycyclopentanoids, can be accessed via a short and effective synthetic route.

The intramolecular arene-alkene meta-photocycloaddition, discovered in 1969 by Morrison and Ferree on photolysis of 6-phenylhex-2-enes,[1] is of a very remarkable, and perhaps unique, nature. In the isomerization process, occurring from the first excited singlet state of the arene, extensive bond reorganization occurs leading to the greatest increase in molecular complexity of any general reaction.[2] The value of the arene-alkene meta-photocycloaddition arises from its capacity to produce tetracyclic reaction products containing up to six new stereocenters from a simple achiral arene-alkene bichromophore, such as (*E*)- and (*Z*)-6-phenylhex-2-ene.[3] Moreover, the cycloadducts can be applied in the synthesis of a variety of commonly encountered structural types, including cylopentanes, cycloheptanes, bicyclo[3.2.1]octanes, and bicyclo[3.3.0]octanes.

SELECTIVITY IN THE INTRAMOLECULAR ARENE-ALKENE META-PHOTOCYCLOADDITION

The photochemical reactivity of (*E*)- and (*Z*)-6-phenylhex-2-ene is very instructive as it clearly shows the selectivity attainable in the intramolecular arene-alkene photocycloaddition reactions. In general, meta-photocycloaddition is preferred over ortho and para modes when the ionization potential of the alkene is similar to that of benzene (9.24 eV).[4] Ortho-photoaddition is generally the preferred process with relatively powerful donor and acceptor alkenes. This predictive rule was confirmed in a detailed study involving orbital interactions by Houk.[5] Mattay developed a rule based on the Weller theory of electron transfer.[6] It was derived that alkenes having poor electron-donor or electron-acceptor abilities preferentially give meta-cycloadducts in photoreactions with benzene if the free enthalpy of electron transfer is higher than 1.4-1.6 eV. When the alkene moiety carries alkyl substituents, meta-photocycloaddition usually prevails.

The regioselectivity induced by substituents on the benzene ring is accounted for by the now generally adopted reaction pathway illustrated in **Scheme 1**.[7] On approach of the alkene to the meta-positions of the arene, the



Scheme 1

vicinal carbon atoms become polarized prior to bond formation. Thus, at the carbon atom between the meta-positions a partial positive charge is developed, while the partial negative charge resides on the remaining vicinal carbon atoms. As a consequence, addition occurs exclusively at the 2,6-positions (**note 1**) of benzenes having electron-donor substituents (e.g. OMe, **1**) and at the 2,4-positions when the substituent is an electron-acceptor group (e.g. CN, **2**) (**Scheme 1**).

According to this mechanism, 6-phenylhex-2-enes should preferably undergo 2,6-meta-photocycloaddition. This is indeed the main reaction (70%) for (*E*)-6-phenylhex-2-ene (**3**).[4,8] The partial positive charge in intermediate **i** is stabilized by the alkyl chain, leading to the formation of diradical **ii**, which is supposed to exist along the reaction pathway. Subsequent reaction may give rise to two vinylcyclopropane isomers. However, only closure of the 1,3-bond takes place yielding photoadduct **5** (1,6-bridged dihydrosemibullvalene, *endo*-methyl), as the adduct formed by closure of the 1,5-bond (1,7-bridged dihydrosemibullvalene) would be severely strained.

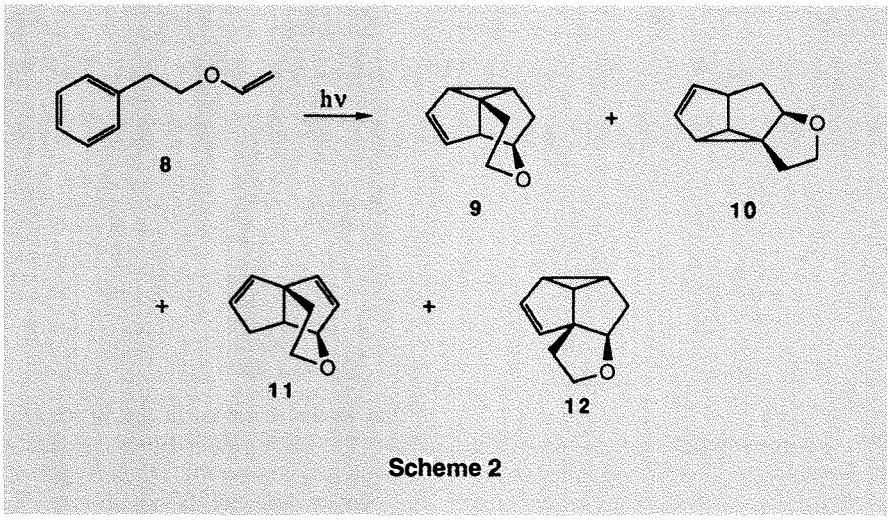
In contrast, (*Z*)-6-phenylhex-2-ene (**4**) only shows 1,3-addition, although no stabilization is present in this mode.[3,4,8] Intramolecular meta-photocycloaddition via intermediates **iii** and **iv** affords both the angular triquinane **6** (5,6-bridged dihydrosemibullvalene, *exo*-methyl) and the linear triquinane **7** (7,8-bridged dihydrosemibullvalene, *exo*-methyl) in a 1 : 1 ratio (80%). The deviating behavior has been ascribed to steric hindrance between the (*Z*)-methyl group and one of the hydrogen atoms at the 2'-carbon of the side chain.[9] It appears that the steric effect is stronger than the electronic effect. Methyl groups at other positions of the side chain affect the ratio 2,6 : 1,3.[10] It has repeatedly been shown that the arene substituents specifically direct the cyclopropane formation,[11] but control of this feature is not straightforward.

It should also be noted that the photocycloadducts, on heating or even on prolonged irradiation, may undergo a vinylcyclopropane-cyclopentene rearrangement. This isomerization is degenerate in the unsubstituted adduct, but it converts one adduct into another if substituents are present.[12]

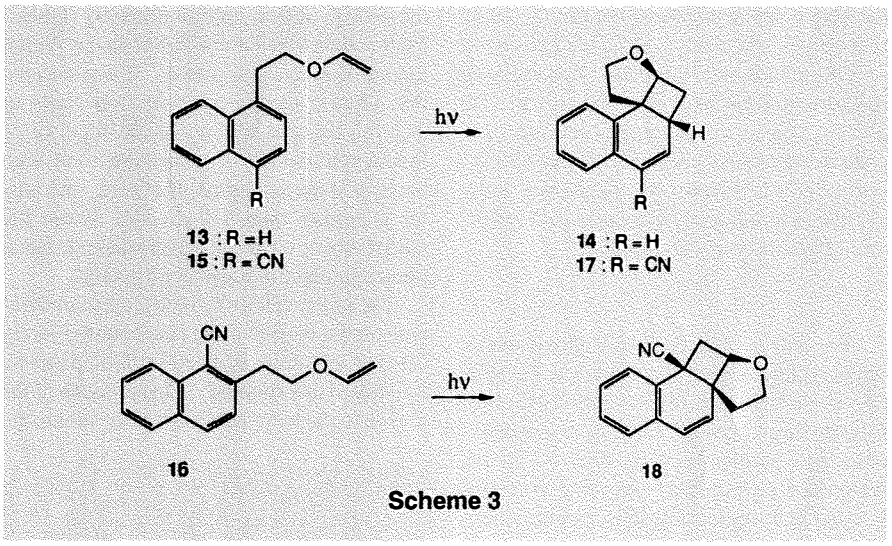
In view of the reaction selectivity, the complexity increase, and the versatile transformation of the adducts, a number of synthetic applications of the photocycloaddition of arenes to alkenes have been reported. Recent reviews by Wender[2b,9a,13] and others[7,14] describe elegant examples of its synthetic utility.

Much less information is available for systems in which the chain connecting the two chromophores contains heteroatoms. In this context, we are mainly interested in the effect of oxygen. Replacement of a methylene group by oxygen will alter the conformation of the side chain due to changed bond length (C-C: 0.154 nm, C-O: 0.141 nm), bond angle (C-C-C: 109°, C-O-C: 111°), Van der Waals radius, and the absence of hydrogen atoms at positions 1', 2', or 3'. The flexibility of the side chain is increased, and thus steric problems may be relieved. Moreover, the presence of an oxygen atom provides a handle for further synthetic elaboration of the photocycloadducts.

The intramolecular meta-photocycloaddition is most successful with molecules having a chain of three atoms between the arene and alkene moieties. We will, therefore, first review the photochemistry of such compounds in which an oxygen atom replaces each of the methylene groups (**note 2**). Next, we will briefly comment on structures having a tether of more or less than three units, but still including an oxygen atom. Furthermore, the tandem Norrish Type I photoreaction and intramolecular arene-alkene meta-photocycloaddition will be highlighted. Finally, some expeditious entries into the synthesis of polycyclopentanoids and other interesting polycarbocyclic skeletons will be explored.



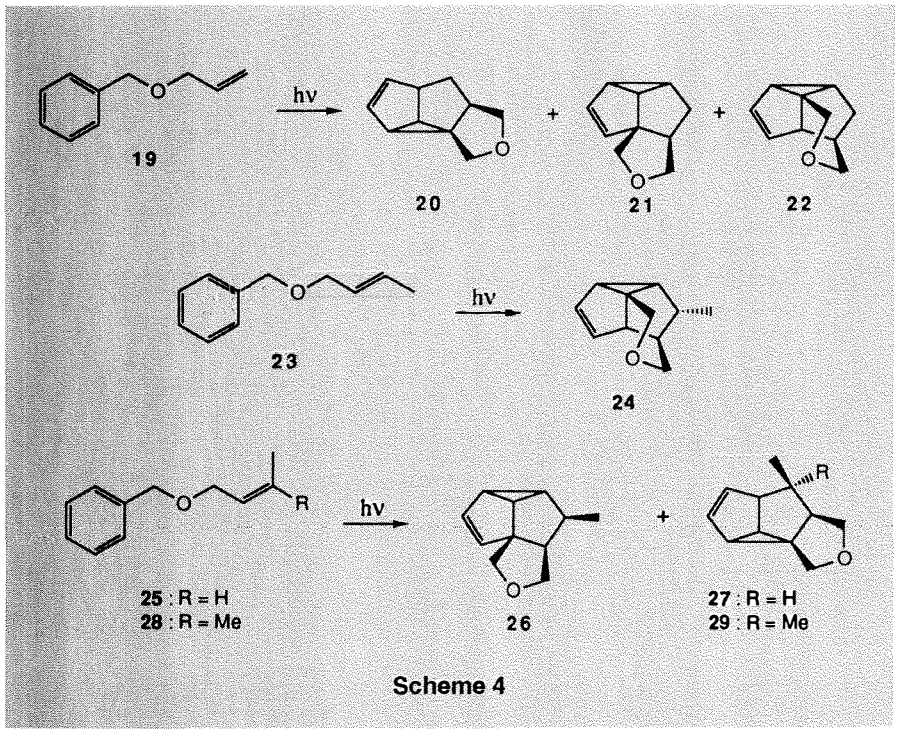
Scheme 2



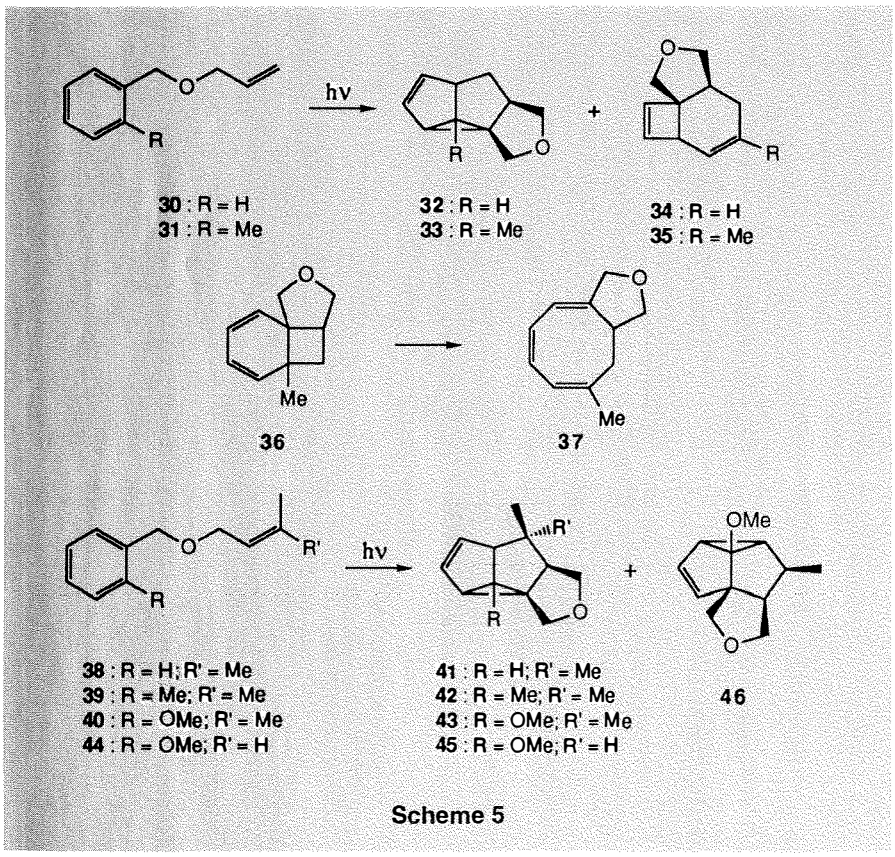
Scheme 3

ARENE-ALKENE BICHROMOPHORES CONTAINING A TETHER WITH OXYGEN AT POSITION 3'

Irradiation of phenethyl vinyl ether (**8**) in cyclohexane affords a mixture of 2,6- and 1,3-meta-adducts.[15] This result, obtained recently by Cornelisse et al., differs from earlier reports.[16] Four photoproducts **9**-**12** were detected in a ratio of **9** : **10** : **11** : **12** = 56 : 16 : 1 : 4 (**Scheme 2**). Compound **9** is a 2,6-meta-adduct and compound **10** is a 1,3-meta-adduct. Photoproduct **11** is formed by a thermal [1,5]-sigmatropic hydrogen shift, a reaction often encountered in compounds of this type.[10] Adduct **12** is most likely the vinylcyclopropane isomer of **10**.



Scheme 4



Scheme 5

Naphthylethyl vinyl ethers were investigated by Gilbert.[17] Thus, the α-naphthyl compound **13** gave only one photoisomer **14** via an intramolecular 1,2-addition from the S_1 state (**Scheme 3**). The β-isomer, on the other hand, was relatively stable under the same conditions. The differences in the photochemical behavior reflect the differing interactions between the chromophores in the excited state, since in the α-isomer the arene fluorescence was quenched to 60% of that of 1-(2-ethoxyethyl)naphthol, whereas in the β-isomer only 15% quenching was observed compared to 2-(2-ethoxyethyl)naphthol. Apparently, the meta-photocycloaddition is obviated or it represents only a very minor reaction pathway.

If a polar substituent in the naphthyl entity is present, such as in the cyano derivatives **15** and **16**, ready conversion was noted and again the major photoproducts were the corresponding ortho-adducts **17** and **18**.[18]

When the oxygen at position 3' is part of an ester function, such as in vinyl phenylacetate, no meta-photocycloaddition occurs. Traces of photoproducts were detected, but the compound appeared to be largely photostable.[19]

OXYGEN AT POSITION 2'

The simplest compound in this series, benzyl allyl ether (**19**), exhibits mainly 1,3-regioselectivity, furnishing the meta-cycloadducts **20** and **21**[19] (**Scheme 4**). A minor reaction pathway led to the 2,6-meta-photocycloadduct **22**. The ratio of **20** : **21** : **22** was 2 : 2 : 1 (59%). Blakemore and Gilbert,[19b] as well as Neijenesch and Cornelisse,[20] studied a number of arene-alkene bichromophores containing oxygen at position 2'.

The benzyl ether **23** in the (*E*)-configuration afforded a single 2,6-adduct **24** having the methyl group in the *endo*-position (29%). The (*Z*)-isomer **25** gave two 1,3-meta-adducts, **26** (30%) and **27** (58%), respectively, carrying an *exo*-methyl group.[20] These results are fully comparable to those obtained for the carbon analogues, (*E*)-6-phenylhex-2-ene and (*Z*)-6-phenylhex-2-ene, respectively, as discussed before. Specific 1,3-attack also occurs for the trisubstituted alkene **28** and the linear triquinane **29** is isolated as the sole photocycloadduct.[19b]

Methyl and methoxy substituents at the ortho position should stabilize the polarized 1,3-intermediates. As expected, compounds **30** and **31** led to cycloadducts **32** and **33**, respectively (**Scheme 5**). However, in both cases, the respective photoisomers **34** and **35** were also formed, presumably involving 1,2-photocycloaddition and disrotatory ring opening of the thermally labile primary ortho-cycloadduct (e.g., **36**) to give the cyclooctatriene isomer **37**. Intramolecular disrotatory photocyclization (ratio **32** : **34** = 4 : 1, 60%; ratio **33** : **35** = 2.25 : 1, 68%) then leads to the observed photoisomers.[19b]

Blakemore and Gilbert also examined the photochemistry of benzyl allyl ethers carrying geminal dimethyl groups at the olefin terminus. The ortho position was either unsubstituted (**38**) or carried a methyl (**39**) or a methoxy (**40**) group. In all cases, the major reaction products were the linear triquinanes **41**, **42** and **43**, respectively. At very low conversions of the bichromophores other photoisomers were detected, but these rapidly disappeared on continued irradiation.

Isolated compounds were derived either from an 'ene' type addition[21] (for **38**) or from 1,2-addition (for **39** and **40**). Surprisingly, the (*Z*)-bichromophore **44** afforded both 1,3-adducts **45** and **46** in 12% and 40% yield, respectively.[20]

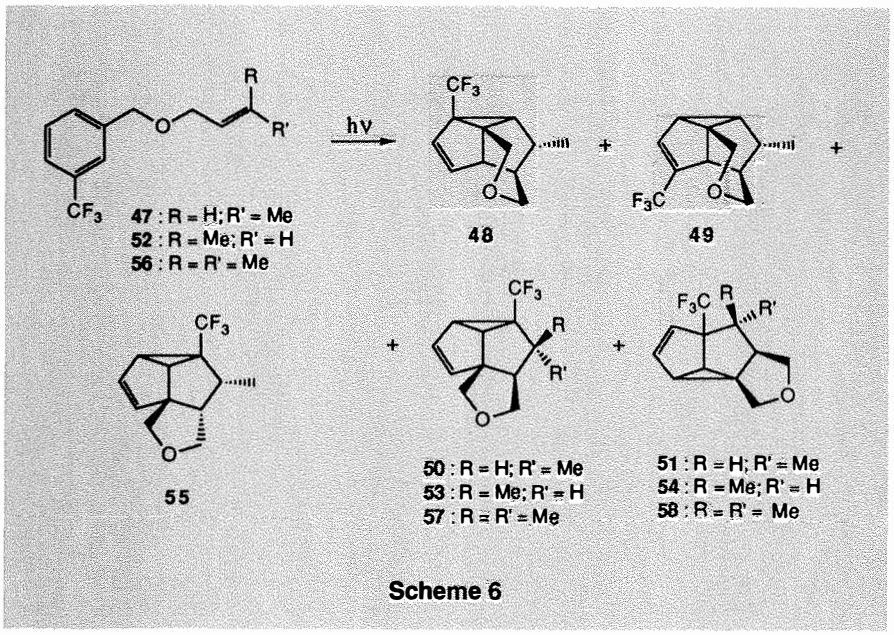
The effect of a trifluoromethyl group in the meta position was studied by Neijenesch.[20] The (*E*)-derivative **47** yielded the 2,6-meta-photocycloadducts **48** (28%) and **49** (2%), together with the 1,3-meta-photocycloadducts **50** (10%) and **51** (8%) (**Scheme 6**). Although the trifluoromethyl group should favor the 2,6-meta-photocycloaddition relative to the parent compound **23**, 1,3-meta-photocycloaddition effectively competes leading to a rather complex reaction mixture. In contrast, the (*Z*)-isomer **52** leads only to the 1,3-adducts **53** (23%), **54** (37%), and the more strained adduct **55** (15%). The same regioselectivity was found in the photoreaction of the homologue **56** giving rise to adducts **57** (17%) and **58** (46%). The presence of other electron-withdrawing groups, such as cyano in position 3 or fluoro in position 4, only led to polymer formation.

Since none of the (*Z*)-compounds give 2,6-meta-adducts, it appears that replacement of a methylene group in position 2' by an oxygen does not relieve the steric strain exerted by the (*Z*)-methyl group during alkene-arene interaction. On the other hand, the oxygen atom does influence the product ratios.

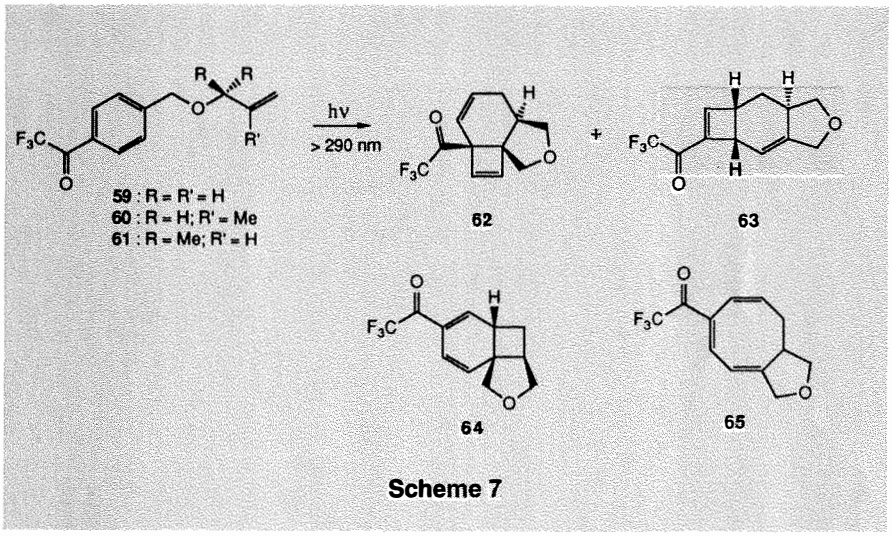
Wagner examined the fluorinated acetophenones **59**, **60**, and **61**, which gave rise, in all cases, to a mixture of two isomeric tricyclo[6.3.0.0]undecadienes, such as **62** and **63** derived from **59** (total chemical yields averaged 60% at 25% conversion)[22] (**Scheme 7**). The overall process results from an intramolecular 1,2-photocycloaddition of the double bond to the π, π^*-triplet of benzene on irradiation at wavelengths above 290 nm to form **64**, which then undergoes electrocyclic rearrangement to **65** followed by $(2\pi+2\pi)$-photocyclization.

The 254 nm induced reactions of indanes (**66**, **67**) and tetrahydronaphthalenes (**68**, **69**) nicely illustrates the considerable influence of the ether linkage on systems in which the benzylic position is constrained[19b,23] (**Scheme 8**). The indanyl compound **66** produced linear triquinane **70** (70%), while the bridged annular isomer **71** was only detected in small amounts from preparative irradiations at low conversions.[19b] In contrast, the dimethyl derivative **67** gave both isomers **72** and **73** (ratio **72** : **73** = 2.3 : 1, 98%). The ratio, however, changes with time, probably as the result of the greater photolability of the angular compared to the linear isomer.

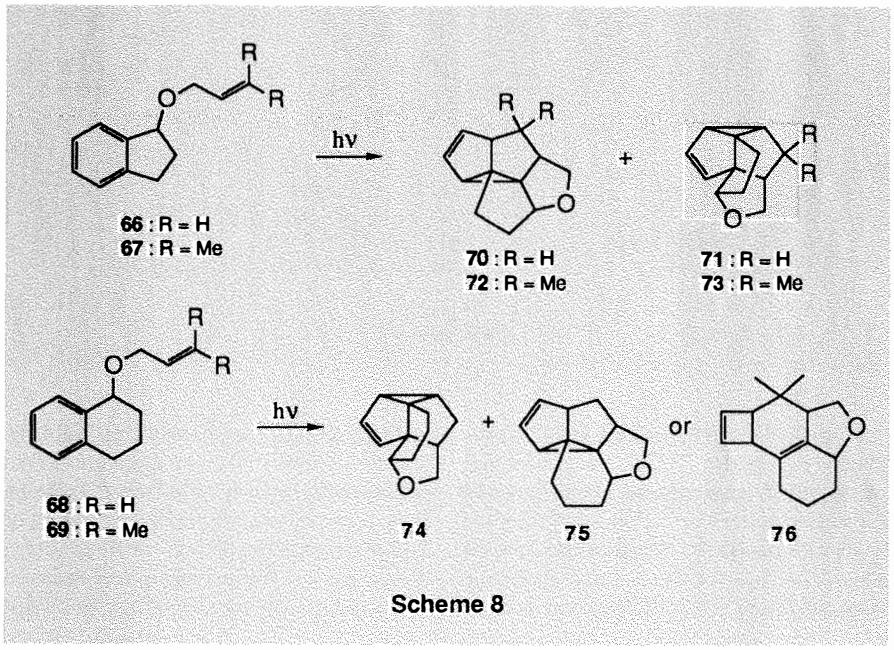
Surprisingly, the angular triquinane **74** is favored over the linear isomer **75** on irradiation of the tetrahydronaphthalene derivative



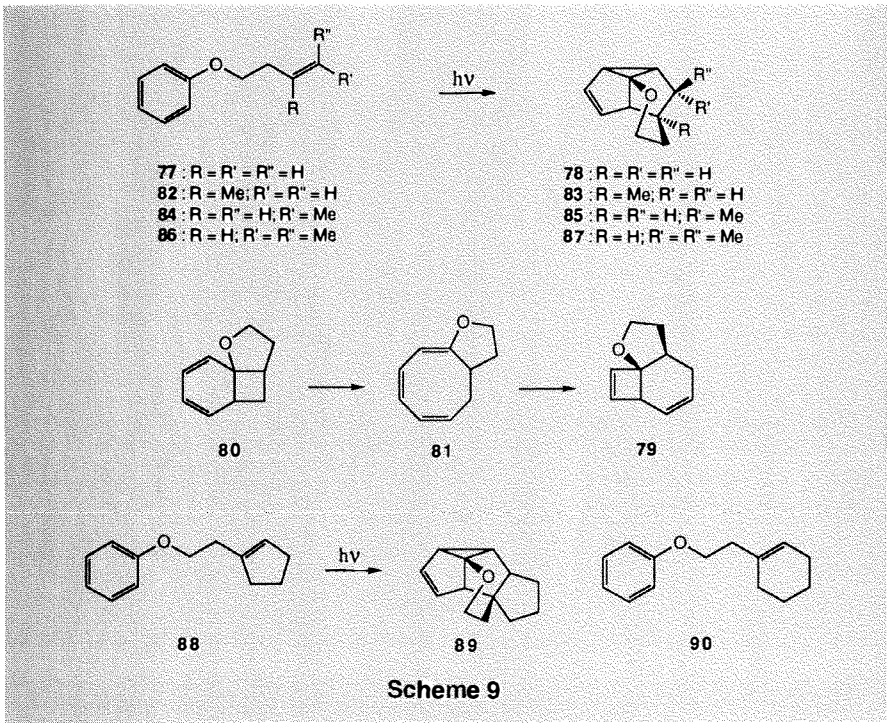
Scheme 6



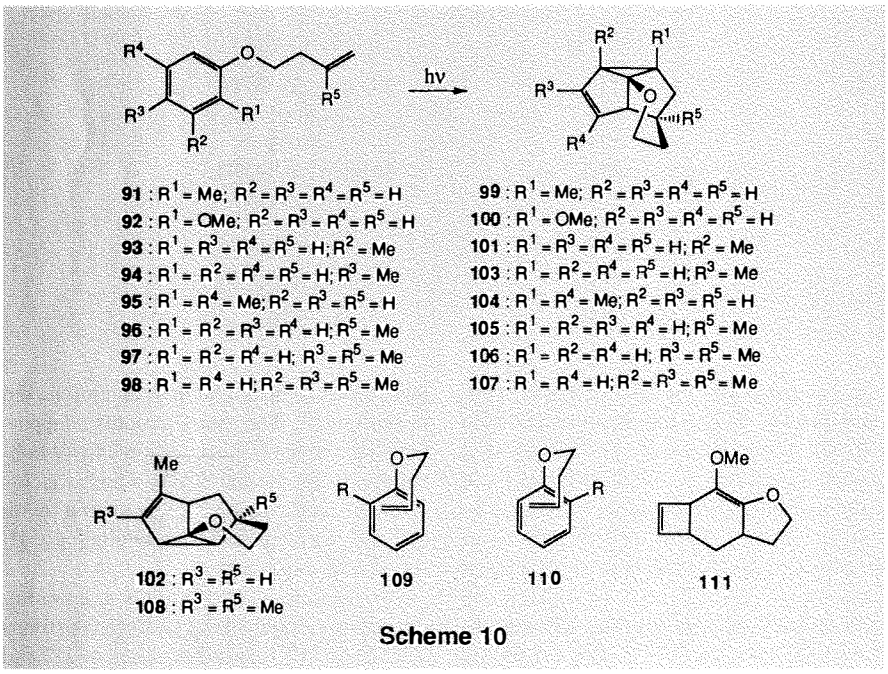
Scheme 7



Scheme 8



Scheme 9



Scheme 10

Table 1. Intramolecular meta-photocycloaddition of bichromophores **91-98** containing electron-donating arene substituents.

Compound	Adduct	Yield (%)
91	**99**	79
92	**100**	21
93	**101 + 102** (1.2 : 1)	75
94	**103**	82
95	**104**	36
96	**105**	55
97	**106**	47
98	**107 + 108** (1.2 : 1)	36

68 (47%). Dimethyl substitution of the alkene again markedly affects the photoreaction and promotes 1,2-cycloaddition to give the isomer **76** in low yield (17%).

It should also be noted that benzyl acrylate, in which oxygen in 2'-position is part of an ester function, does not produce meta-photocycloaddition.[19]

OXYGEN AT POSITION 1'

Irradiation of the alkyl phenyl ether **77** leads to adduct **78**, derived from 2,6-meta-photocycloaddition, in high yield (82%). The alkoxy tether indeed maximizes the stabilization of the developing positive charge in the S_1 state on approach of the addends[24] (**Scheme 9**). Structure **79** was assigned to a second photoisomer of **77**. This compound probably arises from initial intramolecular 1,2-addition, followed by disrotatory ring opening of the thermally labile 11-oxatricyclo[6.3.0.$0^{1,6}$]undeca-2,4-diene (**80**) and [2π+2π]-photocyclization of 11-oxabicyclo[6.3.0]undeca-1,3,5-triene (**81**). Electrocyclic rearrangements following initial 1,2-photocycloaddition (irradiation at wavelengths above 290 nm) also occur when acetyl groups are present in ortho or para positions of the arene (via the π,π*-triplet of the benzene ring).[25] The results are comparable to the photocyclizations of fluorinated acetophenones having oxygen at position 2'.[22]

A methyl substituent on the alkene, as in **82**, markedly reduces the efficiency of formation of the 2,6-meta-photocycloadduct **83** (55%) compared with the parent compound. This may be due to the steric repulsion between the methyl group and the arene meta position. This feature may induce a degree of asymmetric distortion of the six-membered ring in a manner similar to that proposed to account for specific 1,3-closure to a cyclopropane in additions of chloroethenes to the benzene ring.[26]

Bichromophore **84** in the (*E*)-configuration affords a mixture of photoproducts as well as much polymer formation. The main reaction product **85** (33%) results from the expected 2,6-meta-photocycloaddition (*endo*-methyl).[20]

The dimethyl homologue **86** showed very similar behavior leading to adduct **87** as the major photoproduct (39%). This is the first example of a compound with a (*Z*)-methyl group yielding a 2,6-meta-adduct on irradiation. Apparently, the strong 2,6-directing effect of the alkoxy group—stabilizing the polarized intermediate—overcomes the steric hindrance between the hydrogen atoms of the (*Z*)-methyl group and the lone pair orbitals on oxygen (or the hydrogen atoms of the methylene group in position 2').

Irradiation of cyclopentene derivative **88** afforded the expected 2,6-product, linear triquinane **89**.[27] In contrast, the cyclohexene derivative **90** only led to a complex reaction mixture.

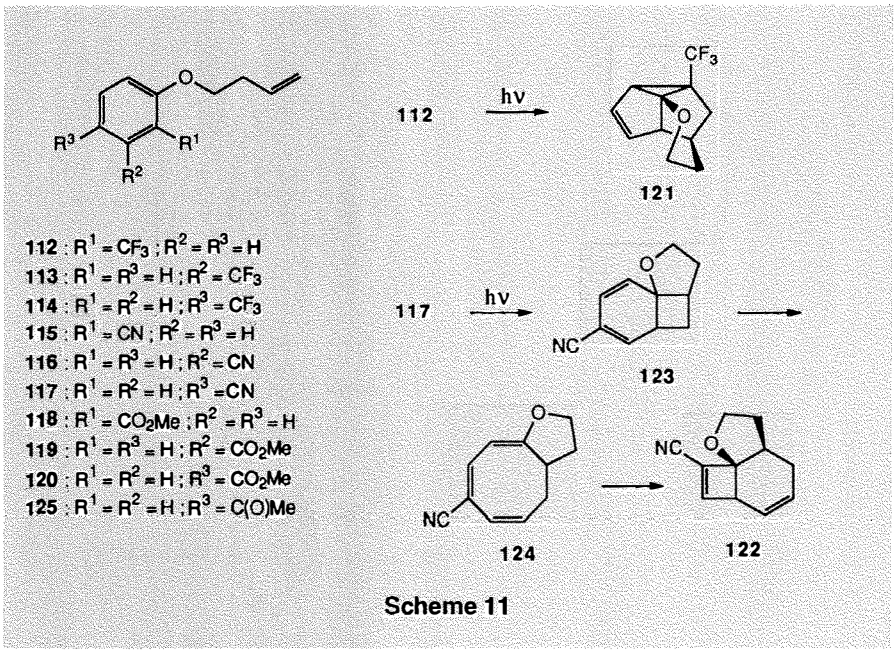
The influence and directing effects of arene substituents on the intramolecular photocycloadditions of (but-3-enyl) phenyl ethers have been studied in detail by Gilbert's and our research groups.[24,27] Let us first consider compounds **91-98** carrying electron-donating groups (**Scheme 10**). The results are summarized in Table 1. It is evident that the cyclopropane ring closure is specifically controlled as, except for **93** and **98**, only the 1,6-bridged dihydrosemibullvalenes **99-101** and **103-107** are formed and not the more strained 1,7-bridged isomers.

Two orientations (**109** and **110**) exist for the tethered alkene when the arene carries a substituent in the ortho position. The 2-methyl and 2-methoxy derivatives **91** and **92** are especially interesting because the competition between the 2,6-control by the tether and the 1,3-directing influence of these electron-donor groups can be explored.

However, as for intermolecular systems,[28] methyl substituents on the benzene ring do not compete effectively with the directing power exerted by the alkoxy group. Furthermore, they have little effect on the efficiency of the intramolecular 2,6-meta-photocycloaddition. On the other hand, the 2-methyl group controls the preferred orientation of the precursor, hence reaction occurs from only conformer **109** for the 2,6-addition. This is probably the result of repulsive steric interactions between the ortho-methyl group and the methylene units in the tether. An increase in the donating ability of the substituent in position 2, as in **92**, favors the ortho mode of photocycloaddition to give the tricyclo[6.3.0.0]undecadiene **111**.

A methyl substituent in meta position of the arene also leads to two possible orientations of attack. Since there are no steric influences to discriminate between the orientations, the 2,6-meta-photocycloaddition of **93** and **98** occurs from both conformations with similar efficiency (adducts **101** and **102** from **93**; adducts **107** and **108** from **98**). The 4-methyl substituent in compound **94** has no substantial influence. As expected, the steric interactions arising from the 2-methyl group in the dimethyl bichromophore **95** dictate a preferred orientation in the precursor conformer and only one 2,6-meta-photocycloadduct (**104**) is formed, albeit in rather low yield. The presence of a methyl group on the alkene (compounds **96** and **97**) also leads to reduced yields of the cycloadducts **105** and **106**, respectively.

Next, it is of interest to examine compounds **112-120** carrying electron-withdrawing substituents on the benzene ring (**Scheme 11**). The results are summarized in Table 2. The presence of a trifluoromethyl group at position 2, as in **112**, does not influence the regiochemistry of the intramolecular reaction, as the directing effect of the alkoxy tether is much more pronounced than the 3,5-direction of attack by trifluoromethyl. Cycloadduct **121** was obtained in 43% yield.[24,27] The positional isomers **113** and **114**, however, did not give clean photoreactions.



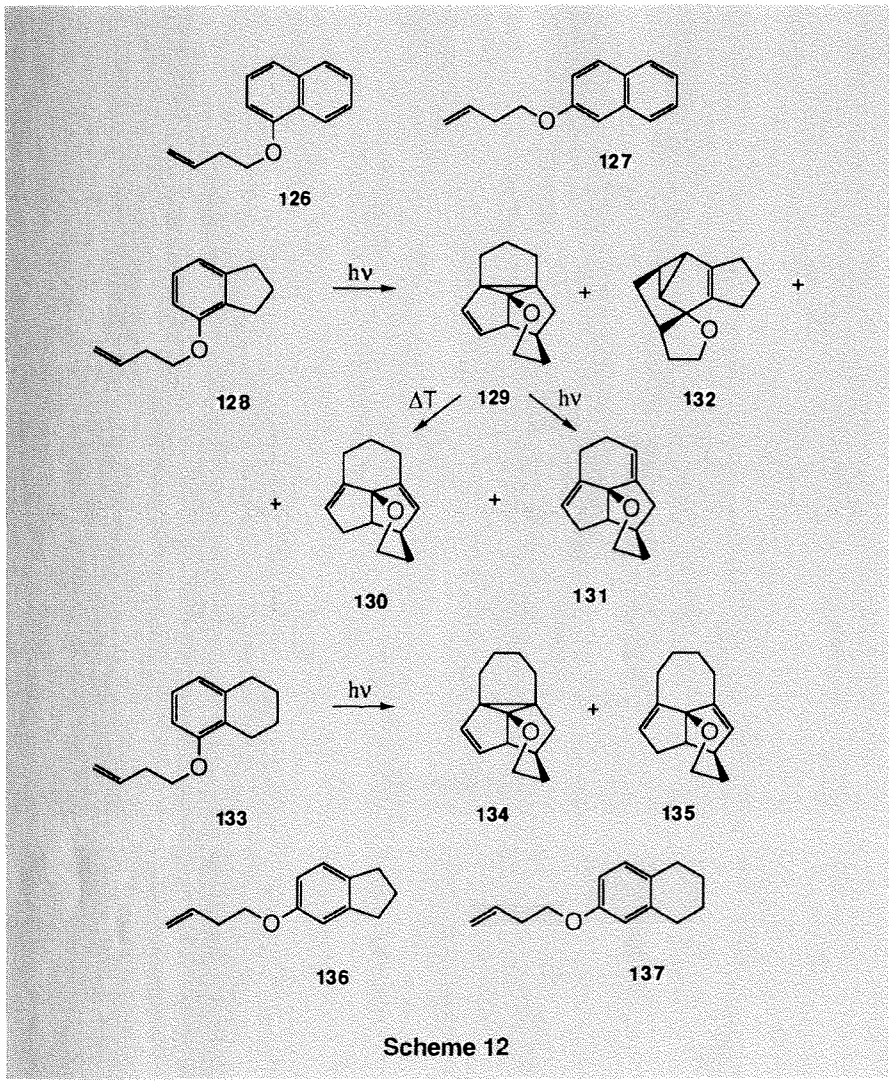
Scheme 11

Table 2. Photoreactions of bichromophores **112-120** containing electron-withdrawing arene substituents.

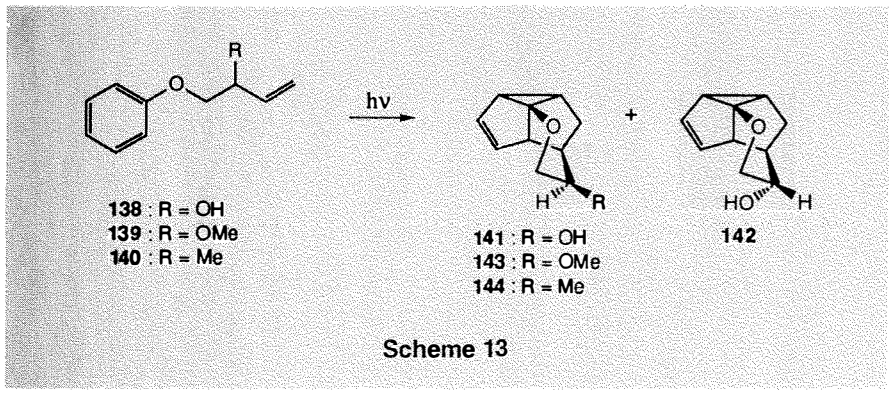
Compound	Photoreaction
112	meta: **121** (43%)
113	mixture
114	mixture
115	ortho: **122** (90%)
116	no reaction
117	ortho
118	ortho
119	no reaction
120	mixture

It is surprising that the photostable 3-cyano-substituted bichromophore **116** does not undergo efficient intramolecular meta-photocycloaddition, as in the intermolecular additions of cycloalkenes to 3-cyanoanisole.[29] Indeed, the 2,6-directing effect of the alkoxy group should be reinforced by the nitrile substituent. A possible explanation is that the reactive S_1 state is depopulated via intersystem crossing, which should not occur in anisole. Indeed, arene-alkene bichromophores, which have a 3-cyanoanisole moiety, do undergo ready intramolecular meta-photocycloaddition even in sunlight.[30] The same rationale is apparently operative for the 3-carbomethoxy-substituted bichromophore **119**, which was essentially unaffected by 254 nm irradiation and was recovered almost quantitatively after 14 days exposure.

Irradiation of compounds containing cyano and carbomethoxy groups in positions 2 (**115** and **118**, respectively) and 4 (**117** and **120**, respectively) at varying wavelengths did not give rise to meta-photocycloaddition.[29b] Instead, ortho adducts appeared to be the primary photoproducts, although all attempts to detect them were unsuccessful. The isolated compounds have an appropriately substituted 11-oxatricyclo[6.3.0.0^{1,4}]-undeca-2,5-diene structure, as illustrated for compound **117**, which afforded **122** in 90% yield. It was suggested that the initial ortho-cycloadduct **123** undergoes extremely rapid disrotatory thermal ring opening to yield the cycloocta-1,3,5-triene **124**, which then readily gives disrotatory photocyclization. These results are in complete agreement with the



Scheme 12



Scheme 13

observations of Wagner for the corresponding 2- and 4-acetyl bichromophores (e.g., **125**). From these findings it is evident that the photoreaction of bichromophores carrying electron-withdrawing substituents with a carbonyl or a cyano unit proceeds by way of the triplet π,π^*-state of the arene moiety.

Naphthyl ethers **126** and **127** are photostable[27] (**Scheme 12**). Irradiation of the indanyl bichromophore **128** led to the formation of four compounds, namely **129**, **130**, **131**, and **132** in a ratio of 2.2 : 1 : 4.1 : 0.8 (50%). Adduct **129** results from 2,6-meta-photocycloaddition, while the minoradduct **132** is formed by a 1,3-meta-photocycloaddition. The other reaction products are dienes derived from the meta adduct **129** by a thermal [1,5]-hydrogen shift (diene **130**) and two successive photochemical [1,3]-hydrogen shifts (diene **131**).

The tetrahydronaphthalene derivative **133** gave photoproducts **134** and **135** in a ratio of 1.5 : 1 (30%). In an analogous manner, as observed for **129**, the initial 2,6-meta-photocycloadduct **134** underwent an *in situ* thermal [1,5]-hydrogen shift to afford diene **135**. Thus, annulation of the arene does not hamper the 2,6-meta-photocycloaddition imposed by the alkoxy chain, but the respective photocycloadducts are prone to undergo regioselective cyclopropane bond cleavage affording more stable diene structures. Surprisingly, the positional isomers **136** and **137** only led to complex reaction mixtures.

As indicated previously, the yields quoted are based on the amounts of photosubstrates converted during irradiation. In our hands, yields of the desired photoproducts were best for conversions between 60% and 80%. Prolonged irradiation (until disappearance) of the starting material usually leads to enhanced decomposition of the reaction products and to much polymer formation. However, introduction of an allylic substituent, such as in **138-140,** dramatically increases the efficiency of the intramolecular meta-photocycloaddition of (but-3-enyl) phenyl ethers[31] (**Scheme 13**). The 2,6-regioselectivity and specific cyclopropane bond formation on irradiation of **138** led to an epimeric mixture of the 2,6-meta-adducts **141** and **142** in a ratio of 7 : 1. Irradiation of **139** and **140** afforded **143** and **144**, respectively, as single photoadducts. Quantitative conversion of the substrates was in all cases readily achieved and yields of the isolated reaction products were between 80% and 90%. The highly efficient complexation of the alkene with the excited arene is evidenced by the almost complete fluorescence quenching compared to anisole.[30]

ARENE-ALKENE BICHROMOPHORES CONTAINING A TETHER OF MORE OR LESS THAN THREE UNITS

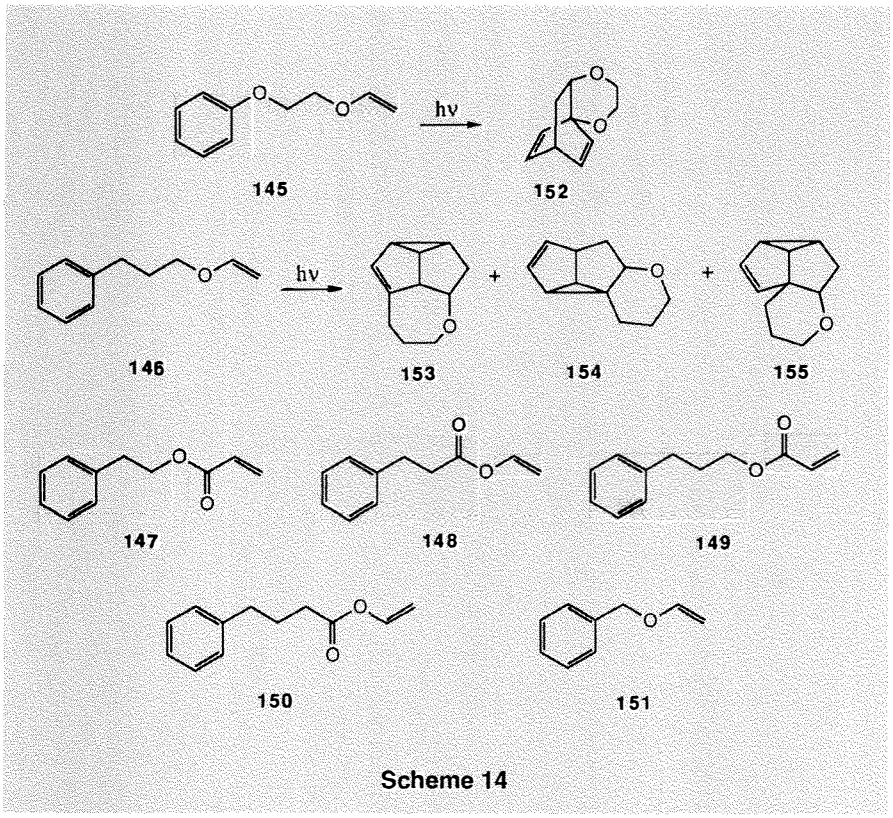
In an extensive compilation published in a recent review by Cornelisse,[7] eight entries pertain to a chain of four atoms, two entries to a tether-length of five atoms, and three entries relate to two atoms. Meta-photocycloaddition was generally not observed and the presence of an oxygen atom replacing a methylene group, such as in compounds **145-146**,[16b,c] **147-150**,[10] and **151**,[16b] had no effect (**Scheme 14**). It may be pointed out that the alkenes are part of either acrylate, vinyl ester, or vinyl ether groups. Diether **145** gave very inefficient 1,4-addition (adduct **152**) along with excessive polymer formation. Vinyl ether **146** afforded the 2,4-meta-photocycloadduct **153** as the major reaction product, along with the 1,3-meta-photocycloadducts **154** and **155** in a ratio of 7:5.

TANDEM NORRISH TYPE I PHOTOREACTION AND INTRAMOLECULAR ARENE-ALKENE META-PHOTOCYCLOADDITION

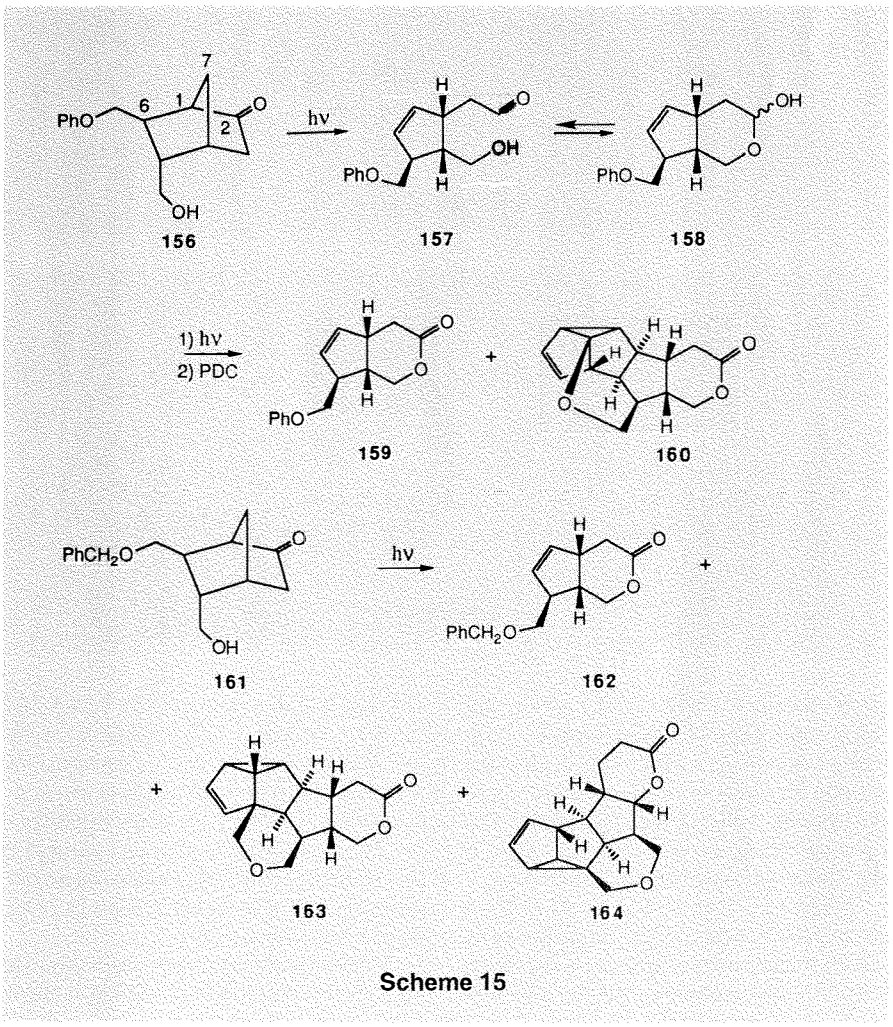
We have discovered that 254 nm irradiation of norbornan-2-ones, substituted with phenoxymethyl or benzoxymethyl groups at C(6), gives rise to a novel type of photochemical tandem reaction.[32] Thus, 6-(*exo*)-phenoxymethyl-5-(*endo*)-hydroxymethylnorbornan-2-one (**156**) is first converted by a Norrish Type I reaction [regiospecific cleavage of the C(1)-C(2) bond followed by abstraction of the *endo*-oriented C(7)-hydrogen atom] to the γ,δ-unsaturated aldehyde **157** in equilibrium with the corresponding lactol **158** (**Scheme 15**). This intermediate can be regarded as a benzene ring substituted with a (cyclopent-2-enyl)methoxy group; hence, this compound belongs to the class of arene-alkene bichromophores containing oxygen at position 1' in the tether. We observed that the Norrish Type I reaction is followed by an intramolecular 2,6-meta-photocycloaddition resulting from the strong directing effect of the alkoxy chain, as already explained before. After oxidation of the crude reaction mixture with pyridinium dichromate, lactones **159** (residual Norrish Type I product, 35%) and **160** (tandem reaction product, 28%) were isolated.[32]

The structure of photocycloadduct **160** was fully elucidated by a detailed NMR study.[33] It is a hexacyclic compound containing nine contiguous stereocenters. Due to the stereochemical features (already present in the norbornan-2-one), the mode and regioselectivity of both the Norrish Type I reaction and the arene-alkene photocycloaddition, the incorporation of the alkene in a five-membered ring, and the steric constraints and the specific formation of the cyclopropane ring, the tandem reaction gives rise to a single photoadduct. The formidable increase in complexity occurring during the one-pot photoisomerization of a rather simple norbornan-2-one to a complex linear triquinane can be appreciated.

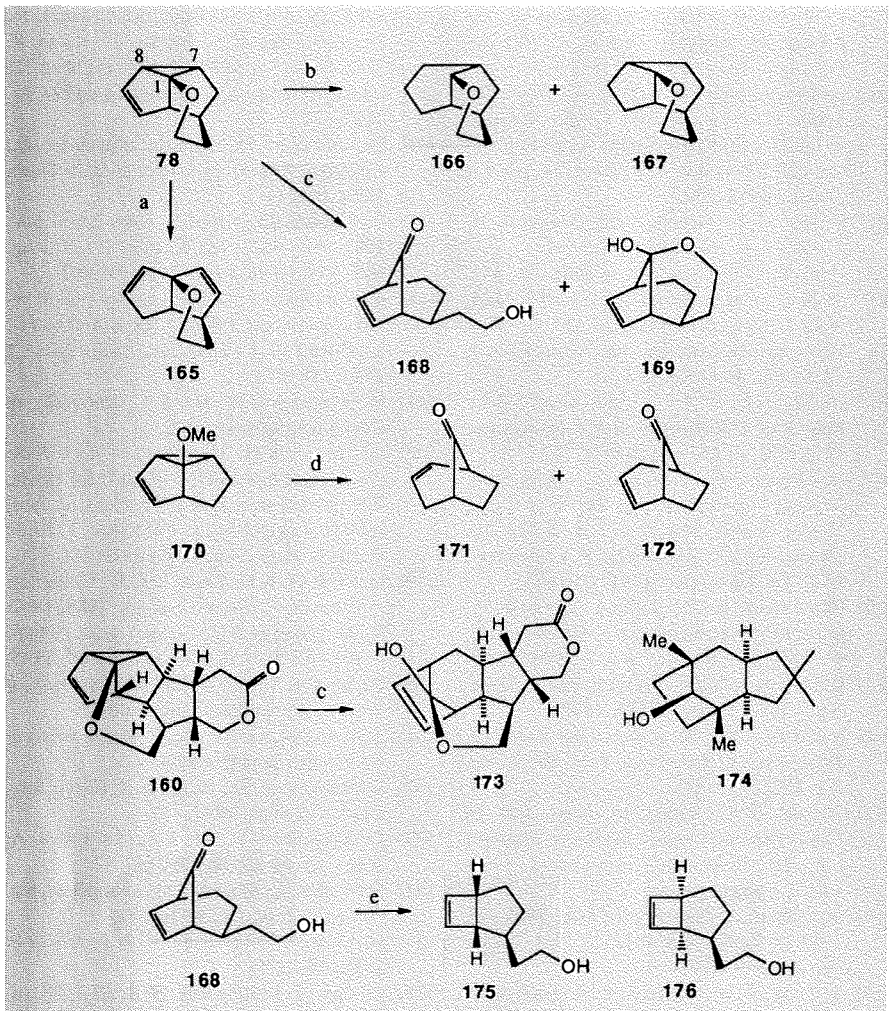
The tandem reaction was also provoked in 6-(*exo*)-benzoxymethyl-5-(*endo*)-hydroxymethylnorbornan-2-one (**161**), the homologue of **156**. Irradiation and oxidation gave the Norrish Type I photoproduct **162** (35%) together with the tandem reaction products **163** and **164** in ratio of 1.4 : 1 (25%). It is quite intriguing that the meta-photocycloaddition still takes place since four units, including an oxygen atom, intervene between the arene and the alkene chromophores. This is perhaps the first example of an efficient intramolecular arene-alkene meta-photocycloaddition when the tether contains more than three units. We further examined the effect of methoxy and trifluoromethyl substituents at different positions.[27] All results



Scheme 14



Scheme 15



Scheme 16

were in accord with the polarized model discussed before. The highest yield (64%) was observed for the trifluoromethyl group in the ortho position. It should also be mentioned that the epimeric norbornan-2-ones, having the phenoxymethyl or benzoxymethyl groups at C(6) in *endo*-configuration, did not produce meta-photocycloaddition since the two chromophores cannot sufficiently interact.

ACCESS TO POLYCYCLOPENTANOIDS

The general synthetic usefulness of the intramolecular arene-alkene meta-photocycloaddition remains essentially unexploited. Its most attractive aspect from a synthetic viewpoint is the creation of fused five-membered rings (polycyclopentanoids). In arene-alkene bichromophores with a tether containing oxygen, the intramolecular meta-photocycloaddition generates either diquinanes or triquinanes (in most instances linearly fused) depending on whether the alkene is acyclic or incorporated into a five-membered ring. Moreover, the tether occurs as an extra heterocyclic ring in the cycloadducts, while a three-membered ring is also present. Although polycyclic structures of this type have extremely interesting synthetic features, applications have emerged only recently.

The cyclopropane ring is evidently a versatile handle for further elaboration and, therefore, it is manipulated for most synthetic applications. Different methods have been developed for cleavage of the allylic cyclopropane bonds.[7,9] In the bichromophoric series containing oxygen at position 1' in the tether, the 2,6-meta-photocycloaddition leads, in general, to a cyclopropyl ether function. This feature allows for straightforward ring opening under conditions where electron deficiency is created at the cyclopropane carbon atom carrying oxygen. Consequently, acidolysis should occur smoothly.

The synthetic potential will be highlighted by a short description of some selective conversions of a simple 2,6-meta-photocycloadduct, such as **78** (2-oxatetracyclo-[5.4.0.0^{1,8}0^{5,11}]undec-9-ene, IUPAC numbering) (**Scheme 16**). Thermolysis causes a [1,5]-hydrogen shift leading to the diquinane **165** (72%).[27] Obviously, bond C(7)-C(8) is cleaved because of its allylic disposition with regard to the double bond in **78** and the hydrogen being transferred. Hydrogenolysis of **78** in the presence of palladium on carbon gave two reaction products, 2-oxatricyclo-[5.4.0.0^{5,11}]undecane (**166**, 66%) and 2-oxatricyclo[6.3.0.0^{5,11}]undecane (**167**, 11%). Compound **166** is formed by preferential opening of the allylic cylopropane bond C(1)-C(8), although hydrogenolysis also occurred to a minor extent via cleavage of the C(1)-C(7) bond.

Treatment of **78** with dilute hydrogen chloride in aqueous acetone afforded compounds **168** and **169** in a ratio of 6 : 1 (90%). The methylated homologues (see Table 1) gave comparable results. Thus, the non-allylic cyclopropane bond C(1)-C(7) was regioselectively cleaved during acidolysis. The special nature and the facility of this reaction are evident from comparison with the simple analogue **170.**[34] While the acidolysis of **78** was complete after 10 minutes at room temperature, the transformation of **170** to the unsaturated bicyclic ketones **171** and **172** under the same conditions required boiling for several hours (80%). Even more striking is the fact that compounds **171** and **172** result from cleavage of an allylic bond. Obviously, the oxyethylene unit bridging the diquinane structure in **78** increases the strain and weakens the non-allylic cyclopropane bond.

This characteristic acidolysis occurs not only in simple meta-photocycloadducts, such as **78**, but was also observed for the complex linear triquinane **160.**[27] Detailed NMR analysis led to complete elucidation of the structure of the lactol **173.**[33] Such a conversion gives direct access to the bullerane skeleton, represented by the naturally occurring (+)-cerapicol **174.**[35]

Finally, it should be noted that compounds such as **168** contain a β,γ-enone functionality which is a well-known photochemically active entity. Irradiation of **168** at 300 nm in methanol gave the bicyclo[3.2.0]hept-6-enes **175** and **176** in a ratio of 1.4 : 1 (80%).[27] This result was confirmed by the similar reactivity observed for the methylated homologues, which revealed that no rearrangement took place. It is, therefore,

most likely that photolysis of **168** occurs via elimination of carbon monoxide to an intermediate cyclohepta-1,3-diene, which is immediately converted to the diastereomeric compounds **175** and **176** by intramolecular [2π+2π]-photocyclization.

CONCLUSION

In general, the introduction of an oxygen atom into the chain linking two chromophores generally enhances the efficiency of intramolecular photocycloadditions.[36] The increased chain flexibility in arene-alkene bichromophores containing oxygen in the tether allows better overlap, enhancing meta-photocycloaddition. The selective formation of meta-photocycloadducts results from a delicate balance between the directing effects of the tether and of arene substituents, and subtle steric features involving alkene substituents and atoms in the tether. The influence of an alkoxy chain as a substituent on the aromatic ring is quite pronounced, while the highest efficiencies are noted when suitable groups are introduced in allylic position, showing the importance of conformational effects. All reported results are in agreement with the polarized benzene model.[7]

Further transformations of the cycloadducts profit from the presence of either the cyclopropane ring carrying a vinyl or an ether group, or other functionalities. Thus, a number of naturally occurring skeletons can be accessed from readily available aromatic substrates in only a few reaction steps. The described photochemical method has a particularly promising synthetic potential for short and efficient construction of polycyclopentanoids.

ACKNOWLEDGMENTS

It is a pleasure to record my thanks to my collaborators Shu-Lin He and Chuan-Yue Wang for their experimental and innovative contributions to these studies. I am very much indebted to André De Bruyn for his invaluable assistance in interpreting the NMR spectra. The inspiring contacts and fruitful discussions with Andrew Gilbert from the University of Reading, UK, and Jan Cornelisse from the University of Leiden, The Netherlands, stimulated very much my endeavors in this fascinating chemistry.

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Notes:

(1) It is important to use a consistent numbering system in order to avoid confusion. Since the meta-photocycloaddition is also named 1,3-addition, as opposed to 1,2- (ortho) and 1,4- (para) addition, confusion may arise when substituted arenes are used. It is therefore appropriate to denote the reaction type as 'meta-photocycloaddition', while the numbers of the carbon atoms of the arene ring are used for identifying the positions of addition. For example, the major mode of intramolecular meta-photocycloaddition of alkoxy-substituted arenes is 2,6. When substitution patterns of intramolecular photocycloadducts have to be compared, the use of IUPAC numbering is often inconvenient. With reference to the arene numbering, the carbon (or oxygen) atoms in the tether and the alkene are designated as 1', 2', 3', etc., starting from the point of attachment to the arene ring.

(2) Irradiations are carried out at 254 nm unless specified otherwise. It is most convenient to use an apolar solvent such as pentane or cyclohexane. When solubility problems arise, a more polar solvent (such as ethyl acetate) may be admixed in small quantities. In polar solvents the formation of complex mixtures is observed. If several photocycloadducts are formed, initial ratios are usually given (i.e. at the shortest exposure time for accurate integration of reaction products). In most cases the yields are not optimized, but values quoted are corrected for amounts of bichromophores unconverted.

ABOUT THE AUTHOR

Denis De Keukeleire was born in Beerlegem, Belgium. He received his B.S. degree in chemistry in 1966, his Ph.D. degree in organic chemistry in 1971 and his Habilitation in 1982 from the University of Gent, Belgium, for work on hop and beer bitter acids. After postdoctoral research with Professor George Hammond at the California Institute of Technology, Pasadena, California and stays at the Universities of Geneva (Professor Schaffner), Bonn (the late Professor Snatzke) and Zurich (the late Professor Schmid), he joined the staff of the Laboratory of Organic Chemistry at the University of Gent as research associate of the National Fund for Scientific Research (Belgium). In 1991 he was appointed as professor at the Faculty of Sciences, Laboratory of Plant Biochemistry and in 1992 he took the chair of Pharmacognosy and Phytochemistry in the Faculty of Pharmaceutical Sciences at the University of Gent.

Professor De Keukeleire has carried on research in a number of areas connected with phytochemistry and photochemistry for over 25 years. His interests include photochemical construction of biologically active polycyclic molecules, along with investigation of various aspects of hop and beer chemistry. He is the author of *Chemistry and Analysis of Hop and Beer Bitter Acids* (Elsevier, 1992) and co-author of *Luminescence Techniques in Chemical and Biochemical Analysis* (Dekker, 1991).

Recently, he started a research project aimed at isolating and identifying pharmacologically active substances from plants used in traditional medicine. His research activities, which have been published in over 100 papers in international scientific journals, have been honoured with a number of prizes and awards.

Professor De Keukeleire, who holds the title of *European Chemist*, is associated with major professional societies, interested in various aspects of chemical education and active in the popularization of sciences. He is acting treasurer-general of the Royal Flemish Chemical Society and editor-in-chief of the monthly Chemic Magazine.

The Trouble with Synthesis[1]

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ABSTRACT

Chemical synthesis is defined as the intentional construction of molecules by means of chemical reactions. The motives of chemists for engaging in synthesis are discussed, together with desirable developments in the art of synthesis and in the publication of its results.

I am honoured to give this lecture, named after my good friend Jerry Price.[2] On two important occasions he has given kind help to our researches; and I will do the best I can with this thank-offering. It isn't the first time that I have given a lecture named after a living man, but the previous one was for my teacher Robert Robinson and I was very apprehensive about what he might say afterwards.

Chemists have been using the word "synthesis" for more than 250 years, so that it predates not only the idea of molecular structure but even Dalton's atomic theory. It comes from the Greek and it means "putting together". As with many other terms that we use, including organic and inorganic, we have been saddled with a not too appropriate word to describe an activity. If we took the word seriously, we would apply it only to addition reactions like the diene synthesis or catalytic hydrogenation; and if we ever demote "synthesis" in favour of some less limiting word like "construction", the category of addition reactions might not be a bad home for it. In truth, nearly all our syntheses depend as much on breaking old bonds as on forming new ones.

There are very few words that don't acquire new meanings as they grow older, and synthesis is no exception. It does not mean making new compositions of matter, new molecules; for it happens that Nature and especially living Nature has exhibited to the chemist a very large variety of molecules. They are there, they are not new; but if we can make them from something else we say that we have synthesized them. And sometimes we proudly call our synthesis a total synthesis.

Briefly, we are then claiming that if we were given adequate supplies of all the chemical elements composing our compound, we could make a specimen of the compound totally derived from the matter supplied. In practice, nobody ever executes a total synthesis and few of the raw materials used have, in fact, been made from their elements. Nineteenth century chemists, notably Berthelot, have shown the way from the elements to the simpler and more abundantly available compounds (often in miserable yields and quite unpractical conditions) and the vast network of transformations relieves the modern chemist even of the need to verify that there is a notional connection between the raw materials and their constituent elements.

But synthesis of compounds from elements is not peculiar to human beings. Other organisms can assimilate elemental hydrogen, nitrogen, oxygen, and sulfur and incorporate them into a wide variety of compounds. So if we claim to have made the first total synthesis of a natural product we are reduced to the rather feeble defence that no organism is known to assimilate elemental carbon (or phosphorus). I would not bet very heavily against the discovery of an organism that will eat buckminsterfullerene (which is undoubtedly elemental carbon), and as for phosphorus it combines spontaneously with oxygen to form compounds that many organisms will certainly assimilate. It is better to admit at once that total synthesis is by restriction a human activity.

This rejection of competition, or even help, from other organisms in the execution of chemical synthesis is another nineteenth-century legacy. The first and slightly dubious synthesis of a natural product—Wöhler's urea—was considered important as a demonstration that compounds produced by living things are in no way different when human beings produce them with no help from other organisms. The doctrine of vitalism, with its idea of a mysterious force pervading living matter and differentiating it from the non-living, is still alive and vocal; even among scientists it died hard.

For example, one might have thought that Louis Pasteur's lovely experiment with racemic acid, when by intelligent inspection of one of its salts he was able to separate the crystals of 'natural' tartrate from those of its mirror image, would have persuaded him that optical activity in the disperse state is not a prerogative of life. Alas, he thought that racemic acid *was* a product of life. His racemic acid had come from grape juice via a factory where some of the tartaric acid in the juice had been racemized by boiling it down in copper pans. When presented with a truly synthetic racemic specimen of malic acid, he would not even try to resolve it, though by that time he had a method which would certainly have worked. Again, he made beautiful experiments to show that, as he put it, 'fermentation is life without oxygen'; but his vitalistic prejudice was probably what prevented him from making Buchner's experiment[3] and showing, 30 years earlier, that lifeless filtrates could also ferment.

We need no more demonstrations that the molecules of life are the same, and have the same biological actions however they were made. So that excuse for indulging in chemical synthesis has long lost its plausibility. Indeed, with our present knowledge of the chemistry of living things and its essential unity with the chemistry that we practise, I can see no reason why we should not welcome enzymes and microbes as friends and colleagues. Since they work for even less money than graduate students, perhaps we should at least acknowledge them in publications. Nevertheless, synthesis directed by the human mind remains a most popular and respected activity among chemists, so what other excuses can we offer?

It is well worth looking at the proposition that chemical synthesis is an art form, needing no justification because it permits self-expression in its creators and produces aesthetic pleasure in those who examine its products. The greatest of synthetic chemists, Robert Burns Woodward, won the Nobel prize in 1965 for — I quote — his contributions to the art of organic synthesis. He accepted the description at the time, but there was no mistaking the Committee's undertone that synthesis may be more of an art than a science, and it is a fact that the prize has

been awarded specifically for synthesis only four times during the 92 years since the first prize was awarded, if one excludes the Bosch-Haber ammonia synthesis, which was not original.

If chemical synthesis is an art, which recognized arts are nearest to it? I think, in their different ways, architecture and chess. An architect's constructive imagination works under constraints imposed by the materials and labour that must be used. A grandmaster of chess creates masterpieces in the face of tough and tenacious opposition. The chemist has materials, an imperfect knowledge of their possibilities and limitations, and an opponent — the truth — who sometimes changes during the work into a teacher and friend.

There are others who think of synthesis as a manifestation of human arrogance, though they usually call it aspiration or endeavour. Elaborate expeditions are launched for the essentially useless feats of treading on the top of a high mountain or on the surface of the moon, or synthesizing a vitamin that will always be easier to get from microbes. Woodward certainly had that feeling very strongly; when he and Eschenmoser had completed the epic synthesis of Vitamin B_{12}, he insisted on completing the final steps with totally synthetic material, though they had already been executed by partial synthesis.[4] And Robert Robinson, no mean mountaineer, certainly had the climber's approach to many of his syntheses.

Comparisons apart, there is no doubt that chemical synthesis can be an immensely challenging, endlessly frustrating, totally stimulating exercise. Art, science, or sport, it holds its devotees; and because it is a rather expensive activity they have to offer what inducements they can to those who alone can provide the money. Such providers usually insist that the synthesis should have some purpose: the situation is perhaps the same as that of the old alchemists who really wanted to get on with their science — they called it the hermetic art, by the way — but who had to dangle the prospect of unlimited gold in front of the medieval prince or baron who then filled the role of the research councils.

A pretext popular in the early years of this century claimed that synthesis was the final proof of structure. I can remember Robert Robinson advancing it when I asked him why he wanted to synthesize cholesterol. The trouble about that excuse was that structures in those days were deduced mainly by interpreting chemical degradations. The reactions used in synthesis were subject to the same interpretation and to similar mistakes. Nowadays, there are many examples of natural products that cannot be crystallized so as to allow the not quite infallible method of X-ray diffraction to be used, and the structure is derived from computer analysis of pulsed NMR spectra. In some of these cases, synthesis has indeed provided final proof that the structures deduced were wrong. So the old excuse can be usefully revived on suitable occasions.

A different line of persuasion, and rather easier to sell, is the notion that by solving a difficult problem of synthesis the chemist is likely to be forced to invent new methods. Robinson would not have invented the ring extension that bears his name,[5] I would not have invented the reduction of 2-methoxynaphthalenes to 2-tetralones,[6] and Birch would not have extended this reduction to the much more generally useful methoxybenzenes[7] if we had not all been working on the synthesis of steroids. The triggering event for Woodward's generalizations on orbital symmetry was a reaction in the B_{12} synthesis that did not go in the sense expected.[8] But the truth is that invention, with its attendant uncertainty, is a last resort for most synthetic chemists whose goal is a natural product. The more reactions we discover, the truer this becomes; and if in the future we entrust the planning of syntheses to computer programs we shall be absolutely dependent on known reactions, the more reliable the better. The reactions we know now were, and still are, largely discovered by accident; and in the days when structures were deduced by chemistry instead of by spectra, natural product chemistry was a very fertile source. Now, new reactions are quite often found by speculative but not purposeless search in particular areas of chemistry. Corey is the master of this genre, but now there are many others.

That brings me to the distinction between a reaction and a synthesis, and the best example I can think of comes from the first half of this century. Richard Willstätter wanted to make cyclooctatetraene to compare its properties with those of benzene. That, in 1905, was a novel and indeed pioneering excuse for synthesis: making a molecule for its theoretical interest. This pretext has been magnificently extended in recent years to create what might be called the chemistry of funny shapes: prismane, cubane, and dodecahedrane are only the more symmetrical examples among a host of bizarre and practically useless molecules that have exacted hard labour from a much larger host of postgraduate and postdoctoral students. But to make cyclooctatetraene was at the time a genuinely valuable exercise. Willstätter wisely chose the line of least effort (**Fig. 1**) and started from an alkaloid provided by the bark of the pomegranate tree. By already known chemistry he arrived at *N*-methylgranatenine, and to this he applied the long-known techniques of exhaustive methylation, addition of bromine, and alkylation of amines. The final exhaustive methylation gave him his product.

Now this was a classic synthesis. It followed a preconceived plan, it used known reactions, it gave a miserable overall yield, and it took nearly 10 years to finish.[9] It also proved its point: benzene and cyclooctatetraene have completely different properties.

In 1940, J.W. Reppe and his team were studying industrially useful reactions of acetylene, taking advantage of techniques for safely handling this potentially explosive gas. When acetylene was pressed into a warm suspension of nickel cyanide and calcium carbide in tetrahydrofuran (THF), the product was cyclooctatetraene in up to 90% yield[10] (**Fig. 2**).

Was this a synthesis? Technically, it fulfils the most rigorous criteria. It can even be called a total synthesis, which Willstätter's was not; indeed, it is only two steps from the elements, since acetylene can be made from carbon and hydrogen. Also, both steps are pure additions: it is truly a putting together. But I will bet that Reppe thought of it as a reaction of acetylene, and I would disqualify it as a synthesis because there was no *purpose* to make cyclooctatetraene.

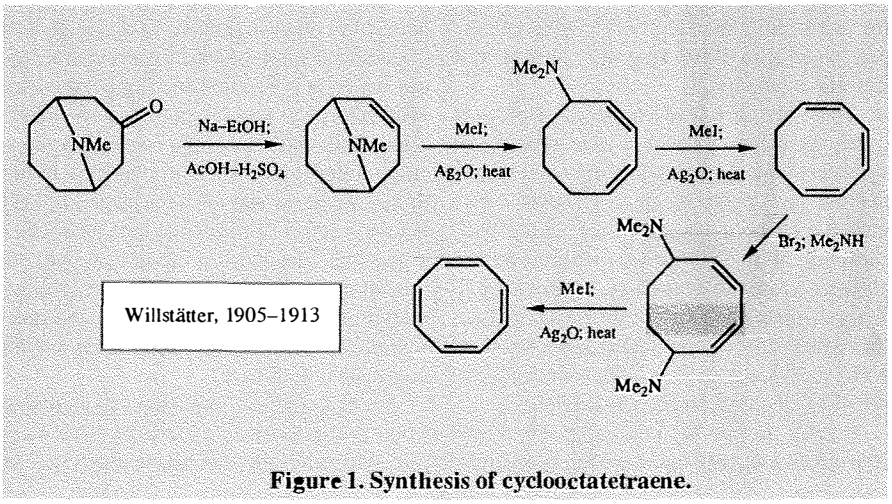

Figure 1. Synthesis of cyclooctatetraene.

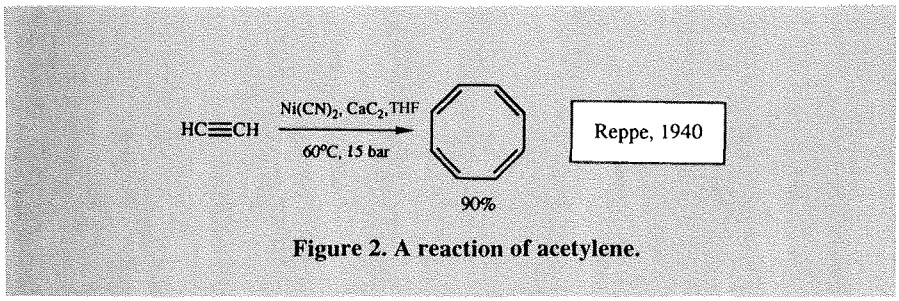

Figure 2. A reaction of acetylene.

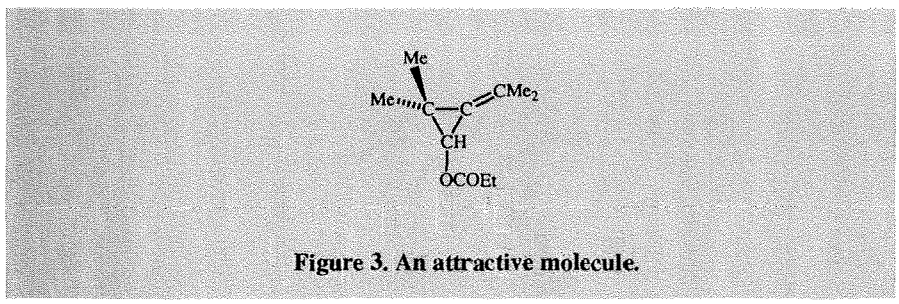

Figure 3. An attractive molecule.

From some points of view it is no disgrace to have a reaction rather than a synthesis. Turning again to the list of Nobel prizes in chemistry, we find half a dozen laureates — Grignard, Sabatier, Diels, Alder, Brown, Wittig — whose citations refer to the discovery of reactions, and a larger number who studied their mechanisms or stereochemistry.

I think we have come far enough now to attempt a modern definition of chemical synthesis as *the intentional construction of molecules by means of chemical reactions*. And it is my purpose now to show the intentions and the reactions interfering with each other. The Why and the How, in other words, are inseparable except in those syntheses that are purely artistic or sporting and, therefore, have any How and no Why.

A nice example comes from the 1960s. A team in the United States was studying the sex attractant of the female American cockroach. Warm air was passed over a very large number of these animals and then through a cold trap. By further refining, a minute amount of active material was obtained and a structure was proposed[11] on the basis of physical measurements (**Fig.3**). There was then, as now, a considerable number of chemists looking hungrily for an excuse to synthesize something, and the effect of this structure was rather like that of a dead horse dropped into a lake of piranha fish. Here was a small molecule asking for the application of up-to-date reactions, and the excuse for synthesizing it was the most grantworthy: an adequate supply of the stuff, obviously not available from natural sources, might plausibly play its part in controlling a noxious pest. Within three years, six approaches were reported, all most ingenious. Two of them[12,13] were successful, the others were honourable near misses. So the molecule was well and truly synthesized and the compound became readily available. There was only one snag — the proposed structure was wrong and the synthetic material inactive. A lady I know remarked at the time that, although this molecule wasn't very good at attracting male cockroaches, it certainly attracted a lot of organic chemists. Perhaps it would be kinder to say that synthesis here was the final proof of non-structure. And there are happier endings to many another story of this kind, for example, in the fields of perfumes and flavours, where a component present only in traces may have a dominant effect. In such cases the versatility and power of modern synthetic methods, acting on information provided by modern analytical methods and motivated by the economic or biological importance of the target, can be invaluable.

All this is just part of the ballet between Chemistry and Nature that has been danced now for more than a hundred years. Nature produces something that humanity wants or needs, but doesn't make enough of it; or, if she does, makes it too expensive to extract or makes it in a country whose people charge too much for it. Europe once imported indigo and madder, both ancient dyestuffs from plants, from the East and Middle East. Chemistry found out how to make both from coal tar, a by-product of the coke ovens and the old gasworks; in fact, the fraction of coal tar containing anthracene came to be called 'Turkey Red oil". The old indigo syntheses have some fascinating chemistry that is a little obscure even now. In that case, Chemistry won. What it did, of course, was to use dead plants — coal — instead of live ones. But sometimes, Chemistry switches from one live plant to another, as when the turpentine from pine trees becomes the raw material for making the perfumes of flowers.

It was my lot to take part in several of these dances, but the most enthralling was the first: penicillin. My wife and I were graduate students at Oxford when the first concentrates from Fleming's fungus were painfully got together at the School of Pathology, and when the first trials with human patients were made at the Radcliffe Infirmary. At the Dyson Perrins Laboratory, Robinson accepted the chemical challenge and the nucleus of the team was formed: Ted Abraham and Ernst Chain from Pathology, and Wilson Baker with Robert from the Dyson Perrins. By 1943, when we joined the team, the scene was set. Here was a chemical substance — we didn't know then what it was — enormously effective against bacterial infections including some that sulfonamides could not cure, and obtainable only in traces and with great labour from the broth in which an obscure mould had grown. Chemistry had scored a notable success in the fight against bacterial disease when it developed the sulfonamides. Perhaps it could find out the structure of penicillin and then synthesize it. In time of war, even a costly synthesis, if it could produce enough, would serve.

The carbon in penicillin (**Fig. 4**) occurs in three blocks. During 1943, they were all identified and the variability of the side chain was established. I guessed the structure of another part — penicillamine — and did the synthesis and optical resolution in six weeks. Before the year's end, synthesis could be concentrated on two different but almost equivalent structures. The international effort that extended over the next three years is recorded in *The Chemistry of Penicillin*,[14] published in 1949. There was so much work, and it was so badly abstracted, that rediscoveries of some of it were being made 20 years later, and for all I know still are. But the limit of success was a synthesis in about 0-1% yield.

Meanwhile, Nature with human aid was not idle. Better nutrient media were found for the mould, techniques were perfected for growing it in deep tanks instead of in anything shallow that could be sterilized and plugged. Better still, another species of *Penicillium* was found to outperform the Fleming strain; and best of all, when mutants were induced and selected, the yields went up by three orders of magnitude. With more penicillin in the broth, extraction procedures became simpler: penicillin became cheap as well as abundant. Even penicillamine, when it turned out to be useful in lead poisoning and in some other disturbances of metal metabolism, was easier to make by degrading natural penicillins than by synthesis. And when, in 1957, John Sheehan's persis-

tence produced a rational synthesis of penicillin,[15] this was far from viable economically. Thus far, Nature had won hands down; but the balance was restored in a rather curious way.

It was discovered that certain conditions of fermentation could produce a penicillin with no side chain, and that this could be provided by chemistry with any side chain desired.[16] And some of these side chains gave penicillins with superior properties. At present, most of the penicillins used in medicine are hybrids, half natural and half synthetic. So the ballet has finished in a triumphal *pas de deux*. But with many (not all) of the useful antibiotics, Nature is still supreme, though that has not prevented chemists from trying to synthesize them.

During the period of which I have been speaking, biochemists began to learn about the actual chemical processes of life. This development was generated partly by better methods of separating and identifying small amounts of material, but above all it owed its impetus to the availability of stable and radioactive isotopes and of the analytical techniques to detect and measure them. It became possible to study the actual workings of a living cell, and I well remember the excitement of reading Rudolf Schoenheimer's little book, *The Dynamic State of Body Constituents*, in which he shows that throughout our lives we have little more stability or permanence than a flame. More to the present point, it became possible to put loaded questions to a living organism, or to one of its functional systems, by presenting it with an isotopically labelled version of something that it would eat. And the more that was understood about the chemistry of the organism, the more subtle became these questions, and organic synthesis began to play an ever more useful part in loading them.

For work of this kind, synthesis is often delimited by which isotopes are wanted for labelling and at which position. I have had a long love affair with mevalonic acid, the precursor of terpenoids (**Fig. 5**). Altogether, we labelled this molecule in 17 different ways using ten different syntheses, eight of them novel at the time; and very recently we added an eleventh synthesis for an eighteenth labelling mode. There were compelling reasons for choosing each of these syntheses, but I have time for only one example. Here, the label had to be ^{13}C and a high proportion of molecules had to have isotopic atoms at both labelling positions.[17]

The reason behind this requirement was a skeletal rearrangement occurring when lanosterol, a precursor of cholesterol, is formed from squalene or rather, as is now known, from squalene epoxide. The question to answer was whether the rearranged methyl

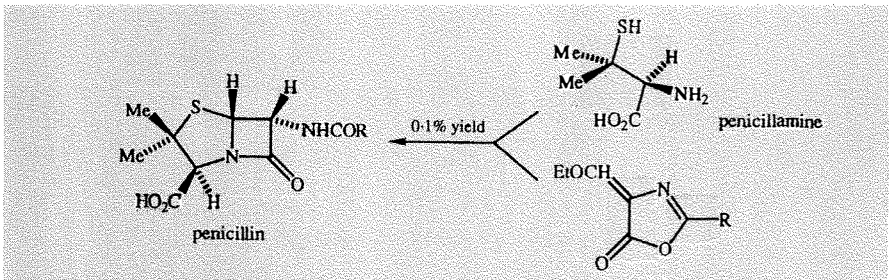

Figure 4. The first synthesis of penicillin.

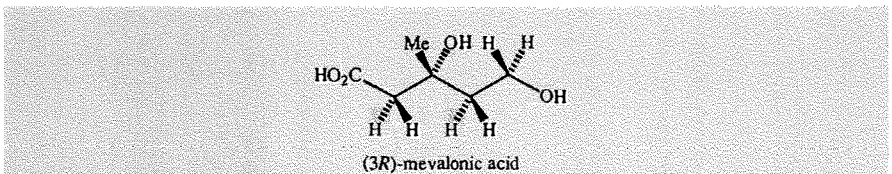

Figure 5. Mevalonic acid.

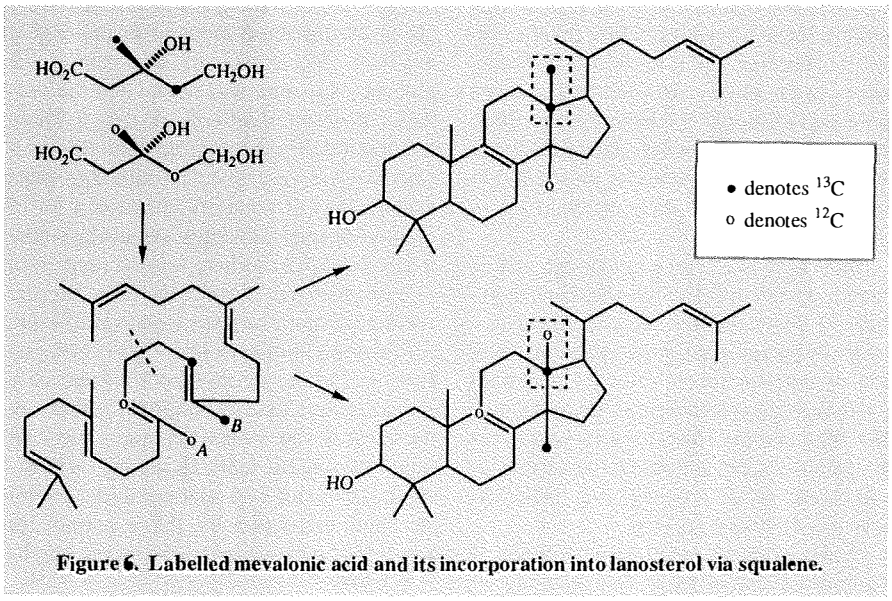

Figure 6. Labelled mevalonic acid and its incorporation into lanosterol via squalene.

group in lanosterol came from position A or position B in squalene (**Fig. 6**). Six molecules of mevalonic acid go to make one molecule of squalene and the pattern of incorporation was known. Ordinary isotopic labelling of the migrating group would not distinguish between the two modes of rearrangement because of the symmetry of the squalene molecule about its midpoint. The same symmetry would defeat ordinary double labelling at both the migrating group and its receptor position. But if the statistical distribution of the two labels was skewed by dilution with non-isotopic mevalonic acid, an intramolecular rearrangement within a group of atoms originating from one mevalonic acid molecule would produce an excess of lanosterol doubly isotopic at adjacent positions, and chemical degradation of this lanosterol to separate those two carbon atoms would allow measurement of that excess. That was the basis of the experiment and the imperative for synthesis (**Fig. 7**).

One interesting effect of isotopic synthesis is to take us back closer to the classic ideal of synthesis from the elements. Here, we had to start from isotopic potassium cyanide. By one-carbon chemistry this was turned into methyl-labelled acetyl chloride, which was treated, in ether, first with triethylamine at reflux and then with lithium aluminum hydride at -70 °C. In this three-step reaction, ketene is formed first and dimerizes to diketene, which is reduced to 4-hydroxybutan-2-one labelled at positions 1 and 3. To skew the distribution of isotopic species, this was diluted with about an equal weight of unlabelled 4-hydroxybutan-2-one, then treated twice with ketene: once to acetylate the hydroxy group, then in the presence of

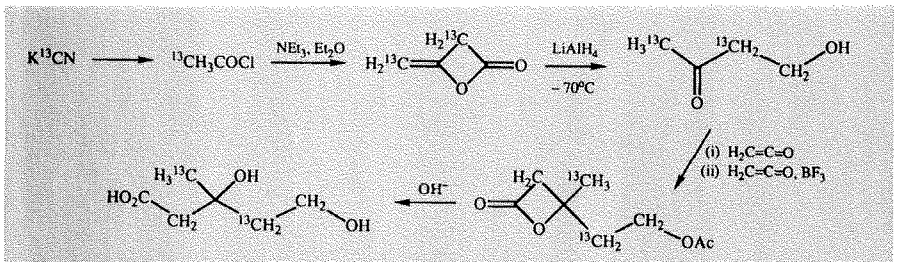

Figure 7. Synthesis of doubly isotopic mevalonic acid.

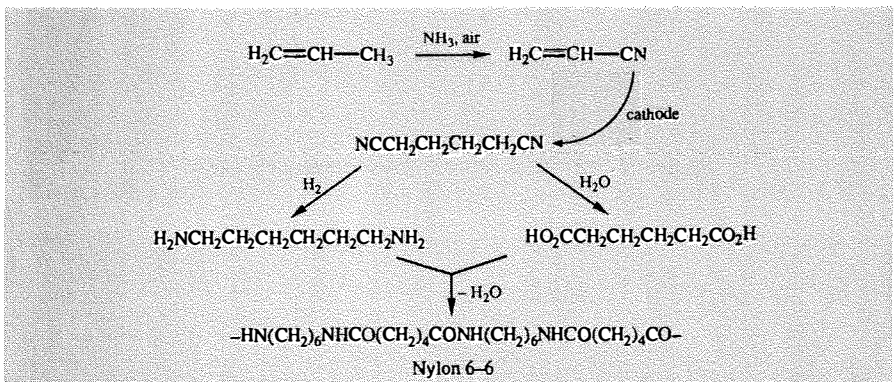

Figure 8. Industrial synthesis of Nylon 6-6.

boron trifluoride to form a β-lactone which yielded the labelled mevalonic acid on hydrolysis. Curiously, this synthesis resembles quite closely the biosynthesis of mevalonic acid, with ketene taking the place of acetylcoenzyme A; but we could not have claimed it as a biomimetic synthesis since that horrible word had yet to be invented. As it happens, this is also one of the best ways to make unlabelled mevalonic acid in quantity if the hydroxybutanone is prepared less exotically.

I should not leave the subject of isotopic synthesis without mentioning tachosynthesis, in which the 20-minute half-life of the positron-emitting carbon-11 has forced the development of a fascinating branch of chemistry requiring an ion accelerator, a radiochemical laboratory, and a hospital in close proximity to each other, and subordinating all other considerations to one imperative — speed.[18]

Probably, most of the chemical synthesis done today is carried out in industrial laboratories, much of it aimed to produce new pharmaceuticals, agrochemicals, additives, and materials of many uses. One major reason for aiming at a particular type of molecule is that a competitor has, or is suspected of having, a successful product of that type and this generates what I call interstitial synthesis — trying to find loopholes in a patent, for example. Again, industrial laboratories usually have screening programs designed to review large numbers of compounds in search of some desired property. When one compound is so detected — and rather seldom has it been made with that particular property in view — a program of synthesis may be directed to variations on the theme compound. The synthesis, unlike the screening, is not entirely random; but above all, the object is to maximize the number of compounds made and to minimize the time taken. This puts a premium on known and reliable synthetic methods and it discourages both innovation and the exploitation of unexpected findings. In contrast, when a candidate for commercial development arises some very interesting synthesis is often initiated, since the object here is to find the shortest, cheapest, cleanest route to the target. Innovation becomes desirable, bold short cuts are tried, and some of these syntheses are among the neatest pieces of chemistry I know. The synthesis of Nylon 6-6 from propene, ammonia, air, hydrogen, and water (**Fig. 8**) is beautiful in its seeming simplicity, but our academic standards would disqualify it because all of it was not found out by the same people.

The larger the scale, and the cheaper the product has to be, the more factors must be taken into consideration when choosing the winning method — or, not infrequently, for rejecting them all. Problems about pollution from the by-products of a process are nowadays taken into consideration in the planning, not tackled retrospectively. And no nonsense about the pure ideal of total synthesis limits the choice of raw materials or methods. Anyone who has helped to plan an industrial synthesis tends to pity the poverty of the criteria that an academic synthesis must meet. Work of this sort ought to be held in greater respect and published more often than, alas, it is.

Returning to the rarefied atmosphere of academic synthesis, we can identify some different constraints. For the most part, synthesis in university laboratories is executed by learners: graduate students and inexperienced postdoctorals. It has become accepted that the supervisor's role is to plan and inspire, not to participate. As one who has been a bench worker almost continuously for 60 years and who has been learning all that time about the best ways to carry out chemical experiments I find this sad, though I know the constraints on the supervisors. The effect has been to stereotype practical methods and to limit the choice available. I am far from decrying the values of chemical synthesis as intellectual training, but I know that in its practice, the hands and brain must work together as in few other disciplines. Every experiment is a new experiment, no matter how often others — and you — may have done it before. To put it no higher, the use of stereotyped procedures tends to add to the expense of research as well as being of less benefit to the trainee.

Perhaps this is the place to comment on the publication of chemical syntheses. It has become customary — I blame Bob Woodward more than any other for making it so — to report a synthesis in a preliminary note or in a sequence of notes, and to defer full publication with proper description of intermediates and methods for years or for ever. Some of Woodward's best syntheses were never reported in detail, and never will be. And if in the beginning this was principally a disease of multistep synthesis, it has spread to the reporting of new reactions and of the increasing number of compounds that are synthesized for specific purposes such as catalysis or complexation. These are useful activities; but as time goes on the value of a chemical paper tends to reside more and more in what was actually done and made, not in why it was done. As it is, there are now thousands of claims to novel compounds that are verifiable only by the repetition of the work, because it cannot be done by comparison or analysis of published properties. It is a poor tribute to chemical synthesis to say that it has been pouring a large volume of unpurified sewage into the chemical literature, but that is too near the truth for comfort. I do not know what can be done about this, though I would support a conspiracy of editors to

refuse to publish a preliminary note if the full publication from a previous note was still outstanding after an agreed interval.

Now, what of the future of chemical synthesis? There is no doubt that it remains a most popular activity: picking up at random a recent *Chemical Communications* I found that 40% of the articles had to do with synthesis or synthetic methods. Clark Still has pointed out that there is practically no imaginable small molecule of reasonable stability that cannot be made by existing methods in sufficient quantity to examine its properties — given enough time, money, and effort. Advance in photochemistry, in free-radical chemistry, and in the use of auxiliary elements, notably silicon, offer an almost embarrassingly wide choice of procedures; and Corey[19] has pioneered effective, programmable rules for combining them into strategies for synthesis. Much attention is rightly being given to stereospecific synthesis and the control of chirality. Success here has come from better understanding of preferred conformations during reactions, from the now predictable stereochemistry of electrocyclic reactions, and from the much greater use of transition and other elements to hold reactants in desired conformations or to coordinate reagents on the same metal atom.

To illustrate the advance of chiral catalysis over the years one can go back to the original example of absolute asymmetric synthesis (**Fig. 9**). Bredig[20] found in 1912 a small anisochirality[21] in mandelonitrile formed from benzaldehyde and hydrogen cyanide in the presence of what seems to have been a crude preparation of cinchona alkaloids. The industrial importance of a related mandelonitrile stimulated a search for more efficient chiral catalysts and the best of them gave an impressive result[22] even when applied to benzaldehyde rather than the targeted 3-phenoxybenzaldehyde, which was still better. One could only wish it possible to find such catalysts by prediction but, alas, our powers in this direction are still infantile.

Other advances have nearly perfected the art of the protecting group. Name any functional group that you want to shield temporarily from your operations on another part of the molecule and there is a menu of reagents, artfully tuned for ease of attachment and selectivity of removal. Add to these the selective reagents that discriminate between similar functional groups and you have so many acronyms that you already need a glossary to sort them out.

So far, so good. Now let us look at the other face of the coin. We are in danger of being limited by our own powers. In the chemistry of natural products it is becoming rather unusual to carry out any chemistry on a product that you isolate. Spectroscopy or X-ray diffraction gives you the answer to the structural problem, and if you need to modify the structure you use well understood reactions. But in the days when it was actually necessary to do some chemistry to solve the structural problem, natural product chemistry was one of the most prolific sources of new reactions. I suggest that this was because the people trying the reactions did not know what to expect. Similarly, if you plan a synthesis and leave its execution to less skilled people who have been told what to expect, you are likely to miss observations and opportunities that you would not miss if you allowed yourself to be taught by the experiments instead of trying to teach Nature how she should behave. And if you boast too loudly that you can devise a synthesis of anything, those who use your work may relegate you to the rank of a technician: oil in the machinery, indispensable but expendable. It is better to have good reasons of your own for your syntheses — reasons that others accept but do not choose.

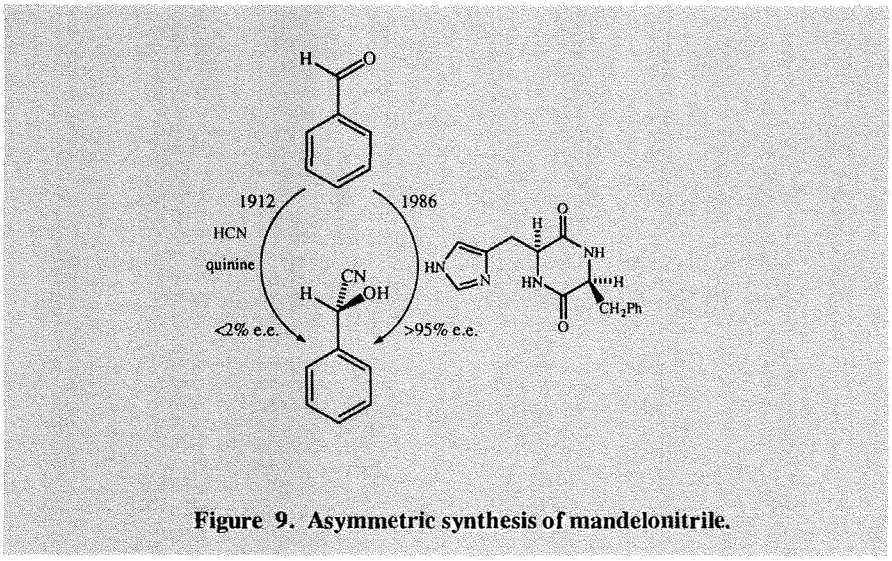

Figure 9. Asymmetric synthesis of mandelonitrile.

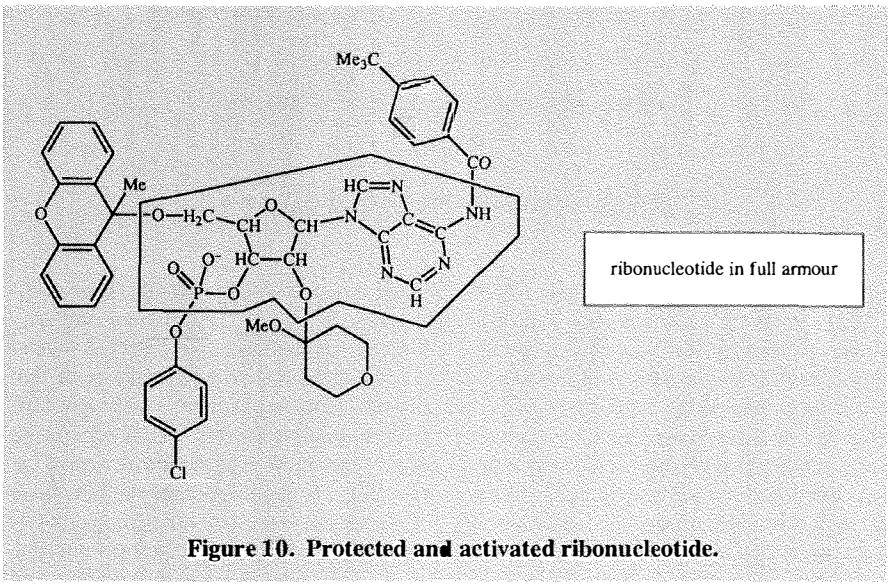

Figure 10. Protected and activated ribonucleotide.

The infrastructure of knowledge and analytical technique on which we base our present syntheses is highly impressive, but I suspect — indeed, I hope — that in the future it may come to be regarded much as we regard the mechanisms drawn by Heath Robinson or Rowland Emett: quaint. It is nice to have a choice of protecting groups, but using one means two more steps in the synthesis. Also, some protecting groups and some reactions are so expensive that there is no chance of their being used outside a chemical or biochemical laboratory. How much better if we begin to regard their use as an imperfection, an artistic failure if you like, and try to eliminate them. The methods which we use to synthesize the oligopeptides or oligonucleotides (**Fig. 10**) needed by our friends the biochemists and molecular biologists are by present standards most ingenious, but they do some-

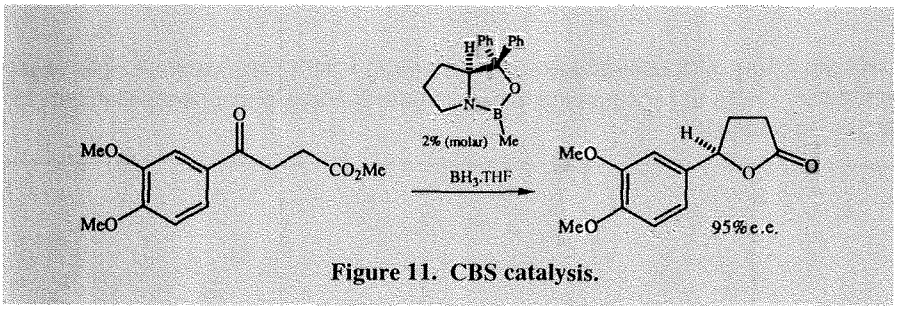

Figure 11. CBS catalysis.

times remind me of a medieval knight buckling on a hundredweight of armour before being hoisted onto a carthorse to go into battle.

We have before us all the time the example of the enzymes, which handle substrates with many unprotected functional groups and select unerringly their target group because their specific catalysis is based not on obstructing the wrong reaction but enormously accelerating the right one. Perhaps there is a prospect of things to come in Corey's development of the so-called CBS catalysts[23] (**Fig. 11**). These chiral oxazaborolidines do not themselves reduce carbonyl groups, and diborane in tetrahydrofuran is a poor reductant, but the two together form a complex that reacts fast and with high anisochirality. The analogy of the catalyst to an enzyme and of diborane to a coenzyme is quite close, and the only thing lacking here is further catalysis of the reaction by specific binding of the substrate. As it is, the selectivity is achieved by obstruction, not positive binding.

We have not had as much time as the enzymes to develop their approach to synthesis — not by some seven powers of 10 — but we are supposed to be more purposeful. And we have to use the old methods of synthesis to construct the new world of specific catalysis, and we have not at present much idea of what we should be making. We need to know a lot more about intermolecular associations; and enzymes, though they certainly have a lot to teach us, are not very talkative. Still, I suppose we shall learn; and luckily there are many excellent reasons why we should make the attempt: the problem is not How or Why, but What. May I live to see, and better to share, more than the limited success that so far has been achieved.

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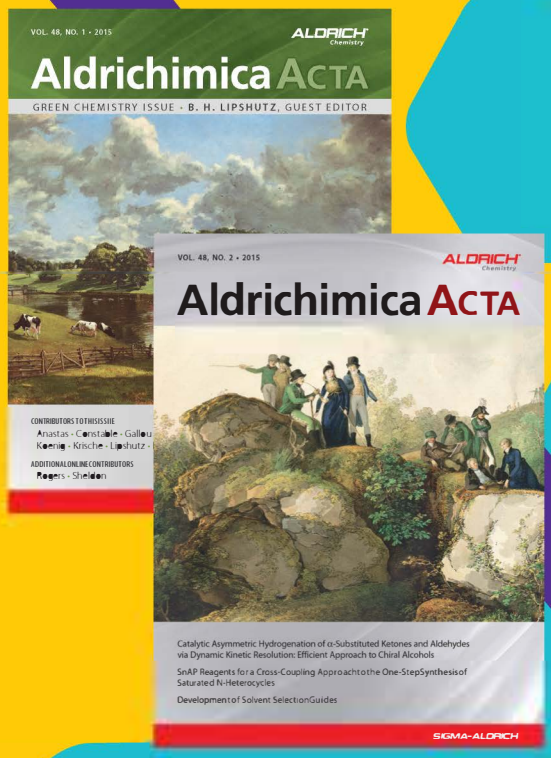

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