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Chiral Dirhodium Carboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams

3-Formylchromone as a Versatile Synthon in Heterocyclic Chemistry

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This painting, *Fantaisie sur Tivoli* (oil on canvas, 241.1 x 193.4cm), is one of four landscapes by Hubert Robert that were commissioned by Grand Duke Serge Alexanderovitch in 1789. It displays Robert's typical combination of romantic rusticity and ancient ruins. The small round temple is based on the design of the temple of Vesta at Tivoli where Robert and Fragonard enjoyed the hospitality of the Abbé de St. Non at the Villa d'Este in the summer of 1760. The temple was well known to tourists of the Roman area and had been the subject of artists' attention since the seventeenth century.

The painting is in the collection of The Saint Louis Art Museum, Gift of Mrs. Frederic W. Allen.

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If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this illustrated catalog. It contains twenty-four paintings that have been reproduced on our *Aldrichimica Acta* covers, and five that have been on our catalog covers.

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To clean and extend the life of your solid state ISE probes, try cleaning them with a mild abrasive such as a non-fluorinated toothpaste. Use your finger to apply the toothpaste and lightly rub the surface. After a sufficient amount of time, completely rinse the probe and recalibrate.

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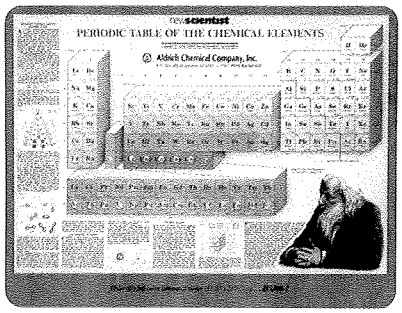

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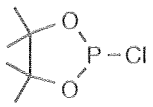

Professor Dimitris S. Argyropoulos (McGill University-Paprican) kindly suggested that we make this dioxaphospholane that is a phosphitylation reagent used in the quantitative analysis of hydroxyl groups in lignins by ^{31}P NMR spectroscopy. The reagent provided excellent resolution of the various phenolic hydroxyl environments including those belonging at the C5 condensed phenolic units.

Granata, A.; Argyropoulos, D.S. *J. Agric. Food Chem.* **1995**, *43*, 1538.

Naturally, we made this useful assay reagent. It was no bother at all, just a pleasure to be able to help.

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Chiral Dirhodium Carboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams

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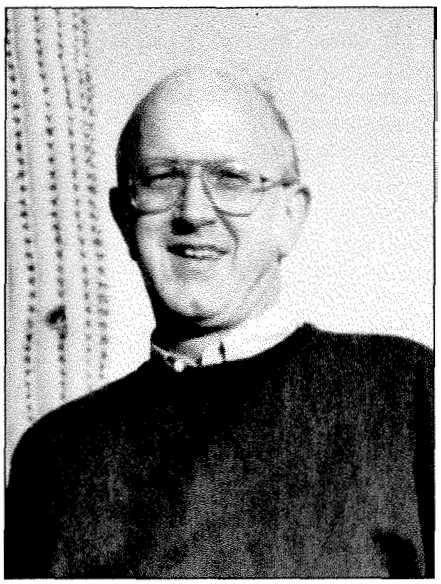
Abstract

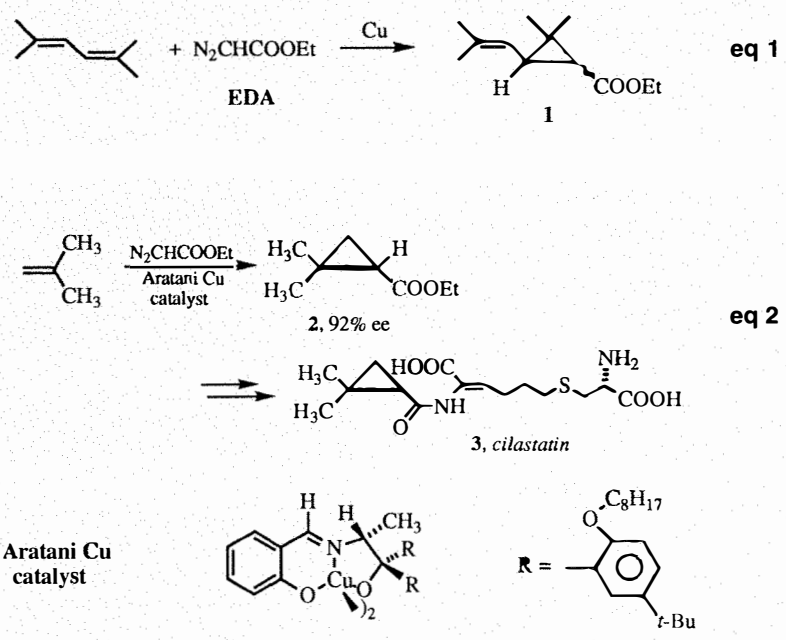
Asymmetric catalysis of metal carbene transformations with unique chiral dirhodium(II) carboxamides provides highly enantioselective, diastereoselective, and regioselective syntheses of lactones and lactams via cyclopropanation and carbon-hydrogen insertion reactions of diazoacetates and diazoacetamides. Constructed from a dirhodium(II) core with bridging chiral pyrrolidone, oxazolidinone, or imidazolidinone ligands, these catalysts are especially effective for intramolecular transformations. Reactions characteristically occur with high turnover numbers, and products are formed in high yield with enantiomeric excesses that are generally greater than 90%.

Introduction

Originating in investigations conducted nearly a century ago,[1] transition metal catalysis of diazo decomposition has provided a diversity of transformations applicable to chemical synthesis. Commercial uses of this methodology are well established for: the construction of chrysanthemic acid esters (**1**) in pyrethroid syntheses (eq 1);[2] the preparation of enantiomerically pure ethyl 2,2-dimethylcyclopropanecarboxylate (**2**) for the synthesis (eq 2) of cilastatin (**3**), an in vivo stabilizer of the antibiotic imipenem (*N*-formimidoylthienamycin);[3] and the critical N-H insertion process (eq 3) that is the ingenious key step in the Merck synthesis of thienamycin (**5**).[4] Suitable catalysts possess an open coordination site at which electrophilic addition to the diazo compound occurs.[5] Extrusion of nitrogen gas from the resulting diazonium ion intermediate generates a highly reactive metal carbene whose reactivity resembles that of a metal-stabilized carbocation. Transfer of the carbene to the reacting substrate regenerates the catalyst to complete the catalytic cycle. Since diazocarbonyl compounds, especially diazoesters and diazoamides, are readily prepared and are generally stable at temperatures ≤ 100°C,[6] they are the preferred substrates for these transition metal catalyzed transformations.

Dirhodium tetraacetate is widely recognized as the catalyst of choice for the vast majority of metal carbene reactions that occur with diazocarbonyl compounds.[7-9] First applied by Teyssie and co-workers in 1973 to reactions of ethyl diazoacetate with alkenes,[10] this catalyst and its subsequently developed ligand variants have been employed for transformations as diverse as cyclopropanation, cyclopropenation, insertion, and ylide generation (**Scheme 1**).[9,11-16] By changing the dirhodium(II) ligand from acetate to perfluorobutyrate (pfb) or caprolactam (cap), catalyst applications have demonstrated enormous diastereoselectivity, regioselectivity, and chemoselectivity.[17-20] Based

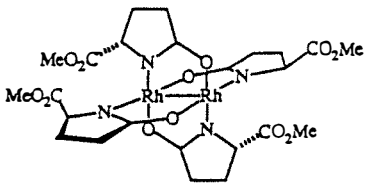




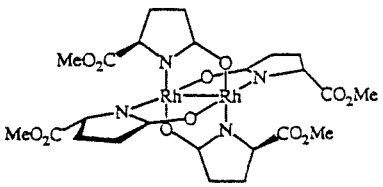
on electronic influences emanating from the dirhodium(II) ligands, $Rh_2(pfb)_4$ is the most reactive and $Rh_2(cap)_4$ is the least reactive towards diazo decomposition. However, $Rh_2(cap)_4$ offers the highest level of substrate discrimination. Recent reviews have documented the synthetic diversity and versatility of these catalysts for reactions of diazocarbonyl compounds in both intermolecular and intramolecular transformations.[7-9,11-16,20]

Chiral Dirhodium(II) Carboxamidates

Our development of efficient syntheses for carboxamidate ligated dirhodium(II) has made possible the construction of a unique set of chiral catalysts whose applications have already demonstrated exceptional enantiocontrol for intramolecular and certain intermolecular reactions of diazoacetates and diazoacetamides.[15,21-25] In their novel design, exemplified by dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate], $Rh_2(5S\text{-MEPY})_4$, and its



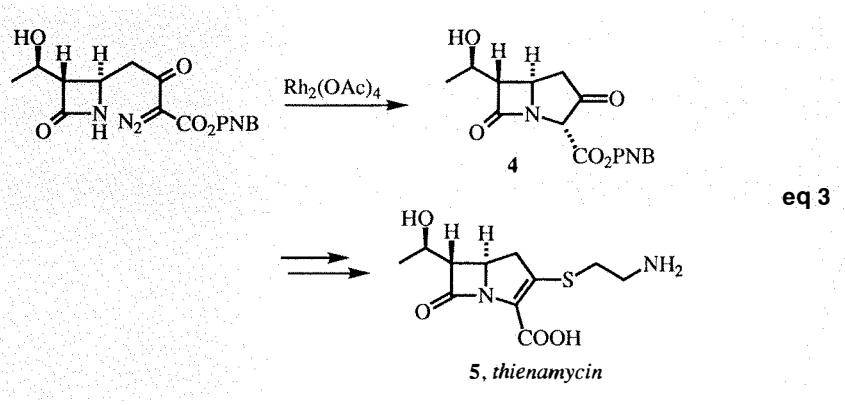
$Rh_2(5S\text{-MEPY})_4$



$Rh_2(5R\text{-MEPY})_4$

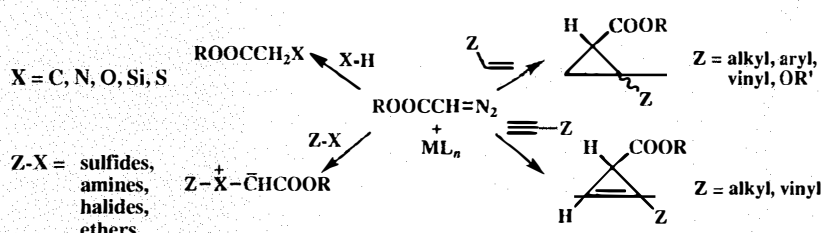
enantiomer $Rh_2(5R\text{-MEPY})_4$, the dirhodium(II) core is surrounded by four bridging amide ligands so that two nitrogen and two oxygen donor atoms bonded to each rhodium are oriented cis (2,2-*cis*). The chiral center of the ligand is the carbon atom directly bonded to nitrogen so that the functional attachment, COOMe in the case of $Rh_2(MEPY)_4$ catalysts, lies in a spatial region that influences both the orientation of the bound carbene and the approach of the substrate to the carbene center.

The X-ray crystal structure of $Rh_2(5R\text{-MEPY})_4(CH_3CN)_2$, in which acetonitrile ligands occupy the axial coordination sites (**Figure 1**), confirms these features of the catalyst.[26] The ligand carboxylate attachments are positioned with a clockwise orientation on each end of the rhodium(II)



eq 3

5, *thienamycin*



Scheme 1

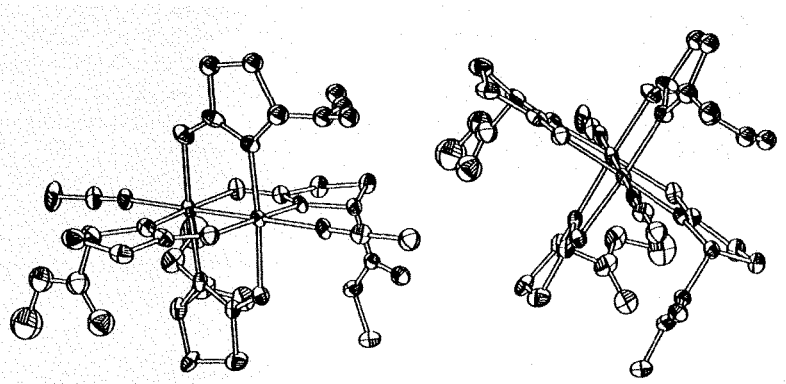
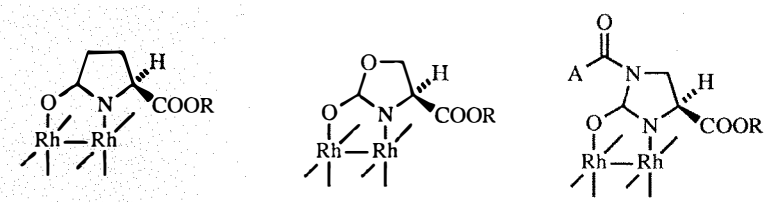
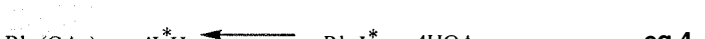


Figure 1. Two views of the X-ray structure of $Rh_2(5R\text{-MEPY})_4(CH_3CN)_2$.



6 **7** **8**



eq 4

complex, offering open access to approach onto the axially-bound carbene ligand. Chiral dirhodium(II) carboxamidates that provide the highest levels of enantiocontrol are constructed from 2-oxopyrrolidine (**6**), oxazolidinone (**7**), and imidazolidinone (**8**) ligands which possess a carboxylate group on the chiral center adjacent to the amide nitrogen. Each complex has the (2,2-*cis*) structural arrangement of ligands. Changing the structure of the ester R from methyl to isopropyl to neopentyl to octadecyl

generally has little effect on enantioselectivity but does change the solubility characteristics of the catalyst; for example, **6** with R = octadecyl is soluble in pentane.

More than 20 structurally different chiral dirhodium(II) carboxamidates have been prepared and characterized. In general, those with carboxylate attachments provide higher enantiocontrol than those with alkyl (Me, *i*-Pr, or Bn) or aryl attachments in the same position.[26] Reactions that are difficult to perform with $Rh_2(OAc)_4$ often occur readily with chiral dirhodium(II) carboxamidates.[19] The achiral dirhodium(II) caprolactamate, $Rh_2(cap)_4$, is a suitable model for the chiral carboxamidates and is generally the catalyst of choice to obtain racemic mixtures for transformations that are to be examined with the use of its chiral analogs.

Dirhodium(II) carboxamidates are prepared from $Rh_2(OAc)_4$ by a facile ligand substitution (eq 4). Using a Soxhlet extraction apparatus, the liberated acetic acid is trapped by sodium carbonate, thus driving the equilibrium to $Rh_2L_4^*$ and requiring only a modest excess of the chiral ligand to effect complete substitution. Large-scale syntheses of both $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ have been developed by Regis Technologies, Inc., who have also found that axial nitrile ligands stabilize these dirhodium(II) compounds and provide them with long shelf lives. Acyclic amides, such as those derived from amino acids, do not undergo facile ligand substitution, presumably because syn orientation of the amide carbonyl and N-H are mechanistic requirements.

General View of Enantioselection

Looking down the Rh-Rh axis **(Scheme 2)**, the rhodium face can be divided into four quadrants of which two are occupied by the ligands' chiral attachment (e.g., COOMe for $Rh_2(MEPY)_4$). The third quadrant is filled by the carboxylate group of the carbene leaving the fourth quadrant open for the substrate to approach the carbene center. Calculations have suggested that the preferred conformation of the carbene associated with $Rh_2(5R\text{-MEPY})_4$ in the transition state for carbenoid transformations is that depicted in **9**.[26] For intramolecular reactions catalyzed by $Rh_2(5R\text{-MEPY})_4$, the reacting substrate bond (Z) approaches the rhodium-bound electrophilic carbene through a counterclockwise movement, whereas with $Rh_2(5S\text{-MEPY})_4$ the movement is clockwise (**10**).

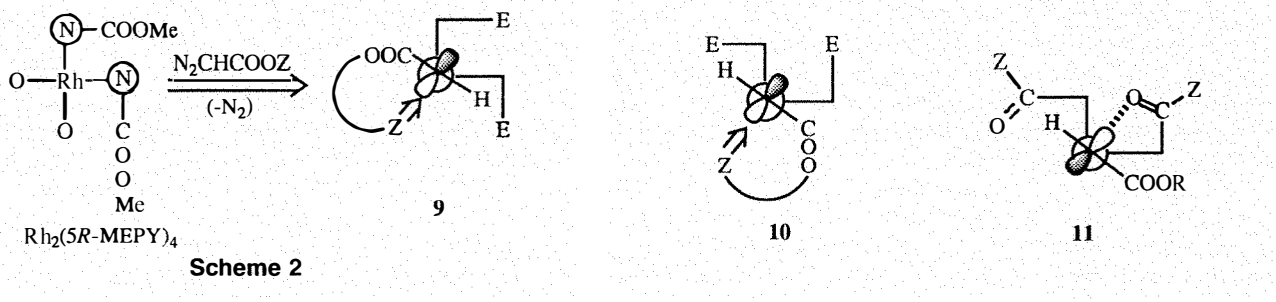
Alternative conformations that model the transition state have also been evaluated by computational methods and are higher in energy.[26] The importance of the ligand's carboxylate attachment appears to be associated with both orientation of the carbene and its stabilization by dipolar forces since dirhodium(II) catalysts with alkyl or aryl (*i*-Pr, Ph, or Bn), rather than a carboxylate attachment, always give significantly lower enantiocontrol.[21,26] Surprisingly, dirhodium(II) tetrakis[*N*,*N*-dimethyl-2-pyrrolidone-5(*S*)-carboxamide], $Rh_2(5S\text{-DMAP})_4$, whose amide substituents were expected to have a stronger force of dipolar attraction, did not exhibit a higher level of enantiocontrol in metal carbene reactions; X-ray structural analysis demonstrated that the ligand carbonyl groups, which were expected to interact with the intermediate carbene (**11**), were not in position to do so.[27] The *N*-acyl attachment of imidazolidinone ligands (**8**) further restricts substrate occupation on the axial face of rhodium(II) and affords additional stereochemical control for carbene transformations that will be evident in their applications.

Highly Enantioselective Intramolecular Cyclopropanation

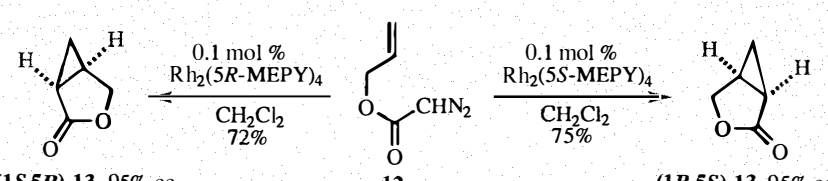
The effectiveness of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ catalysts for asymmetric induction has been demonstrated by the exceptional enantiocontrol that has been achieved with their uses in intramolecular cyclopropanation reactions of allylic diazoacetates,[28] homoallylic diazoacetates,[28] and selected *N*-allylic[28] and *N*-homoallylic diazoacetamides.[29] With the simplest system, 2-propen-1-yl diazoacetate (**12**), use of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ in catalytic amounts as low as 0.1 mol % (1000 turnovers) causes the formation of the enantiomeric 3-oxabicyclo[3.1.0]hexan-2-ones (**13**) with 95% ee in good yields following distillation (eq 5).

cis-Disubstituted diazoacetate systems (**14**) undergo catalytic cyclopropanation with such high enantiocontrol that only one enantiomer could be detected by NMR methods with the use of chiral shift reagents, and this high level of enantiocontrol (≥ 94% ee) was independent of the 3-(*Z*)-substituent (eq 6).

Similar high enantiocontrol characterizes trisubstituted allylic diazoacetates that include those prepared from nerol (93% ee) and geraniol (95% ee), but with *trans*-disubstituted systems use of the $Rh_2(MEPY)_4$ catalysts provides ee's as low as 68% (eq 7). However, dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)imidazolidin-2-one-4(*S*)-carboxylate], $Rh_2(4S\text{-MPPIM})_4$, offers significant enhancements in the % ee, so that even with *trans*-disubstituted allylic diazoacetates (**16**), ≥ 95% ee's can be achieved.[30] Other significant challenges for selectivity



Scheme 2



(1*S*,5*R*)-13, 95% ee **12** **(1*R*,5*S*)-13**, 95% ee

eq 5

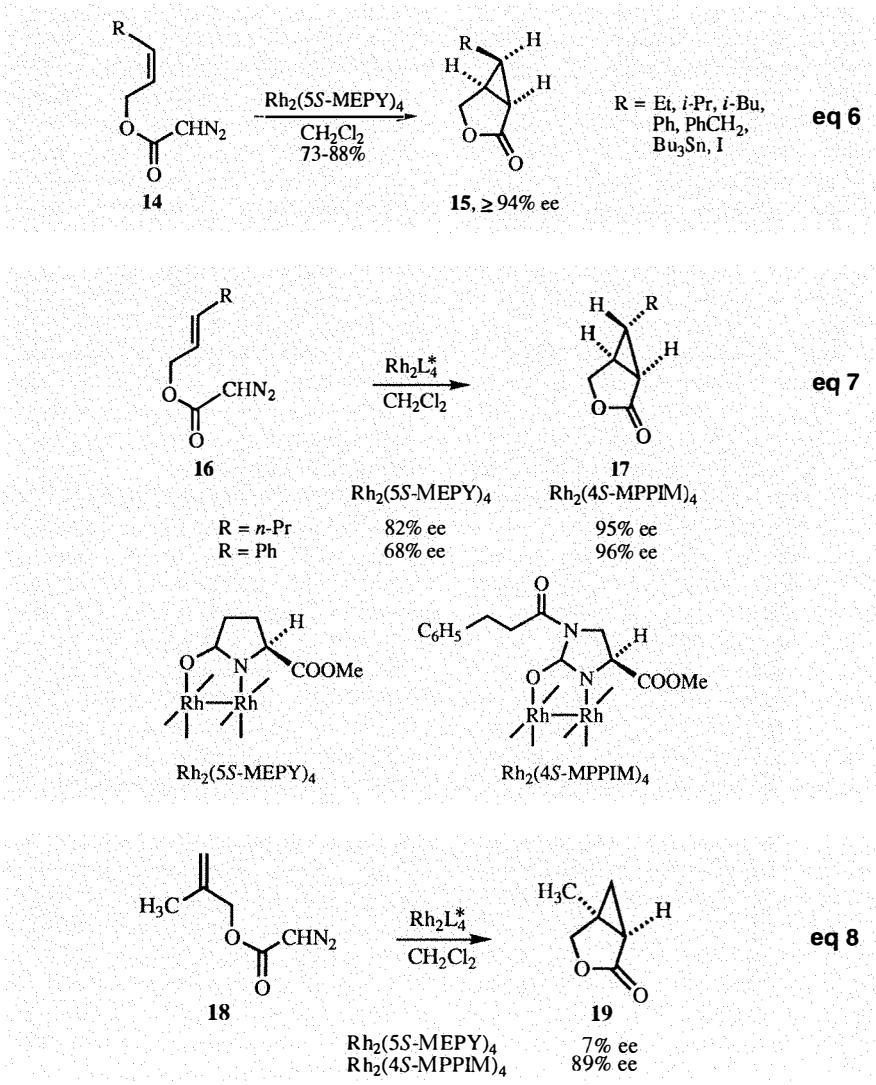
enhancements can be met by an appropriate ligand modification on the dirhodium(II) core. One such example is the enhanced % ee observed when $Rh_2(4S\text{-MPPIM})_4$ is employed instead of $Rh_2(5S\text{-MEPY})_4$ for intramolecular cyclopropanation of 2-methyl-2-propen-1-yl diazoacetate (eq 8).[30]

Extension of this methodology with $Rh_2(5S\text{-MEPY})_4$ by Martin and co-workers to homoallylic systems has shown that there is a moderate reduction in enantioselectivity (71-90% ee) for similarly substituted substrates.[28] However, they are subject to more uniform enantiocontrol than their allylic counterparts. For example, in contrast to results with 2-methyl-2-propen-1-yl diazoacetate (eq 8), 3-methyl-3-buten-1-yl diazoacetate gave the corresponding cyclopropanation product in 83% ee using $Rh_2(5S\text{-MEPY})_4$. Results with *N*-homoallylic diazoacetamides[29] generally paralleled those with homoallylic diazoacetates. The absolute configurations of the bicyclic cyclopropane derivatives formed from homoallylic diazoesters and diazoamides are the same as those from their corresponding allylic systems, and a comprehensive mechanistic explanation for this stereocontrol has been provided.[28a] Enantiomeric excesses of these and other products from intramolecular cyclopropanation were obtained with baseline enantiomer separation on chiral GC columns (±1-2%) or by NMR analysis with the use of chiral shift reagents (±3%).

Among the pharmacologically relevant compounds whose syntheses have been reported using this methodology, with either or both $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ (**Scheme 3**), are 1,2,3-trisubstituted cyclopropanes as conformationally restricted peptide isosteres for renin (**20**)[31] and collagenase[32] inhibitors, presqualene alcohol (**21**)[33] from farnesyl diazoacetate, and the GABA analog 3-azabicyclo[3.1.0]hexan-2-one (98% ee) formed by intramolecular cyclopropanation from *N*-allyldiazoacetamide.[28a] In addition, 6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one, a precursor to *cis*-chrysanthemic and permethrenic acids,[28] has been produced in 98% ee.

Following from the demonstration by Martin and co-workers that diazoacetate esters of chiral secondary allylic alcohols exhibit diastereocontrol as high as 20:1 with the appropriate match of $Rh_2(5S\text{-MEPY})_4$ or $Rh_2(5R\text{-MEPY})_4$,[34] we have found that highly efficient kinetic resolution of racemic secondary allylic diazoacetates in intramolecular cyclopropanation reactions is achieved using, optimally, dirhodium(II) tetrakis-[methyl 2-oxazolidinone-4(*S* or *R*)-carboxylate], $Rh_2(4S\text{-MEOX})_4$ or $Rh_2(4R\text{-MEOX})_4$.[35] In reactions catalyzed by $Rh_2(4S\text{-MEOX})_4$, for example, (1*S*)-cycloalk-2-en-1-yl diazoacetates undergo cyclopropanation (up to 40% isolated yields), whereas (1*R*)-cycloalk-2-en-1-yl diazoacetates form 2-cycloalkenones and 1-methylene-2-cycloalkenes, the latter being the products from intramolecular hydride abstraction from the allylic position alpha to oxygen (**Scheme 4**).[36]

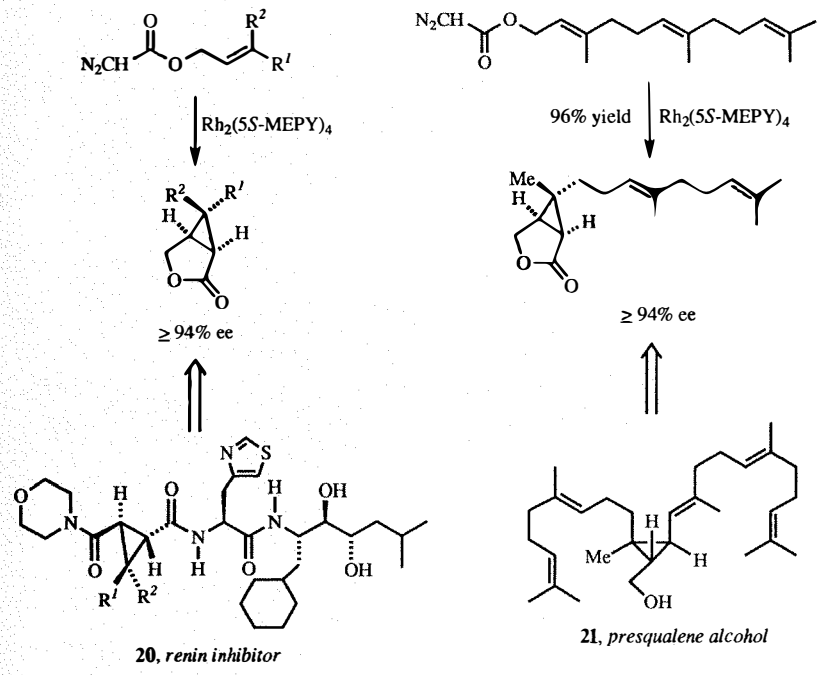
The mirror image isomers are formed from reactions catalyzed by $Rh_2(4R\text{-MEOX})_4$. With acyclic racemic secondary allylic diazoacetates, enantiomer differentiation occurs through the formation of *exo*- and *endo*-diastereoisomers whose opposite preferential configurations, (4*R*)-*endo* and (4*S*)-*exo* from reactions with $Rh_2(4S\text{-MEOX})_4$, demonstrate enantiomer differentiation (70-92% ee).



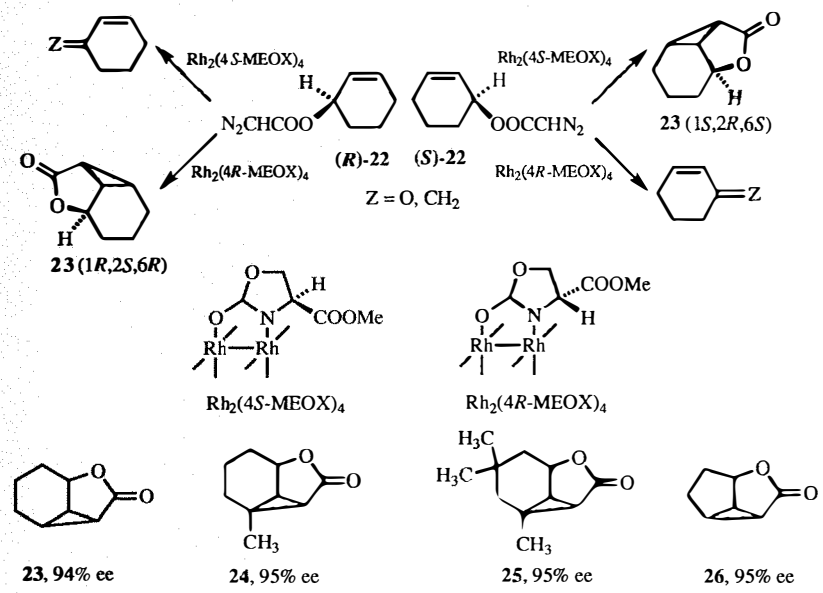
Intermolecular Addition Reactions

Copper(I) catalysts that possess chiral semicorrin or C_2-symmetric bis-oxazoline ligands are generally effective for high enantiocontrol in intermolecular cyclopropanation of alkenes, especially monosubstituted and 1,1-disubstituted.[37-39] In contrast, chiral dirhodium(II) carboxamidates provide limited enantiocontrol in these same reactions with diazoacetate esters.[40-42] Neither Cu(I) nor Rh(II) catalysts provide effective diastereocontrol for reactions performed with monosubstituted alkenes except when diazoacetate esters with bulky substituents are used such as 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate (BDA).[18] Most often, Cu(I) and Rh(II) catalysts produce mixtures of *cis* and *trans* cyclopropanecarboxylates.

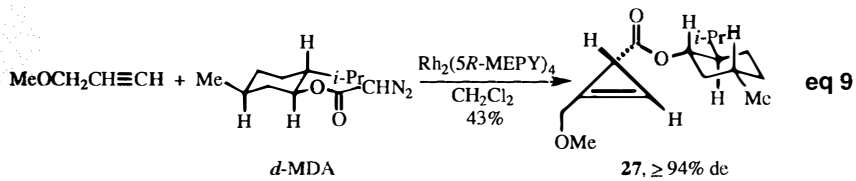
However, $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ are effective catalysts for intermolecular addition to terminal acetylenes of diazoesters and -amides leading to cyclopropenes.[43] Diastereoselectivities achieved from the appropriate match of catalyst configuration with *d*- or *l*-menthyl diazoacetate (MDA) are 77 to ≥ 94% de



Scheme 3



Scheme 4



(e.g., eq 9). Enantioselectivities up to ≥ 98% ee have been obtained with 3-methoxy-1-propyne (reaction with *N,N*-dimethyldiazoacetamide) and 3,3-diethoxy-1-propyne (reaction with methyl diazoacetate, eq 10), yet cyclopropenation of 1-hexyne occurred with 78% ee.

N,N-Dimethyldiazoacetamide provides a higher level of enantiocontrol than do diazoesters, but reactions generally occur in lower yields. The absolute configurations of the cyclopropene products have been established.[43b] Use of $Rh_2(5S\text{-MEPY})_4$ produces 1-substituted-1-cyclopropene-3-carboxylates having the (*S*)-configuration, whereas $Rh_2(5R\text{-MEPY})_4$ provides these cyclopropene products in the (*R*)-configuration. Diimide reduction or catalytic hydrogenation of these enantiomerically enriched cyclopropene compounds, produces the corresponding *cis*-disubstituted cyclopropane esters exclusively in the moderate to high enantiomeric/diastereomeric excesses achieved by cyclopropenation. This catalytic methodology provides a direct route to chiral cyclopropenes and, following reduction, to chiral *cis*-disubstituted cyclopropanes of moderate to high optical purity, neither of which are generally accessible by alternative catalytic routes.

Recently, Davies has demonstrated that the chiral dirhodium(II) *N*-(arenesulfonyl)-prolinate catalysts developed by McKervey[44] are effective for the highly enantioselective intermolecular cyclopropanation of vinyldiazoacetate esters with monosubstituted olefins.[45] Corey has employed this methodology (**Scheme 5**) in an efficient synthesis of the antidepressant sertraline (**29**).[46] However, the high enantiocontrol with chiral dirhodium(II) carboxylates appears to be limited to olefin addition reactions of vinyldiazoacetates.

Highly Enantioselective Intramolecular Carbon-Hydrogen Insertion Reactions

Dirhodium(II) compounds are the catalysts of choice for intramolecular carbon-hydrogen insertion reactions of diazocarbonyl compounds.[7-9,12,13,15] Although there are notable exceptions,[11b,22,47] five-membered ring formation is preferred,[11] and regioselectivity is generally subject to specific electronic effects.[17,19,48] Early applications of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ to alkyl diazoacetate decomposition have demonstrated the feasibility of these catalysts for highly enantioselective and regioselective C-H insertion reactions (e.g., eq 11).[49] Insertion into a C-H bond α to an ether oxygen is a facile process.[48] With

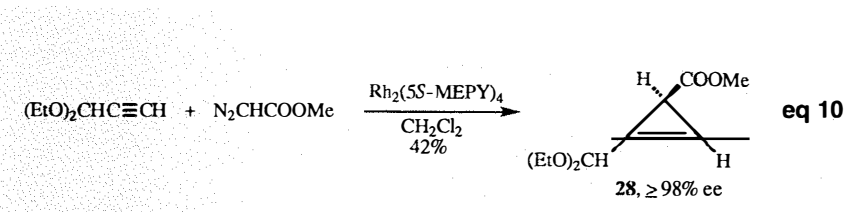
R = benzyl (Bn), hydrogenolysis generates the 4-hydroxy derivative (**31**, R = H). With primary alkyl diazoacetates other than **30**, C-H insertion reactions catalyzed by Rh_2(5*S*-MEPY)$_4$ or Rh_2(5*R*-MEPY)$_4$ occur with selectivities that are < 70% ee. However, the use of Rh_2(4*S*-MPPIM)$_4$ or Rh_2(4*R*-MPPIM)$_4$ significantly enhances enantiocontrol, provides exceptional regiocontrol, and as is exemplified in **Scheme 6**, provides a facile route to (+)- or (-)-enterolactone and other lignan lactones.[50] Enantiomeric excesses of these and other products from intramolecular C-H insertion were obtained with baseline enantiomer separation on chiral GC columns.

This methodology has been extended to C-H insertion reactions of secondary cycloalkyl diazoacetates where diastereoselectivity in the formation of *cis*- and *trans*-fused bicyclic lactones is a critical control feature.[51] Use of Rh_2(5*S*-MEPY)$_4$ or its enantiomer produced insertion products with a high degree of enantiocontrol, but diastereocontrol was only 3:1 (e.g., eq 12). However, both high enantiocontrol and nearly complete diastereocontrol were achieved with recently developed dirhodium(II) tetrakis[methyl 1-acetylimidazolidin-2-one-4(*S*)-carboxylate], Rh_2(4*S*-MACIM)$_4$ (**8**, A = R = Me). The oxazolidinone analog of Rh_2(5*S*-MEPY)$_4$, Rh_2(4*S*-MEOX)$_4$, facilitated high enantiocontrol but significantly lower diastereocontrol: (**36**)/(**37**) = 55/45.

Similarly high enantio- and diastereoselectivities have been achieved with cyclopentyl through cyclooctyl diazoacetates, with *cis*- or *trans*-4-alkylcyclohexyl diazoacetates where preferential insertion into equatorial C-H bonds (e.g., **38** and **39**) has been demonstrated,[51,52] and with 2-adamantyl diazoacetate (**40**).[53] In these cases, however, Rh_2(MEOX)$_4$ catalysts provided the highest levels of enantiocontrol. Exceptionally efficient enantiomer differentiation is also provided by Rh_2(MEOX)$_4$ catalysts in reactions involving racemic *cis*- and *trans*-2-methylcyclohexyl diazoacetates (up to 99% ee).[54]

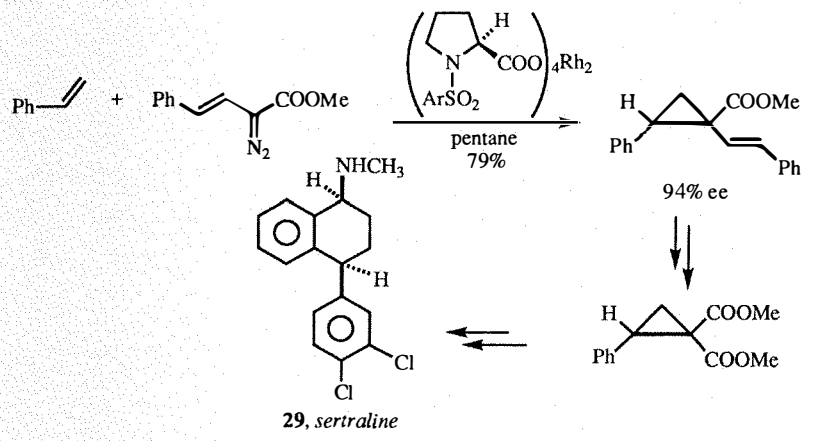
High enantio- and diastereocontrol in Rh_2(MEPY)$_4$-catalyzed C-H insertion reactions of glycerol-derived diazoacetates (e.g., **41**) have provided a convenient synthesis of pure 2-deoxyxylolactone (**44**, **Scheme 7**).[55] The reactant diazoester was conveniently prepared from commercially available 1,3-dichloro-2-propanol. As little as 0.1 mol % of the catalyst was required to effect complete reaction (1000 turnovers).

The success of these C-H insertion reactions is based on ether oxygen activation of adjacent C-H bonds.[13,48,56] In the absence of α-ether oxygens, enantioselectivity remains high but diastereocontrol using Rh_2(MEPY)$_4$ is much lower. However, Rh_2(4*S*-MPPIM)$_4$



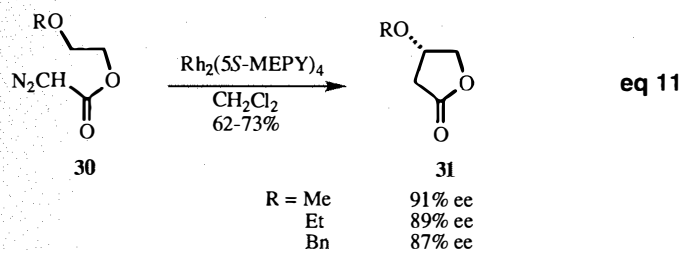
28, ≥ 98% ee

eq 10



29, *sertraline*

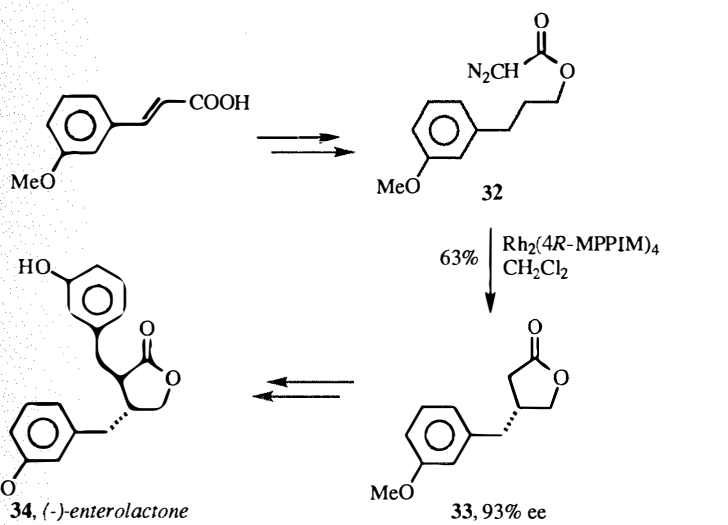
Scheme 5



30 **31**

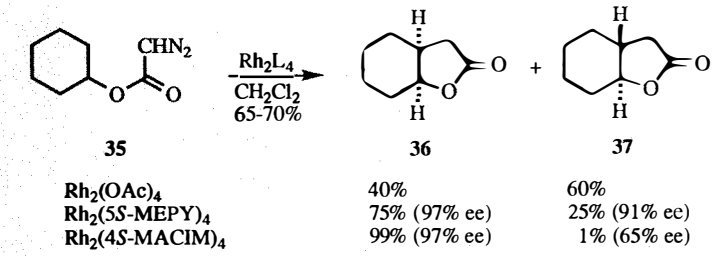
R = Me	91% ee
Et	89% ee
Bn	87% ee

eq 11



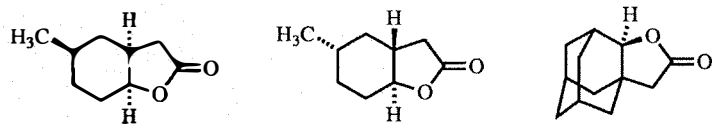
34, *(-)-enterolactone* **33**, 93% ee

Scheme 6

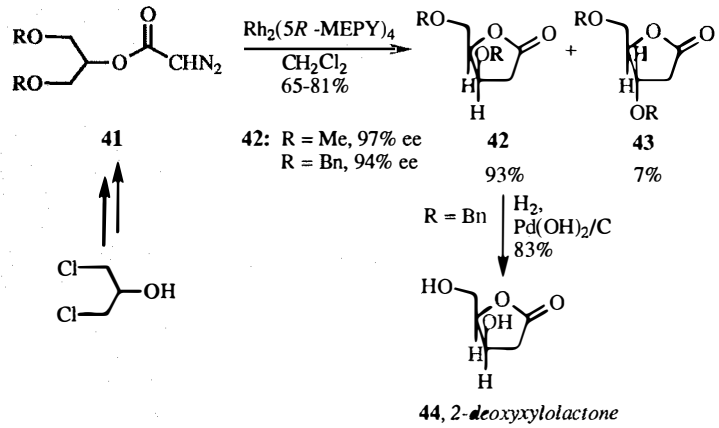


35 **36** **37**

$Rh_2(OAc)_4$	40%	60%
$Rh_2(5S\text{-MEPY})_4$	75% (97% ee)	25% (91% ee)
$Rh_2(4S\text{-MACIM})_4$	99% (97% ee)	1% (65% ee)



$Rh_2(4S\text{-MEOX})_4$: **38**, 98% ee **39**, 95% ee **40**, 98% ee



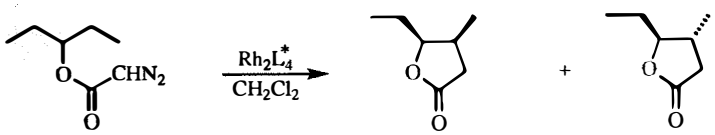
41

42: R = Me, 97% ee
R = Bn, 94% ee

42 93% **43** 7%

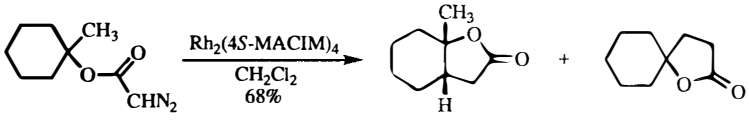
44, *2-deoxyxylolactone*

Scheme 7



45 **46** **47**

	yield, %		
$Rh_2(4S\text{-MPPIM})_4$	81	97 (99% ee)	3
$Rh_2(4S\text{-MACIM})_4$	81	94 (86% ee)	6 (36% ee)
$Rh_2(5S\text{-MEPY})_4$	70	78 (98% ee)	22 (71% ee)
$Rh_2(4S\text{-MEOX})_4$	75	69 (98% ee)	31 (92% ee)



48 **49** (90% ee) **50**

provides extraordinary diastereocontrol and impressive enantiocontrol, as exemplified in the reactions of 3-pentyl diazoacetate (eq 13).[30] These results suggest that the high level of stereocontrol characteristic of C-H insertion reactions for cycloalkyl diazoacetates can now be successfully extended to acyclic diazoacetates.

Tertiary alkyl diazoacetates also undergo facile C-H insertions catalyzed by chiral dirhodium(II) carboxamidates, but here regiocontrol is an important consideration.[57] Enantiocontrol, which is highly dependent on the chiral ligand of the catalyst, is greatly enhanced by the use of $Rh_2(4S\text{-MACIM})_4$ (eq 14; **49**:**50** = 90:10). Regioselectivity, even when competitive C-H insertion is with an electronically unfavorable primary C-H bond, varies with the catalyst and application, and conformational restrictions may be responsible for overriding electronic preferences.[19]

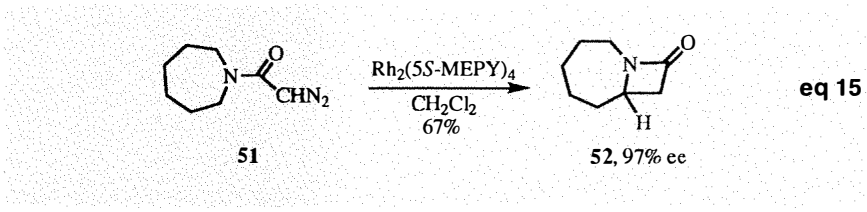
Although 5-membered ring formation is usually preferred, conformational influences and/or heteroatom activation of a C-H bond for insertion can cause selective production of 4-membered rings.[17] For diazoacetamides, 5-membered ring formation is preferred, whereas β-lactam formation is virtually exclusive in catalytic reactions with diazoacetoacetamides. Diazo decomposition of *N-tert*-butyl-*N*-alkyldiazoacetamides catalyzed by chiral dirhodium(II) carboxamidates results in the production of mainly or exclusively γ-lactams in up to 78% ee.[58] Since the conformational flexibility accorded to acyclic *N*-alkyldiazoacetamides provides favored access to β-C-H bonds for insertion to form γ-lactam derivatives, we expected that diazoacetamides derived from cyclic amines would prefer β-lactam production. As is evident in equations 15 and 16, this regiocontrol has been realized in selected cases.[59] Use of $Rh_2(5R\text{-MEPY})_4$ provided the enantiomers of **52** and **54** with the same high % ee values as were achieved with the use of $Rh_2(5S\text{-MEPY})_4$. Product yields for these and previous reactions were determined after distillation or chromatography.

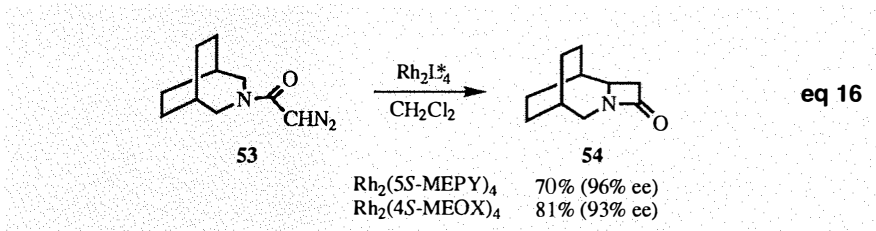
Preparation of Diazoacetates and Diazoacetamides

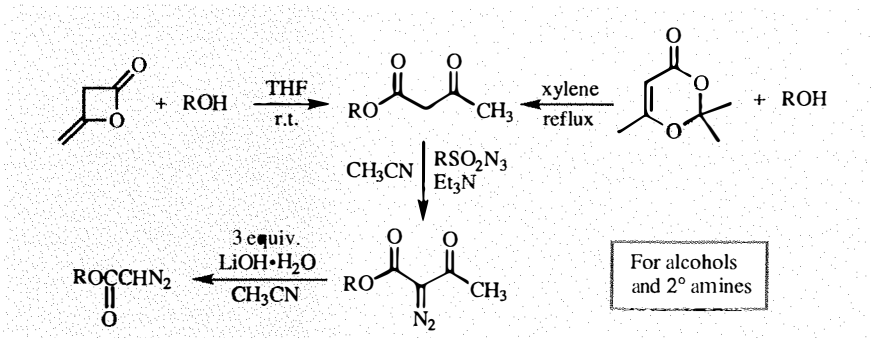
The most common and generally successful methodology for the synthesis of diazoacetates and *N,N*-disubstituted diazoacetamides is a three-step procedure involving condensation with diketene (or with its acetone adduct), followed by diazo transfer, most often from a sulfonyl azide, and subsequent deacylation (**Scheme 8**).[17,19,26,53]

Although the first step is generally successful with primary amines, subsequent diazo transfer and deacylation, which are often made to occur in one pot, are severely limited. A variety of azides, including methanesulfonyl azide (not distilled),[60] *p*-acetamidobenzenesulfonyl azide,[61] and *p*-dodecylbenzenesulfonyl azide[62] have been employed for diazo transfer, the latter to reduce to a minimum the concern over impact sensitivity.

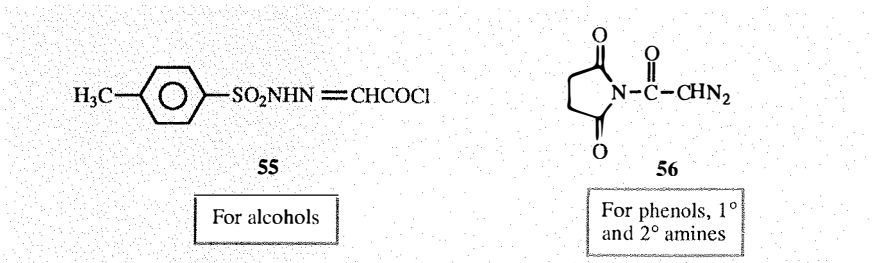
The Corey-Myers procedure[63] using *p*-toluenesulfonylhydrazone (**55**) provides direct access to diazoacetates from alcohols without necessitating the use of azides. However, this reagent is ineffective with amines. A recently reported diazoacetylating reagent, succinimidyl diazoacetate (**56**),[64] is especially effective with amines and phenols, but reactions with alcohols do not occur unless the alkoxide is employed. Other methods are also available,[6,9] but these complements have provided access to all but one of the diazoacetates and diazoacetamides that have been employed in our investigations.







Scheme 8



Catalyst Recovery and Reuse

A polyethylene-bound, soluble, recoverable dirhodium(II) 2-oxopyrrolidine-5(*S*)-carboxylate, PE-Rh_2(5*S*-PYCA)$_4$, has been prepared from Rh_2(5*S*-MEPY)$_4$ and demonstrated to undergo highly enantioselective intramolecular cyclopropanation and C-H insertion reactions even at 80°C.[65] The catalyst was recovered and reused seven times without significant loss of enantiocontrol. Catalyst effectiveness in reuse is optimized by treating the spent catalyst with as little as 3 mol % of the chiral ligand. Chromatographic purification of chiral dirhodium(II) catalysts or their separation from organic products has been achieved in moderate-scale syntheses at Regis Technologies, Inc.

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About the author

Born and raised in Minneapolis, Minnesota, Michael P. Doyle received his B.S. degree from the College of St. Thomas in 1964 and his Ph.D. with W.S. Trahanovsky from Iowa State University in 1968, where he was a U.S. Public Health Service Predoctoral Fellow. He was a postdoctoral associate with J. Rocek and an instructor at the University of Illinois at Chicago before he began his academic career at Hope College in the fall of 1968. He advanced to the level of Professor in six years, and in 1982 he was appointed the first Kenneth G. Herrick Professor at Hope College. In 1984, he moved to Trinity University as the first Dr. D.R. Semmes Distinguished Professor of Chemistry.

Dr. Doyle has received the Camille and Henry Dreyfus Teacher-Scholar Award (1973-78) and the Chemical Manufacturers Association Catalyst Award (1982), and in 1988 he was the third recipient of the American Chemical Socicty Award for Research at Undergraduate Institutions sponsored by the Research Corporation. He has been elected Doctor *Honoraris Causa* of the Russian Academy of Sciences (1994), and he received an Alexander von Humboldt Research Award for Senior U.S. Scientists (1995). His professional activities include, among others, boards or committees of the American Chemical Society, the National Research Council, IUPAC, the Research Corporation, and the Council on Undergraduate Research. He is the coauthor of two textbooks for organic chemistry and one monograph, and he and his students have coauthored more than 170 research publications. Undergraduate student coauthors number 110, and nearly half of these students are credited with two or more publications. Dr. Doyle's current research interests include the design of chiral catalysts for highly enantioselective chemical transformations, the development of new synthetic methods involving metal carbenes, and catalytic carbonylation reactions.

3-Formylchromone as a Versatile Synthon in Heterocyclic Chemistry

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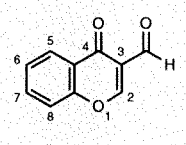
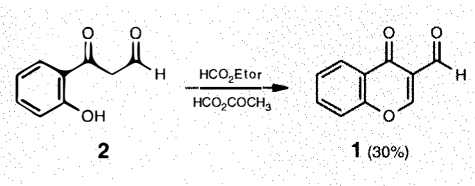
Introduction

Since 1973, when a convenient synthesis of 3-formylchromone (**1**) by the Vilsmeier method[1] was first reported, the potential of this molecule in the synthesis of fused heterocyclic systems has attracted the attention of chemists worldwide. Much of the synthetic utility of **1** derives primarily from the reactivity of its three electron-deficient centers at C-2, C-4, and the C-3 formyl group. 3-Formylchromone can serve as a Michael acceptor with concomitant opening of the pyrone ring. It can act as a heterodiene as well as an ideal dienophile. Bifunctional nucleophiles can react at any two of the three active centers to provide a fused heterocyclic compound directly. It is also possible to use two different nucleophiles to obtain a new heterocycle.

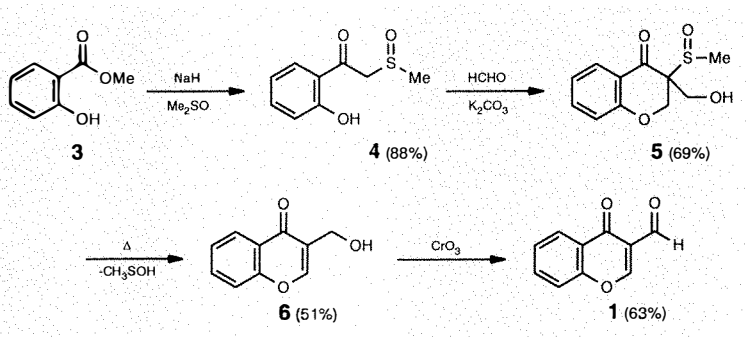
This review will cover the synthetic exploitation of nucleophilic additions, cycloadditions, cyclocondensations, and other important reactions with 3-formylchromone as well as methods for its preparation.



1
3-Formylchromone



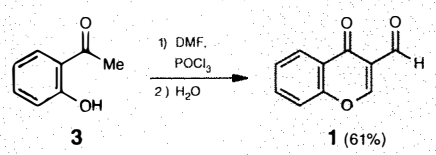
2 **1** (30%) eq 1



3 **4** (88%) **5** (69%)

6 (51%) **1** (63%)

Scheme 1



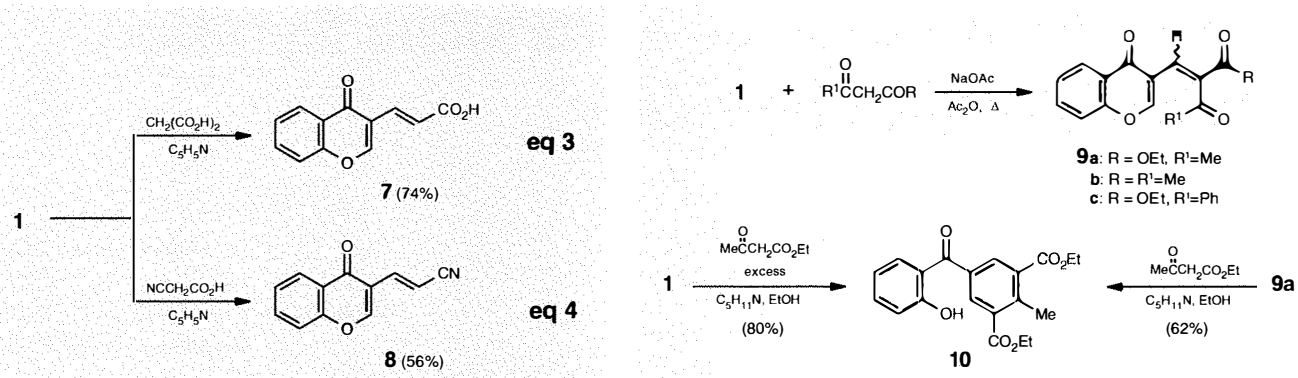
3 **1** (61%) eq 2

An earlier review on the synthesis, properties, and reactions of **1** appeared in 1983;[2] however, the continuing interest in 3-formylchromone prompted this comprehensive review which covers the recent literature to 1994.

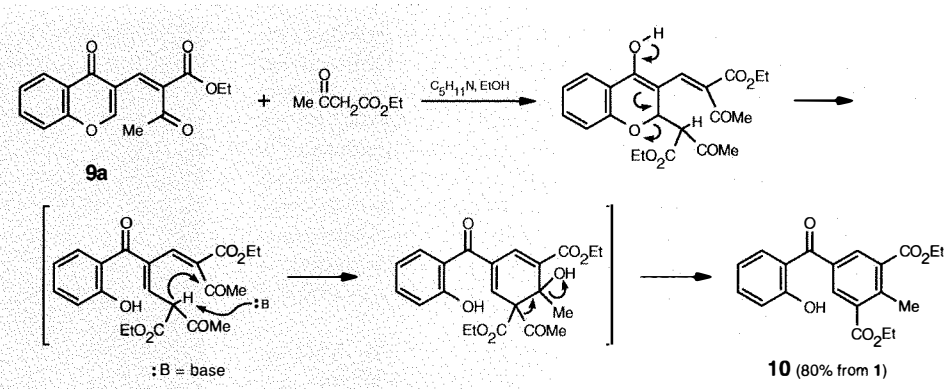
Synthesis

3-Formylchromone can be synthesized by the reaction of *o*-hydroxy-ω-formyl acetophenone (**2**) with ethyl formate[3,4] or acetic-formic anhydride (eq 1).[5] Compound **1** can also be obtained in four steps starting with sodium methylsulfinyl-methide and methyl salicylate (**3**) (**Scheme 1**). The *o*-hydroxy-ω-(methylsulfinyl)acetophenone (**4**) thus produced is treated with formaldehyde, in the presence of base, to give 3-(hydroxymethyl)-3-(methylsulfinyl)-4-chromanone (**5**). Thermal elimination of CH_3SOH gives 3-hydroxymethylchromone (**6**),[6] which is readily oxidized to 3-formylchromone.

By far the most convenient method of synthesizing **1** is by the Vilsmeier-Haack reaction as shown in equation 2.[1,7,8]



Scheme 2



Scheme 3

Reactions

Nucleophilic Addition

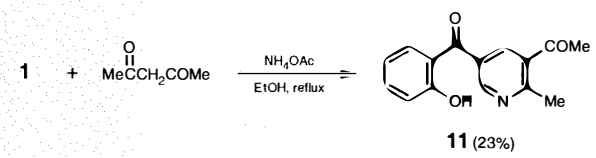
The majority of reactions with 3-formylchromone are nucleophilic additions leading mainly to condensation products. These additions can be classified into the following two types: reactions with monofunctional nucleophiles and reactions with bifunctional nucleophiles.

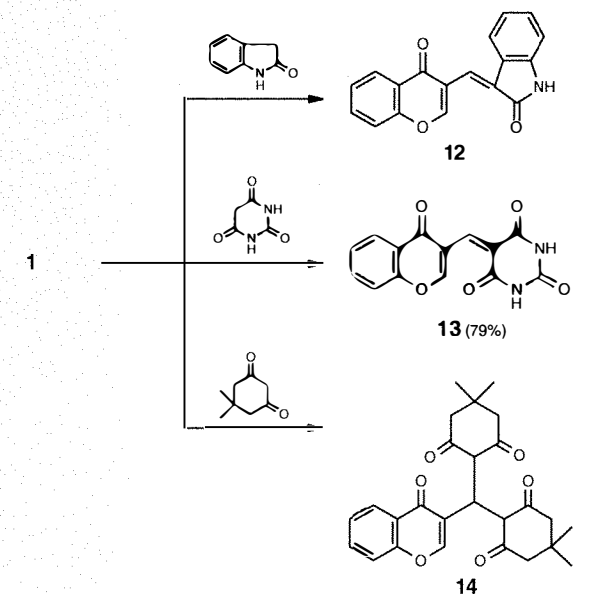
(i) Reactions with monofunctional nucleophiles

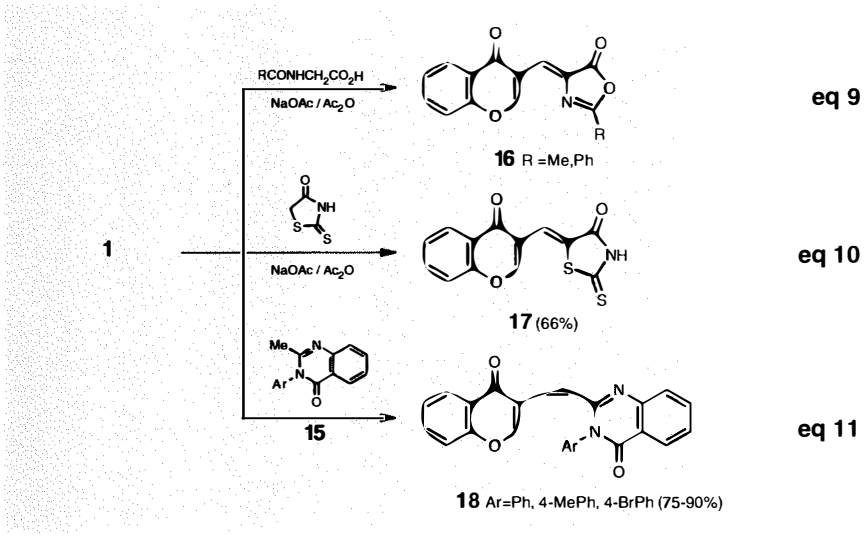
With active methylene compounds

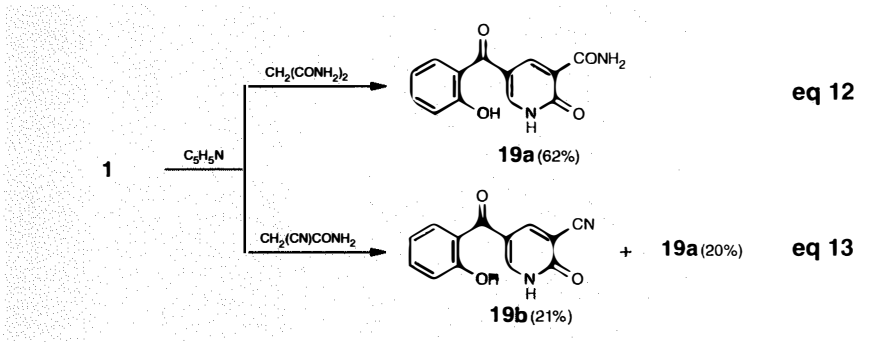
Active methylene compounds readily react with **1** in the presence of base. For example, reaction of **1** with malonic acid (eq 3) or cyanoacetic acid (eq 4) in the presence of pyridine followed by decarboxylation gives *trans*-β-(4-oxo-4*H*-1-benzopyran-3-yl)acrylic acid (**7**), which displays antiallergic activity,[9] and *trans*-β-(4-oxo-4*H*-1-benzopyran-3-yl)acrylonitrile (**8**),[10,11] respectively.

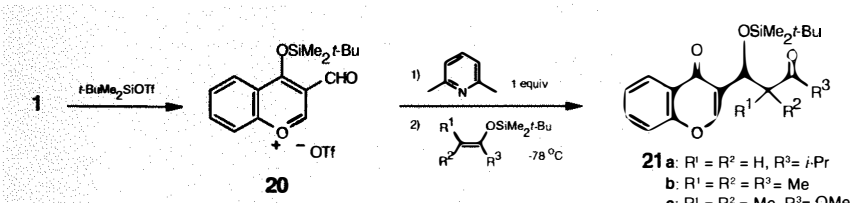
Base-catalyzed condensation of **1** with ethyl acetoacetate, 2,4-pentanedione, or ethyl benzoylacetate, provides the expected condensation products, **9a-c**, respectively (**Scheme 2**). Further reaction of **9a** with ethyl acetoacetate in the presence of piperidine-EtOH gives the substituted benzophenone **10**, which can also be obtained directly with excess ethyl acetoacetate as indicated in **Scheme 2**.[12] The formation of **10** is rationalized in **Scheme 3**.



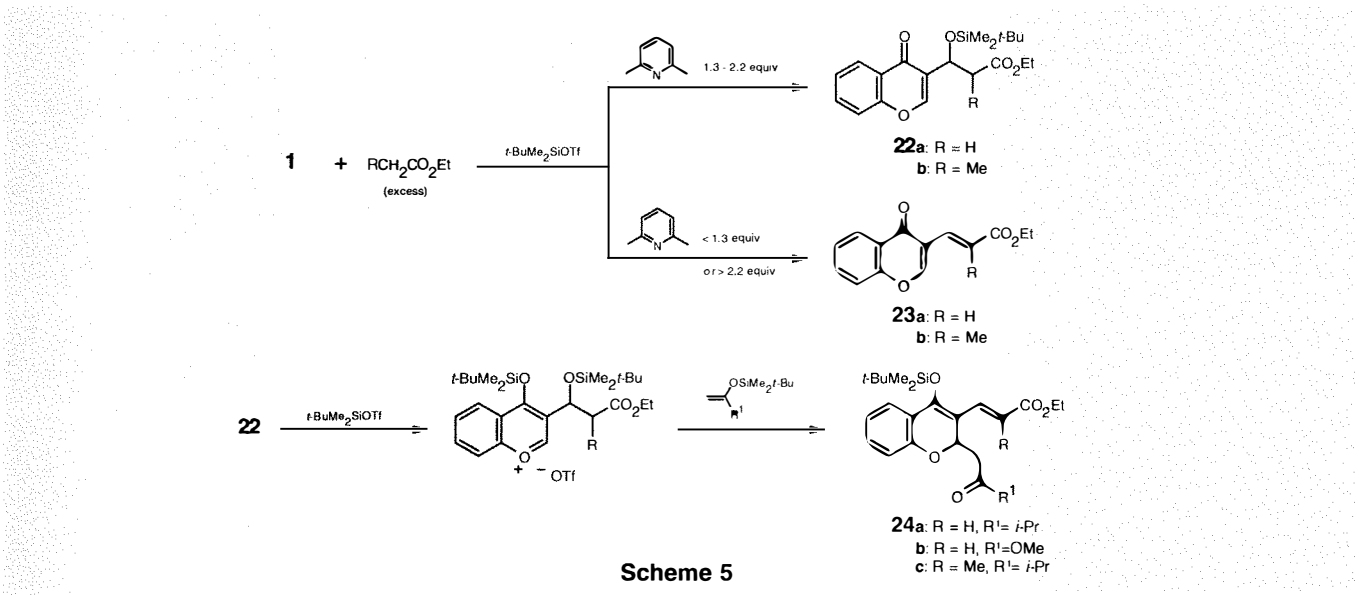








Scheme 4



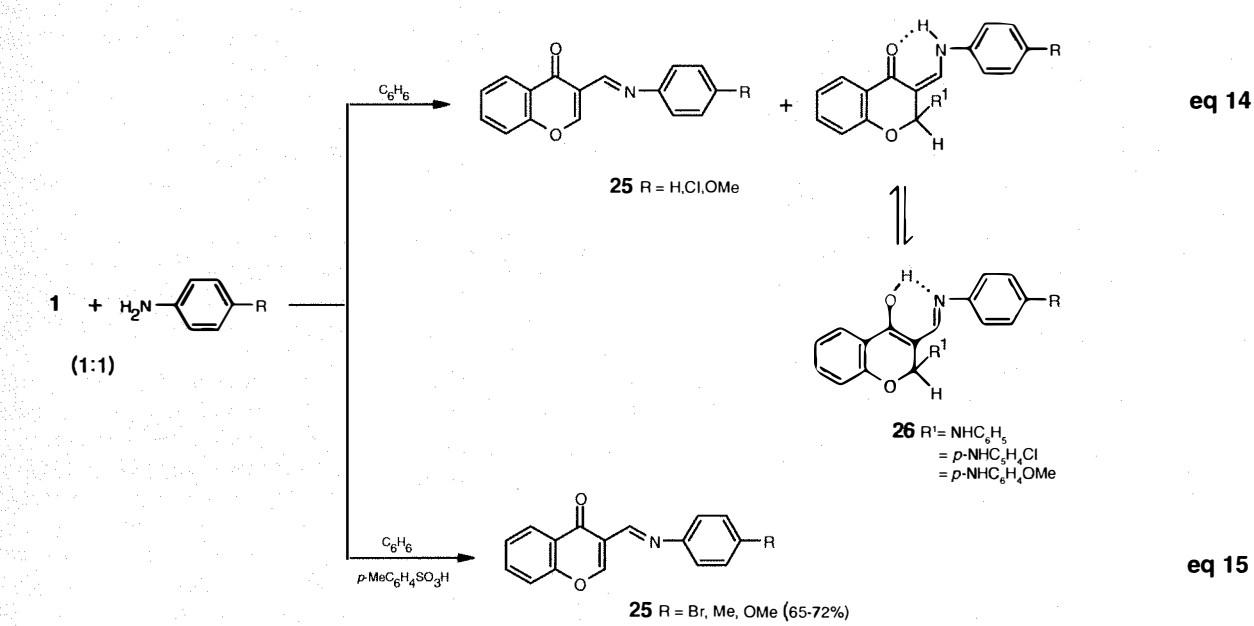
Scheme 5

The reaction of **1** with excess 2,4-pentanedione in the presence of ammonium acetate in boiling ethanol gives the pyridine analog **11** (eq 5).[13]

Condensation of **1** with oxindole[14a] or barbituric acid[14] provides the expected monoadducts **12** (eq 6) and **13** (eq 7); however, when dimedone is used the 2:1 adduct **14** is formed (eq 8).[3] Analogous reactions of **1** with *N*-acetylglycine,[15a] *N*-benzoylglycine,[15b] rhodanine,[15b] or 3-aryl-2-methyl-4-(3*H*)-quinazolinone (**15**)[16] leads to condensation products **16** (eq 9), **17** (eq 10), and **18** (eq 11).

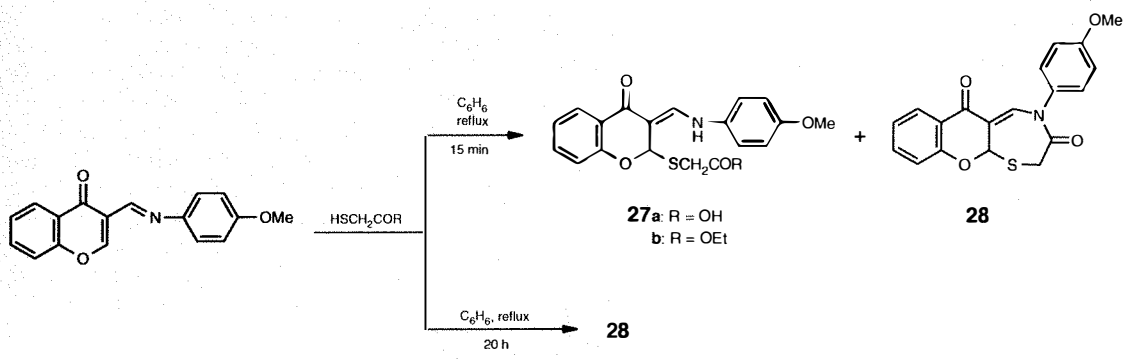
In the presence of pyridine, amides such as malonodiamide and cyanoacetamide react with **1** to produce pyridones such as **19a** (eq 12) and a mixture of **19a** and **19b** (eq 13).[17]

Iwasaki and co-workers[18] reported a facile route to 2,3-disubstituted chromones via *O*-silyl-3-formylchromone triflate **20** formed by reaction with one equivalent of *t*-butyldimethylsilyl triflate at 160 °C. This salt reacts rapidly with silyl enol ethers to give adducts **21a-c (Scheme 4)**. Although the yields of **21a-c** are low, they can be improved by reaction of **1** with excess ethyl acetate or ethyl propionate in the presence of two equivalents of triflate and 1.3-2.2 equivalents of 2,6-lutidine. In this way, **22a** and **22b** are obtained in >90% yields (**Scheme 5**). Use of less than 1.3 equivalents of lutidine or more than 3 equivalents results in elimination, giving **23a** and **23b**. A second group can be introduced into the C-2 position of **22a** and **22b** by further silylation and subsequent reaction with silyl enol ethers (**Scheme 5**).



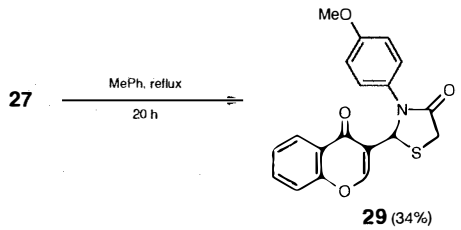
eq 14

eq 15

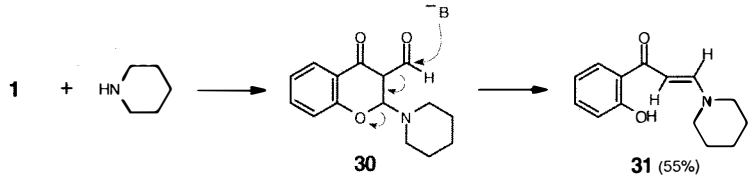


eq 16

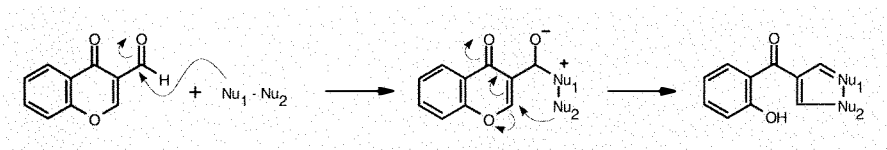
eq 17



eq 18

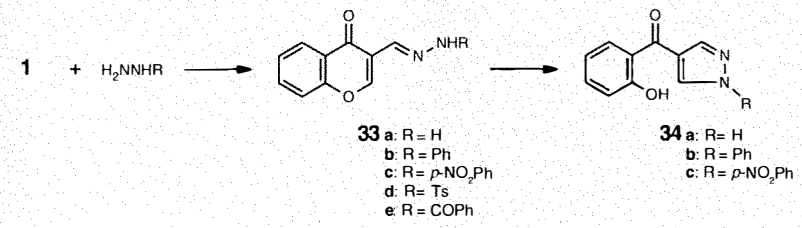


Scheme 6



32

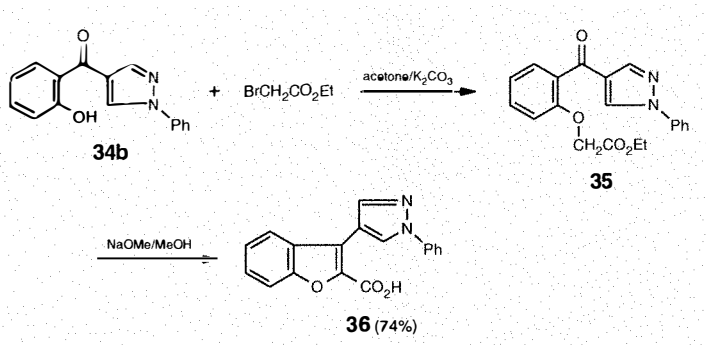
Scheme 7



33 **a**: R = H
b: R = Ph
c: R = *p*-NO_2Ph
d: R = Ts
e: R = COPh

34 **a**: R = H
b: R = Ph
c: R = *p*-NO_2Ph

Scheme 8



34b

35

36 (74%)

Scheme 9

With nitrogen nucleophiles

3-Formylchromone readily reacts with primary aromatic amines to give a mixture of the anil **25** and the 1,4-adduct **26,** formed by further addition of the amine to **25** (eq 14).[19,20a] However, if moisture is present some of the anil hydrolyzes and the liberated amine adds to the unchanged **25**, thus enriching the yield of the 1,4-adduct. The pure anil can be obtained by performing the reaction in the presence of *p*-toluenesulfonic acid (eq 15). *p*-Methyl- and *p*-bromoanalogs of **25** have also recently been prepared using this procedure.[20b] The 1,4-adduct **26** is stabilized by a hydrogen-bonded ketoamine interaction as indicated in equation 14. Any base strong enough to remove this hydrogen bonded proton causes elimination of the C-2 amino substituent. Aromatic amines are not strong enough bases to deprotonate **26**, and thus these crystalline adducts are stable in their presence.

For steric reasons, secondary aromatic amines do not add to **25.** Primary aliphatic amines are too strongly basic to form the adduct. For example, *n*-propylamine caused instant decomposition of the aromatic amine adducts **26**. Secondary nonaromatic amines like dimethylamine and piperidine form adducts only in solution, as evidenced by UV absorption analysis. However, after solvent evaporation these adducts break apart.

Anils **25** are very reactive toward alcohols, phenols, and thiols, often producing interesting C-2 addition compounds as well as new heterocyclic rings. Alcohols readily add to **25** to give crystalline adducts. However, due to steric hindrance, *t*-butyl alcohol gives an unstable adduct. When heated, these alcohol adducts undergo elimination to the corresponding anils. While thiophenols give stable solid adducts, adducts derived from phenols are stable only in solution.

Thiols add to anils in higher yields than alcohols. Occasionally, the thiol adducts undergo further reaction to produce heterocycles. For example, Fitton and co-workers[21] reported that reaction of **25** (R = OMe) with thioglycolic acid or its ethyl ester in boiling benzene for 15 minutes gave the adducts **27a** and **27b**, respectively, as well as fused thiazepinone **28** (eq 16). When the reaction was prolonged for 20 hours only **28** was isolated (eq 17). Significantly, the same authors reported the formation of thiazolidinone **29** in 34% yield when **27** was heated at reflux in toluene for 20 hours (eq 18).[21] The nature of the substituent at the *para* position in the amine portion of the anil affects this cyclization since an electron withdrawing group in **25** (R = Cl) gave no cyclization product.

When 3-formylchromone (**1**) is treated with secondary amines like piperidine, an unstable 1,4-adduct **30** is formed (**Scheme 6**). This adduct undergoes base-catalyzed deformylation to give the enamino ketone **31**.[22] Enamino ketones are useful intermediates for the synthesis of chromones,[23] 3-halochromones,[23] and *o*-hydroxyphenylpyrazoles.[24]

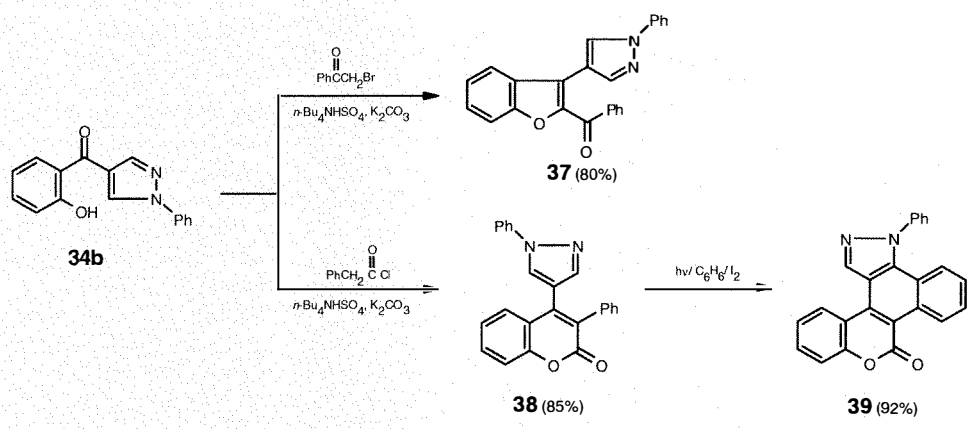
(ii) Reactions with bifunctional nucleophiles

Reaction of **1** with bifunctional nucleophiles (e.g., Nu_1-Nu_2) results in the formation of a new heterocyclic ring. Thus, reaction of **1** at the formyl carbon gives, initially, intermediate **32** which, following intramolecular attack by Nu_2 at the reactive C-2 position, results in ring-forming/ring-opening, as shown in **Scheme 7**.

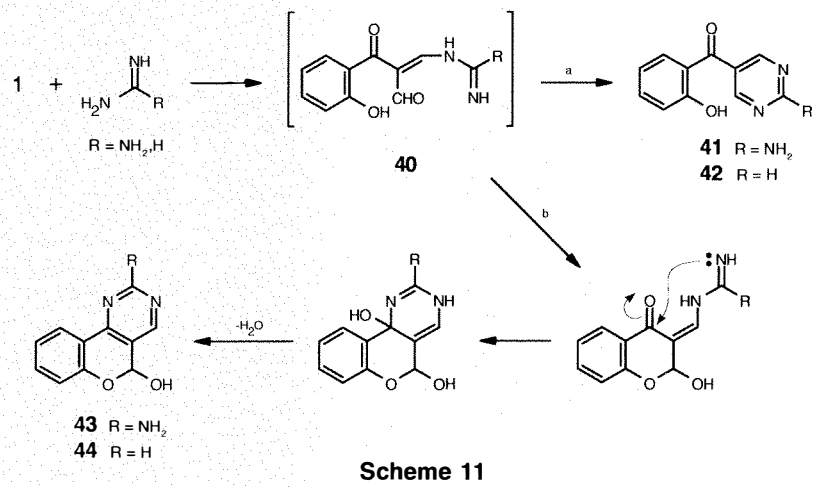
An example of this generalized scheme is the reaction of 3-formylchromone with hydrazine to give initially hydrazone **33a**, which then reacts further at the C-2 position to give 4-(2-hydroxybenzoyl)pyrazole (**34a**).[25a] Similarly, reaction with a number of aryl hydrazines gives hydrazones **33b-e**[26] which are converted under varying conditions to the corresponding pyrazoles **34b,c** (**Scheme 8**).[25a] Other interesting hydrazines, acid hydrazides, and even thiosemicarbazide have recently been reported to react with **1** to produce hydrazones.[25b]

Pyrazole **34b** is a useful intermediate in the synthesis of other heterocyclic systems such as benzofurans and coumarins. For example, reaction of **34b** with ethyl bromoacetate and K_2CO_3 in acetone results in the phenoxy ester **35**. Treatment of **35** with NaOMe/MeOH gives 3-(1-phenyl-1*H*-pyrazol-4-yl)benzofuran-2-carboxylic acid (**36**) after hydrolysis of the ester group during aqueous workup (**Scheme 9**).[27]

A similar sequence of reactions of **34b** with phenacyl bromide under phase transfer catalysis (PTC) conditions furnishes 2-benzoyl-3-(1-phenyl-1*H*-pyrazol-4-yl)benzofuran (**37**) in 80% yield (**Scheme 10**).[28] 3-Phenyl-4-(1-phenyl-1*H*-pyrazol-4-yl)-coumarin **(38)**[29] is synthesized by reaction of **34b** with phenylacetyl chloride under identical PTC conditions. Compound **38**, possessing a reactive conjugated triene system, undergoes photocyclization, as expected, to give the novel fused heterocyclic system,



Scheme 10



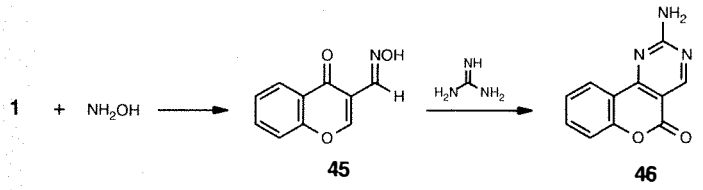
Scheme 11

3-phenylbenzo[*g*][1]benzopyrano[4,3-*e*]-indazol-8(3*H*)-one (**39**) (**Scheme 10**).[29]

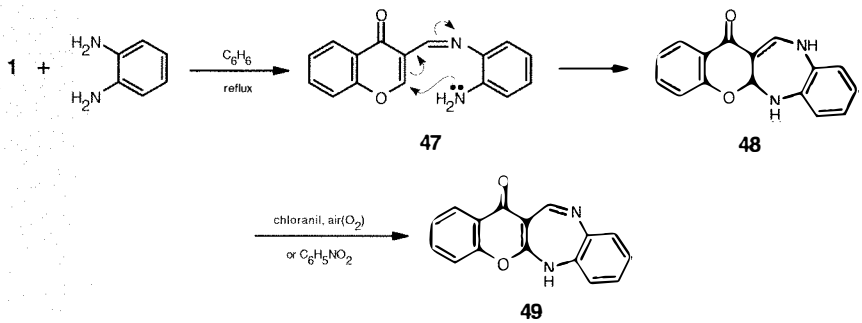
Reaction of **1** with guanidine provides a mixture of 2-amino-5-(2-hydroxybenzoyl)-pyrimidine (route a, **41**) and 2-amino-5-hydroxy-5*H*[1]-benzopyrano[4,3-*d*]-pyrimidine (route b, **43**) via the intermediate **40** as shown in **Scheme 11**.[30,31] Similarly, reaction of **1** with formamidine gives, as expected, pyrimidine **42** and benzopyranopyrimidine **44**.[32] Oxime **45**, formed from **1** and hydroxylamine, reacts with guanidine to give 2-amino-(5*H*)-[1]benzopyrano-[4,3-*d*]pyrimidine-5-one (**46**) (**Scheme 12**).[33]

o-Phenylenediamine was initially reported to react with **1** in boiling benzene providing anil **47** which then ring-closed to diazepinone **48** (**Scheme 13**).[34] Dehydrogenation of **48** by chloranil, air, or nitrobenzene reportedly provided **49**.[35,36]

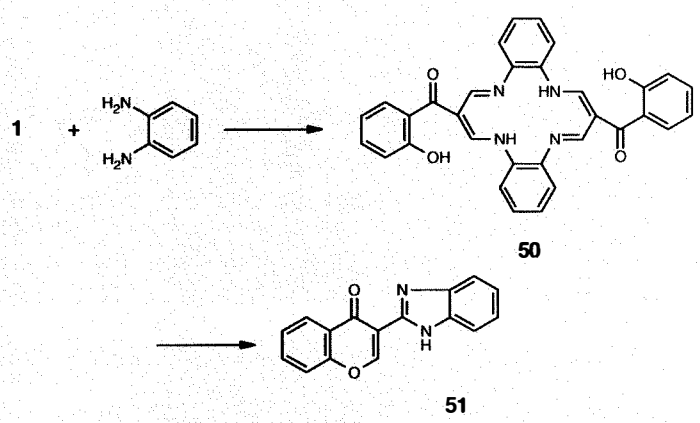
The actual sequence of reactions with *o*-phenylenediamine and **1** was later reported to follow the path outlined in **Scheme 14**.[37] The initially formed product dihydrotetraaza[14]annulene (**50**) was determined by



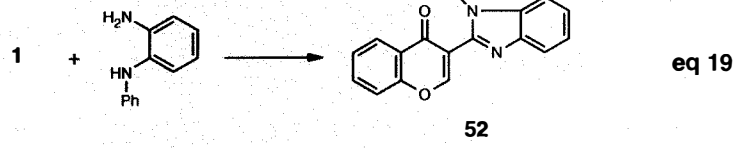
Scheme 12



Scheme 13



Scheme 14



eq 19

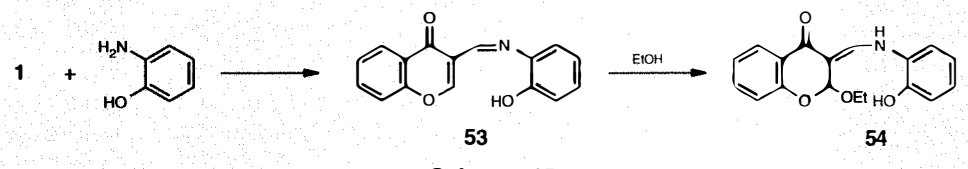
^{1}H NMR analysis. Oxidation of **50** produced 3-(2-benzimidazolyl)chromone (**51**). The structures for **50** and **51** were established by X-ray crystallography.[38]

N-substitution of *o*-phenylenediamine also results in benzimidazole-type products. Winkler and co-workers reported that reaction of **1** with *N*-phenyl-*o*-phenylenediamine provides 3-(1-phenyl-2-benzimidazolyl)-chromone (**52**) (eq 19).[37,38]

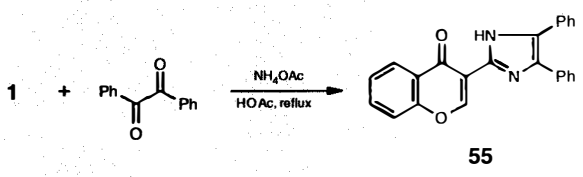
Condensation of *o*-aminophenol with **1** leads to 3-(2-hydroxyphenyl)iminomethyl-chromone (**53**), which on crystallization with ethanol produces **54** by 1,4-addition (**Scheme 15**).[37,38]

When **1** is refluxed with benzil and ammonium acetate in glacial acetic acid, 4,5-diphenyl-2-(4-oxo-4*H*-1-benzopyran-3-yl)imidazole (**55**) is obtained (eq 20).[39]

Pyridines are formed when 3-formylchromone is condensed with methyl or ethyl aminocrotonate giving initially dihydropyridines **56** and **57**, which are readily oxidized by MnO_2 to **58** and **59**, respectivcly (**Scheme 16**).[40,41]



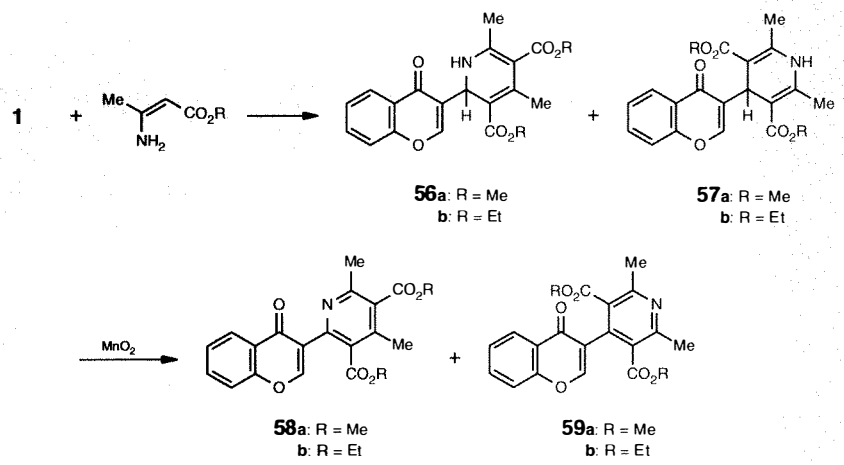
Scheme 15



eq 20

Fused-ring pyridines **60** can be prepared by treating **1** with enaminonitriles and enaminoketones, such as 3-aminocrotononitrile and 2-amino-4-oxopent-2-ene. Oxidation with CrO_3 then gives **61** (**Scheme 17**).[42]

Reaction of 3-formylchromone with 4-amino-3-mercapto-5-phenyl-1,2,4-triazole



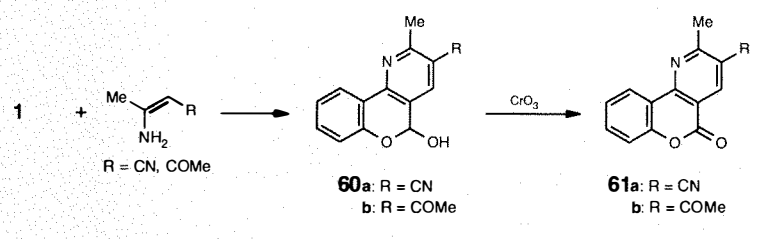
Scheme 16

under phase transfer conditions yields the ring-opened thiadiazepine **63** via the intermediate **62** (**Scheme 18**).[43]

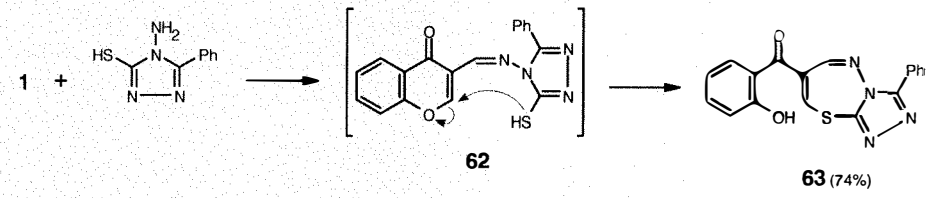
Cycloaddition Reactions

(i) As a Heterodiene

3-Formylchromone behaves as a heterodiene in [4+2] cycloaddition reactions. Such reactions are facilitated by the electron withdrawing carbonyl group at the α-position of



Scheme 17



Scheme 18

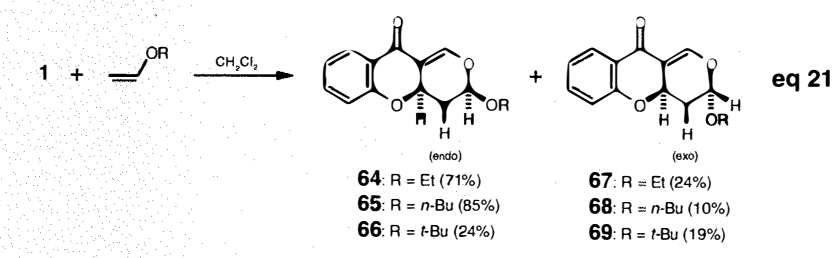
the heterodiene system. Thus, treatment of **1** with ethoxyethylene in dichloromethane at room temperature gives a mixture of two adducts **64** and **67** (eq 21),[44] formed by endo and exo addition of the dienophile, with the former predominating. Similarly, reactions with *n*-butoxyethylene, *t*-butoxyethylene, and 2-methoxypropene give mixtures of endo and exo cycloadducts (eq 21 and 22) with endo products predominating.[45] Not suprisingly, a quantitative yield of a single cycloadduct **72** results when **1** is reacted with 1,1-dimethoxyethylene (eq 23).[46]

Reaction of **1** with dihydropyran at 115°C produces the isomeric tetracyclic compounds pyrano[2',3':6,5]pyrano[4,3-*b*][1]benzopyranones **73** and **74** (eq 24) in which the enol ether geometry is retained;[45] once again **73** slightly predominates over **74.**

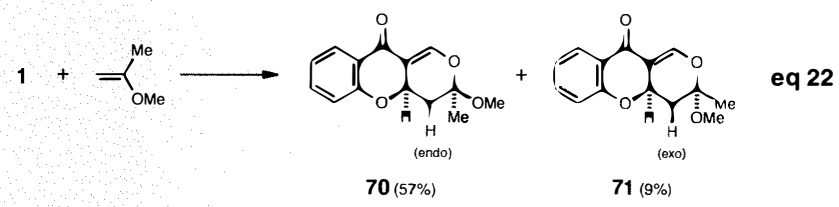
Similarly, [4+2] cycloaddition of **1** with keteneacetals **75**, derived from 1,2-diarylethane-1,2-diols **78**, gives a mixture of cycloadducts **76**, which on acid-catalyzed methanolysis, undergo transesterification and retro-Claisen deformylation giving **77** and regenerating the 1,2-diol **78.** When the keteneacetal derived from (*S,S*)-hydrobenzoin was used, the optically enriched methyl 3,4-dihydro-4-oxo-2*H*-[1]benzopyran-2-yl acetate (**77**) was formed. The byproduct **78** was recycled as shown in **Scheme 19**.[47]

(ii) As a Dienophile

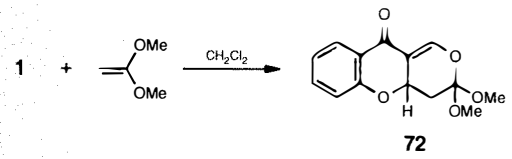
3-Formylchromone can also function as a dienophile in [4+2] cycloaddition. Thus, treatment of **1** with 2,3-dimethylbutadiene in boiling dichloromethane containing a catalytic quantity of $TiCl_4$ gives a mixture of



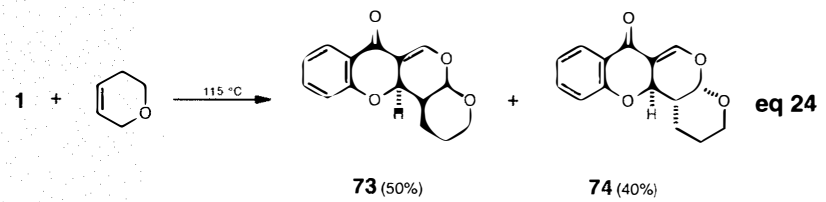
eq 21



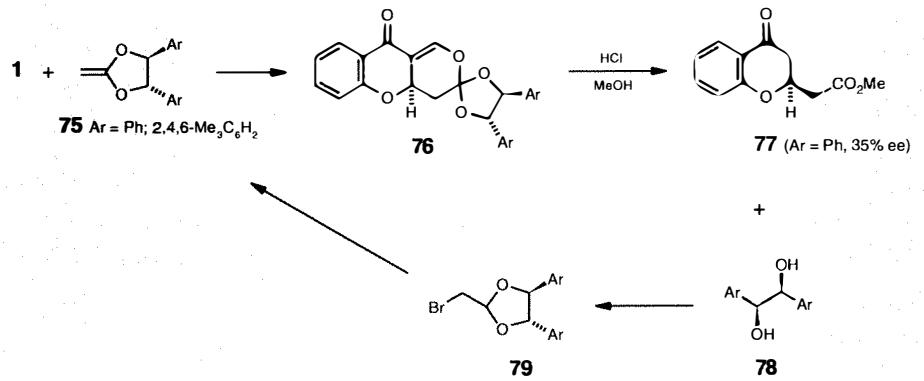
eq 22



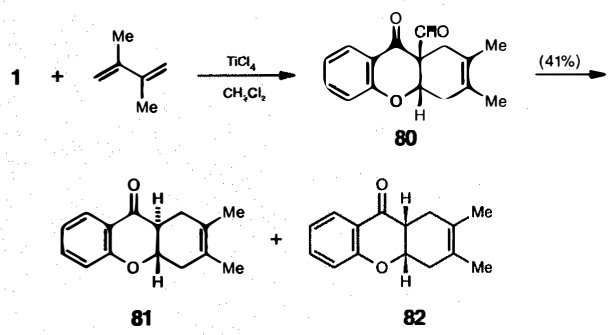
eq 23



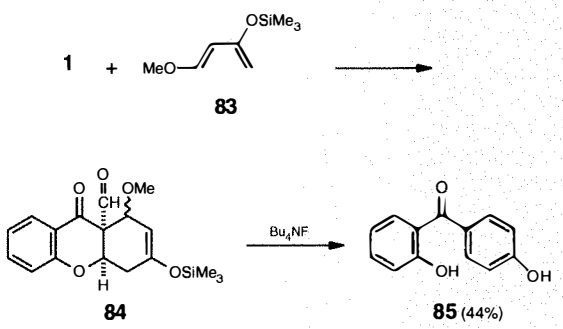
eq 24



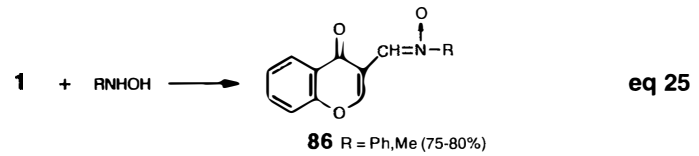
Scheme 19



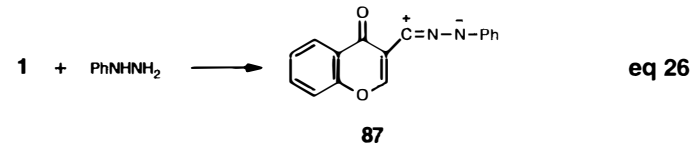
Scheme 20



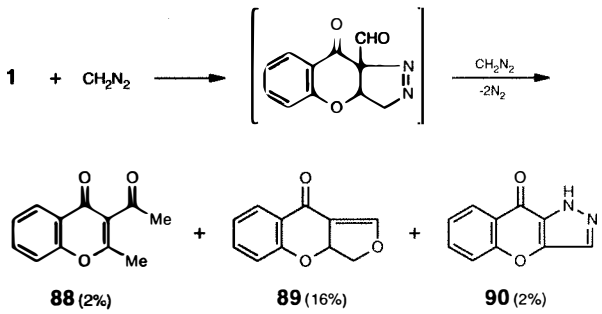
Scheme 21



eq 25



eq 26



Scheme 22

trans- and *cis*-2,3-dimethyl-1,4,4a,9a-tetrahydroxanthone (**81** and **82**), resulting from cycloaddition-decarbonylation (**Scheme 20**).[48] The reaction of **1** with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**83**) gives a quantitative yield of the isomeric cycloadducts **84** in the absence of a Lewis acid catalyst (**Scheme 21**). Treatment of the mixture of these adducts with tetrabutylammonium fluoride causes desilylation, decarbonylation, and aromatization to give 2,4'-dihydroxybenzophenone (**85**) in 44% yield.[48]

Within the context of 1,3-dipolar cycloaddition, 3-formylchromone functions as both a precursor for 1,3-dipoles such as **86** (eq 25) and **87** (eq 26)[49,50] and as an activated olefin substrate for cycloaddition—as in its reaction with diazomethane (**Scheme 22**). A mixture of products results from this reaction. 3-Acetyl-2-methylchromone (**88**) (2%), 3,3a-dihydro-9-oxo-9*H*-furo[3,4-*b*][1]-benzopyran (**89**) (16%) and 9-oxo-9*H*-[1]-benzopyrano[2,3-*d*]pyrazole (**90**) (2%) were isolated.[51]

Cyclocondensation Reactions

Wallace and co-workers[52] reported a one-step annulation procedure, wherein **1** reacts with 2-iodoethanol to produce

tetrahydrofuro[2,3-*b*][1]benzopyran-4-one (**93**) as shown in **Scheme 23**.

Fused pyridine derivatives **94-100**[14a] are obtained when 3-formylchromone is reacted with a variety of acyclic, alicyclic, and heterocyclic enamines in acetic acid, pyridine, or DMF as shown in **Scheme 24**.

A cyclocondensation reaction occurs when **1** is reacted with dichloroketene, eliminating HCl to give the tripyran **101** (eq 27).[53]

Miscellaneous Reactions

3-Formylchromone undergoes a very interesting reaction with acrylonitrile/iodotrichlorosilane to give directly the 3-aminoprop-2-enal derivative **102** in 45% yield (eq 28).[54]

Nohara and co-workers[55,56] reported a novel route to 3-halochromones. Reaction of **1** with NaOCl in acetic acid at room temperature gives 3-chlorochromone (**103**) in 86% yield, along with a small quantity (1%) of 2-acetoxy-3,3-dichlorochromanone (**104**) (eq 29). However, when **1** is treated with NaOBr, 3-bromochromone (**105**) and 2,2,3',5'-tetrabromo-2'-hydroxyacetophenone (**106**) are produced in 9% and 30% yields, respectively (eq 30). Product **106** obviously arises out of a radical reaction. When the same reaction is carried out in the dark, ostensibly to avoid formation of radicals, **105** is obtained in 32% yield, along with 2-acetoxy-3,3-dibromochromanone (**107**) in 29% yield (eq 31).

Conclusion

The above discussion demonstrates the versatility of 3-formylchromone, and molecules derived from it, as starting materials for preparing novel heterocyclic systems. The chemistry of 3-formylchromone is indeed rich, and its exploration is increasing worldwide.

Acknowledgements

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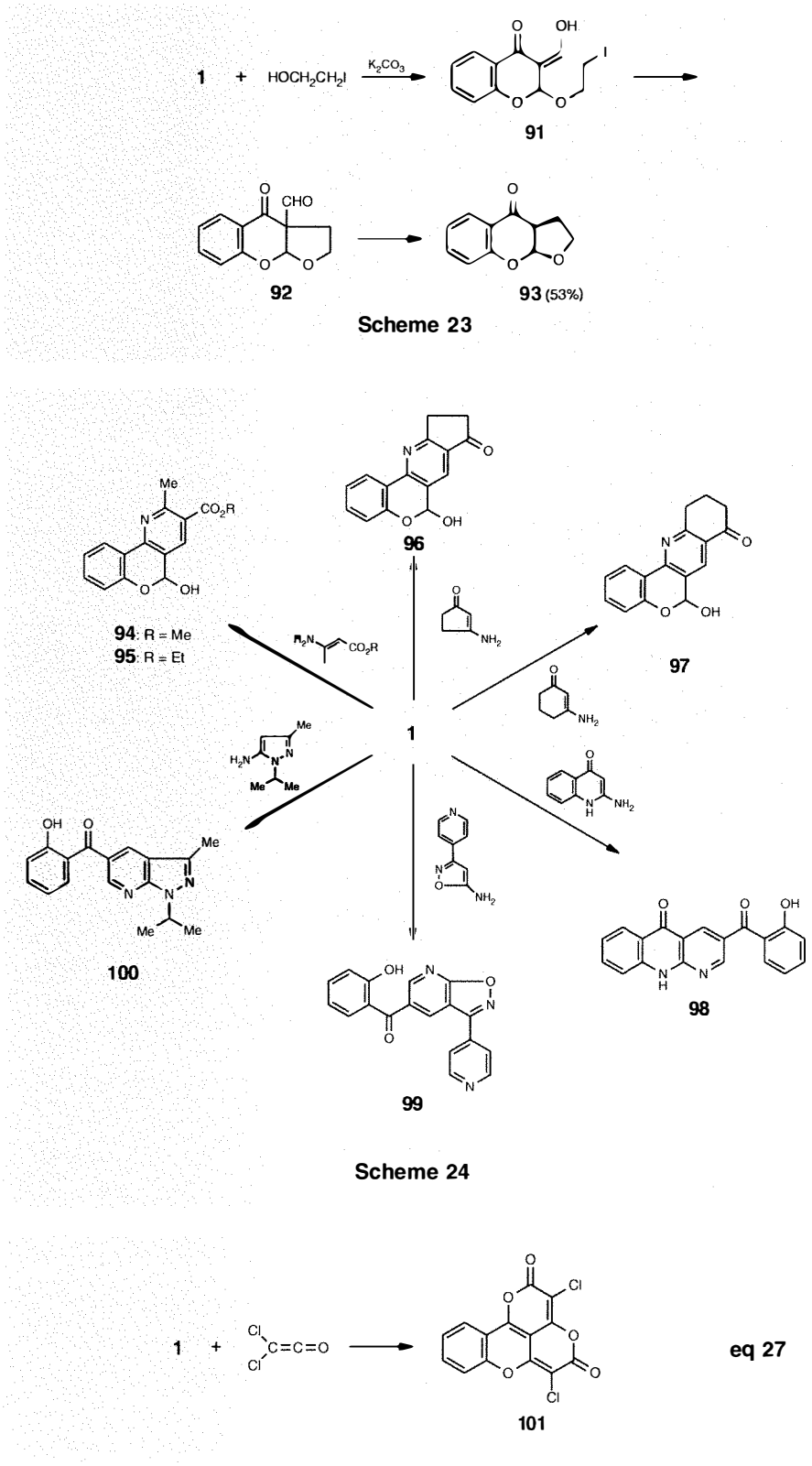
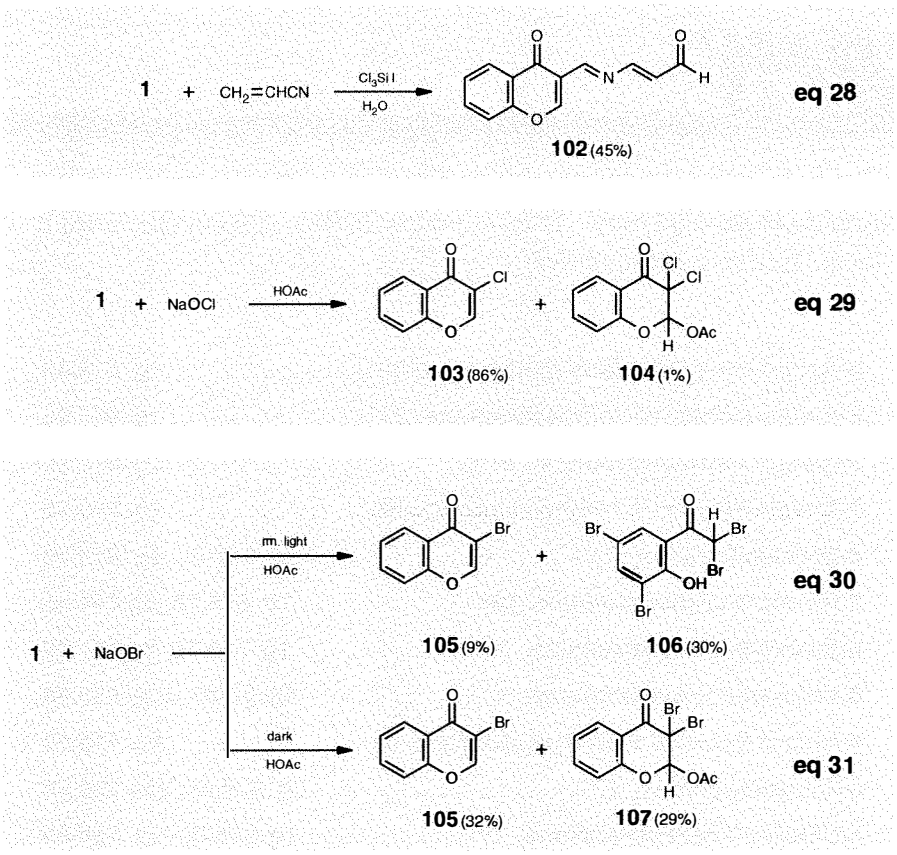


Scheme 23

Scheme 24

eq 27



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Gowravaram Sabitha was born in Karimnagar, India in November 1959. She obtained her B.Sc. and M.Sc. degrees from Osmania University, Hyderabad in 1978 and 1980, respectively. She received her Ph.D. in 1987 from the same university with a thesis entitled "Investigations on Phase Transfer Catalysis: Synthesis of Some Heterocyclic Compounds of Physiological Interest" under the supervision of Professor A.V. Subba Rao. This work was based mainly on 3-formylchromone derived products.

After a period of teaching, she joined Osmania University as UGC Research Associate in January 1989. In August of that year, she became a Visiting Research Fellow at Princeton University, where she worked with Professor Edward C. Taylor on "*de novo* biosynthetic pathway inhibitors as anticancer agents" for one and a half years. Presently, she is a Scientist at the Indian Institute of Chemical Technology in Hyderabad. Her present interests include process development and the synthesis of new chemical entities (NCE's).

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The painting on our cover, *Fête Galante* (oil on canvas, 54.3 x 66 cm), was painted by Jean-Baptiste Joseph Pater (1695-1736). Pater was a close follower of Jean-Antoine Watteau, a compatriot from Valenciennes and eleven years Pater's senior, with whom he worked for two periods of time. Together they shared an unreal, dream-like, elusively musical imagery as their common characteristic. Less profoundly provocative than Watteau, Pater's work achieved a decorative delicacy all his own of which this painting is a fine example. Typically, Pater's imagery includes elegantly dressed ladies, gentlemen, and children amusing themselves with conversation, music, and wine in pastoral settings embellished with decorative sculpture.

The painting is part of the collection of French paintings at The Saint Louis Art Museum.

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Thank you,
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(1) Levine, S.G. *J. Chem. Educ.* **1996**, *73*, 77.

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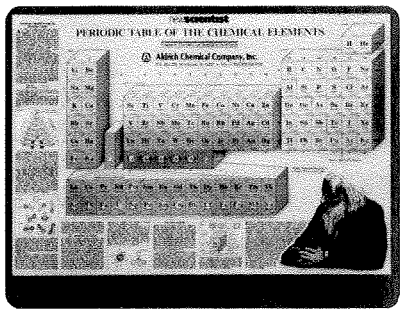

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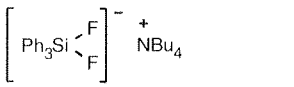
"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



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Pilcher, A.S.; Ammon, H.L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

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Nonnatural Products Nonpariel

Dedicated to Professor Philip E. Eaton on the occasion of his sixtieth birthday

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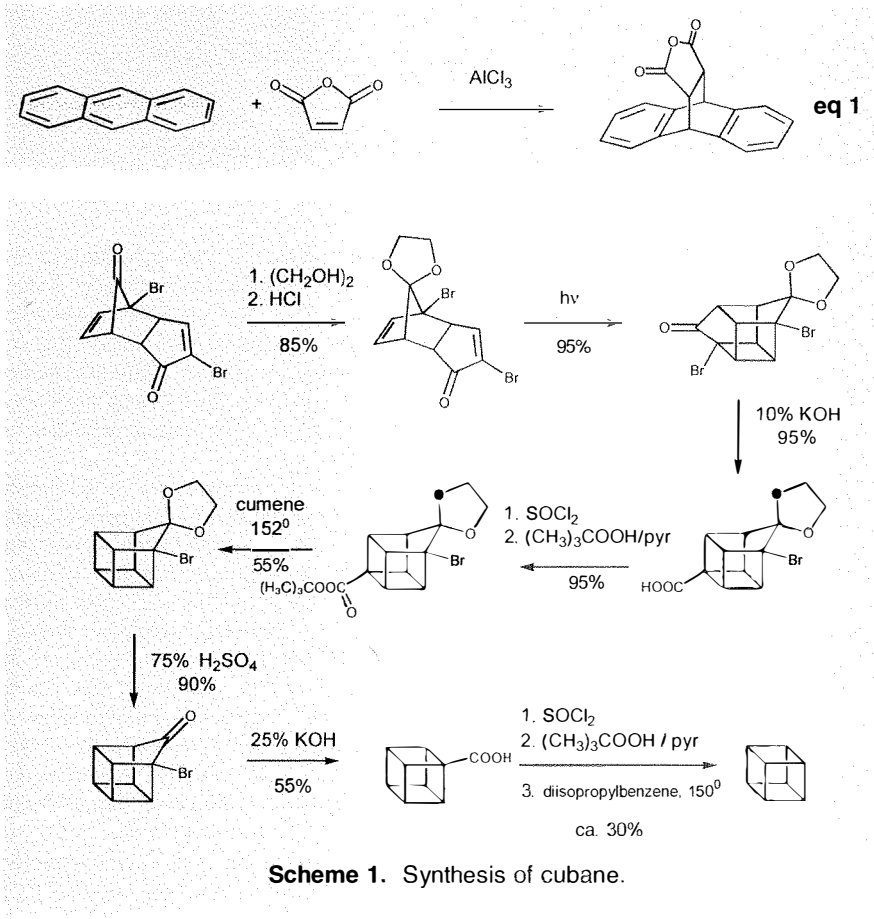
Professor Philip E. Eaton



Scheme 1. Synthesis of cubane.

Building Blocks

It doesn't take long before a student of organic chemistry becomes acquainted with the beauty and marvel of cubane, and fascination with this extraordinary molecule continues more than three decades after its discovery. Before then, it was said that this was one carbocycle that could *not* be synthesized. It took the vision and persistence of Philip Eaton to forge this molecule and, as a consequence, redefine the limits of synthetic and structural chemistry, as he has done since then so many times and in such breathtaking ways.

Philip Eaton's higher education began at Princeton, and in 1957 continued at Harvard in the laboratory of Peter Yates, where he wrote his dissertation on the subjects of *"Isomerizations in the Dicyclopentadiene Series, Acceleration of the Diels-Alder Reaction by Lithium Chloride, and Studies in the Chemistry of Perchloro Compounds"*,[1] indeed, enough material for several theses! These were seminal studies on the effect of Lewis acids upon the rates and selectivities of the Diels-Alder reaction, and greatly clarified the nature and scope of this renowned mode of catalysis (**eq 1**).[2] After his appointment at the University of California-Berkeley in 1960, Eaton studied, among other things, the [2+2] cycloadditions of cyclopentenones.[3] The groundwork for cubane synthesis was thus being laid in other ways, as the Eaton group had discovered how to steer the Diels-Alder reactivity of cyclopentadienone ketals,[4] the source of all eight cubane carbons.

In 1964, Tom Cole, now President of Atlanta University, was still in his first year of graduate school at the University of Chicago, the new location of the Eaton group since 1962, when he prepared a cubane for the first time (dimethyl 1,4-cubanedicarboxylate). An extremely effective [2+2] cycloaddition would form the cage, and the now famous final Favorskii reaction would

snap the cube shut (**Scheme 1**).[5] Reflecting on the cubane synthesis, Roald Hoffmann wrote:[6]

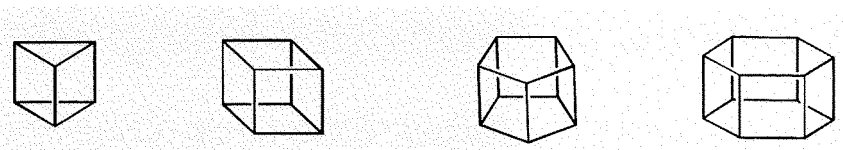
There is a high logic in synthetic strategy. The design of a multistep synthesis resembles the making of a chess problem. At the end is cubane—the mating situation. In between are moves, with rules for making them. The rules are much more interesting and free than those of chess. The synthetic chemist's problem is to design a situation on the chessboard, ten moves back, which has the most ordinary appearance. But from that position, one player (or a team of chemists), by a clever sequence of moves, reaches the mating position no matter what the recalcitrant opponent, the most formidable opponent of all, Nature, does.

Eaton and Cole had won the match.

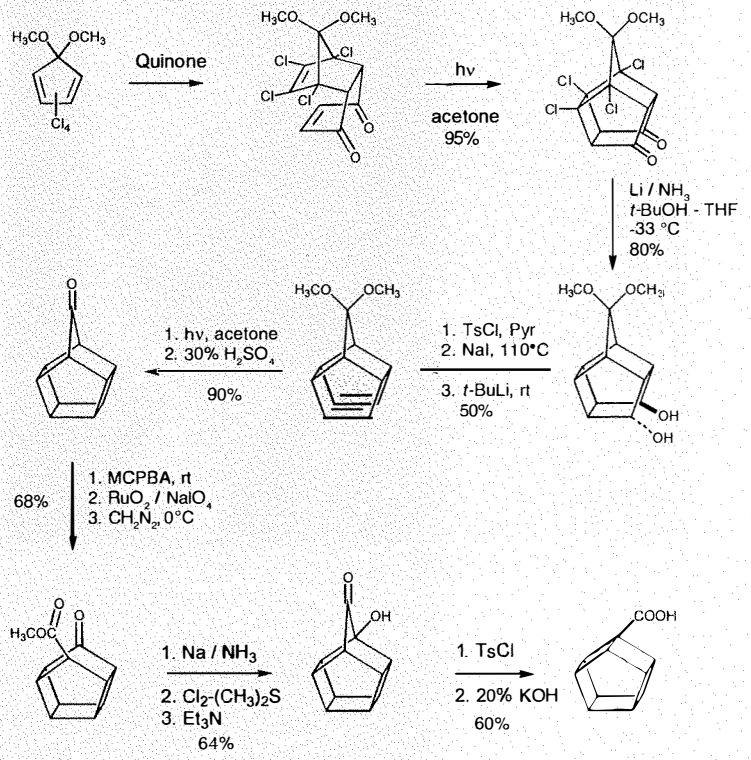
"No synthesis of a new ring system can be considered complete until the parent hydrocarbon has been prepared and characterized," Eaton later wrote.[7] Indeed, cubane itself was obtained by radical decomposition of the corresponding *tert*-butyl perester.[8] Since then, numerous subtle improvements have enabled the preparation of this cage structure in kilogram quantities; however, the basic synthetic sequence remains true to the original conception in all its essential details. Richard Hudson, a student of Eaton and colleague of Tom Cole, described the atmosphere at the time this way:[9]

I remember that Saul Winstein came to Chicago as the Kharasch Lecturer during our first winter in the Eaton lab and was treated to the first NMR spectrum of cubane as the spectrum was being observed. Professor Winstein could not imagine what the fuss was about as he observed the single peak, thinking that for some strange reason, five or six students were crowded around Professor Eaton to observe the NMR spectrum of benzene. Professor Eaton and Tom Cole were using an old A-60 at maximum amplification to determine the ^{13}C-H coupling in cubane. In those days, we simply ran the pen over the noisy spectrum many times until the noise in the spectrum averaged and we could see the peaks.

Professor Closs had been walking around with Professor Winstein to show him the department and introduce him to people. They stopped in the NMR lab and the rest of the story is related above. Professor Winstein was shocked and pleased to be looking at the first NMR spectrum of cubane, and, as I recall, demanded to know the whole story on the spot. So, Professor Closs's tour came to an end!



Scheme 2. The first four members of the prismane series.



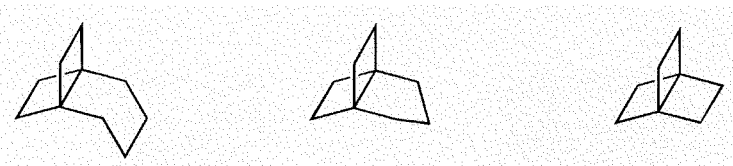
Scheme 3. Synthesis of pentaprismanecarboxylic acid.

The Homologous Series

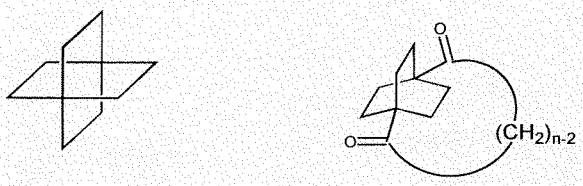
In the 1840s, the French chemist Charles F. Gerhardt systematized the notion of the homologous series: compounds that differed by a fixed number of methylene groups but were otherwise alike. This idea formed one basis for the classic systematic organization of chemical structures in *Beilstein's Handbuch der Organischen Chemie*.[10] Eaton expanded the idea structurally to include cage systems, and infused physical meaning into the concept by the incremental perturbation of carbon hybridization and bonding. After cubane had been mastered, the natural extension would be to a *series* of prismanes (**Scheme 2**).

The synthesis of pentaprismane was achieved by Or, Branca, and Eaton in 1981.[11] The strategy retains the flavor of the cubane preparation, but the route to pentaprismane requires a bit more work to span the additional cyclobutane bridge (**Scheme 3**). An α-substituted ketone required for the final Favorskii contraction step was obtained after skillful manipulation; years later, Eaton and Spitz developed a very efficient solution to this general problem (*vide infra*). Reductive decarboxylation of pentaprismanecarboxylic acid to pentaprismane itself was accomplished as in the cubane synthesis in 42% yield.

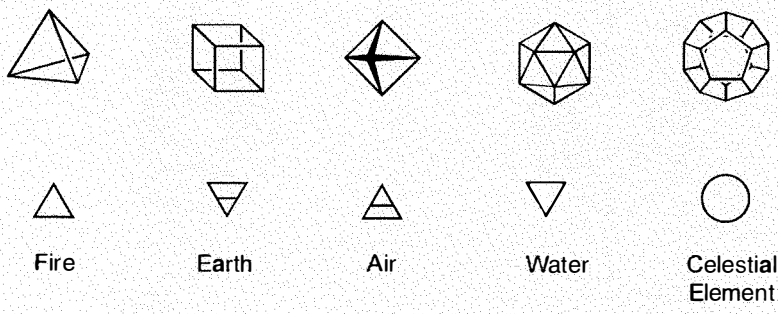
One does not always know at the outset that an Eatonesque structure is stable enough to make, nor if the architecture is even accessible by available methods of construction. These are the very reasons for selection of a particular structure. Consequently, the synthesis of such nonnatural products can be an extraordinary test of will and fortitude. Fortunately, the rationality of the homologous series tempers this challenge. Consider the propellanes (**Scheme 4**). The [4.2.2] system, prepared first, and the [3.2.2] system are stable for hours at 160 °C.[12] This can be quite encouraging for the chemist nominated to take on the [2.2.2]



Scheme 4. [4.2.2]-, [3.2.2]-, and [2.2.2]propellane systems.



Scheme 5. Tricyclo[2.2.2.2]decane and [n.2.2.2]paddlane.



Scheme 6. The Platonic Solids.

system. It is a good thing, too, for it turns out that [2.2.2]propellane dimethyl amide has a half-life of only 28 minutes at room temperature, and its existence could well be overlooked under standard conditions of preparative organic synthesis.[13]

A long-standing goal of physical organic chemistry has been understanding planar tetravalent carbon. Tricyclo[2.2.2.2]decane is a prime theoretical construct for examining this situation (**Scheme 5**). If perhaps not a realistic synthetic target (with a projected strain energy of over 300 kcal/mol!),[14] it would certainly be a superb synthetic *trajectory*, as Eaton had argued, and the philosophy of incremental change presented by the homologous series of [n.2.2.2]paddlanes was the way to go. With successively smaller and smaller rings, one could systematically observe the changes in carbon hybridization and determine the point at which these "contortionist" molecules could simply take no more strain. Incidentally, the smallest paddlane made by the Eaton group thus far is the [10.2.2.2] system, which has already shown signs of strain even with a still rather lengthy connecting chain.[15]

Platonica Chimica Acta

According to Plato's metaphysical, geometric theory of matter, the four terrestrial material principles of fire, earth, air, and water were associated with the four regular solids: the tetrahedron was associated with fire, the cube with the earth, the octahedron with air, and the icosahedron with water (**Scheme 6**).[16] It would take over two millennia for the modern atomic theory to develop, and for chemists to replicate the Platonic elemental symbols (at least the three that are possible) using the atomic elements of carbon and hydrogen. A tetrahedron was made in 1978,[17] and of course, the cube had been prepared in 1964 as described previously. But Plato spoke of yet another element, a celestial or heavenly one, which came to be represented by the dodecahedron. With the twentieth century waning, chemistry was still awaiting the synthesis of dodecahedrane.[18]

Dodecahedrane represented a towering synthetic challenge, and therefore a completely natural one for Philip Eaton to tackle. After years of steroid chemistry, the synthetic community had become better acquainted with how to manipulate five-membered rings. The Eaton group was in the thick of the battle (**Figure 1**).[19] Randall Millikan captures the spirit in an interchange between Professor Eaton and postdoctoral fellow Steve Branca, now Vice President of Chemical Manufacturing at Aldrich:[20]

Steve, working at the time on peristylane- and pentaprismane-related problems, presented a total synthesis of a natural product at our group meeting, and introduced the "Branca Scale" for evaluating a total synthesis according to three categories: Conceptual elegance, technical aplomb, and the lack of 5-membered rings—which were peculiarly absent in the target under discussion. This amused all present, but Professor Eaton was not about to let this be the last word. While Steve was describing a crucial step near the end of the synthesis, Professor Eaton inquired about the solvent. Branca replied innocently "THF", whereupon Professor Eaton took great satisfaction in replying, "There's the crucial 5-membered ring!"

In the Eaton labs, the approach to dodecahedrane would not be one of mass action of scores of students and co-workers, (after all, cubane was made by one student and pentaprismane by only a few), nor one of sheer force of will on an anemic strategy. If the synthesis of dodecahedrane were to be achieved, it would have to be through ingenuity.

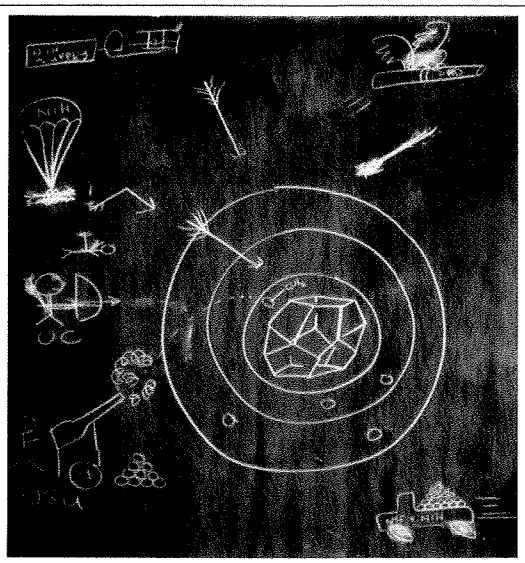


Figure 1. The assault on dodecahedrane as depicted by Eaton co-workers (ca. 1980).

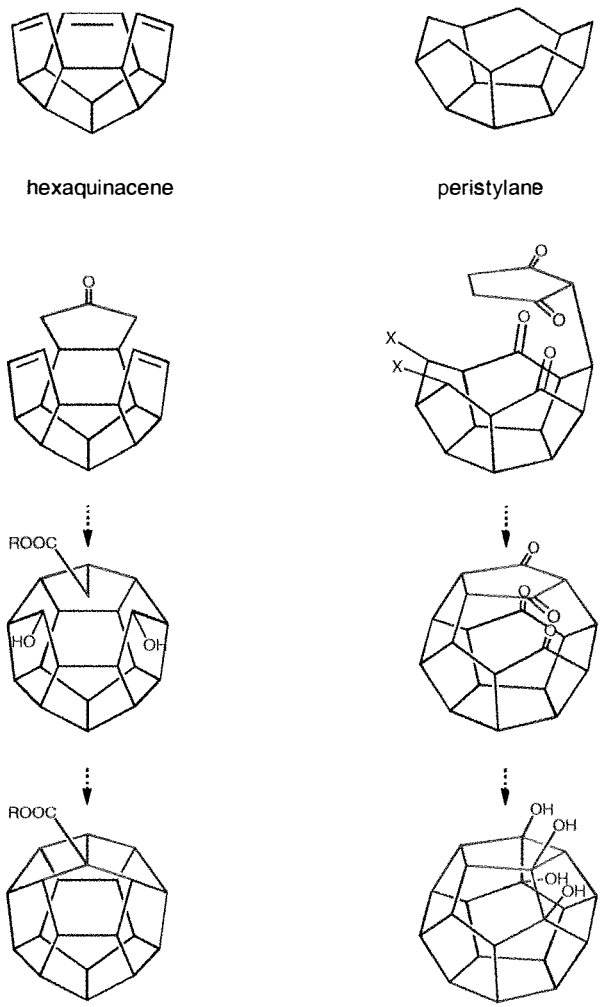
Two general strategies were pursued (**Scheme 7**). One was based on the critical intermediate hexaquinacene, and would require stitching in four additional carbon atoms to form the cage.[18,21] This route was eventually supplanted by a second approach that was based on peristylane, a colonnade-like molecule on which Eaton envisioned laying a cyclopentane roof.[18,22]

As Roald Hoffmann wrote:[23]

A chemical synthesis is obviously a building process. One therefore sees architectonic considerations and the aesthetics of architecture figuring prominently...Synthesis is a building process, but what a marvelous, "hands-off" kind of building!

True to his chemical tastes, Eaton has also maintained an abiding interest in art and architecture, whether it be in the design of new laboratories in the Searle and Kent buildings at the University of Chicago, or his home in Indiana.

Connection of the final carbon-carbon junctures between peristylane and its roof evaded synthesis, however, and so did dodecahedrane, until Leo Paquette and his group at Ohio State University secured the structure through their own landmark synthesis reported in 1983.[24] In the meantime, however, practical syntheses for both hexaquinacene and peristylane were developed, an enormous amount was taught to the chemical community concerning cyclopentannulations, and the exercise formed the training ground for a number of dedicated and inspired students and postdocs who have gone on to successful careers.

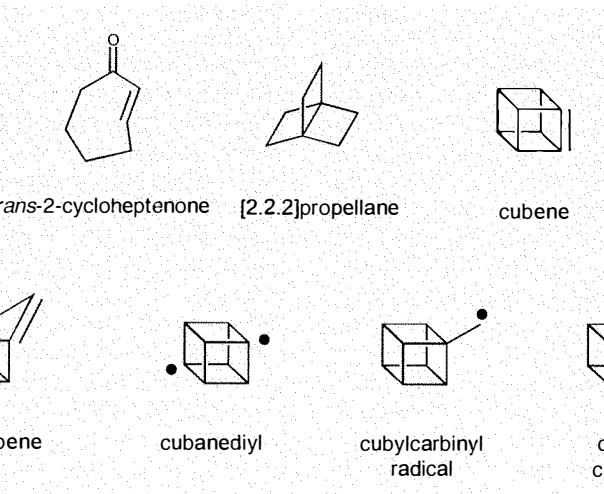


Scheme 7. The hexaquinacene- and peristylane-based strategies for dodecahedrane synthesis.

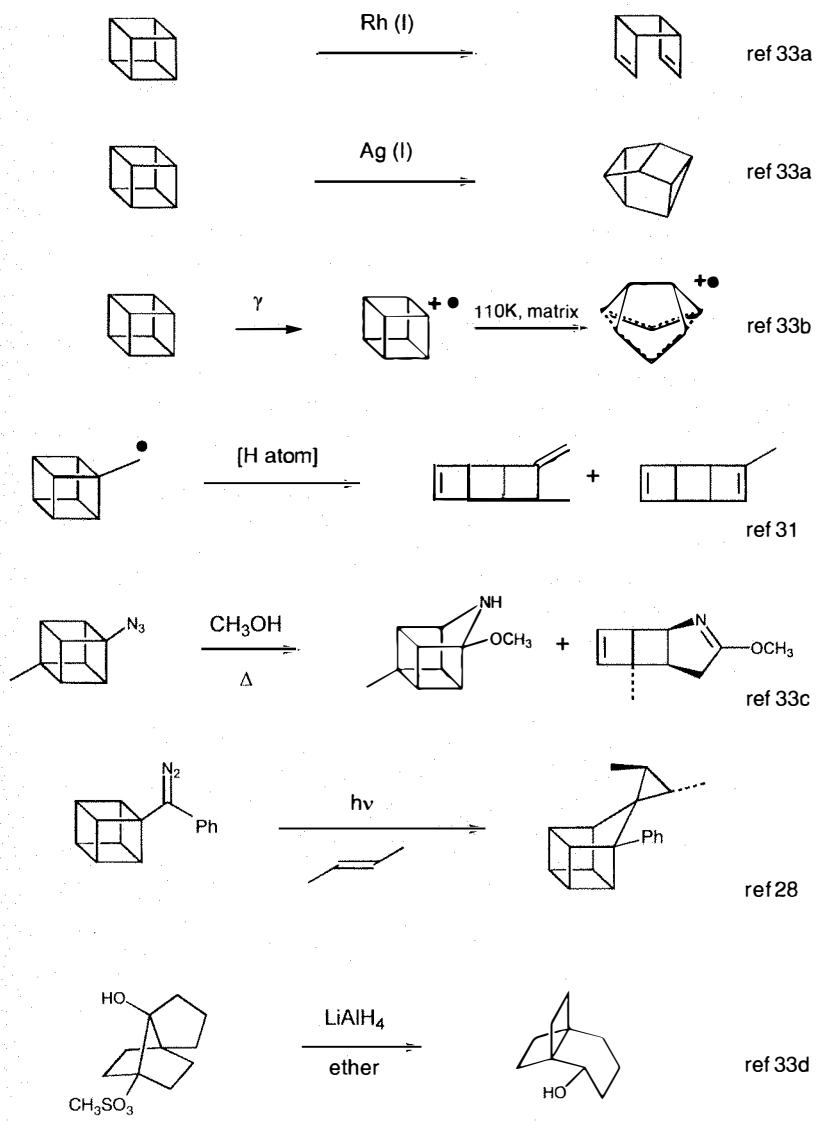
Hot Picks

There was a time when The University of Chicago football team led the Big Ten, but sports at this extraordinary institution have not always thrived. The late Robert M. Hutchins, former University of Chicago chancellor, promoted the pursuit of intellectual goals almost to the exclusion of physical rejuvenation. University of Chicago students are well-acquainted with the Hutchins dictum: "Whenever I feel the urge to exercise coming on, I lie down and rest until it passes over."[25]

Alas, sports in the chemistry department also had setbacks. When one Eaton student broke his ankle while running to catch a flyball, baseball was effectively discontinued in the group, and students reconsidered their involvement in any athletic activity involving airborne projectiles. Creative ergonomic arrangements were always found to facilitate uninterrupted laboratory activity for sports-injured chemists in our group.



Scheme 8. Reactive molecular species.



Scheme 9. Instructive molecular rearrangements.

Conditions

Starting Material ⟶ **Products** **eq 2**

Years later, across town from Hyde Park, the Chicago Cubs would play late afternoon baseball. The game times then were perfectly suited for a virtually complete day of lab work and evening work, and most suitably to our research advisor, watching baseball was a far better alternative to playing it. Perhaps to guide his students toward more cerebral forms of entertainment, the Professor would freely pass out opera tickets, which were duly appreciated.

Far from being placid, chemistry is an exciting field, and all the more so when the molecules under study barely hold together. Highly reactive molecules and fleeting intermediates have a long tradition in the Eaton laboratories (**Scheme 8**). It began with *trans*-2-cyclooctenone,[26] and *trans*-2-cycloheptenone,[27] prepared by Kang Lin, and continued with the [2.2.2]propellane system. When cubane chemistry was taken up again in the mid-1980s, the Eaton group began to use this scaffold as a tool to study intermediates of unusual geometry. Bredt's rule was challenged with the twisted double bond of homocubene,[28] and cubene[29] tested extreme double bond pyramidalization. Cubanediyl[30] addressed the issue of transcage bonding, and cubylcarbinyl radical[31] was found to be one of the fastest radical clocks known. Sometimes an intermediate turned out to be much tamer than expected (e.g., the cubyl cation).[32] Whether or not expectation coincides with experimental fact, all of these structures and their observed reactivities teach us a great deal about the nature of bonding.

Molecular Gymnastics

Anyone who has heard an Eaton lecture has appreciated its beauty and clarity of delivery, and anyone who has studied under Professor Eaton has certainly been as much impressed by the quality and intensity of his pedagogics as by his scholarship. A take-home assignment in his course on total synthesis would invariably be returned with comments that would send the student back to the library for additional research. This would be followed by yet another round of corrections from the Professor so that by the end of the course, palytoxin had been prepared—at least on paper! Strained molecules, fascinating in their own right, also tend to display unusual chemistry, and the efforts to understand their reactivity and rearrangements also served as superb pedagogical exercises not only for his own students, but also for several generations of students of organic chemistry in general. **Scheme 9** offers but a glimpse of the remarkable rearrangement chemistry of Eaton molecules.[28,31,33]

Experimental Measurements

Of course, given inputs for all the variables of the classical synthetic formulation (**eq 2**), it is always possible to rationalize why the reaction in question happens to take the course that it does. Explanations which are comprehensive or quantitative, however, are held in especially high regard. But when one is in the midst of assigning structures to the products of reactions like those of **Scheme 9**, the intellectual exercise of mechanistic chemistry becomes absolutely grueling. Lengthy sessions in which professor and student would sit thoughtfully, silently staring at a freshly acquired NMR or mass spectrum are legendary. Disbelief abounds. This is an extremely important, but less appreciated, hallmark of nonnatural product synthesis.

As a teacher, Eaton impressed upon his students the absolute need for experimental verification. Work from his own laboratory and from his collaborations with illustrious physical, analytical, and theoretical chemists resulted in answers to many of the mechanistic and other physical chemistry questions raised by these molecules. Throughout his career, Eaton has enjoyed travel, which in turn has fostered numerous collaborations, many of them international. The few article titles shown below illustrate this point:[34]

Photodimerization of Cyclopentenone. Singlet or Triplet?
P. Eaton, W. Hurt

The Electronic Structure of Pentaprismane as Revealed by its Photoelectron Spectrum
E. Honegger, P. Eaton, B.K.R. Shankar, E. Heilbronner

The Geometries of Pentaprismane and Hexaprismane. Insights From Molecular Mechanics
N. Allinger, P. Eaton

Bond Lengths and Quadratic Force Field for Cubane
L. Hedberg, K. Hedberg, P. Eaton, N. Nodari, A. Robiette

Kinetic Acidity of Cubane
R. Dixon, A. Streitweiser, P. Williams, P. Eaton

On the Nature of Cubyl Cation
P. Eaton, J.P. Zhou

Long-Distance Electron Transfer Through Rodlike Molecules with Cubyl Spacers
B. Paulson, K. Pramond, P. Eaton, G. Closs, J. Miller

Formation of the Radical Anion of Cubene and Determination of the Heat of Formation, Heat of Hydrogenation, and Olefin Strain Energy of Cubene
P. Staneke, S. Ingemenn, P. Eaton, N. Nibbering, S.Kass

Eaton's molecules have spawned quite a number of independent investigations by other chemists as well.

Esotericism and Pragmatism

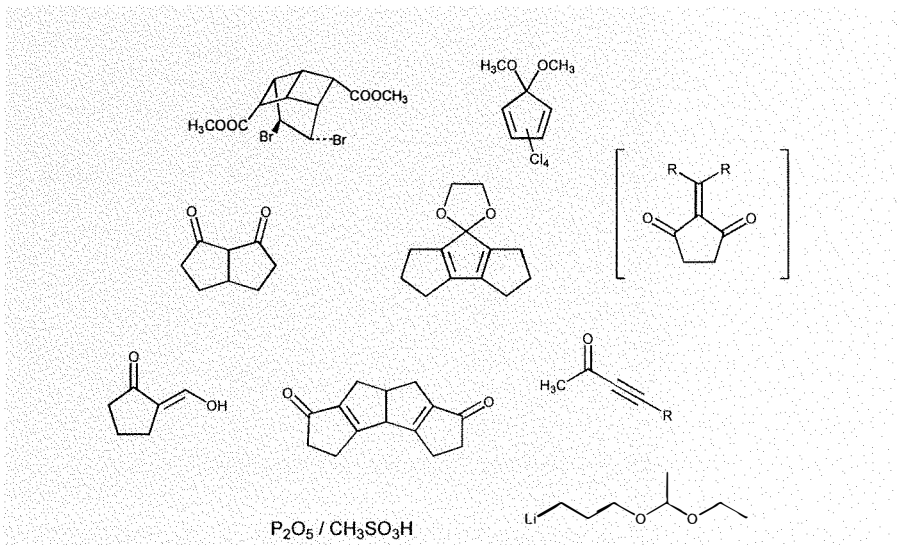
"The synthesis of substances occurring in Nature, perhaps in greater measure than activities in any other area of organic chemistry, provides a measure of the condition and power of the science...It can scarcely be gainsaid that the successful outcome of a synthesis of more than thirty stages provides a test of unparalleled rigor of the predictive capacity of the science, and of the degree of its understanding of its portion of the environment."[35]

If these oft-quoted words of R.B. Woodward are sufficient justification for natural products synthesis, then they certainly apply *a fortiori* to the synthesis of nonnatural products, not only because they test the "predictive capacity of the science", but also because they invigorate the science and have practical applications.

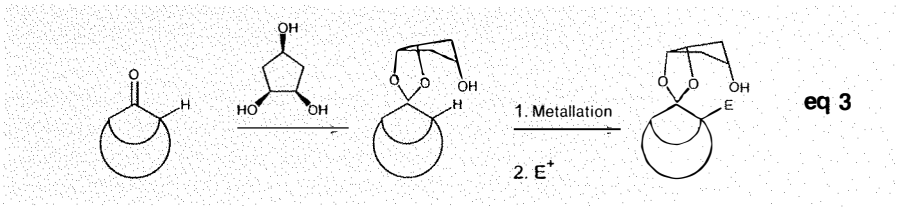
Whether making natural products in an academic environment or performing polymer synthesis in an industrial lab, one may turn to numerous practical synthetic procedures and intermediates that have originated in the Eaton labs (**Scheme 10**). The utility of cyclopentadienone ketals[4,36] is well-known to a large degree as a result of cubane and pentaprismane; quite a few cyclopentanoids, previously hard to come by, now have practical syntheses as a result of the dodecahedrane effort at Chicago.[22,37] Functionalized nortwistbrendanes are extremely interesting intermediates.[38] Acetylenic ketones were developed by the Eaton group in its early years,[39] as was a useful alkyllithium for hydroxypropylation.[40] Jobe and Eaton's preparation of 2-hydroxymethylene cyclopentanone was a vast improvement over previous methods,[41] and "Eaton's reagent", a mixture of methanesulfonic acid and phosphorous pentoxide, is a terrific alternative to polyphosphoric acid.[42]

Spitz and Eaton developed *cis,cis*-1,3,5-trihydroxycyclopentane as an elegant auxiliary for bridgehead functionalization of non-enolizable ketones (**eq 3**).[43] Wicks and Eaton developed dimethyldioxirane as a reagent for the direct conversion of isocyanates to nitro compounds (**eq 4**).[44]

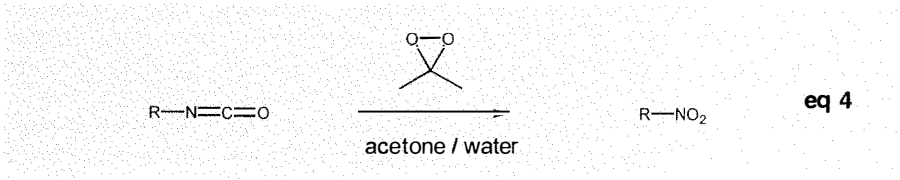
Since the mid-1980s, Eaton chemists have developed an enormous body of information on the functionalization of cubane,[45] which has led to indispensable strategies



Scheme 10. Useful synthetic intermediates.



eq 3

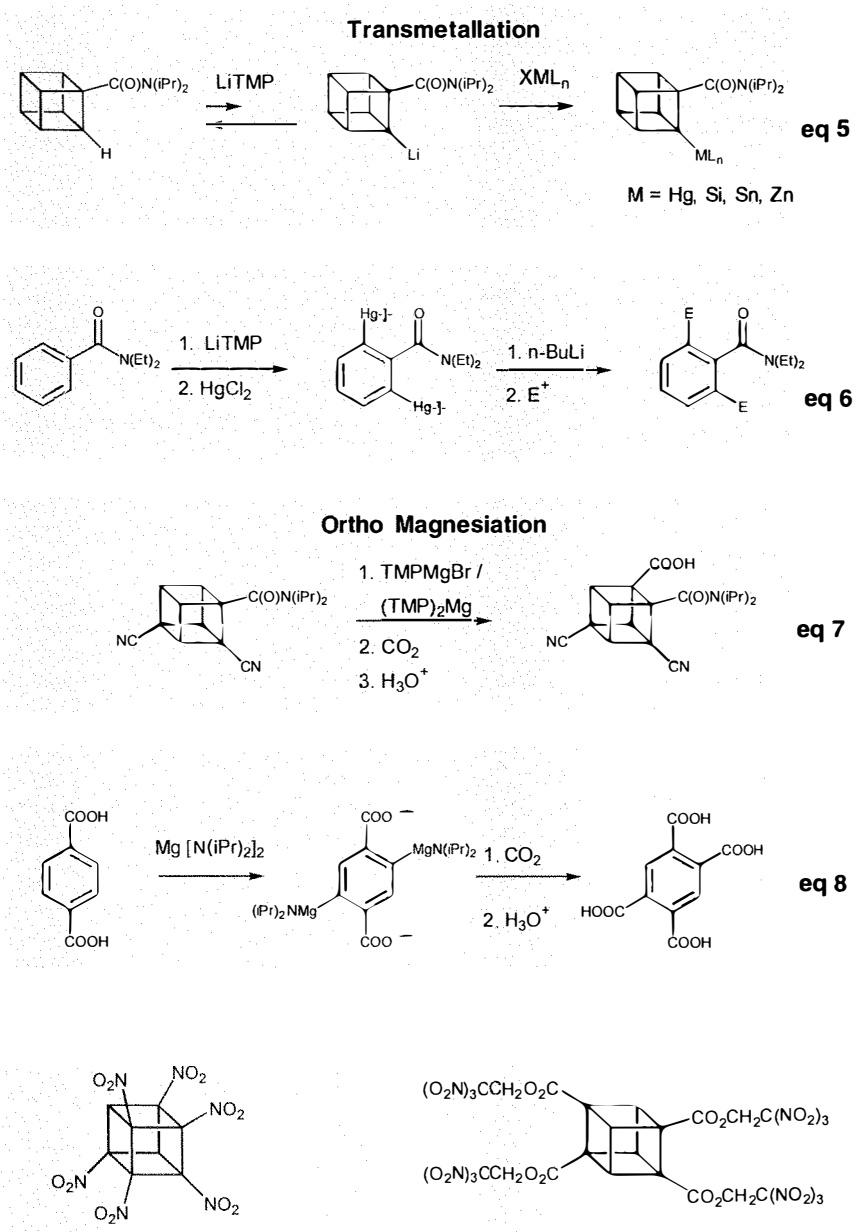


eq 4

for substitutions in arenes and cyclopropanes. One may speak fundamentally of two related methods, even though there are variations and valuable adjunctive methodologies too numerous to describe here; a third method is described in the accompanying article. The first two strategies involve organometallic deprotonations. The first, a metallation/transmetallation, relies on alkyllithium ortho deprotonation of an amide-bearing cubane, followed by trapping of the small equilibrium quantity of deprotonated species with a mercury halide, or alternatively with an organotin, organosilicon, or zinc halide (**eq 5**).[46] The resultant organomercury compound may itself be recursively mercuriated at additional sites, substituted with a halide, or exchanged again for lithium and subsequently with any of a wide range of electrophiles. Applied to benzamides, this methodology permits efficient simultaneous ortho, ortho' substitution (**eq 6**).[47]

The second strategy, ortho magnesiation, also relies on ortho deprotonation but this time by R_2NMgBr (a Hauser Base) or $(R_2N)_2Mg$, long-known reagents revived to an even longer life of utility (**eq 7**). Applied to arenes, this procedure permits the use of an unprotected carboxyl group or even an ester group as the activating functionality (**eq 8**).[48] This is extremely useful in light of the hydrolytic stability of the amides traditionally used in ortho lithiation. As a result of these and other developments, cubanes can be prepared essentially at will with virtually any substitution desired—a remarkable collective achievement of Eaton'sstudents, postdocs, and collaborators.

Why cubanes? Eaton himself, as well as others, have argued convincingly for their application in medicinal chemistry and materials science.[45] The case for medicinal chemistry is based on the rigid and unique presentation of a pharmacophore in three-dimensional space, as well as the potential for generation of highly reactive species in vivo. Indeed, cubylmethylamine has been utilized to help sort out the mechanism of monoamine oxidase inhibition.[49] The argument for application in materials science also lies in the rigidity and strain energy of cubanes. Applications in optics certainly come to mind. Cubanes are high-energy materials, and polynitrated cubanes are some of the highest energy materials known, with uses as propellants or explosives. Thanks to the Eaton group and to other groups (accompanying article) molecules of this class *are* being made available (**Scheme 11**).[50] It remains for the chemical community to determine how to use them productively.



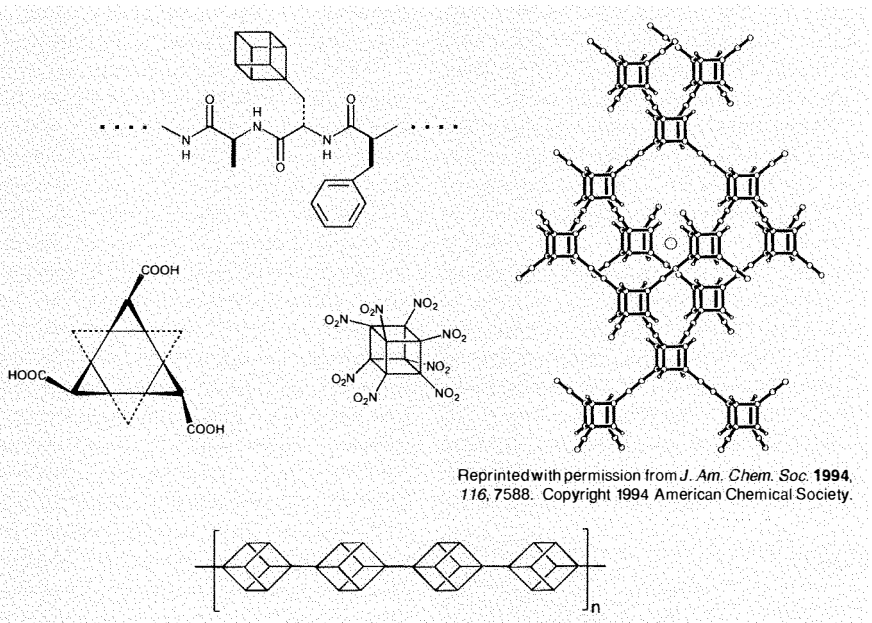
Scheme 11. High-energy cubanes.

Supranatural Products

The road less traveled is all the more toilsome when it is a nonnatural one, and all the more impressive when one such as Eaton has traversed it. Still, there lies ahead an expansive vista (**Scheme 12**),[45,51] as Berthelot envisioned more than a century ago with astounding clarity:[52]

Thus, synthesis extends its conquests from the elements up to the domain of the most complicated substances without our being able to assign any limit to its progress. Indeed, if we envision in our minds the almost infinite number of organic compounds, from the substances which our art knows how to produce, such as [hydrocarbons], alcohols, and their derivatives, up to those which still exist only in nature, such as the sugars and the nitrogenous principles of animal origin, we pass from one term to the other by insensible degrees, and we cannot see any absolute barrier or break that we may with any appearance of certitude fear to find unsurpassable.

If patterns of bonding and reactivity permit an indefinite, if perhaps not infinite, number of molecular possibilities, we find ourselves thoroughly humbled indeed. Yet it is still the goal of organic synthesis to widen this envelope, and we are fortunate to have scholars like Phil Eaton with the courage and persistence to try this in the most unusual ways—and succeed. Happy Birthday, Phil. We sincerely wish you many more to come.



Scheme 12. Just a few supranatural products in various stages of realization.

Acknowledgement

I wish to express my gratitude to Steve Branca, A. Bashir-Hashemi, Glenn Carlson, Ravi Sidhu, Esteban Bornancini, and Elena Galoppini for editorial assistance, William Wulff and William Bunnelle have graciously provided archival information. I am indebted to James Altena for help with historical research.

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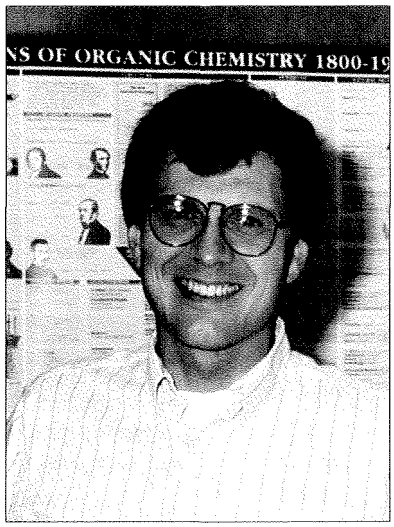

About the Author

Robert E. Hormann obtained a B.S. degree in biochemistry at Dartmouth College. After joining the Eaton group, he devised a preparation for azidocubanes, and examined the photo- and thermal rearrangements of methylcubyl azide in solution and under low-temperature matrix isolation conditions, completing his Ph.D. dissertation in 1987. He then moved to the laboratories of Duillio Arigoni at the E.T.H. in Zürich, Switzerland, and, with Professor Arigoni, developed the first method for assigning the stereochemical configurations of *tert*-butyl groups with isotopically-engendered chirality. Presently, Dr. Hormann is on the staff in the Exploratory Agrochemicals Department, Rohm & Haas Company, where he is engaged in the discovery and design of novel and safe agents for crop protection. He resides in the Delaware Valley with his wife Susana, and three daughters, Noemi, Rebecca, and Ruth.

Oxalyl Chloride in Photochemical Chlorocarbonylation of Cage Compounds

Dedicated to Professor Philip E. Eaton on the occasion of his 60th birthday

A. Bashir-Hashemi, Gerald Doyle*
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Introduction

The elegant synthesis of cubane by Eaton and Cole in 1964 opened up a new era in the exploration of nonnatural "platonic" compounds.[1] This compound, previously thought impossible to synthesize, possesses a unique structure and a very high strain energy derived from its unusual bond angles and lengths.[1,2]

Despite intensive interest in cubanes in academic research, industrial applications have not progressed significantly, mainly due to the short supply of cubane compounds. The real challenge, to functionalize the cubane skeleton, was surmounted in the last decade. Eaton and Castaldi used a brilliant approach, a reverse transmetallation, to replace the acidic hydrogens of cubane with functional groups ortho to the amido groups.[3] This approach was modified by us at ARDEC, employing cubyl Grignard intermediates to give a wide variety of substituted cubanes in much simpler and larger scale processes.[4]

In this review, we present a photochemical approach for the synthesis of a variety of polysubstituted cubanes. The synthetic potential of photochemical chlorocarbonylation and its extension to adamantanes and other compounds are also discussed.[5]

By classical methods and employing ortho-directed metallation, the synthesis of 1,3,5,7-cubanetetracarboxylic acid (**1**) requires more than twenty synthetic steps starting from commercially available 1,4-dicarbomethoxycubane.[6] Similarly, synthesis of 1,3,5,7-adamantanetetracarboxylic acid (**2**) from Meerwein's ester requires several lengthy synthetic steps and time-consuming processes.[7]

These tetrasubstituted cage hydrocarbons with tetrahedral symmetry are potential precursors for "energetic materials", dendrimers, star-shaped macromolecules, and molecules of interest in combinatorial chemistry.[2] They can now be prepared in one step by the photochemical reactions of oxalyl chloride and readily available starting materials (**Figure 1**).

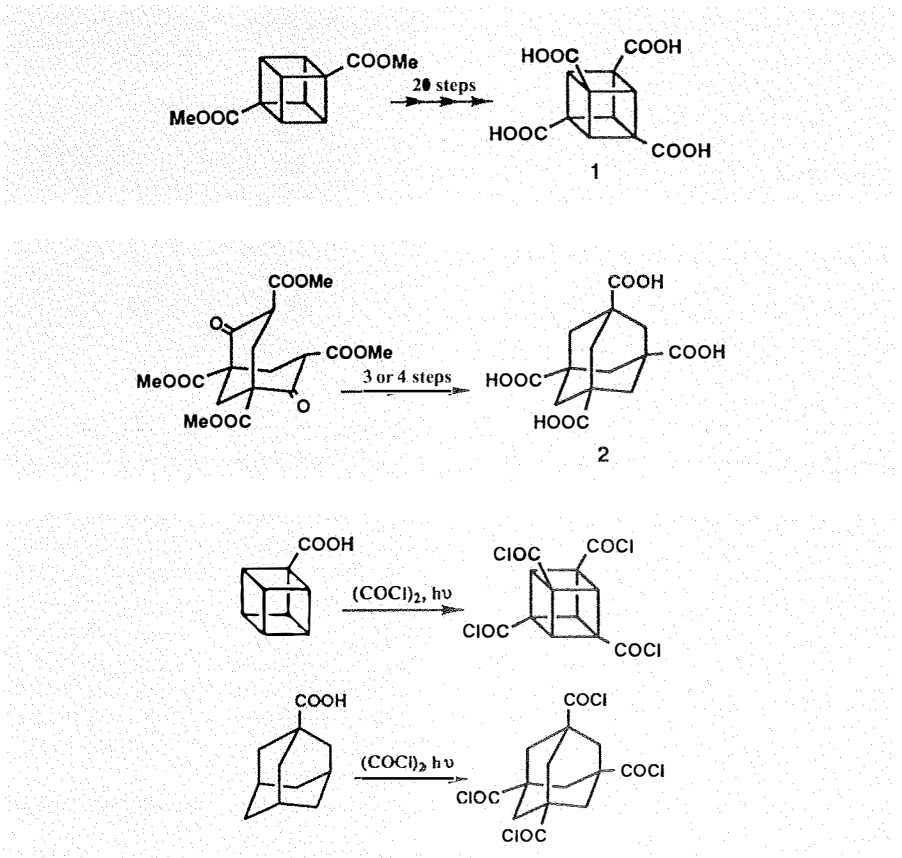
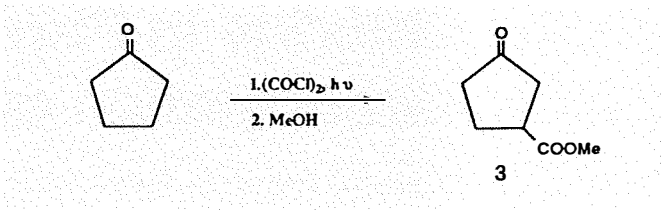


Figure 1

Mechanistic Aspects of Chlorocarbonylation

Investigations of the chlorocarbonylations of cyclopentanone, cyclobutanone, 3-pentanone and 3-methylbutanoic acid led to a more complete understanding of the nature of these processes.[8] Chlorocarbonylations of these reactants can give a number of easily identified isomeric substitution products. For example, α-chlorocarbonylation of cyclopentanone would yield, after methanolysis, methyl 2-oxocyclopentanecarboxylate; β-substitution would afford methyl 3-oxocyclopentanecarboxylate[9a] (**3**). Keto ester **3**, an important intermediate for the synthesis of agrochemicals, is difficult to prepare by current methods.[9b] Similarly, the synthesis of the pharmaceutically important intermediate, methyl 3-oxocyclobutanecarboxylate (**4**), is a multistep process using conventional methods.[10]



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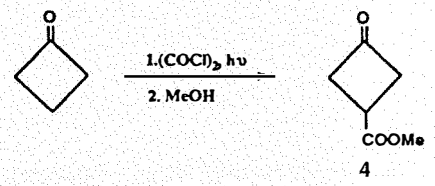

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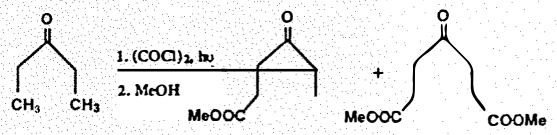
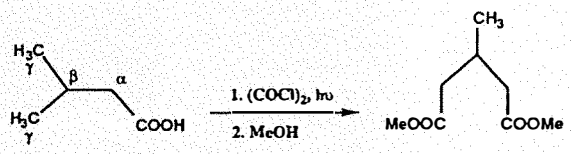


5 **6**

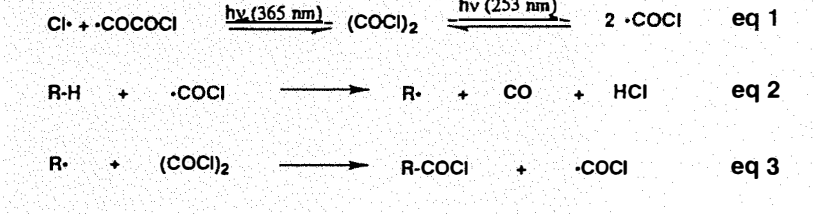


7

Irradiation of cyclopentanone in oxalyl chloride for 24 hours, followed by esterification with methanol, gave **3** only—no evidence for the formation of the α-substituted product was observed. This suggests that the resonance stability of the α-radical does not play a decisive role in the regioselectivity of this chlorocarbonylation. As is the case with most photochemical reactions, the yield of **3** was highly dependent on reaction temperature, concentration, and wavelength of the light used. The best yield (60%) was obtained when the reaction was run at 0-5°C and a concentration of 0.1-0.2*M* in a quartz flask placed in a Rayonet photochemical reactor (each lamp 2.2W, 2537Å).[5c]

Similarly, photolysis of cyclobutanone in oxalyl chloride followed by esterification produced **4** as the major product. In this case, with only two β hydrogens present, chlorocarbonylation was much slower than when cyclopentanone was used; after 24 hours of irradiation only 50% of cyclobutanone had been consumed. The slower reaction rate and lower yield (10-20%) may be attributed to the increased C-H bond strength in the smaller four-membered ring ketone, and the proximity of the β-position to the carbonyl group.[11]

Chlorocarbonylation was extended to two acyclic compounds, 3-pentanone, and 3-methylbutanoic acid. These compounds were chosen based on the anticipated differences of the C-H bond reactivities and the ease of characterization of the reaction products by NMR spectroscopy. Photochemical chlorocarbonylation of 3-pentanone with oxalyl chloride proceeded slowly at room temperature, and after 24 hours of irradiation followed by methanolysis the mono- and dicarbonylated products, methyl 4-oxohexanoate (**5**) and dimethyl 4-oxopimelate (**6**), were obtained in an 8:1 ratio.[5c]



When a mixture of 3-methylbutanoic acid and oxalyl chloride was irradiated at room temperature for 24 hours, substitution occurred preferentially at the γ-position resulting in the formation of dimethyl 3-methylglutarate (**7**) after methanolysis.[5c] Clearly, attack took place at the least hindered γ- rather than β-position, which would have been expected to give rise to a more stabilized tertiary radical. Moreover, statistical factors (six γ-hydrogens *versus* one β-hydrogen) also favor substitution in the γ-position.

In free-radical substitution reactions with oxalyl chloride and derivatives, it is commonly accepted that the overall process is initiated by the dissociation steps shown in equation 1.[8] Subsequent steps likely involve abstraction of a hydrogen atom from the substrate molecule by either a chlorocarbonyl radical (eq 2) or a chlorine atom, followed by the chain propagation step depicted in equation 3.

Our data suggest that either the electrophilic chlorocarbonyl (ClCO•) or chlorine (Cl•) radical, perhaps as a complex with oxalyl chloride, preferentially abstracts a hydrogen from the least electron-deficient carbon atom distant from the carbonyl group. In the case of 3-methylbutanoic acid, despite the familiar decrease in C-H bond strength from primary to secondary to tertiary, the substitution occurs at the methyl group. This preference, which may also be reinforced by steric effects as well as statistical factors, infers a kinetically-controlled process for these reactions.

The preceding studies illustrate the remarkable regioselectivities of photochemical chlorocarbonylations of certain carbonyl compounds. The methodology can be used to introduce a chlorocarbonyl group at a remote site (β or γ) and makes possible the efficient synthesis of compounds that are otherwise difficult to prepare.

Chlorocarbonylation of Cubanes

Cubane and its derivatives belong to a class of strained cage compounds which have been at the forefront in the search for new

high-energy materials over the past decade.[2,12] The cubane structure, in which functional groups would possess unique spatial arrangements in a rigid framework, should have applications in pharmaceutical and polymer chemistry. Other potential applications of current interest are in the areas of dendrimer and combinatorial chemistry. Anionic reactions as well as radical and cationic reactions have been used in the synthesis of substituted cubanes, although the cubyl radical[13] and cubyl cation[14] have unfavorable, nonplanar geometries. The multifunctionalization of the cubane skeleton, however, remains a challenging task for organic chemists.

By virtue of the cubane geometry and its exceptionally high strain energy (165 Kcal/mol), the carbon-hydrogen bonds in cubane contain a high s-character. Ortho-Directed metallation of amidocubanes has until now been the dominant approach to the synthesis of the polycarboxycubanes.[15] However, the lengthy reaction sequences required have limited the usefulness of this approach.

Other electron-withdrawing groups, notably carboxyl groups, can also have a profound effect on the regioselectivity of photochemical chlorocarbonylations.[16] This observation was provisionally interpreted in terms of an electron-withdrawing field effect of the carboxyl group resulting in retarded cleavage of the α C-H bonds, and thus leading to predominant chlorocarbonylation at the β-positions (**Figure 2**).

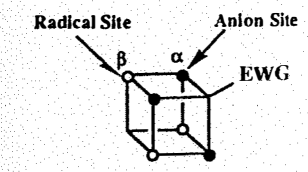
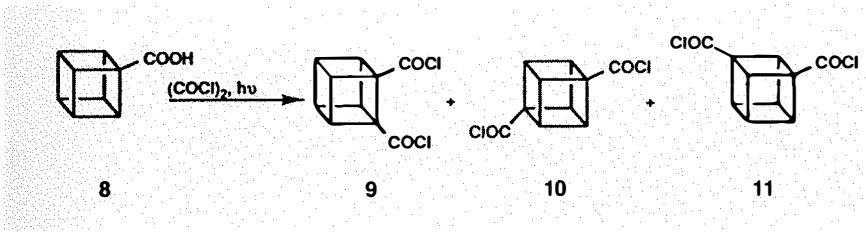


Figure 2



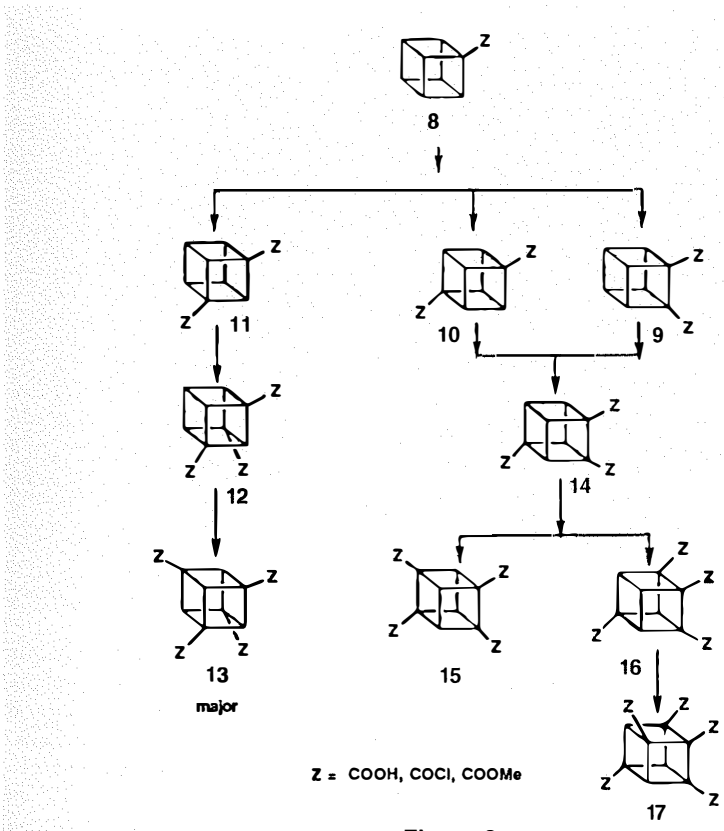


Figure 3

Cubanecarboxylic acids have now been synthesized by photochemical chlorocarbonylation.[17] Mixtures of polysubstituted cubanes can be obtained easily in a single operation from carboxycubane. In this methodology an electron-withdrawing group (or polar group) is used to direct substitutions predominantly to positions other than the ortho position. For example, a solution of carboxycubane **8** and oxalyl chloride was irradiated in a Rayonet photochemical reactor at 35-40 °C and the progress of the reaction was monitored by ^{1}H NMR. The starting material was completely consumed in 30 minutes and 1,2-, 1,4- and 1,3-disubstituted cubanes **9**, **10**, and **11** were formed in approximately a 1:1:3 ratio.[5b] This ratio is explained by statistical factors (three ortho, three meta, and one para position) and polar effects.[18] The electrophilic chlorocarbonyl or chlorine radicals preferentially abstract a hydrogen from the least electron-deficient carbon atom. Steric influences on the substitution pattern are minimal since the cubane skeleton contains long C-C bonds (1.57 Å) and wide external C-C-H angles (126°).[1]

The conversion of disubstituted cubanes to tri- and higher substituted cubanes followed a similar course (**Figure 3**). After an irradiation period of 8 hours, the ^{1}H NMR spectrum of the reaction product was consistent with the presence of tetrasubstituted cubanes **13**, **15**, and **16** in an approximate 55:10:35 ratio, respectively. Compound **13**, in which chlorocarbonylation occurred at the alternate 1, 3, 5, and 7 positions, was the major product and was separated from other isomers in 40-50% yield by triturating the reaction mixture with ether.[5b]

The rates of substitution decrease as the reaction progresses. After 18 hours of irradiation, pentasubstituted cubane **17** was obtained with only trace amounts of hexa- and heptasubstituted cubanes (GC-MS). Assignment of the structure of the C_3V symmetrical **17** (R = COOMe) was based on the simplicity of its proton NMR spectrum, which showed a single resonance at 4.64 ppm for the cubane protons.[5b] The origin of **17** must be the tetrasubstituted cubane **16**. Compound **16** is the only one of the three tetrasubstituted compounds in which substitutions occur ortho to only one carbonyl group. In compounds **13** and **15** the unsubstituted carbons are ortho to three and two carbonyl groups, respectively.

Compounds **15** and **17** were obtained in much better yields (36% and 45% respectively) from the photochemical reaction of commercially available 1,4-dicarbomethoxycubane and oxalyl chloride, followed by esterification with methanol (**Figure 4**).[5b]

Interestingly, the photochemical reactions of compounds **13** or **15** with oxalyl chloride at higher temperatures and for longer reaction times gave only chlorinated products. When a solution of **13** or **15** in oxalyl chloride was irradiated for two days at 60 °C, chlorocubanes **18** and **19** were obtained in 28% and 35% yields, respectively.[5b]

The chlorination might be due to an increased concentration of the chlorine radical formed from cleavage of •CO-Cl under the reaction conditions (eq 1). The amounts of chlorinated products also increase under Pyrex®/sunlamp and reflux conditions. The increase may be attributed to the predominant carbonyl-chlorine bond cleavage of oxalyl chloride at longer wavelengths (365 nm) and higher temperatures.

An important application of the chlorocarbonylation methodology is the functionalization of nitrocubanes. Considerable effort in recent years has been directed toward the synthesis of polyfunctionalized nitrocubanes because of their potential uses as explosives, propellants, fuels, and binders.[12] Irradiation of 1,4-dinitrocubane (**20**) with oxalyl chloride (Rayonet, 0-5 °C, quartz) produced, after esterification with methanol, 2-carbomethoxy-1,4-dinitrocubane (**21**) and 2-chloro-1,4-dinitrocubane (**22**) in 84% and 16% yields, respectively.[5b, 25]

Increasing the polarity of the directing groups increases the regioselectivity of the substitution (**Figure 5**). For example, chlorocarbonylation of nitrocubane gave predominantly 1-nitro-3,5,7-tris(chlorocarbonyl)cubane with very minor amounts of other tetrasubstituted isomers (^{1}H NMR). However, attempts at photochemical chlorocarbonylation of 1,3,5,7-tetranitrocubane under various reaction conditions failed. The lack of reactivity of the tetranitrocubane toward photochemical substitution could be due to a combination of increased C-H bond strength relative to the monosubstituted cubanes and a large polar effect arising from three nitro groups that surround each C-H bond.

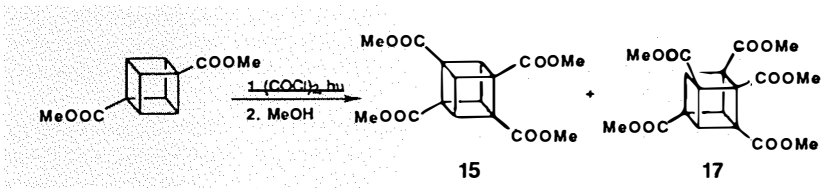
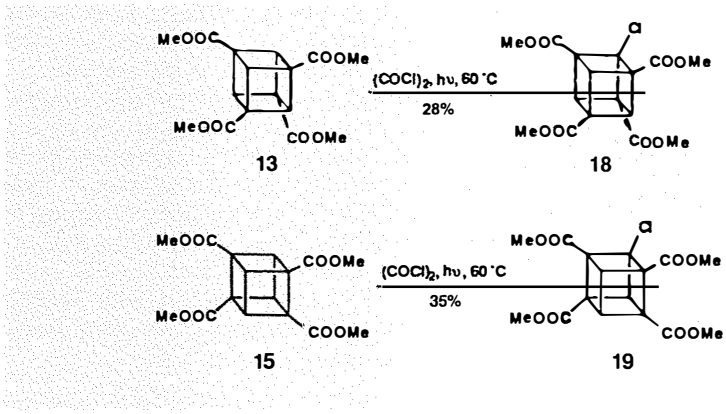
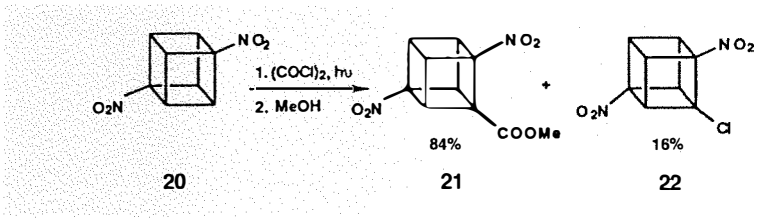


Figure 4





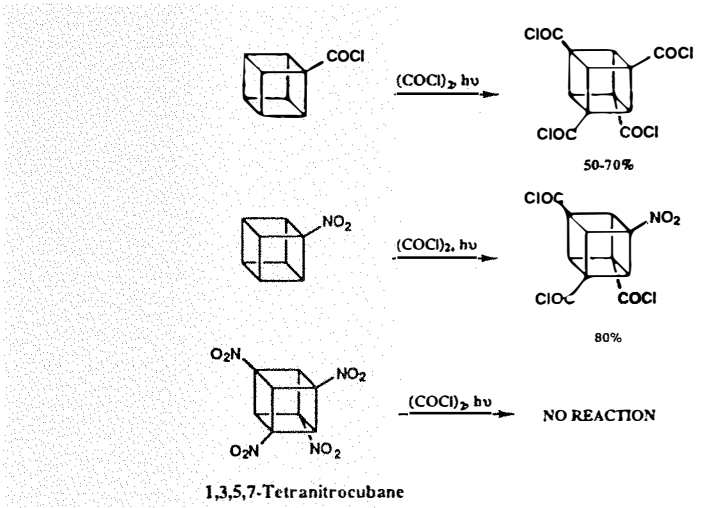


Figure 5

Chlorocarbonylation of Adamantanes

There has been renewed interest in the chemistry of adamantanes since some of their derivatives, particularly nitroadamantanes, have promise as high-density energetic materials.[19] Recent interest in adamantanes also extends into the areas of host-guest compounds,[20a] combinatorial chemistry, optically active organic molecules,[20b] and dendritic macromolecules.[21]

Several approaches have been applied to the synthesis of 1,3,5,7-adamantanetetracarboxylic acid.[22] The most recent method requires multiple synthetic steps involving high-pressure and high-temperature bomb reactions, and, therefore, is greatly limited for scaled-up production.[7] The direct functionalization of adamantanes is most often achieved by ionic substitution which gives predominantly bridgehead products, whereas free-radical processes generally yield both bridgehead and bridge products. Positional selectivity (relative reactivity of bridgehead H/bridge H) for chlorocarbonylation is 3.7/1 for adamantane.[23]

The photochemical reaction of adamantane with oxalyl chloride followed by methanolysis produced only a small

amount (<5%) of 1,3,5,7-tetracarbomethoxyadamantane (**24**) along with many other products.[5d, 24] Given this less-than-satisfactory precedent, we reasoned that the prepositioning of a carbonyl function at a bridgehead increases the possibility of chlorocarbonylation at other bridgehead positions, since hydrogens ortho to a chlorocarbonyl group are less susceptible to radical abstraction.

Irradiation of a solution of commercially available 1-adamantanecarboxylic acid (**23**) and oxalyl chloride in a Rayonet photochemical reactor for 1 hour, followed by esterification of the reaction product with methanol gave 1,3,5,7-tetracarbomethoxyadamantane (**24**) as a colorless solid in 20-30% yield along with other carbomethoxyadamantane isomers.[5d] This is considerably more practical than the best stepwise preparation of **24**.[7]

When commercially available 1,3-adamantanedicarboxylic acid (**25**) was similarly reacted with oxalyl chloride, followed by treatment of the reaction product with methanol, the yield of 1,3,5,7-tetracarbomethoxyadamantane (**24**) increased to 40%.[5d] Multi-gram quantities of compound **24** can be isolated by triturating the reaction mixture with methanol.

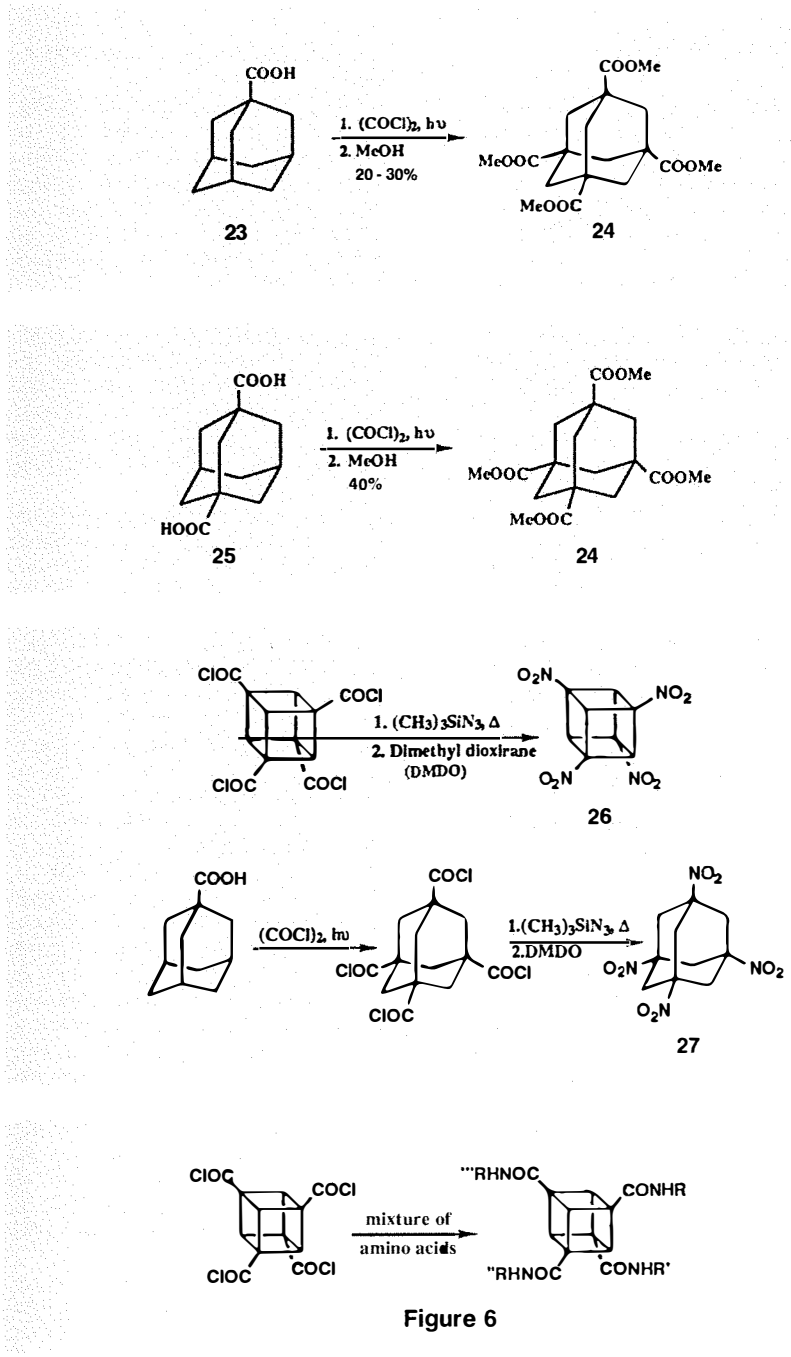


Figure 6

Applications

Perhaps the most important application of the chlorocarbonylation process is the simple synthesis of strongly energetic materials such as tetranitrocubane (**26**) and tetranitroadamantane (**27**). Preliminary experiments suggest that the tetranitro derivatives are actually less sensitive but more powerful than predicted. Energetic materials of this type have applications in volume-limited devices such as warheads and rocket engines.

The most recent conventional synthesis of 1,3,5,7-tetranitroadamantane requires many synthetic steps, and the material has been very difficult to prepare in large amounts.[19] The syntheses of 1,3,5,7-tetranitrocubane and 1,3,5,7-tetranitroadamantane were simplified by employing the photochemical chlorocarbonylation methodology. For example, adamantanetetraacyl chloride, obtained directly from irradiation of 1-adamantanecarboxylic acid and oxalyl chloride, was converted easily to the corresponding tetranitroadamantane via adamantanetetraisocyanate.[25]

In one approach, chlorocarbonyl groups were directly placed on the cage and the excess oxalyl chloride was recycled and reused without further purification. Gram quantities of tetranitrocubane and tetranitroadamantane are now produced in simple, safe, and environmentally friendly processes.[12b] Very recently, Eaton and co-workers have synthesized penta- and hexanitrocubanes from now readily accessible tetranitrocubane.[26]

Despite intensive interest in cubanes and adamantanes as energetic materials, other applications of these fascinating molecules still await exploration. Cubane 1,3,5,7-tetraacyl chloride has been targeted for combinatorial chemistry studies in bioorganic chemistry.[27] A cubane with four chlorocarbonyl groups, for example, can react with a mixture of twenty natural amino acids to generate thousands of molecules (**Figure 6**). This mixture offers a suitable environment for reaction with the AIDS virus or cancer cells to facilitate discovery of new drugs to treat these diseases. Some cubane derivatives have already shown moderate anti-AIDS and anti-cancer activities without affecting healthy cells.[2]

Carbonyl chlorides of adamantane, like their cubane analogues, can also be candidates for combinational chemistry studies. A number of functionalized cage compounds, notably adamantyl amides, amines, and sugars have shown antiviral and antitumor activities.[28] The value of the cage substituent seems to lie in its ability to increase the

lipophilicity of the rest of the molecule, which facilitates transport across membranes.

Another area of much recent interest is the synthesis of star polymers.[29] Generally speaking, star polymers have higher thermal stabilities, Tg's, and solubilities than linear polymers. The bulkiness of adamantane tends to inhibit packing of chains which ultimately decreases crystallinity and increases solubility. Tetrasubstituted cubanes and adamantanes with tetrahedral symmetry are also ideal cores for the preparation of hydrocarbon-based dendrimers. The combination of these core molecules with proper building blocks may create new macromolecules which show promise as surfactants, coatings, and bioactive molecules.[21]

In recent work,[29] functional moieties such as (−)-cholesterol, Disperse Red 1 (DR1), and nematogens were attached to 1,3-adamantanedicarboxylic acid and 1,3,5,7-adamantanetetracarboxylic acid cores in order to evaluate the glass-forming abilities of the resultant amorphous and mesogenic molecular systems. Although both di- and tetrasubstitution on adamantane with (−)-cholesterol and DR1 were found to contribute to glass formation, tetrasubstitution resulted in systems with superior morphological stabilities; namely, elevation in Tg's and absence of recrystallization upon heating of the corresponding quenched glasses.

Interestingly, the first stable tetrahedral tetracarboxonium ions of an adamantane and a cubane have been prepared (**Figure 7**).[30] Analogues of these intermediates could also be core units for the construction of interesting polymers and dendritic macromolecules.

In conclusion, a simple and efficient photochemical procedure using oxalyl chloride has been used for the direct chlorocarbonylation of cubane and adamantane skeletons. This methodology places new functionalities at remote sites and makes possible synthesis of a wide range of substituted cage compounds. These unique molecules are potential starting materials for energetic substances, small-molecule libraries, star polymers, and dendrimers.

Acknowledgements

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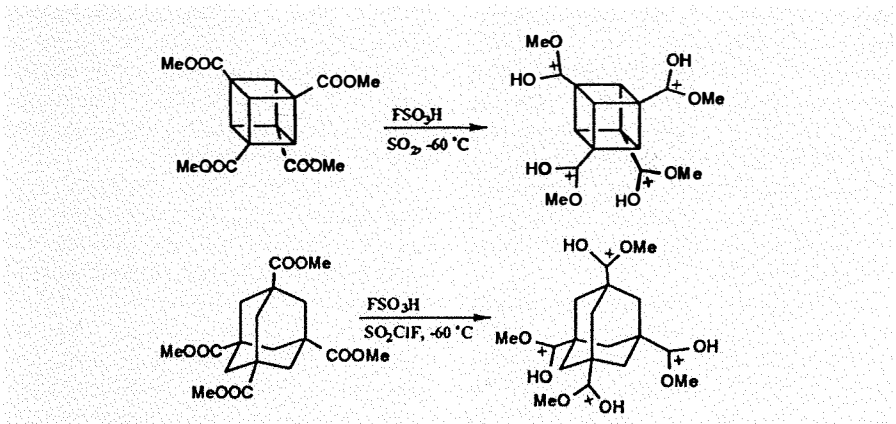

Figure 7

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Atlas of Organic Conversions: An Aid in Perspective†

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Abstract

The teaching of organic chemistry, with its ever changing content, has undergone revolutionary changes over the past few decades. One of the areas in which undergraduate students encounter difficulties is solving problems based on organic functional group transformations—especially multistep conversions. The main thrust in designing this perspective aid is to reduce these difficulties and add another dimension to the teaching and learning of organic chemistry. The Atlas organizes reactions systematically so students can compare and extrapolate them. The "seeds" for designing these charts were "sown" during my fifteen years of classroom experience. The charts themselves are the result of over four years of rigorous research in chemical education.

Introduction

Students at the undergraduate level may find it difficult to learn organic chemistry because of the large number of compounds and reactions involved. Friedrich Wöhler describes the complexity of organic chemistry in an 1835 letter to his mentor, J.J. Berzelius:

> *Organic chemistry just now is enough to drive one mad. It gives me the impression of a primeval tropical forest, full of the most remarkable things; a monstrous and boundless thicket, with no way of escape, into which one may well dread to enter.*

Over the past few decades, however, organic chemistry has achieved a considerable degree of systematization.

Objectives and a Brief Description of the Charts

The study of organic chemistry comprises concept-building chapters such as structural theory, nomenclature, reaction mechanisms, stereochemistry, and spectroscopy. Once a student understands these fundamental concepts, subsequent study becomes easier as it involves application of these concepts to different chemical classes.

Emphasis is usually placed on problem-solving as an aid to learning. While students invariably encounter difficulties in working out problems based on organic functional group conversions, it is these conversions that constitute a major part of organic chemistry. Textbooks usually provide a summary of preparations and properties of chemical classes at the end of each chapter. In fact, preparations and chemical properties are interlinked and thus constitute organic conversions. The Atlas of Organic Conversions is designed to show this connectivity and highlight multi-step strategies for synthesizing simple molecules. This adds a new dimension to the teaching and learning of organic chemistry and helps minimize difficulties in solving problems related to functional group transformations (**Figure 1**).

The Atlas is made up of two parts: Part I consists of 595 acyclic and alicyclic structures (including some simple heterocycles). Part II has 495 aromatic structures (benzene and its derivatives). A considerable number of name reactions and type reactions are covered in both charts.

In Part I, structures and reagents are represented in black, and a particular class of compounds is found in the specified portion of the chart (**Scheme 1, Figure 2**). In Part II, structures are also drawn in black

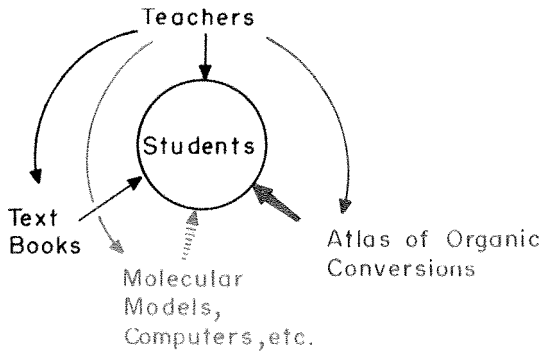
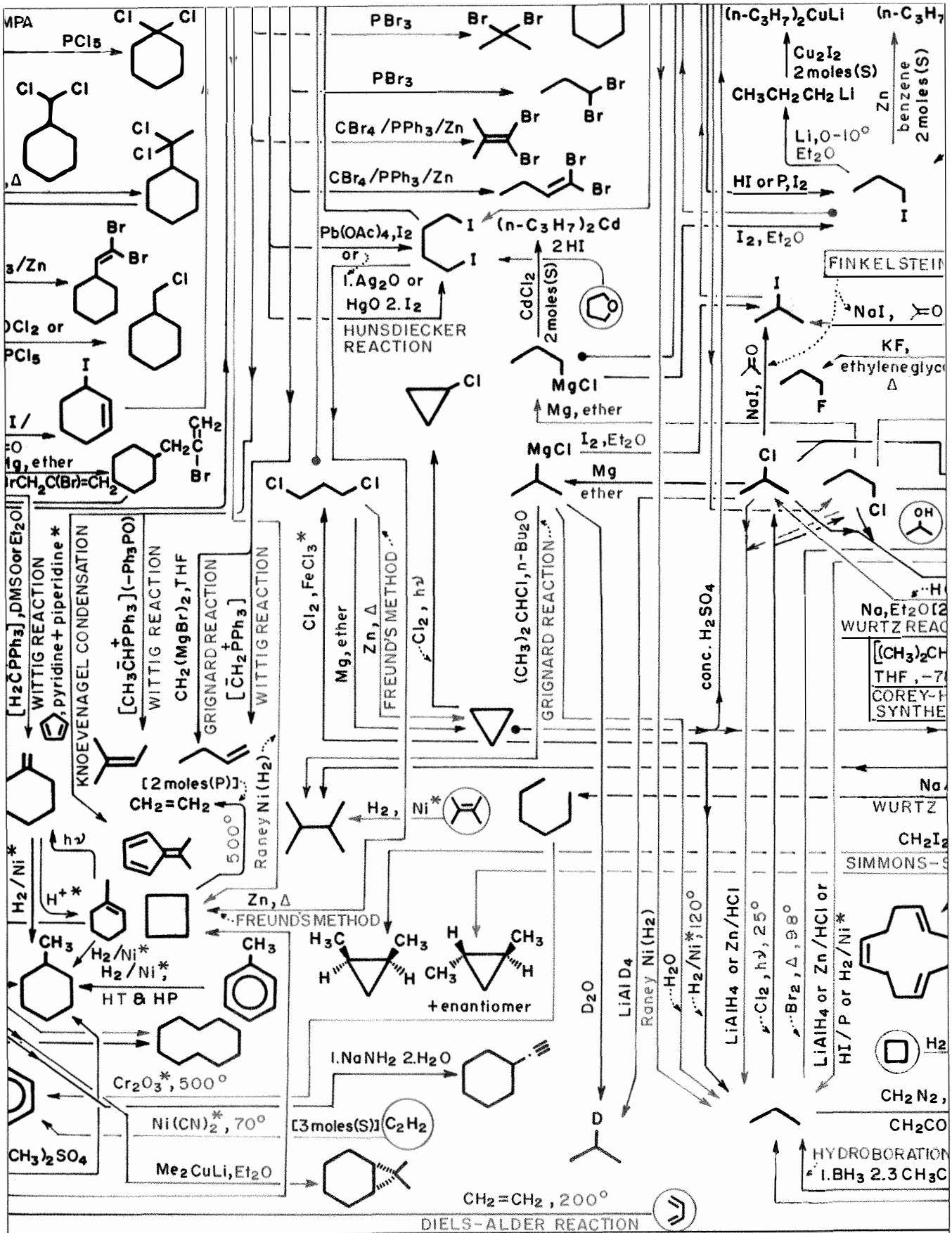
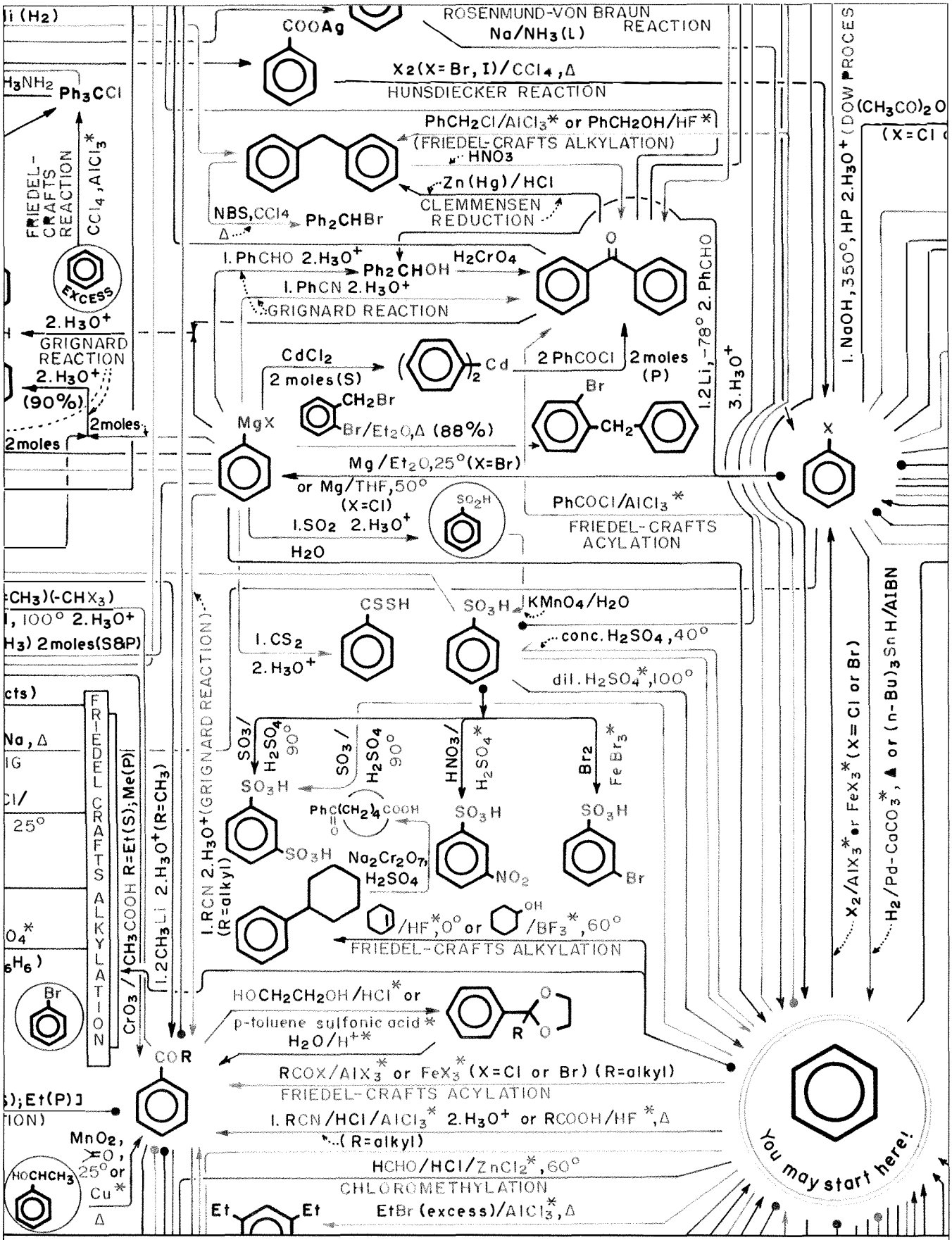


Figure 1. Interactive relationships among various components of teaching and learning.

† Presented in part at the 200th & 203rd American Chemical Society National Meetings, Washington, D.C., 1990 (Paper No. 1996) and San Francisco, 1992 (Paper No. 287), and at the "Workshop on Teaching Aids", Osmania University, Hyderabad, India (1989).



Scheme 1. Atlas of Organic Conversions: Part I. Aliphatic Compounds (*partially shown; original chart consists of 595 structures*).



Scheme 2. Atlas of Organic Conversions: Part II. Aromatic Compounds (*partially shown; original chart consists of 495 structures*).

while heteroatom functional groups are red for immediate perception; each class of compounds is spread out but still remains connected. Solvents in both charts are indicated in blue, and catalysts are blue with a red asterisk (**Scheme 2, Figure 3**).

Structures in both charts are represented as condensed and line-angle formulas, or a combination of the two. One can easily observe the various methods of formation of a particular compound (convergent transformations) and the various ways a particular compound reacts to give products (divergent transformations). Each type of reaction illustrates a combination of electronic, steric, temperature, or solvent effects. Stereo-, regio-, and chemoselectivity are highlighted where applicable. Examples of organometallic, photochemical, and pericyclic reactions are also presented. In a broader sense, the conversions include functionalization, functional group interconversions, isomerization, homologation, defunctionalization, and a combination of two or more of these types.

In aliphatic systems, emphasis is placed on ring-forming, ring-opening, ring-expansion, and ring-contraction reactions. In aromatic systems, ring-substitution reactions are stressed, as well as special reactions of functional groups resulting from the presence of the aromatic ring. If a particular conversion involves two or more equivalents of substrate (S) or product (P), it is indicated along the arrow [e.g., 2 moles (S) or 2 moles (P)]. A detailed key defining the Atlas's objectives and conventions is provided at the bottom of each chart. The charts are outlined, divided, and designated alphabetically (A to I) along the x-axis, and numerically (1 to 8) along the y-axis (1 to 9 in Part II)(**Figures 2 & 3**). These axes provide a reference grid for locating compounds.

The overwhelming number of reactions are tailored to suit the needs of undergraduate students and designed to give a quick overview. The interconversions are shown in all possible paths. The Atlas illustrates a broad spectrum of organic conversions and is based on an integrated approach.

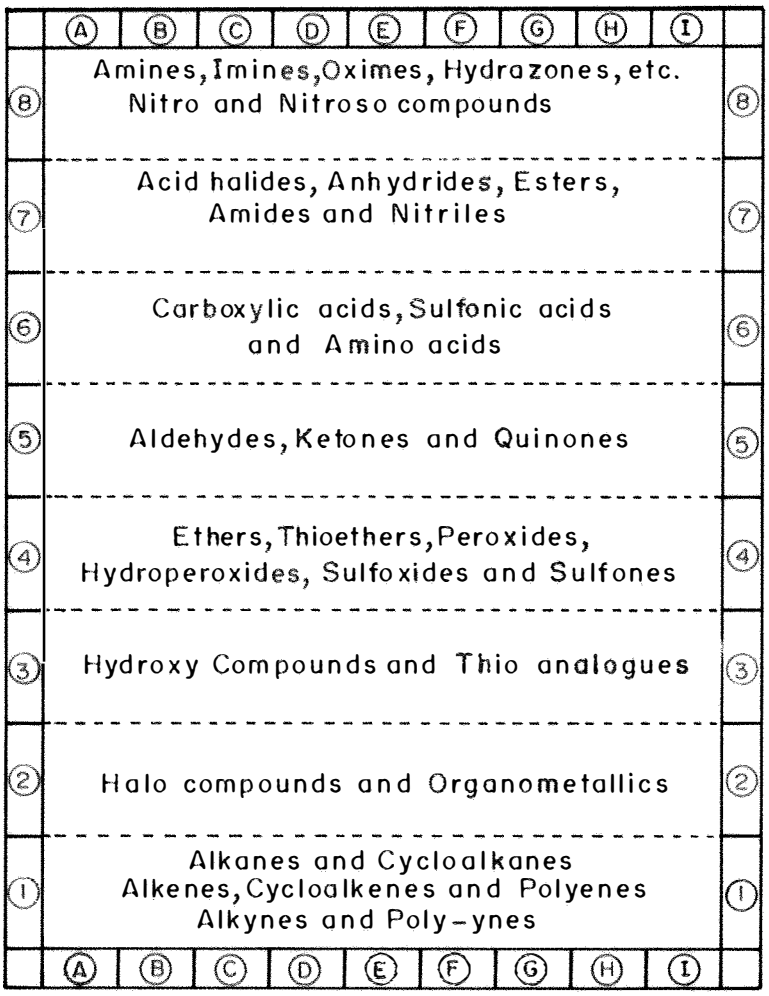


Figure 2. In the Atlas of Organic Conversions (Part I) a particular class of compounds is found in the specified portion of the chart.

Learning aids

The wall charts are intended for display in libraries, classrooms, and research labs. Students can use the charts in the following ways:

- Read the "Key to Understanding" at the bottom of each chart.
- Organize into small groups (4-5 students) and have one of the students act as 'quiz-master' by asking others to identify reactant(s), product(s), or reagent(s) after masking any one of them.
- Study these charts progressively after attending lecture(s) on, and studying the assigned reading for, a particular topic.
- Engage in other activities such as the 'name game' and the 'game of reaction mechanisms': writing or reciting IUPAC names (or alternative names) for structures or writing reaction mechanisms.
- Construct study sheets for each class of compounds using a representative example.

Teaching aids

It gives me immense pleasure to share my experiences with my fellow teachers. The primary role of the teacher is to impart the best possible education to the students. These perspective aids are designed as part of, and in pursuit of, this goal. The teacher could explain to a set of students a broad spectrum of organic reactions involving a few lectures. For a large classroom situation, alternatively, slides would be helpful. The charts also act as a 'prototype' for framing various problems based on organic conversions (one-step and multistep conversions). A model problem-sheet is provided in the manual.

Conclusions

The motivation behind these perspective aids is to arouse interest among students, whet their appetite, and broaden their horizons through stimulated and systematic learning. These charts are the result of fifteen years of classroom experience and over four years research in chemical education. They are classroom-tested and should catalyze understanding, learning, and thinking about organic transformations. I am confident that students will find the Atlas rewarding and, as a result, will be better able to solve organic synthesis problems. The charts will also better prepare students for academic and professional examinations.

Acknowledgements

I am especially grateful to Professor David Krupadanam (Osmania University) for his invaluable suggestions. My thanks go to Ghulam Mohiuddin, D. Vijay Prasad, and P. Jaya Prasad for their comments, and Giridharan Bhartwaj for his professional drawings. To my students, I offer my acknowledgment and appreciation for their participation and contribution to this project.

Dedication

To the chemists responsible for growth and development of the subject.

To my teachers who motivated and enlightened me.

To my students who taught me how to teach organic chemistry.

To Kanakatara, Kranti, and Sputnik.

About the Author

Vara Prasad R. Koganti hails from Macharam, Andhra Pradesh (India). He completed his education (BSc., MSc., MPhil) at Osmania University, India, in 1988 with a doctorate thesis on the "*Chemistry of 4H-Imidazo[2,1-c][1,4]benzoxa(thia)zines*". He joined the faculty of New Science College in 1979, where he has been an Associate Professor since 1992.

Dr. Koganti's research interests include synthetic organic chemistry, spectroscopy and chemical education. He has played an active role in designing and modernizing the Undergraduate Organic Chemistry Curriculum at Osmania University. Currently, he is also engaged in crafting innovative methodologies for teaching and learning organic chemistry.

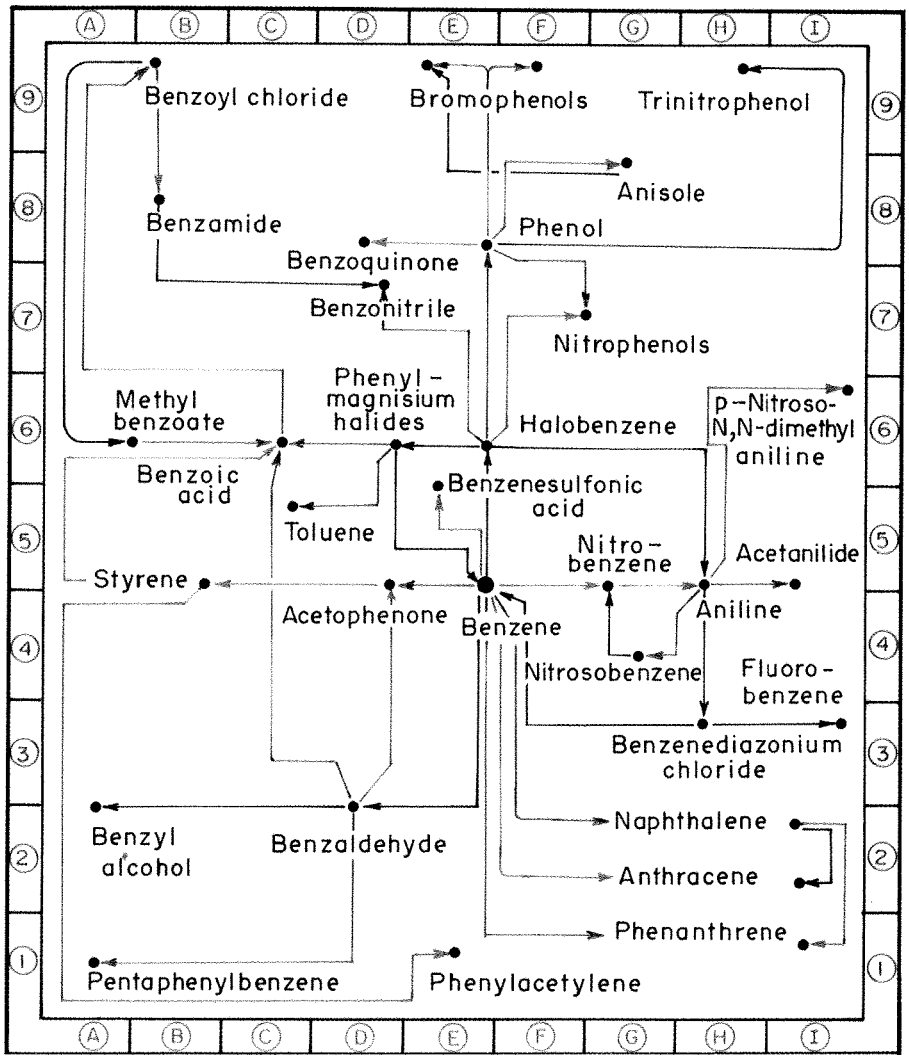


Figure 3. In the Atlas of Organic Conversions (Part II) various classes of compounds are spread out but remain closely connected.

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Aldrichimica Acta

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New Possibilities in Organic Synthesis

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This painting is part of the collection of French paintings at The Saint Louis Art Museum.

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Lab Notes

Column chromatography on silica gel is a widely used general purification method in organic chemistry, and hexane/ethyl acetate is one of the most common solvent systems. However, using this method, chemists often encounter undesirable "tailing", especially in the case of large-scale purifications. It is not unusual to have long tails during chromatographic separation, even if on a TLC plate the substance has a nice round spot. This problem not only makes purification longer and consumes large volumes of solvents, it may also affect the recovery and purity of the desired substance.

The reason for this tailing is usually a slow adsorption-desorption equilibrium on the surface of the silica gel. This problem is well known to those working with normal phase HPLC. In HPLC, the problem can be solved easily by addition of a small amount of isopropyl alcohol (~0.1%) to the mobile phase, assuming the mobile phase had not originally contained it. Such a small amount of isopropyl alcohol does not essentially increase the polarity of the mobile phase. Therefore, retention times do not change and resolution is not affected, but tailing is greatly reduced due to the increased equilibration speed.

We found that the same method works very well with regular column chromatography when hexane/ethyl acetate or a similar solvent system is used as an eluent. In this case, however, methyl alcohol is more convenient for obvious practical reasons. Depending on the substance to be purified, 0.1-0.3%, and sometimes even 0.5% (v/v) of methanol could be added to the mobile phase. This method was found to be a real timesaver during large-scale chromatographic separations.

I hope this hint proves useful to many synthetic organic chemists.

Yours sincerely,

Dr. Vladimir Khlebnikov
Shiga Research Laboratories
Roussell Morishita Co., Ltd.
1658, Ohshinohara, Yasu-gun, Yasu-cho
Shiga-ken, Japan

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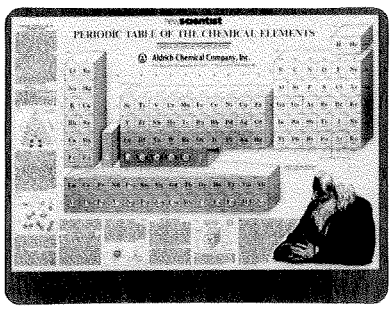

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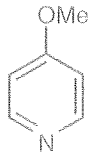
by Jai Nagarkatti

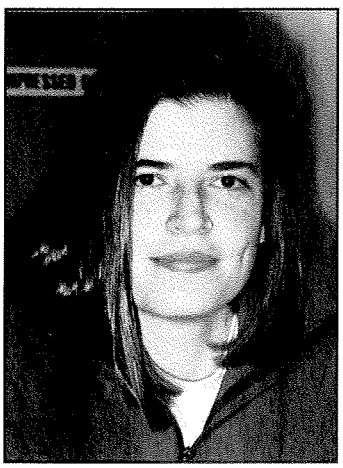
Jai Nagarkatti, President



Professor Daniel D. Comins of North Carolina State University kindly suggested that we make this valuable heterocyclic building block. It is readily converted to 2-substituted-2,3-dihydro-4-pyridones by acylation of the nitrogen and reaction of the resulting salt with a Grignard reagent. An asymmetric version of this reaction was used in the syntheses of a number of naturally occurring alkaloids.[1,2]

(1) Comins, D.L.; Joseph, S.P.; Goehring, R.R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (2) Comins, D.L.; Joseph, S.P. *Advances in Nitrogen Heterocycles*; JAI: Greenwich, CT, 1996; Vol. 2, p 251.

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.



Aldrich Chemical Company Fellow

We are pleased to announce that Janet L. Gunzner has been selected as the 1996/1997 Aldrich Chemical Company Fellow by the Organic Division of the American Chemical Society.

Ms. Gunzner is starting her fourth year of graduate study in the laboratory of Professor K.C. Nicolaou at The Scripps Research Institute, La Jolla, California. Her research is focused on new methodologies for, and synthetic routes to, the polycyclic ether maitotoxin isolated from *Gambierdiscus toxiscus* (a marine natural product of unprecedented complexity). She has previously received the Roche Award for Excellence in Organic Chemistry and the Wiener Graduate Fellowship. Additionally, as an undergraduate at Reed College, Janet was the recipient of the American Chemical Society-Portland Section Scholarship.

Congratulations, Janet! Aldrich is proud to help the research efforts of a young scientist such as yourself.

New Possibilities in Organic Synthesis

Teruaki Mukaiyama
Department of Applied Chemistry,
Faculty of Science,
Science University of Tokyo,
Kagurazaka, Shinjuku-ku, Tokyo 162

1. Introduction

In Japanese universities the mandatory retirement age is 60 to 65 years. Of these universities, only the University of Tokyo and the Tokyo Institute of Technology set their retirement age at 60.

After I retired from the University of Tokyo in 1987, I accepted a position at the Science University of Tokyo (SUT), a private university where professors are allowed to work beyond the mandatory retirement age. Here I continue my work with graduate students and co-workers from Industry. I formed a new research team to continue studying "Chiral Lewis Acids" in the "Crossed Aldol Reaction", an area we had been working in for a long time.

Because our research has made considerable progress during the past nine years, we have now become interested in three topics:

(i) *The chiral Lewis acid mediated asymmetric aldol reaction*: preparation of chiral polyoxy compounds useful in the synthesis of various monosaccharides and taxol®. The chiral Lewis acid in this case is a tin(II) triflate-chiral diamine complex.

(ii) *Efficiency in fundamental and useful synthetic reactions*: (a) esterification using equimolar amounts of free carboxylic acid and alcohol; (b) glycosylation of 1-hydroxy sugars with several nucleophiles using a catalytic amount of acid activators.

(iii) *Oxygenation of olefins*: hydration and enantioselective epoxidation of olefins catalyzed by transition-metal complexes containing diketone-type ligands.

Topics (i) and (iii) are discussed in this review.

2. The Chiral Lewis Acid Mediated Asymmetric Aldol Reaction

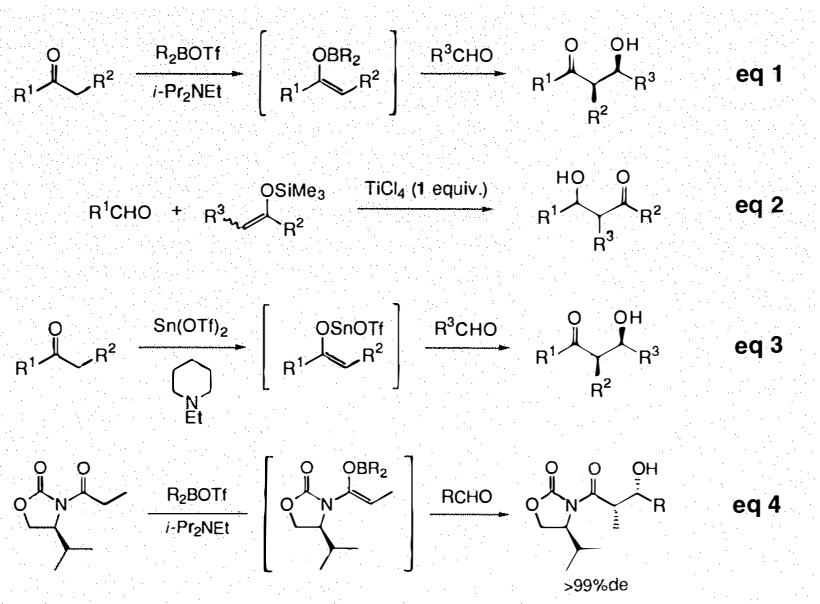
While I was at the Tokyo Institute of Technology and the University of Tokyo, we explored some new possibilities for realizing the "crossed aldol reaction" (1973-1987). We began with enol borates,[1] moved on to silyl enol ethers,[2] and eventually into tin(II) enolate chemistry (**eq 1-3**).[3] The availability of four vacant orbitals on tin(II)—which is not very likely with the other Lewis acids (Li, B, Sn(IV), Ti, etc.)—led us to the "Chiral Lewis Acid" concept.

2.1. Design of the Catalytic Asymmetric Aldol Reaction

The asymmetric aldol reaction is one of the most powerful tools for the construction of new carbon-carbon bonds and for control of the absolute configurations of the newly created chiral centers.[4] The utility of the reaction has been demonstrated in the synthesis of natural products such as macrolide and polyether antibiotics, carbohydrates, and others.[5]

Conventional asymmetric aldol reactions have been performed mostly in a diastereoselective manner by using chiral enolates and achiral carbonyl compounds as starting materials.[6-11] For example, the chiral boron enolate (generated in situ from the corresponding chiral oxazolidone derivative, dialkylboron triflate, and

diisopropylethylamine) reacts stereoselectively with aldehydes to afford the corresponding aldol adducts in good yields (**eq 4**).[6b] While these reactions proceed with excellent diastereoselectivities, they require additional steps for introducing a chiral center into the starting material and for



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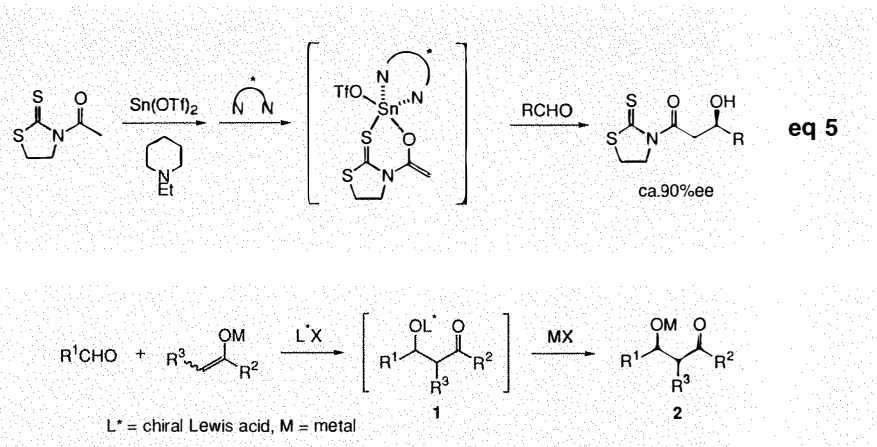
removing such a center after the aldol reaction is completed. In contrast, examples of the direct preparation of chiral aldols from achiral enolates and achiral aldehydes have been reported.[3,12] For example, the tin(II) enolate derived from achiral 3-acetylthiazolidine-2-thione creates an asymmetric environment with the aid of a chiral diamine and then reacts with achiral aldehydes to give the corresponding aldol adducts in high enantioselectivities by a one-pot procedure (**eq 5**).[12b] In these reactions, optically active aldol adducts are obtained in high enantiomeric excesses by using a *stoichiometric* amount of a chiral auxiliary.

The development of the asymmetric aldol reaction which proceeds in a *catalytic* manner with high diastereo- and enantioselectivities has been a challenging task in organic synthesis.[13] Although the use of a chiral Lewis acid is one of the most promising ways to solve the problem, less progress has been made here than in the case of the chiral Lewis acid catalyzed Diels-Alder and related reactions,[3] probably owing to the greater difficulty in controlling the asymmetric environment in the aldol reaction.

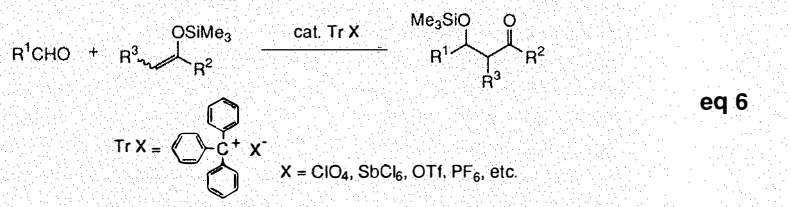
The catalytic asymmetric aldol reaction between a simple achiral ketone or ester and an aldehyde was planned as shown in **Scheme 1**. A chiral Lewis acid (L*) coordinates to an aldehyde to form an asymmetric environment, and then an enolate attacks this aldehyde from the less hindered side of the enantioface of the aldehyde to produce initially the aldol adduct **1**. For the reaction to be catalytic, an exchange reaction between L* and M must take place to give product **2** and regenerate the chiral Lewis acid.

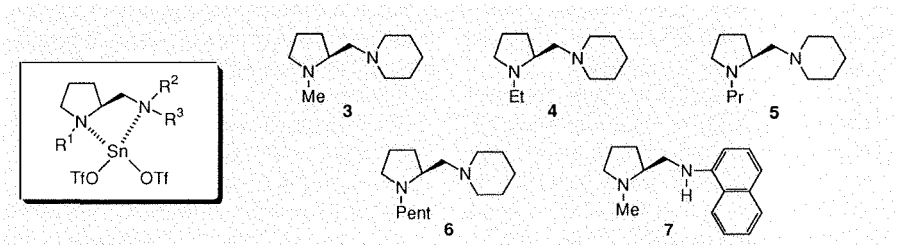
Thus, we reported initially on the titanium tetrachloride-mediated aldol reaction of silyl enol ethers with aldehydes (**eq 2**),[2,14] and then showed that a trityl salt, represented by trityl perchlorate, was an efficient catalyst in this reaction (**eq 6**).[15] While the original reaction required a stoichiometric amount of titanium tetrachloride, 5-10mol % of trityl salt was sufficient to drive the reaction to completion. The interesting finding in this reaction was that *silyl* enolates reacted with aldehydes to give the corresponding aldol adducts as their *silyl* ethers.

For us, the next and quite important step was the choice of the chiral Lewis acid. While as early as 1989 some chiral Lewis acids were already being used successfully in the Diels-Alder and related reactions, the chiral Lewis acids employed consisted of rather strong Lewis acids and hard metals such as aluminum and titanium. Since these metals strongly coordinate to oxygen, the smooth exchange between the metal and silicon would hardly take place. For this



Scheme 1. Design of the Catalytic Asymmetric Aldol Reaction.





Scheme 2. Chiral Tin(II) Lewis Acids.

reason we chose chiral tin(II) Lewis acids, which were prepared in situ by the coordination of chiral pyrrolidine derivatives to tin(II) triflate (**Scheme 2**). Divalent tin has vacant *d* orbitals, easily forms complexes with amines,[16] and has an affinity for sulfur atoms. One favorable feature of such chiral tin(II) Lewis acids is that the metal is coordinated to the chiral auxiliary. After the coordination of two nitrogen atoms to tin(II), one vacant orbital remains and tin(II) can thus bond to an aldehyde as a Lewis acid without losing the favorable asymmetric environment created by the chiral ligand.

2.2. The Asymmetric Aldol Reaction of Aldehydes with Silyl Enolates Derived from Acetic Acid Thioesters

As a preliminary experiment, the Lewis acidity of tin(II) triflate coordinated to tetramethylethylenediamine (TMEDA) was examined, since the coordination of two nitrogens to tin(II) was expected to reduce the Lewis acidity of the tin. Nevertheless, the resulting aldol adduct was obtained in 78% yield when the trimethylsilyl enol ether of *S*-ethyl ethanethioate (**8**) was allowed to react with benzaldehyde at -78 °C in the presence of a stoichiometric amount of TMEDA-coordinated tin(II) triflate. This result showed that the diamine-coordinated tin(II) triflate had enough Lewis acidity to promote the aldol reaction. Next, the same aldol reaction was tried using (*S*)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**3**)-coordinated tin(II) triflate. The reaction proceeded smoothly, but no enantiomeric selection was observed.

The reason for the absence of chiral induction in the above example was explained as follows: The chiral diamine-coordinated tin(II) triflate activated benzaldehyde and might have created an efficient chiral environment, but the silyl enol ether attacked the aldehyde quite freely, resulting in a low enantiofacial selectivity. Therefore, we

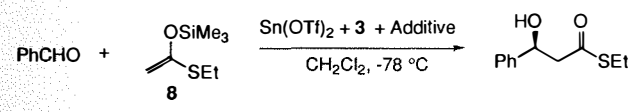


Table 1. Effect of Additive on the Reaction of **8** with Benzaldehyde.

Entry	Additive	Yield %	ee %
1	—	74	0
2	AlF_3	76	0
3	MgF_2	72	0
4	*n*-Bu_3SnCl	80	0
5	*n*-Bu_3SnF	78	82

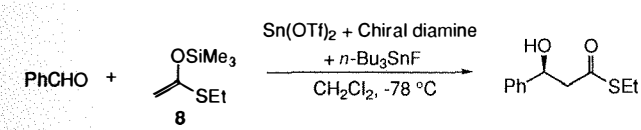


Table 2. Effect of Chiral Diamine on the Reaction of **8** with Benzaldehyde.

Entry	Chiral diamine	Yield %	ee %
1	**3**	78	82
2	**4**	67	83
3	**5**	58	83
4	**6**	75	88
5	**7**	52	92

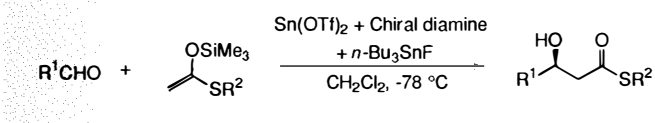
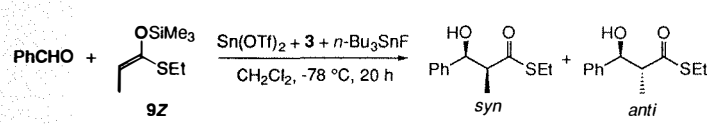


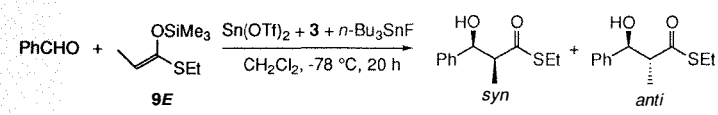
Table 3. Asymmetric Aldol Reaction of Silyl Enolates of Acetic Acid Thioesters.

Entry	R^1	R^2	Chiral diamine	Yield %	ee %
1	Ph	Et	**3**	78	82
2	Ph	Et	**7**	52	92
3	Ph	*t*-Bu	**3**	73	86
4	$Ph(CH_2)_2$	Et	**3**	70	78
5	$Ph(CH_2)_2$	Et	**7**	50	81
6	$Ph(CH_2)_2$	*t*-Bu	**3**	71	85
7	*i*-Pr	Et	**3**	77	95
8	*t*-Bu	Et	**3**	90	>98



80% yield, *syn*/*anti* = 93/ 7, 80%ee (*syn*)

eq 7



30% yield, *syn*/*anti* = 59/41, 30%ee (*syn*)

eq 8

searched for an additive that would connect the promoter more effectively with the silyl enolate. Since a second Lewis acid was expected to interact with tin(II) triflate, some Lewis acids that contain fluoride and have a strong affinity for silicon were examined as additives.

When **8** was treated with benzaldehyde in the presence of stoichiometric amounts of tin(II) triflate, **3**, and some metal fluorides such as magnesium fluoride (MgF_2) or aluminum fluoride (AlF_3), the aldol reaction proceeded at -78 °C, but the enantiomeric excess was zero. However, when **tributyltin fluoride** (***n*-Bu_3SnF**) was employed, the same aldol adduct was obtained in 78% chemical yield and 82% ee.[17] The importance of tributyltin fluoride is obvious from the observation of no enantiomeric selection when tributyltin chloride was used, even though the chloride promoted the same reaction to the same extent (**Table 1**). Next, chiral diamines were examined in order to improve the enantioselectivity of the reaction. The 1-alkyl groups of the pyrrolidine ring system were found to have a strong influence on the enantiomeric excesses. When (*S*)-1-pentyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**6**) was employed, the enantiomeric excess rose to 88%. The maximum ee (92%) was obtained when (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine (**7**) was employed as the chiral diamine (**Table 2**).[18]

Several examples of this asymmetric aldol reaction are shown in **Table 3**. In every case, the corresponding aldol adducts were obtained in good yields and high enantioselectivities. In particular, very high enantiomeric excesses (≥95%) were attained in the reaction with bulky aldehydes such as isobutyraldehyde and pivalaldehyde.[17-19]

2.3. The Asymmetric Aldol Reaction of Aldehydes with Silyl Enolates Derived from Propionic Acid Thioesters

The synthesis of *syn*-α-methyl-β-hydroxy thioesters was then studied. The reaction of benzaldehyde with the silyl enol ether **9** was chosen as a model and several reaction conditions were examined in the presence of tin(II) triflate, chiral diamine **3**, and tributyltin fluoride. The double bond geometry of the silyl enol ether was found to influence both reactivity and selectivity strongly. The *Z* enolate **9Z** reacted smoothly with benzaldehyde to give the corresponding aldol adduct in high yield with high *syn* stereoselectivity (**eq 7**), while the corresponding *E* enolate **9*E*** reacted more slowly producing the aldol adduct in lower yield and lower stereoselectivity (**eq 8**).[20]

The effect of chiral diamines on the diastereo- and enantioselectivity in this reaction is summarized in **Table 4**. When (*S*)-1-ethyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**4**) was employed, the *syn*/*anti* ratio was slightly lower while the enantiomeric excess was rather improved as compared to **3**. Dramatic improvements in both reactivity and selectivity were observed when **7** was used; only the *syn* aldol was obtained with excellent enantioselectivity. The faster reaction rate observed in the case of chiral diamine **7** (entry 4) is attributed to the weaker coordination of the nitrogen atom of the naphthylamino group in **7** to tin. This weaker coordination enhances the Lewis acidity of the chiral diamine **7**-coordinated tin(II) triflate catalyst complex as compared to the Lewis acidity of the other

1-alkyl-2-[(dialkylamino)methyl]pyrrolidine-coordinated tin(II) triflates.[18]

Next, the effects of tin(IV) compounds other than tributyltin fluoride were investigated.[21] The reaction was postulated to proceed equally well by using a tin(IV) compound additive that had oxygen atoms, since these were also expected to show strong affinity toward the silicon atom of silylated nucleophiles. Thus, tin(IV) alkoxides and tin(IV) carboxylates were examined by using the reaction of silyl enol ether **9Z** with benzaldehyde as a model (**Table 5**). In most cases, the reactions proceeded smoothly to give the corresponding aldol adducts in good-to-high yields with good-to-high

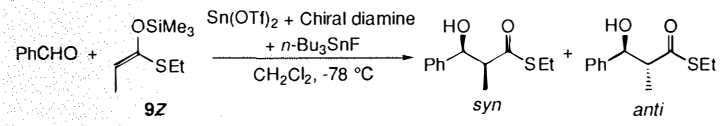
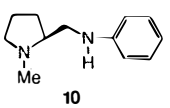


Table 4. Effect of Chiral Diamine on the Reaction of **9Z** with Benzaldehyde.

Entry	Chiral diamine	Time (h)	Yield %	*syn/anti*	ee % (*syn*)
1	**3**	20	80	93/ 7	80
2	**4**	20	85	91/ 9	96
3	**5**	20	85	93/ 7	96
4	**7**	3	86	100/ 0	>98
5	**10**	3	58	88/12	42
6	**11**	3	79	100/ 0	84



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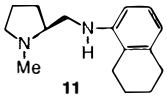

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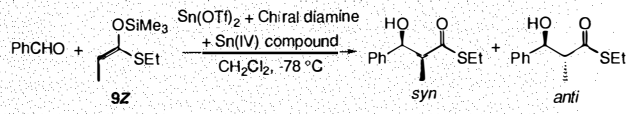


Table 5. Effect of Sn(IV) Compounds on the Reaction of **9Z** with Benzaldehyde.

Entry	Sn(IV) compound	Chiral diamine	Yield %	*syn/anti*	ee % (*syn*)
1	*n*-Bu_3SnF	**3**	80	93/ 7	80
		7	86	100/ 0	>98
2	*n*-Bu_2SnF_2	**3**	0	—	—
		7	90	100/ 0	88
3	*n*-Bu_3SnOAc	**3**	65	63/37	55
		7	81	98/ 2	90
4	*n*-$Bu_2Sn(OAc)_2$	**3**	86	89/11	77
		7	85	100/ 0	>98
5	*n*-$BuSn(OAc)_3$	**3**	90	94/ 6	82
		7	93	100/ 0	75
6	*n*-Bu_3SnOMe	**3**	74	80/20	65
		7	0	—	—
7	*n*-$Bu_2Sn(OMe)_2$	**3**	54	95/ 5	75
		7	0	—	—
8	*n*-$Bu_2Sn(OCOPh)_2$	**7**	65	100/ 0	>98
9	*n*-$Bu_2Sn(OCOCH_2Cl)_2$	**7**	91	97/ 3	92

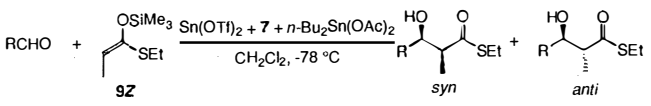
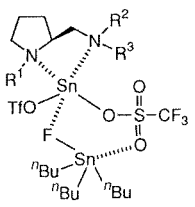


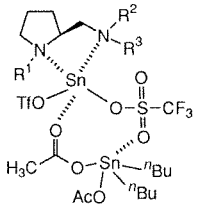
Table 6. Asymmetric Aldol Reaction of **9Z** with Various Aldehydes.

Entry	R	Yield %	*syn/anti*	ee %
1	Ph	85	100/ 0	>98
2	*p*-Cl C_6H_4	96	100/ 0	>98
3	*p*-$CH_3C_6H_4$	92	100/ 0	>98
4	*p*-$CH_3OC_6H_4$	95	100/ 0	>98
5	$CH_3(CH_2)_6$	90	100/ 0	>98
6	*c*-C_6H_{11}	90	100/ 0	>98
7	*i*-Pr	70	100/ 0	>98
8	*i*-Bu	86	100/ 0	>98
9	(*E*)-CH_3CH=CH	92	100/ 0	>98
10	(*E*)-PhCH=CH	91	100/ 0	>98
11	(*E*)-*n*-PrCH=CH	91	100/ 0	>98
12		93	100/ 0	>98
13		92	100/ 0	>98

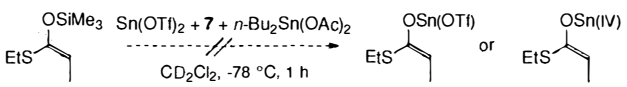
diastereo- and enantioselectivities. Our findings can be summarized as follows: (i) tin(IV) carboxylates gave better chemical yields than tin(IV) alkoxides; (ii) higher stereoselectivities were obtained when tin(IV) dicarboxylates were employed as compared with tin(IV) monocarboxylates; (iii) tin(IV) carboxylates with electron-withdrawing groups resulted in lower stereoselectivities. The optimal conditions for obtaining a high yield and perfect stereochemical control were achieved by the combined use of tin(II) triflate, chiral diamine **7**, and **dibutyltin diacetate**.[22]

A wide variety of aldehydes including aliphatic, α,β-unsaturated, and aromatic aldehydes underwent this reaction (**Table 6**). In every case, the aldol adducts were obtained in high yields with almost perfect stereochemical control. These results make





Scheme 3. Assumed Three-Component Promoter.



eq 9

it clear that tin(IV) diacetate is superior as an additive to the other tin(IV) compounds including tributyltin fluoride.[18,22]

In these aldol reactions, the formation of an active complex consisting of three components—tin(II) triflate, chiral diamine, and tributyltin fluoride (or dibutyltin diacetate)—was assumed (**Scheme 3**).[18] This assumption was supported by the observation that the mixture of these three components was completely soluble in dichloromethane, while tin(II) triflate or tributyltin fluoride was only sparingly soluble under these conditions.

The ^{1}H NMR spectra of the mixture of the chiral, three-component promoter and the silyl enol ether at -78 °C showed that no exchange was taking place from silicon to tin(II) or from silicon to tin(IV). Thus, to a dichloromethane-d_2 solution of tin(II) triflate, **7**, and dibutyltin diacetate, was added silyl enol ether **9Z** in dichloromethane-d_2 at -78 °C. The singlet at δ 0.15 corresponding to the trimethylsiloxy group of **9Z** did not change within 1 hour under these reaction conditions. This observation supports the hypothesis that the reaction does not proceed via tin(II) or tin(IV) enolates formed by silicon-metal exchange, and that the aldehydes are attacked directly by the silyl enol ethers (**eq 9**).[18] However, the three-component complex would be able to activate both the aldehyde and the silyl enol ether (double activation). That is, the chiral diamine-coordinated tin(II) triflate Lewis acid activates the aldehyde while the electronegative fluoride or acetoxy oxygen atom in the tin(IV) compound interacts with the silicon atom of the silyl enol ether.

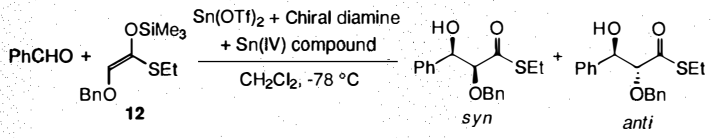
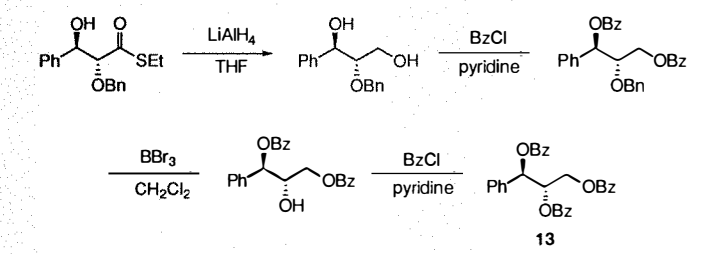


Table 7. Effect of Chiral Diamine on the Reaction of **12** with Benzaldehyde.

Entry	Chiral diamine	Sn(IV) compound	Yield %	*syn/anti*	ee % (*anti*)
1	**3**	*n*-Bu_3SnF	70	1 /99	97
2	**4**	*n*-Bu_3SnF	54	1 /99	99
3	**5**	*n*-Bu_3SnF	54	1 /99	99
4	**6**	*n*-Bu_3SnF	38	1 /99	97
5	**7**	*n*-Bu_3SnF	69	26/74	97
6	**3**	*n*-$Bu_2Sn(OAc)_2$	74	1 /99	96
7	**4**	*n*-$Bu_2Sn(OAc)_2$	83	1 /99	96



Scheme 4. Conversion of Aldol Product to Tribenzoate **13.**

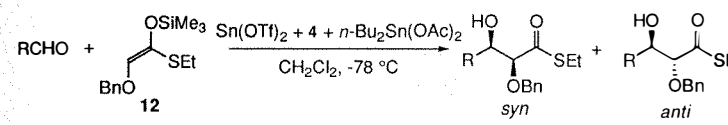


Table 8. Scope of the Asymmetric Aldol Reaction of **12**.

Entry	R	Yield %	*syn/anti*	ee %(*anti*)
1	Ph	83	1 / 99	96
2	CH_3CH_2	72	2 / 98	97
3	*c*-C_6H_{11}	59	9 / 91	96
4	(*E*)-PhCH=CH	88	2 / 98	98
5	(*E*)-CH_3CH=CH	85	2 / 98	97
6	(*E,E*)-CH_3CH=CHCH=CH	83	2 / 98	95

2.4. Asymmetric Synthesis of syn- and anti-1,2-diol Derivatives

Optically active molecules containing 1,2-diol units are often observed in nature (e.g., carbohydrates, macrolides, polyethers). Recently, several excellent asymmetric olefin oxidation reactions using osmium tetroxide and a chiral ligand have been developed to introduce these 1,2-diol units with high enantioselectivities.[23,24] However, some challenges still remain such as the preparation of optically active *anti* 1,2-diols. For this reason, the asymmetric aldol reaction of the silyl enol ether **12** with aldehydes was developed to introduce two vicinal hydroxyl groups simultaneously with stereoselective carbon-carbon bond formation.

First, the reaction of **12** with benzaldehyde was carried out in dichloromethane by using the chiral promoter consisting of tin(II) triflate, **7**, and tributyltin fluoride (**Table 7**, entry 5). The reaction proceeded smoothly at -78 °C, afforded the corresponding aldol adduct in 69% yield, and showed preference for the *anti* aldol diastereomer. The enantiomeric excesses of the *syn* and *anti* aldols were 30% and 97%, respectively. Several chiral diamines were then examined in order to improve the diastereoselectivity (**Table 7**). When (*S*)-1-ethyl-2-[(piperidin-1-yl)methyl]-pyrrolidine (**4**) was employed, the aldol adduct was obtained in 54% yield with excellent diastereo- and enantioselectivities. Furthermore, the yield was improved without any loss of stereoselectivity by the combination of tin(II) triflate, **4**, and dibutyltin diacetate.

The absolute configuration of this aldol product was determined by comparison with an authentic sample after elaboration into tribenzoate **13** (**Scheme 4**). Reduction by lithium aluminum hydride, benzoylation, removal of the benzyloxy group with boron tribromide, and a second benzoylation gave **13**. The optical rotation of this synthetic sample was in complete agreement with that in the literature.[25]

The results from applying the present asymmetric aldol reaction to several kinds of aldehydes are shown in **Table 8**.[26] In every case, *anti*-α,β-dihydroxy thioesters

are obtained in high yields with excellent diastereo- and enantioselectivities. The aldol adducts (optically active *anti*-α,β-dihydroxy ester derivatives) thus obtained are generally difficult to prepare by the conventional asymmetric oxidative procedure because the required starting materials, *cis*-α,β-unsaturated ester equivalents, are not easily available. Moreover, a consideration of the mechanistic model of the asymmetric dioxyosmylation indicated that preparation of *anti*-1,2-diols in high enantiomeric excesses is hardly achieved by this method.[27] In the present aldol methodology, two vicinal, *anti* hydroxyl groups can be introduced stereoselectively and concomitantly with the formation of a new carbon-carbon bond.

The high *anti* selectivities attained in the reaction of **12** with aldehydes were unexpected and interesting results, especially since the aldol reaction of **9Z** with aldehydes using the above chiral promoter proceeded with *syn* preference in excellent diastereo- and enantioselectivities (**Table 6**). A consideration of the transition states of these aldol reactions led us to postulate that coordination of the oxygen atom of the α-benzyloxy group of the silyl enol ether **12** to tin in tin(II) triflate is essential in the *anti* selective transition state. Thus, the absence of this interaction in the reaction of **9Z** leads to the opposite diastereoselectivity.

To test this hypothesis, we prepared the silyl enol ether **14** in which the bulky *tert*-butyldimethylsilyl group sterically hinders the coordination of the oxygen atom to tin(II). As expected, the *syn* aldol was obtained in high stereoselectivities under these reaction conditions [tin(II) triflate, chiral diamine **7**, dibutyltin diacetate, and benzaldehyde] (**Table 9**, entry 7). When the reaction was carried out using other chiral diamines, it was found that (*S*)-1-*n*-propyl-2-[(piperidin-1-yl)methyl]-pyrrolidine (**5**) gave the most favorable result (**Table 9**, entry 4).

Several examples of this *syn*-selective aldol reaction are shown in **Table 10**. In every case, the reaction proceeded smoothly affording the aldol adducts in good yields and very high *syn* selectivities. The enantiomeric excesses of the *syn* isomers were greater than 90% in most cases.[28]

In light of the preceding results, it now becomes possible to control the enantiofacial selectivity of the silyl enol ethers derived from α-alkoxy thioesters by selecting the appropriate protective group of the alkoxy part of the silyl enol ether. Both diastereomers of optically active α,β-dihydroxy thioesters can be synthesized this way (**Scheme 5**).

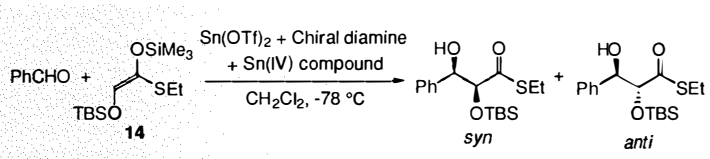
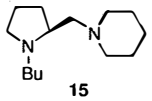


Table 9. Effect of Chiral Diamine on the Reaction of **14** with Benzaldehyde.

Entry	Chiral diamine	Sn(IV) compound	Yield %	*syn/anti*	ee % (*syn*)
1	**3**	*n*-Bu_3SnF	81	86/14	49
2	**3**	*n*-$Bu_2Sn(OAc)_2$	83	91/ 9	49
3	**4**	*n*-$Bu_2Sn(OAc)_2$	83	86/14	90
4	**5**	*n*-$Bu_2Sn(OAc)_2$	86	88/12	90
5	**15**	*n*-$Bu_2Sn(OAc)_2$	75	87/13	89
6	**6**	*n*-$Bu_2Sn(OAc)_2$	63	83/17	89
7	**7**	*n*-$Bu_2Sn(OAc)_2$	73	73/27	94



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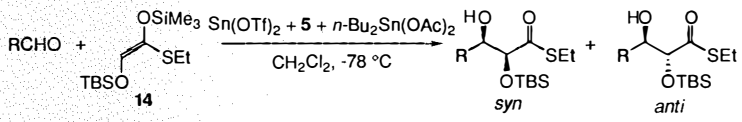
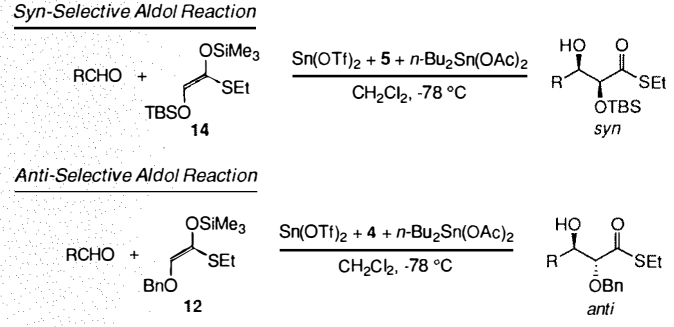


Table 10. Scope of the Asymmetric Aldol Reaction of **14**.

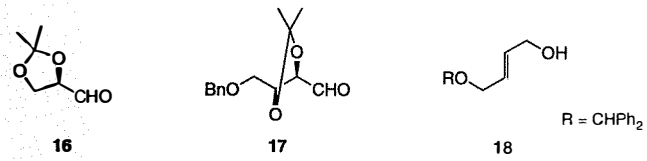
Entry	R	Yield %	*syn/anti*	ee %(*syn*)
1	Ph	86	88/12	90
2	CH_3CH_2	46	92/ 8	82
3		93	94/ 6	93
4	(*E*)-PhCH=CH	76	90/10	92
5	(*E*)-CH_3CH=CH	75	97/ 3	94
6	(*E*,*E*)-CH_3CH=CHCH=CH	83	93/ 7	94



Scheme 5. Synthesis of Optically Active *syn*- and *anti*-1,2-Diol Derivatives.

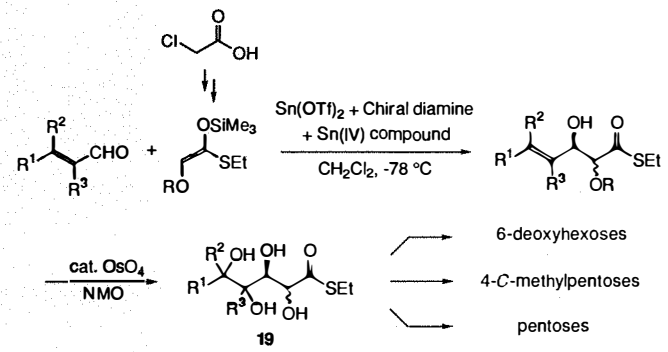
2.5. Synthesis of Monosaccharides

Chemical synthesis of monosaccharides made a great advance in the last decade based on the stereoselective addition reactions of 2,3-*O*-isopropylidene-D or L-glyceraldehyde (**16**)[29] or 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (**17**)[30] with enolate components or allyl nucleophiles. Many examples of the effective synthesis of sugars, including natural and unnatural forms, were reported. One of the starting materials in these syntheses, glyceraldehyde or a threose derivative, is prepared from a natural chiral pool, mannitol or tartaric acid, respectively.

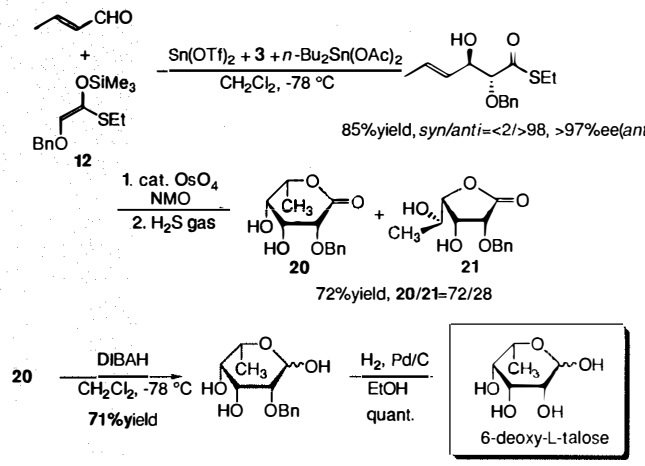


16 17 18

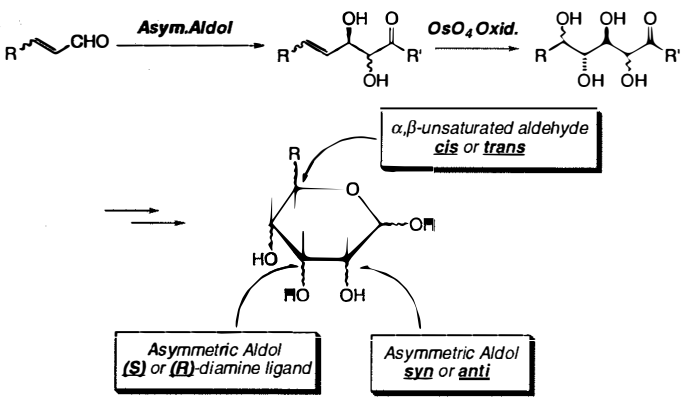
Scheme 6. Starting Materials for the Stereoselective Synthesis of Monosaccharides.



Scheme 7. Asymmetric Aldol Synthetic Route to Monosaccharides.



Scheme 8. Synthesis of 6-Deoxy-L-talose.



Scheme 9. General Synthetic Route to Monosaccharides.

Masamune and Sharpless recently reported the synthesis of L-hexoses starting from the achiral monoprotected allylic diol **18** using the Sharpless epoxidation as a key step.[31]

The plan to synthesize monosaccharides by the present asymmetric aldol reaction methodology is shown in **Scheme 7**. The achiral starting materials are α,β-unsaturated aldehydes and the silyl enol ethers of α-alkoxy thioesters, which are readily prepared from chloroacetic acid. The chiral induction in the aldol reaction between the α,β-unsaturated aldehydes and the silyl enol ethers is accomplished by using the chiral promoterconsisting of tin(II) triflate, a chiral diamine, and a tin(IV) compound. Subsequent oxidation of the olefinic part of the aldol adduct produces tetrahydroxy thioester derivatives **19**, which are useful precursors for the synthesis of various monosaccharides, including rare sugars.

One application of this methodology, the synthesis of 6-deoxy-L-talose, is shown in **Scheme 8**.[32] The asymmetric aldol reaction between crotonaldehyde and the silyl enol ether **12** was carried out in the presence of tin(II) triflate, chiraldiamine **3**, anddibutyltin diacetate. The corresponding aldol product was obtained in 85% yield with >97% enantiomeric excess. The subsequent oxidation of this chiral intermediate in acetone-water (8/1) at room temperature in the presence of a catalytic amount of osmium tetroxide and a stoichiometric amount of *N*-methylmorpholine oxide (NMO) resulted in the formation of the corresponding lactones **20** and **21** in 72% yield. The major lactone **20** was isolated and reduced with diisobutylaluminum hydride (DIBAH) in dichloromethane at -78 °C. Cleavage of the benzyl group with hydrogen over Pd/C in ethanol gave the desired 6-deoxy-L-talose in quantitative yield.

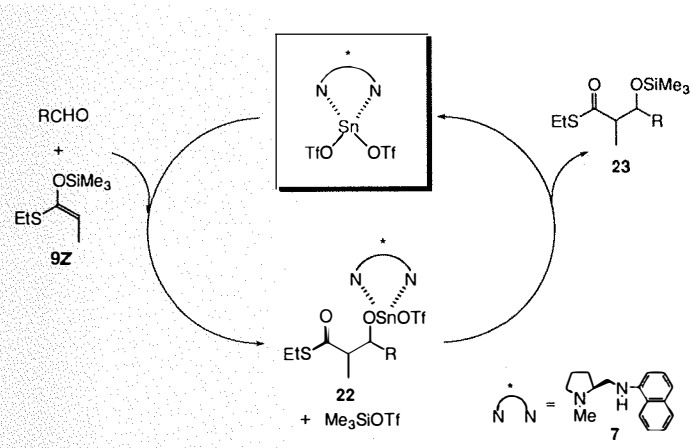
Several monosaccharides, including branched, deoxy, and amino sugars, were synthesized by this method.[33] Since the key asymmetric reactions—asymmetric aldol reaction and subsequent dihydroxylation—offer some flexibility in controlling the newly created chiral centers, the present method is expected to provide useful routes to various monosaccharides from achiral unsaturated aldehydes and chloroacetic acid, that is, without using any starting materials from the natural chiral pool (**Scheme 9**).

2.6. The Catalytic Asymmetric Aldol Reaction

In the previous sections, highly diastereo- and enantioselective aldol reactions of silyl enol ethers with aldehydes using a novel promoter system [stoichiometric amounts of tin(II) triflate, chiral diamine, and

tributyltin fluoride or dibutyltin diacetate] were described. Optically active aldol adducts were easily prepared in these reactions from achiral aldehydes and achiral silyl enol ethers, but a stoichiometric amount of a chiral auxiliary was still required. In the course of investigations to characterize the promoter system, the following catalytic cycle was envisaged to clarify the mechanism of these reactions and develop a truly catalytic aldol process (**Scheme 10**).[34]

Tin(II) triflate coordinated with a chiral diamine [a chiral tin(II) Lewis acid] interacts with an aldehyde; the silyl enol ether **9Z** then attacks the activated aldehyde to produce tin(II) alkoxide **22** and trimethylsilyl triflate (TMSOTf). When the exchange between tin(II) and silicon takes place smoothly



Scheme 10. The Catalytic Cycle of the Asymmetric Aldol Reaction.

Table 11. Synthesis of *syn*-α-Methyl-β-hydroxythioesters (solvent: CH_2Cl_2).[a]

Entry	R	Yield %	*syn/anti*	ee % (*syn*)
1	Ph	86	93/ 7	91
2	*p*-Cl C_6H_4	80	93/ 7	93
3	*p*-$CH_3C_6H_4$	82	78/22	80
4	$CH_3(CH_2)_6$	75	100/ 0	>98
5	*c*-C_6H_{11}	31	>99/ 1	74
6	(*E*)-CH_3CH=CH	51	84/16	77
7	(*E*)-$CH_3(CH_2)_2CH$=CH	62	81/19	74

a) Slow addition of **9Z** and aldehyde to the catalyst in dichloromethane over 9h at -78°C.

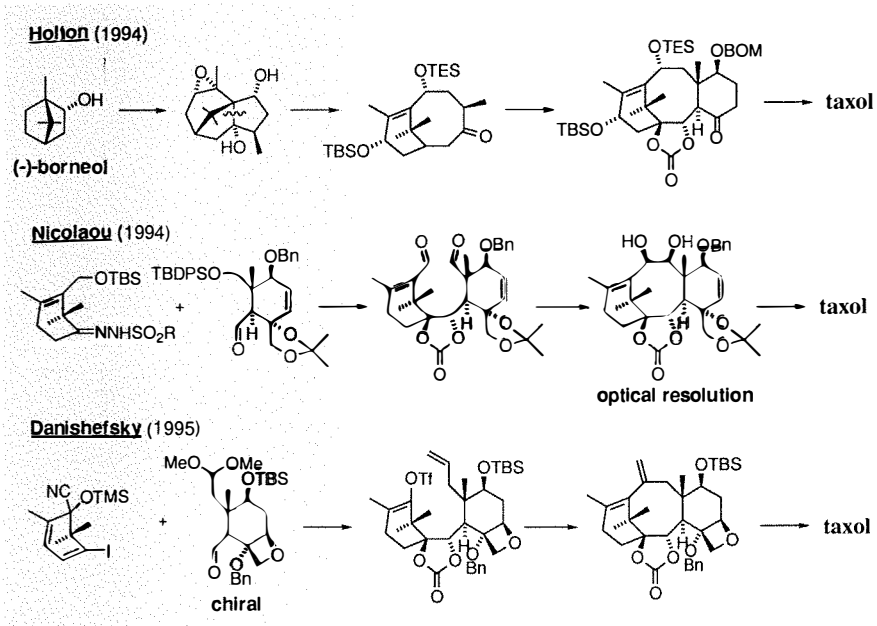
Table 12. Synthesis of *syn*-α-Methyl-β-hydroxythioesters (solvent: C_2H_5CN).

Entry	R	Addition Time/h	Yield %	*syn/anti*	ee % (*syn*)
1	Ph	3	77	92/ 8	90
2	*p*-ClC_6H_4	4.5	83	87/13	90
3	*p*-$CH_3C_6H_4$	3	75	89/11	91
4	$CH_3(CH_2)_6$	4.5	80	100/ 0	>98
5	*c*-C_6H_{11}	3	71	100/ 0	>98
6	(*E*)-CH_3CH=CH	3	76	96/ 4	93
7	(*E*)-$CH_3(CH_2)_2CH$=CH	3	73	97/ 3	93

in **22**, the corresponding aldol adduct is obtained as its trimethylsilyl ether **23** and the catalyst complex is regenerated. However, if the Sn ↔ Si exchange occurs slowly, an undesirable TMSOTf-promoted reaction takes place affording the achiral aldol adduct and resulting in a lower selectivity.[35]

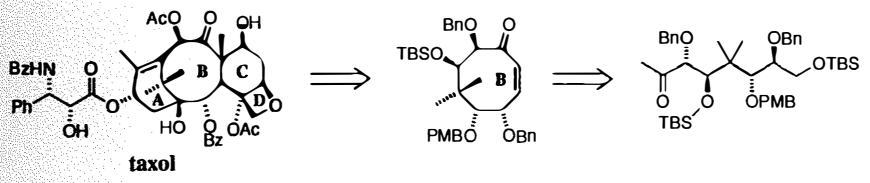
Based on these considerations, the substrates were slowly added to a solution of the catalyst in order to keep the trimethylsilyl triflate concentration as low as possible during the reaction: A dichloromethane solution of **9Z** and an aldehyde were added over 9 hours to a dichloromethane solution of the catalyst (20 mol%) (**Table 11**).[36] As expected, aldol adducts were obtained in good yields with excellent enantiomeric excesses and high diastereoselectivities in some cases. The selectivities were not as high, however, when *p*-tolualdehyde, α,β-unsaturated aldehydes, or cyclohexanecarboxaldehyde were used.

The lower selectivities were attributed to the incompleteness of the catalytic cycle, especially to the slowness of the Sn ↔ Si exchange between **22** and trimethylsilyl triflate. In order to accelerate this exchange, various polar solvents with low melting points (below -78 °C) were carefully examined using the reaction of **9Z** with

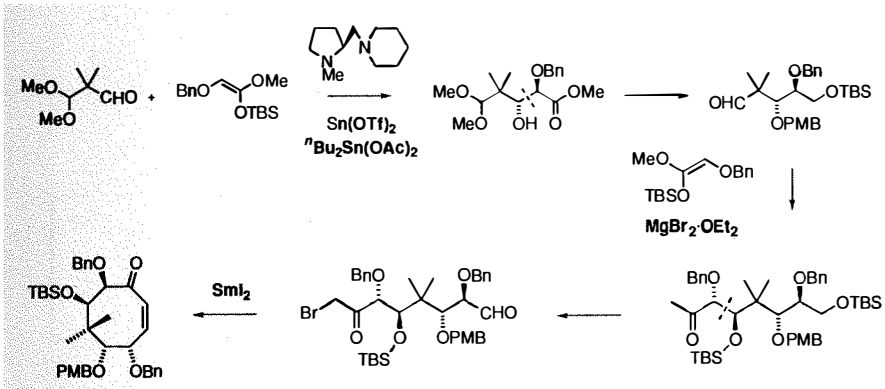


Scheme 11. Previous Syntheses.

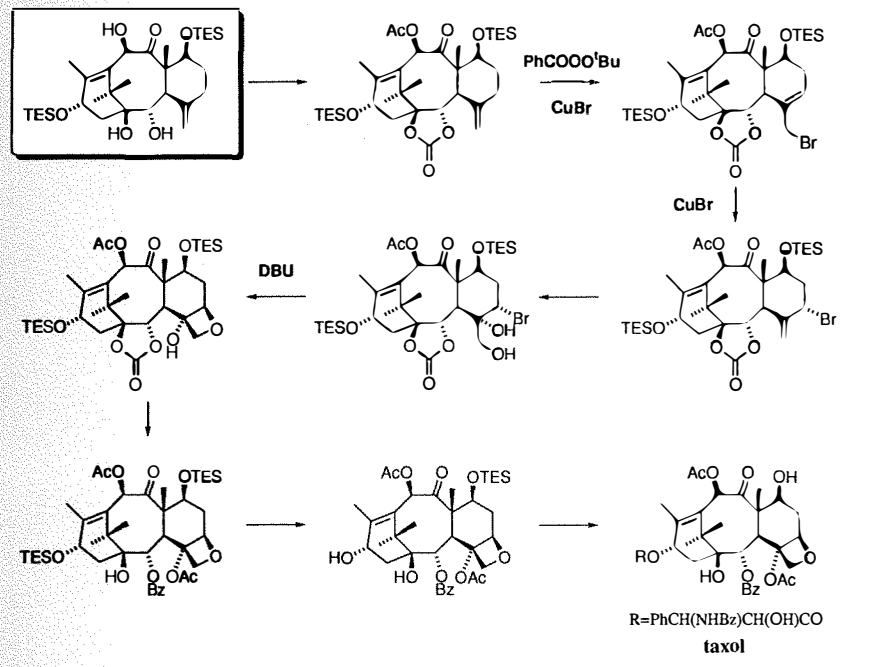
benzaldehyde as a model. Of these solvents, **propionitrile** (C_2H_5CN) was found to be the most effective.[37] An examination of the addition time (addition of the reactants to a solution of the catalyst) revealed that the rate of the Sn ↔ Si exchange is faster in propionitrile than in dichloromethane. While an addition time of 9 hours was necessary to attain the best results in dichloromethane, comparable selectivities were achieved when



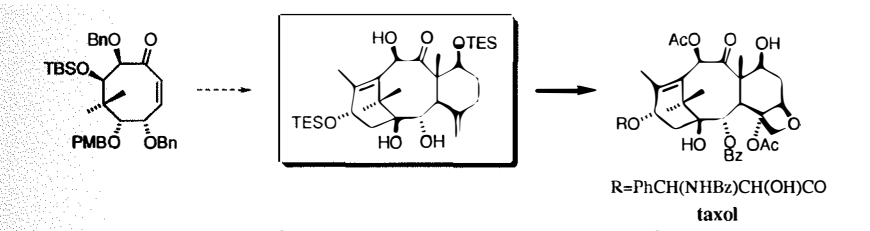
Scheme 12. Retrosynthesis.



Scheme 13. Synthesis of the B Ring System.



Scheme 14. Synthesis of the ABCD Ring System from Novel Taxoids.



Scheme 15. Synthetic Approach via the B Ring System.

the reactants were added to the catalyst over 3 hours in propionitrile.

It is worth noting that tin(II) triflate is more soluble in propionitrile than in dichloromethane, suggesting that the coordination of the nitrile group to tin(II) is rather strong. Nevertheless, when the chiral diamine is added to this propionitrile solution of tin(II) triflate, the ligand exchange of the diamine for the nitrile takes place smoothly to form the desired chiral Lewis acid. Although tin(II) triflate is also soluble in tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME), the aldol reaction that uses chiral diamine **7** did not proceed at -78 °C in either of these two solvents.

This catalytic asymmetric aldol reaction was carried out using aromatic, aliphatic, and α,β-unsaturated aldehydes, and the desired products were obtained in good yields with high selectivities (>90%ee, **Table 12**). In particular, the lower yields or selectivities previously observed in the reaction of *p*-tolualdehyde, (*E*)-crotonaldehyde, (*E*)-2-hexenal, and cyclohexanecarboxaldehyde, were remarkably improved by using propionitrile as a solvent. High selectivities were also achieved even when 10 mol% of the catalyst was employed.[38]

2.7. An Approach to the Asymmetric Synthesis of Taxol

Taxol, a substance isolated from the Pacific yew tree, was found to have anticancer properties, and its complex structure has long been a tempting target for synthetic chemists. Total syntheses of taxol were reported by Holton and Nicolaou in 1994, and by Danishefsky in 1995 as sketched in **Scheme 11**.[39]

Our strategy for synthesizing the basic skeleton of taxol is based on our recently established, highly controlled enantioselective aldol reaction. It involves assembling first the chiral B ring system from an optically active polyoxy unit, and then fusing the A and C ring systems onto it. This plan has flexible possibilities since the key intermediate, the B ring system, is synthesized from a chiral linear compound.

The chemistry described in **Schemes 12-16** is not a completed total synthesis of taxol; information on the steps marked with solid lines is given in the references.[40] The dotted lines represent reaction steps that had not yet been completed when this manuscript was submitted.

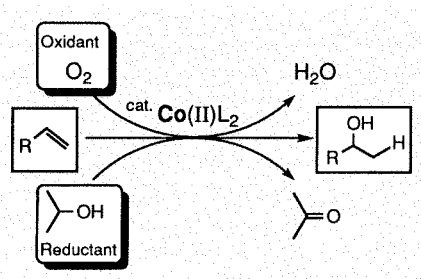
3. Catalytic Oxygenations of Olefins with Molecular Oxygen

In the fall of 1987, Mitsui Petrochemical Industries, Ltd. (MPC) opened a research

laboratory named "Advanced Technology Center" in the Chiba area (about 80 minutes from Tokyo by train). I was asked by the president of the company, Mr. Shogo Takebayashi, to start a basic synthetic chemistry research laboratory there. Kindly enough, the company offered me four excellently equipped laboratories and a staff of five selected from its employees.

I was very anxious at first about choosing the most suitable topic that would satisfy one's purely scientific interest and still have industrial benefits. Soon I figured that if I were to pick the chemistry of olefins, the topic might bring profitable results for the sponsoring petrochemical company while still stirring my personal interests. The study of metal complex catalysts that allow one to control reactivity and regioselectivity by the judicious choice of their ligands would be of particular interest. Therefore, I started out by studying the oxygenation of olefins with molecular oxygen using as a catalyst a metal complex containing a 1,3-diketone ligand.

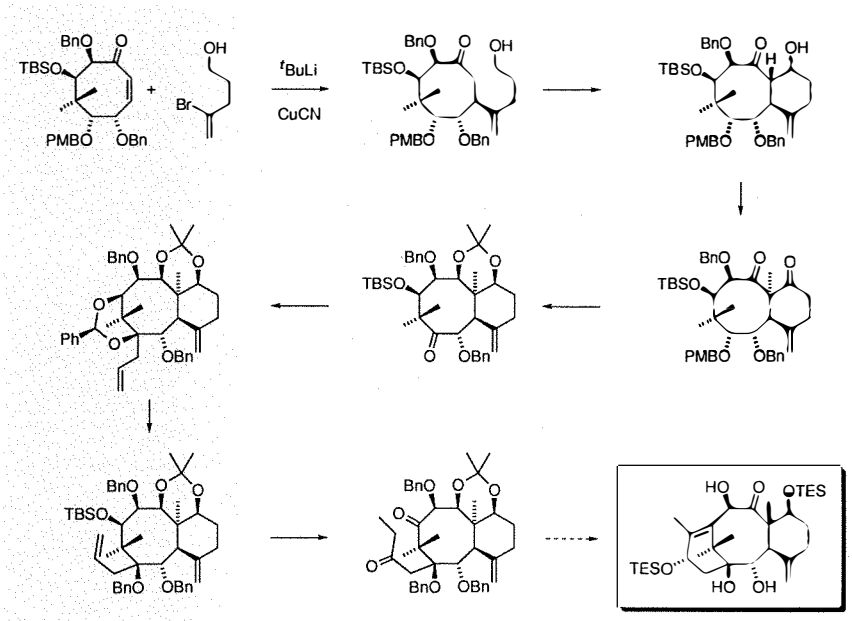
Molecular oxygen is the most readily available oxidant for chemical processing and is successfully employed even in mass production. However, such oxygenation



Scheme 17. Oxidation-Reduction Hydration.

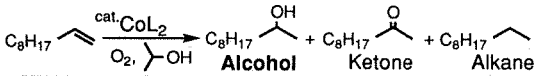
reactions have some limitations since they are carried out under severe conditions of temperature, pressure, or both. All possible efforts must be made then to develop efficient oxygenation reactions that can be performed under mild conditions.

In aerobic oxidations catalyzed by transition-metal complexes the transition-metal complex captures and activates molecular oxygen. The stereochemical and electrochemical properties of such a complex can be tuned by modifying its system of organic ligands. The suitable combination of three components—a transition-metal, organic ligand, and a reductant—offers the possibility of creating an effective oxygenation system in such aerobic reactions. Thus, several reactions that include the combined use of molecular oxygen and reducing agents have been investigated.



Scheme 16. Synthetic Studies on the ABC Ring System.

Table 13. Effects of Ligands in (β-Diketonato)cobalt(II) Complexes.



Entry	Ligand (LH)	Yields % Alcohol	Ketone	Alkane
1	(Hacac)	45	7	22
2	(Hecbo)	72	14	2
3		59	17	15
4	(Hmodp)	74	7	5
5	(Htfa)	81	13	2

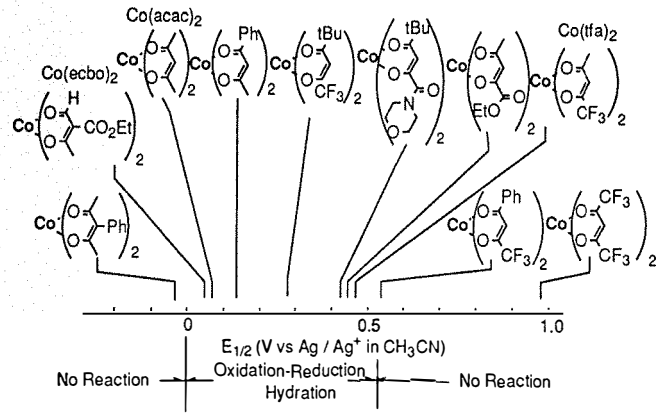


Figure 1. Redox Potential of Co(II) Complexes.

3.1. Cobalt(II)-Catalyzed Oxidation-Reduction Hydration

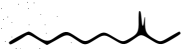
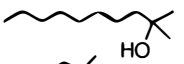
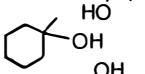
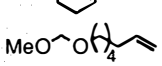
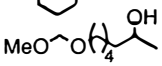
After screening several metals, cobalt(II) complexes with 1,3-diketone ligands were chosen. Various 1,3-diketone derivatives are easily prepared by a conventional synthetic procedure, and they are able to regulate the stereochemical and electrochemical properties of the coordinated complexes.

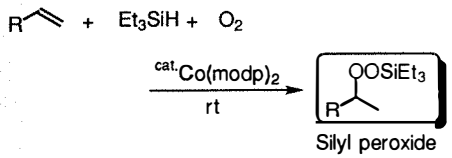
Our research on the oxygenation of olefins with molecular oxygen started with one observation: When 4-phenyl-1-butene was treated with 1 atmosphere of molecular oxygen in the presence of a catalytic amount of bis(acetylacetonato)cobalt(II), an oxygenated product, 4-phenyl-2-butanol, was formed as a major product along with 1-phenylbutane and 4-phenyl-2-butanone. It was suggested that the above reaction would proceed smoothly in secondary alcohols such as 2-propanol.[41] These results indicated that the (1,3-diketonato)cobalt(II)-catalyzed oxygenation reaction afforded mainly the corresponding hydrated product directly from the olefin via concomitant transfer of oxygen and hydrogen atoms, even under neutral and mild conditions. Therefore, both oxidation (oxygenation) and reduction (hydrogenation) proceeded at the same time in this hydration reaction; thus, it was named "Oxidation-Reduction Hydration" (**Scheme 17**).

Examination of the catalytic activity of several cobalt(II) complexes having various 1,3-diketone-type ligands (**Table 13**) indicated that the ratio of the three products—hydrated product (alcohol), oxidized product (ketone), and reduced product (alkane)—was influenced by the structure of the ligand.[42] The selectivity towards hydration was increased when cobalt(II) complexes coordinated with a ligand containing an electron-withdrawing group were employed. Finally, the yield of alcohol was improved to 81% by using bis(trifluoroacetylacetonato)cobalt(II) as the catalyst. To elucidate the effect of ligand on catalytic activity, the redox potentials of the above cobalt(II) complexes were measured (**Figure 1**).[43] Complexes with redox potentials between those of Co^{2+} and Co^{3+}, in the range 0.0 V to +0.5 V, were effective catalysts.

This Oxidation-Reduction Hydration was successfully applied to various olefins. Acyclic and cyclic olefins, trisubstituted and 1,1-disubstituted olefins were converted into the corresponding tertiary alcohols in more than 10,000% yield based on the catalyst (**Table 14**). Since the Oxidation-Reduction Hydration is performed under neutral and mild conditions, olefins containing an acetal group could be transformed into the desired hydrated product in high yield.

Table 14. Oxidation-Reduction Hydration Catalyzed by $Co(ecbo)_2$.

Entry	Olefin	Alcohol	% Yield based on catalyst
1			10,110
2			9,780
3			10,370
4			9,340

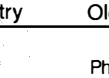
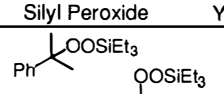
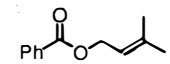
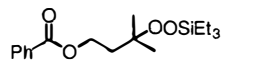
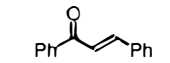
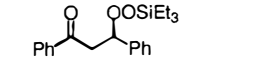


Scheme 18. Direct Peroxygenation of Olefins.

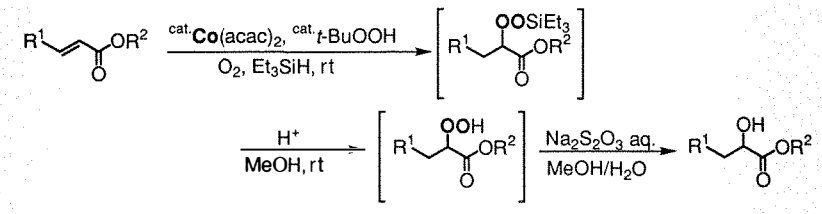
3.2. Catalytic Peroxygenation

Silane is known to be one of the most reliable reductants in organic synthesis.[44] When triethylsilane was employed in place of 2-propanol as a mild reductant,[45] an unexpected peroxygenated product, the triethylsilylperoxy derivative, was obtained.[46] For example, 4-phenyl-1-butene reacted with molecular oxygen and triethylsilane in the presence of a catalytic amount of bis(acetylacetonato)cobalt(II) complex to give the corresponding 1-phenyl-3-(triethylsilylperoxy)butane in good yield. Detailed screening of various cobalt(II) complexes revealed that $Co(modp)_2$ was the most effective catalyst in this type of peroxygenation (**Scheme 18**). The silylperoxy group was introduced into olefins with complete regioselectivity according to Markownikoff's rule (**Table 15**). The present peroxygenation reaction provides a simple and efficient method for the direct introduction of dioxygen into the carbon-carbon double bond of various olefinic compounds under mild conditions.

Table 15. Peroxygenation of Various Olefins Catalyzed by $Co(modp)_2$.

Entry	Olefin	Silyl Peroxide	Yield %
1			95
2			80
3			99
4			75

Besides simple olefins, several α,β-unsaturated esters were also peroxygenated to produce the corresponding triethylsilylperoxy derivatives.[47] In the presence of a catalytic amount of *t*-butyl hydroperoxide, the present peroxygenation proceeded smoothly and regioselectively to afford the corresponding α-triethylsilylperoxy esters in high yields (**Scheme 19**). When phenylsilane[48] was employed in place of triethylsilane, the silylperoxy intermediates formed by peroxygenation of the α,β-unsaturated esters were reduced in a one-pot process to the corresponding α-hydroxy carboxylic acid esters in high yields. Moreover, the manganese(II) complex, bis(dipivaloylmethanato)manganese(II) [$Mn(dpm)_2$], was a more effective catalyst for the



Scheme 19. Hydration of α,β-Unsaturated Carboxylic Acid Esters.

direct hydration of α,β-unsaturated esters than the cobalt(II) complexes (**Table 16**).[49]

3.3. Nickel(II)-Catalyzed Epoxidation

Epoxides are some of the most useful synthetic intermediates for the preparation of natural products or the production of epoxy resins. Peroxy acids are often employed as convenient oxidants in the synthesis of epoxides. Hydroperoxides are also useful oxidants for the epoxidation of allyl alcohols catalyzed by vanadium(IV) complexes.[50] Since peroxy compounds have potentially explosive properties, careful handling is always required. In contrast, molecular oxygen is a fairly safe, clean, and abundant oxidant. Therefore, much effort has gone into developing a direct and selective epoxidation of olefins that uses molecular oxygen.

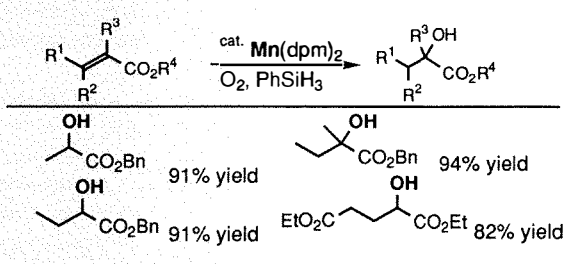
Our observations in the "Oxidation-Reduction Hydration" were that one oxygen atom from molecular oxygen and two hydrogen atoms from 2-propanol were introduced at the same time into the olefin to form the hydrated product. Since the secondary alcohol behaved as an effective reductant in the hydration reaction, it was anticipated to function as a reliable reductant in the epoxidation of olefins with molecular oxygen. Indeed, norbornene analogs were monooxygenated to the corresponding epoxides in good yields in the presence of 2-propanol, molecular oxygen, and a catalytic amount of bis(2-alkyl-1,3-diketonato)oxovanadium(IV) (**Scheme 20**).[51]

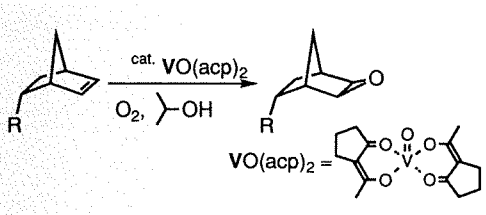
In a search for reductants[52] other than alcohols for the aerobic epoxidation of olefins, aldehydes gave excellent results at room temperature (**Scheme 21**):[53] Various trisubstituted, 1,1-disubstituted olefins, and norbornene analogs were smoothly monooxygenated to the corresponding epoxides in high-to-quantitative yields at room temperature and under an oxygen pressure of 1 atmosphere. It should be stressed that in no case, nor to any extent, did overoxidation at the allylic position or cleavage of the carbon-carbon double bond take place. For the aerobic epoxidation of 1,2-disubstituted olefins, the use of a smaller amount of the nickel(II) complex was sufficient to result in good yields of the corresponding epoxides. Bis[1,3-bis(*p*-methoxyphenyl)-1,3-propanedionato]-nickel(II) [Ni(dmp)$_2$, **Figure 2**] was the most potent catalyst for the present epoxidation of a wide variety of olefins (**Table 17**). Isovaleraldehyde was remarkably effective in the epoxidation of terminal olefins; the corresponding 1,2-epoxyalkanes were obtained in good-to-high yields.[54]

When an iron(III) complex was used as the catalyst, epoxy alcohols were obtained from alkenols in quantitative yield without any overoxidation of the hydroxyl group, whereas nickel(II) complex-catalyzed epoxidation of citronellol stopped halfway, and the yield of the epoxy alcohol was only moderate.[55] Bis(acetylacetonato)-nickel(II) and tris(acetylacetonato)iron(III) exhibited excellent catalytic activities in the epoxidation of aliphatic and aromatic olefins but were ineffective in the oxygenation of α,β-unsaturated carboxamides. In this latter case, bis(dipivaloylmethanato)oxo-vanadium(IV) [VO(dpm)$_2$] was an appropriate catalyst. An α,β-unsaturated carboxamide was oxygenated by the combined use of molecular oxygen and isovaleraldehyde to afford the corresponding epoxide in 87% yield (**Scheme 22**).[56] Although several patents on the use of molecular oxygen and aldehyde are known, the reported yields are not always high.

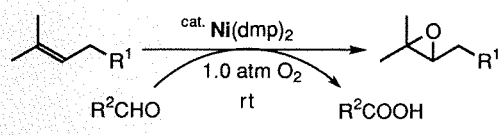
Oxidation of cholesteryl benzoate with peroxy acids such as *m*-CPBA or MMPP (magnesium monoperoxyphthalate hexahydrate) yielded a mixture of the corresponding 5,6-α- and 5,6-β-epoxides in the ratio of 71 to 29 (*m*-CPBA, entry 1 in **Table 18**). In contrast, epoxidation with molecular oxygen and isobutyraldehyde in the presence of a catalytic amount of nickel(II), iron(III), or manganese(II) coordinated by 1,3-diketones led to the formation of

Table 16. Manganese(II)-Catalyzed Hydration of α,β-Unsaturated Esters.





Scheme 20. Vanadium-Catalyzed Aerobic Epoxidation.



Scheme 21. Aerobic Epoxidation by the Nickel(II)-Aldehyde Procedure.

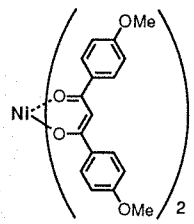
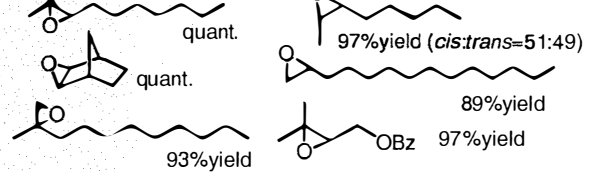
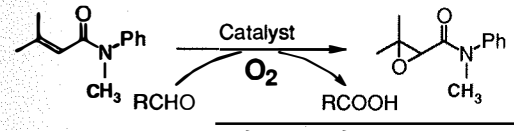


Figure 2. Ni(dmp)$_2$, Catalyst for Aerobic Epoxidation.

Table 17. Nickel-Catalyzed Aerobic Epoxidation of Various Olefins.

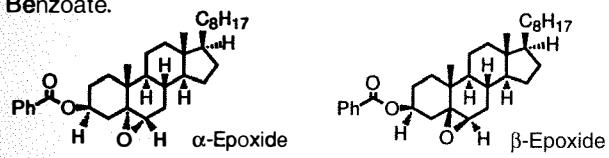




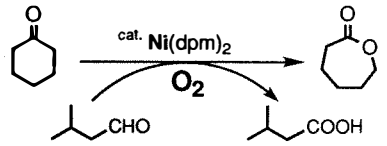
Catalyst	Conversion %	Yield %
$Ni(acac)_2$	—	trace
$Fe(acac)_3$	33	26
$VO(dpm)_2$	92	87

Scheme 22. Epoxidation of an α,β-Unsaturated Carboxamide.

Table 18. β-Stereoselective Epoxidation of Cholesteryl Benzoate.



Entry	Epoxidation reagent	α-Epoxide : β-Epoxide
1	*m*-CPBA	71 : 29
2	cat. $Ni(dmp)_2$, O_2, >CHO	31 : 69
3	cat. $Mn(dpm)_2$ O_2, >CHO	20 : 80



Scheme 23. Aerobic Baeyer-Villiger Reaction.

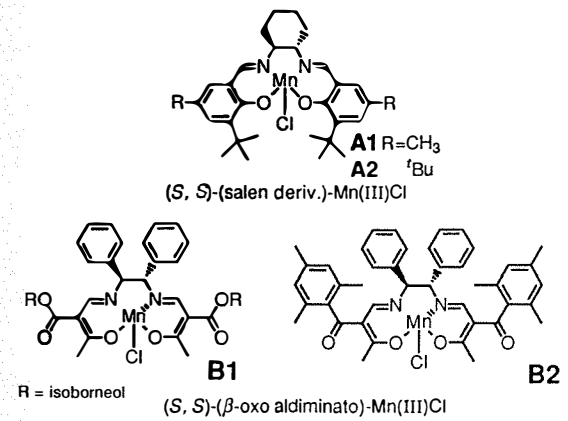
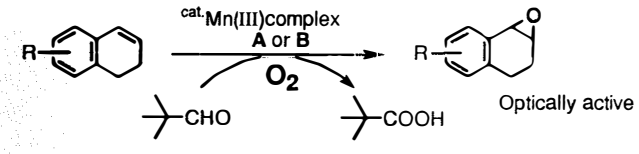


Figure 3. Optically Active Manganese(III) Catalysts for Aerobic Enantioselective Epoxidations.



Scheme 24. Aerobic Enantioselective Epoxidation Catalyzed by Mn(III) Complexes.

the *hindered* 5,6-β-epoxide as the major product.[57] This remarkable reversal of stereoselectivity in the epoxidation of cholesterol indicates that the active oxidant in this case is obviously not a simple peroxy carboxylic acid (generated from the aldehyde in an autooxidative manner), and that the manganese complex participates directly in the oxidation step. An enantioselective aerobic epoxidation should therefore take place when optically active manganese complexes are used as catalysts (see section 3.5).

3.4. Baeyer-Villiger Oxidation

In the preceding aerobic epoxidation reaction, one oxygen atom from molecular oxygen oxidizes a carbon-carbon double bond (substrate) to afford the corresponding epoxide, while the other oxygen atom is captured by an aldehyde (reductant) to form the corresponding carboxylic acid. The Baeyer-Villiger reaction is one of the typical one-oxygen transfer reactions in organic synthesis, and hydrogen peroxide or organic peroxy acids such as peracetic acid and *m*-CPBA are generally employed as the oxygen source. Among several attempts to achieve an aerobic Baeyer-Villiger reaction, the preparation of ε-caprolactone from cyclohexanone by the combined use of an aldehyde and a transition-metal catalyst has been reported, but the selectivity for ε-caprolactone or the conversion of cyclohexanone were not satisfactory.

Cyclohexanone is smoothly converted into ε-caprolactone in the presence of molecular oxygen, isovaleraldehyde, and a catalytic amount of nickel(II) coordinated by 1,3-diketones (**Scheme 23**).[58] Cyclohexanones substituted in the 2 or 4 position were also oxidized to the corresponding ε-caprolactones in high yields without any accompanying overoxidation products.

3.5. Enantioselective Epoxidation of Unfunctionalized Olefins Catalyzed by Chiral Manganese(III) Complexes

Optically active epoxides have received a great deal of attention as versatile intermediates for the synthesis of a wide variety of chiral compounds, including biologically active compounds and functional organic materials. The reliable enantioselective titanium(IV)-catalyzed epoxidation of allylic alcohols is performed by using *t*-butyl hydroperoxide as an oxidant and leads to optically active 2,3-epoxy alcohols with very high enantiomeric excesses. The procedure has been applied widely to the synthesis of a number of natural products. Many approaches to develop efficient, enantioselective epoxidations of unfunctionalized olefins have also been studied. Several biological systems that use an enzymatic catalyst have been employed in the enantioselective epoxidation of terminal alkenes. Nonenzymatic systems such as artificial metal porphyrins have been designed as cytochrome P-450 models that catalyze the enantioselective epoxidation of styrene analogs. Recently, Jacobsen and Katsuki independently reported that manganese(III) salen complexes and terminal oxidants such as iodosylbenzene, sodium hypochlorite,[59] or hydrogen peroxide[60] are effective catalytic systems for the enantioselective epoxidation of unfunctionalized olefins. Except for artificial bleomycin,[61] few have used molecular oxygen for the enantioselective epoxidation of simple olefins.

The aerobic enantioselective epoxidation of unfunctionalized olefins has been performed in the presence of molecular oxygen, pivalaldehyde, and a catalytic amount of optically active manganese(III) complexes of salen derivatives (**A1** and **A2** in **Figure 3**) or (β-oxo aldiminato)manganese(III) complexes (**B1** and **B2** in **Figure 3**) (**Scheme 24**). Various (β-oxo aldiminato)-manganese(III) complexes (type **B1**) were synthesized from the corresponding alkyl(R) acetoacetate[62] and acetophenone derivatives in a few steps. After screening various aldehydes, it was found that the use of pivalaldehyde provided good enantioselection and high

chemical yields. When a salen-type catalyst was used, addition of a catalytic amount of *N*-methylimidazole was effective in improving the optical yield of the epoxide. Interestingly, the absolute configuration of the epoxide obtained was reversed by the addition of *N*-methylimidazole.

As deduced from an X-ray diffraction study,[63] the most potent ligands were rationally designed based on the prediction that bulkiness in the ester moiety of type **B1** ligands would influence the optical yield. Thus, the Mn(III)Cl complexes containing the isoborneol moiety (**B1**) and the mesitoyl side chain (**B2**) were prepared (**Figure 4**).

The present aerobic oxidation system was applied to the enantioselective epoxidations of various simple olefins (**Table 19**). Dihydronaphthalenes were converted into the corresponding optically active epoxides in good yields with moderate-to-good enantioselectivities. The enantioselective aerobic epoxidation of 7-membered cyclic olefins afforded the corresponding epoxides with high enantiomeric excess in the presence of the Mn(III) complex [salen-Mn(III)Cl **A1**: 83%ee, (β-oxo aldiminato)-Mn(III)Cl **B1**: 84%ee]. Chromene derivatives[64] and simple acyclic olefins were also converted into the corresponding optically active epoxides with high enantioselectivities.

It should be pointed out that the (*S,S*)-complex catalyst in the present aerobic epoxidation afforded the (*1R,2S*)-epoxide (entry 1, **Table 20**), whereas the opposite (*1S,2R*)-epoxide was formed by using sodium hypochlorite or iodosylbenzene as the oxidant (entries 2 and 3, **Table 20**). Furthermore, in the presence of a catalytic amount of *N*-methylimidazole the absolute configuration of the epoxide was completely reversed: The epoxide with the (*1S,2R*)-configuration was formed in the *aerobic* epoxidation using the (*S,S*)-complex. These results suggested that the reactive intermediate leading to the (*1R,2S*)-epoxide was different from that giving rise to the (*1S,2R*)-epoxide when *N*-methylimidazole was present. Similarly, the (*1R,2S*)-(+)-epoxide resulted when the epoxidation was carried out by using peracetic acid as the oxidant instead of the combined system—molecular oxygen and pivalaldehyde. The absolute configuration of the epoxide was again reversed to (*1S,2R*)-(-) by addition of *N*-methylimidazole.[65]

Figure 5 shows tentative structures for the presumed intermediates in the present epoxidation. The (acylperoxo)manganese complex **I** is formed in the first step from molecular oxygen, pivalaldehyde, and the manganese(III) complex. In the absence of *N*-methylimidazole, (acylperoxo)-(*S,S*)-salen-Mn(III) complex **I** reacts with the olefin to afford the (*1R,2S*)-(+)-epoxide. Complex **I**, on the other hand, is converted into (oxo)manganese complex **II** in the presence of *N*-methylimidazole by coordination of the latter as an axial donor ligand. Complex **II** is widely accepted as the reactive intermediate in epoxidations employing terminal oxidants. Moreover, reversal of enantiofacial selection was observed in the aerobic enantioselective epoxidation of 1-propenylbenzene catalyzed by chloro(β-oxoaldiminato)manganese(III).[66] These results clearly indicate that the reactive species in the current aerobic, enantioselective epoxidation is different from the (oxo)manganese complex intermediate generated from the chiral manganese(III) catalyst and terminal oxidants such as sodium hypochlorite or iodosylbenzene. Since the combined use of (*S,S*)-(α-aminomethylene-β-diketone)Mn(III)Cl **B2** and peracetic acid also afforded the (*1R,2S*)-epoxide, it is reasonable to assume that the (acylperoxo)manganese complex generated from the optically active manganese catalyst, molecular oxygen, and pivalaldehyde is the key intermediate in this reaction (**I, Figure 5**).

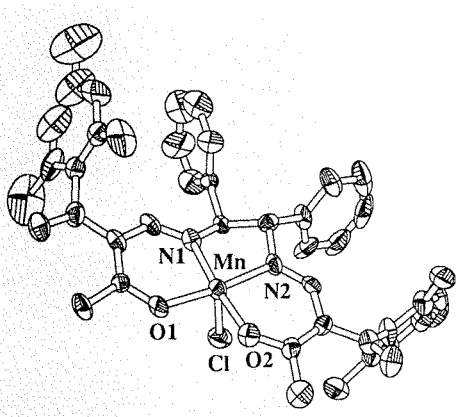


Figure 4. X-ray Analysis of Mn(III) Complex B2.

Table 19. Aerobic Enantioselective Epoxidation of Various Olefins.

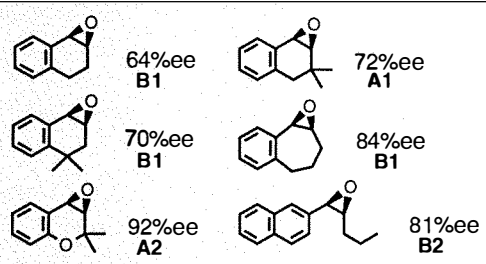


Table 20. Absolute Configuration of Epoxide; Catalyst = [(*S,S*)-salen deriv.]-Mn(III) Complex **A1**.

Entry	Oxidant	Major product
1	O_2, ⟩CHO	(*1R,2S*)-(+)
2	NaClO	(*1S,2R*)-(-)
3	PhIO	

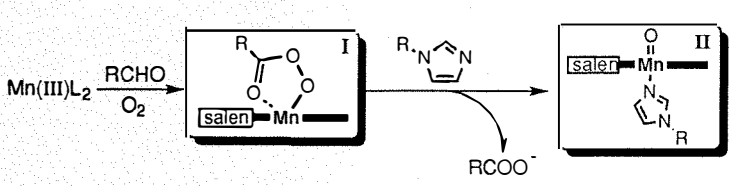
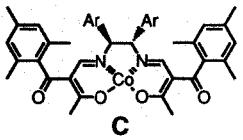


Figure 5. Reactive Intermediates I and II.

4. Enantioselective Borohydride Reduction Catalyzed by Cobalt(II) Complexes

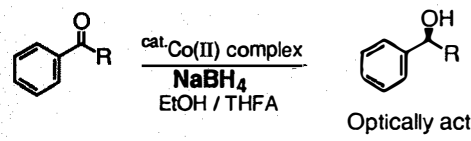
A wide variety of asymmetric reducing agents have been developed for the enantioselective reduction of prochiral ketones; the combination of chiral oxazaborolidine catalysts with borane is most noteworthy.[67] The asymmetric hydrogenation catalyzed by optically active BINAP-Ru(II) complexes has also recently been reported.[68]



C

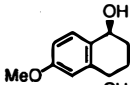
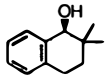
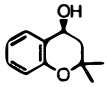
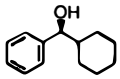
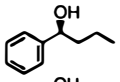
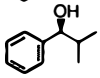
C1 : Ar =phenyl
C2 : 3,5-dimethylphenyl
C3 : 2,4,6-trimethylphenyl

Figure 6. (*S,S*)-(β-Diketonato)-Co(II).

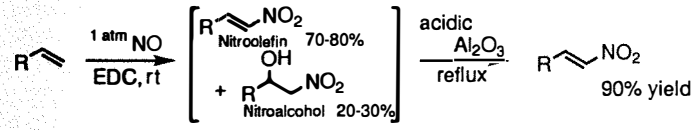


Scheme 25. Enantioselective Borohydride Reduction.

Table 21. Enantioselective Reduction Catalyzed by Optically Active Cobalt(II) Complex.

Entry	Catalyst	Product[a]	Optical yield[b]
1	C2		90%ee
2	C2		93%ee
3	C1		91%ee
4	C2		92%ee
5	C3		95%ee
6	C2		97%ee
7	C2		98%ee

a) (*S,S*)-Complex catalyst was employed.
b) Chemical yields >98%.



Scheme 26. Convenient Nitration of Olefins.

Sodium borohydride is one of the most common industrial reducing agents because of its safe handling and reasonable cost. Its utilization in enantioselective reductions, however, has been limited to only a few examples. Combining $NaBH_4$ with a catalytic amount of β-diketonato cobalt(II) complex **C** (**Figure 6**) provides a novel method for the enantioselective borohydride reduction of prochiral ketones (**Scheme 25**).[69] The optically active β-oxo aldimine ligands were rationally designed and effectively employed in the enantioselective aerobic epoxidation of olefins as mentioned above. Several such ligands containing optically active diamine moieties were prepared, and the corresponding optically active β-diketonato cobalt(II) complexes **C1**, **C2**, and **C3** were synthesized (**Figure 6**). The choice of catalyst and alcohol was critical for achieving high enantioselection.[70] The use of tetrahydrofurfuryl alcohol (THFA) or its derivatives and ethanol (or methanol) with sodium borohydride significantly improved the enantiofacial selectivity.[71]

Using sodium borohydride pre-modified with THFA,[72] ethanol, and a 0.1-1 mol% amount of the above-mentioned cobalt(II) complex catalysts, the enantioselective borohydride reduction of arylketones afforded the corresponding optically active alcohols in quantitative yields and high enantiomeric excesses within a few hours at 0 °C. By optimizing these factors, a practical enantioselective reduction of arylketones was achieved (**Table 21**). Studies of the mechanism of the present reduction system are ongoing.

5. Nitration of Olefins with Nitrogen Monoxide

Nitrogen monoxide (NO) is commercially available and used industrially for the mass production of nitric acid. Its chemistry in the fields of biochemistry, medicine, and environmental sciences has been the focus of considerable attention recently. Nitrogen monoxide is a highly reactive radical that should be a convenient nitrogenating reagent. A few reports on nitrogen monoxide are found in the synthetic organic chemistry literature; for example, the oximation of styrene and α,β-unsaturated amides catalyzed by a cobalt(II) complex.[73]

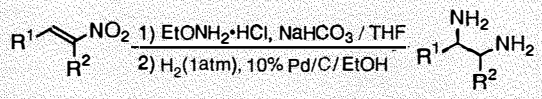
A convenient preparative method for nitroolefins was recently developed.[74] Treatment of various olefins with an atmospheric pressure of nitrogen monoxide at room temperature afforded the corresponding nitroolefins in fairly good yields along with the nitroalcohols in a ratio of about 8:2. The nitroalcohol by-products were converted into the corresponding nitroolefins by dehydration with acidic alumina resulting in high total yields. This simple and convenient nitration procedure was applied successfully to the preparation, in good-to-high yields, of nitroolefins derived from various terminal olefins or styrene (**Scheme 26**).

In the present nitration reaction, the introduction of the nitro group (NO_2) into olefins using only nitrogen monoxide (NO) implies that oxidation-reduction processes are also taking place. Generation of nitrogen was detected by GC analysis, in amounts 1 to 1.4 times that of the olefin consumed. The pH of the reaction solution was weakly acidic at the end of the reaction. Based on the amount of olefin consumed, a stoichiometric amount of nitrous acid (HNO_2) was formed as determined by quantitative analysis. On the basis of these observations, the probable stoichiometry of the reaction was proposed.[75]

Since vicinal diamines are reliable building blocks of various natural products and medicinal compounds, or ligands for metal complexes, several preparative methodologies are known: substitution of the corresponding alkyl halide or alcohol, ring-opening of aziridines, reductive conversion of diazides, or coupling of imines. A convenient, preparative, one-pot synthesis of 1,2-diamines

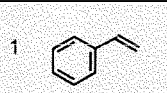
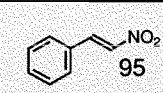
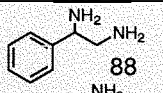
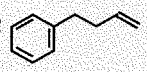
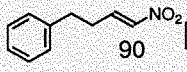
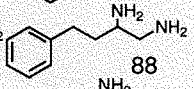
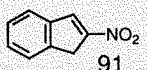
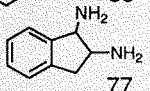
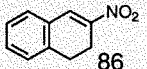
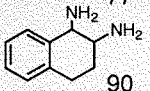
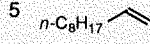
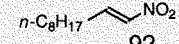
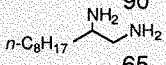
was developed recently. It involves the preparation of the appropriate nitroolefin by the above-mentioned nitration reaction. This is followed by Michael addition of amino group equivalents to the nitroolefin and subsequent reduction to the 1,2-diamine (**Scheme 27**).

After examining various amino group equivalents, *O*-ethylhydroxylamine was found to be excellent for the production of the corresponding 1,2-diamine in good-to-high yields. Michael addition of *O*-ethylhydroxylamine to the nitroolefin proceeded smoothly and was followed by the addition of palladium catalyst (10% Pd/C) and ethanol. This mixture was stirred under an atmospheric pressure of hydrogen at room temperature to afford the desired 1,2-diamine. Thus, the 1,2-diamine is available from the olefin in only two reaction steps (**Table 22**).[76]



Scheme 27. Conversion of Nitroolefins into 1,2-Diamines.

Table 22. Nitroolefins and 1,2-Diamines from Various Olefins.

Entry	Olefin	Nitroolefin Yield %	1,2-Diamine Yield %
1		 95	 88
2		 90	 88
3		 91	 77
4		 86	 90
5		 92	 65

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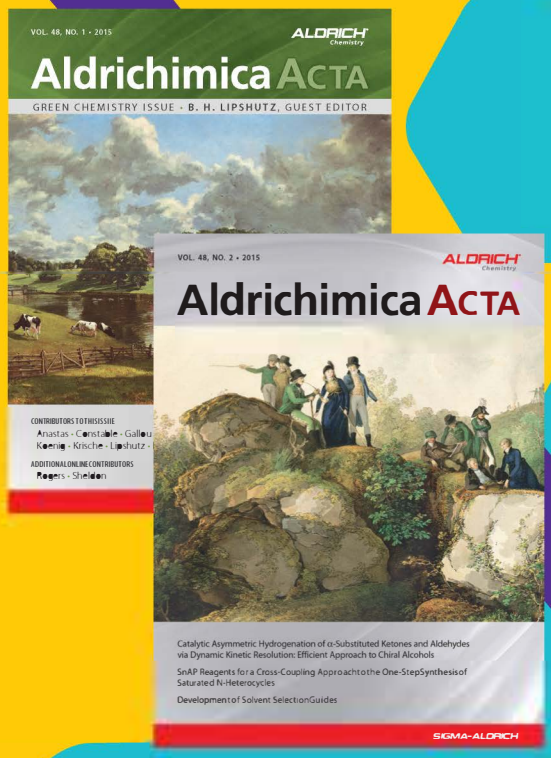

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