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Asymmetric Synthesis Using Rhodium-Stabilized Vinylcarbenoid Intermediates

*Dimethyl Tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3,4-dicarboxylate:
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Aldrichimica Acta



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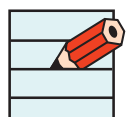
The Simon Vouet (1590–1649) painting on our cover, *The Muses Urania and Calliope* (oil on wood 31 1/8 x 49 3/8 in.), depicts two allegorical female figures reclining in front of a classical portico. On the left is the Muse of Astronomy, Urania, robed in celestial blue, wearing a diadem of six stars, and supported by an astral globe. She is accompanied by one of her eight sisters, Calliope, the Muse of Epic Poetry. Calliope holds a bound volume of Homer's *Odyssey*, one of the best known epic poems she inspired.

In all probability, this tranquil scene is part of a series executed by Vouet for a wealthy Parisian patron in the 1630s. The entire ensemble does not seem to have survived, but four other remaining works suggest that the picture's original context was a decorative scheme illustrating all nine Muses and the god of intellect, Apollo, whom they served. The picture's compositional elegance, figural equilibrium, and delicate color harmonies provided the perfect setting for *salon* life during Louis XIII's reign.

The device of incorporating the Muses in room decor appeared in late fifteenth-century Italy and continued to enjoy popularity in seventeenth-century France. By implication, the presence of the nine goddesses transformed a given architectural space into a Temple of the Muses or *Mouseion*—from which our word *museum* has evolved.

This painting is part of the Samuel H. Kress collection at the National Gallery of Art.

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Lab Notes

Clean and Efficient Procedure for the Complete Removal of Reddish, Colloidal Selenium from Reaction Mixtures

The complete removal of selenium byproducts (notably H_2SeO_3)¹ from a reaction mixture is a nuisance well-known to synthetic chemists using selenium dioxide (SeO_2). Recently, we have engaged in synthesizing some formylpyridine derivatives utilizing SeO_2 , and we have been troubled by the same problem. In our case, it is largely worsened by the coordination of SeO_2 and/or its secondary derivatives with the pyridine nitrogen (observed by NMR).

Though one communication was published in 1978 in your journal dealing with the removal of selenium from a reaction mixture (by briefly heating the mixture in DMF to cause the black tar formed to precipitate out of the solution),² the method does not work well in our experiments, even with extensive silica gel column chromatography.

We wish to report a safe, clean, and efficient procedure for the complete removal of reddish, colloidal selenium by simply stirring the reaction mixture (usually in dioxane) with anhydrous NaHCO_3 powder (to remove selenic acid), anhydrous MgSO_4 (to remove H_2O), then filtering through a thin pad of a 1:1 mixture of Florisil[®] and Celite[®] (both are available from Aldrich Chemical Co.), and rinsing the paste with a suitable solvent such as dichloromethane, ethyl acetate, or acetone. The filtrate usually gives no indication of the existence of selenium species.

(1) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp 992-993. (2) Milstein, S.R.; Coats, E.A. *Aldrichimica Acta* 1978, 11, 10.

Rex X-F. Ren, Ph.D., and
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Leo V. Carr, Lab Manager
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Editor's Note: For a discussion of the issues surrounding the dissolution of starch in water, the reader should consult, among others, the following two references: (1) Mitchell, W.A. *J. Chem. Educ.* 1977, 54, 132, and (2) Green, M.M.; Blankenhorn, G.; Hart, H. *ibid.* 1975, 52, 729.

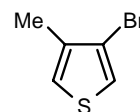
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by

Jai Nagarkatti, President



Professor Mario Leclerc at the Université de Montreal kindly suggested that we offer this thiophene. It has been used to prepare conducting and chromic regioregular polythiophenes.^{1,2}

(1) Faïd, K.; Leclerc, M. *J. Chem. Soc., Chem. Commun.* 1996, 2761. (2) Lévesque, I.; Leclerc, M. *Chem. Mater.* 1996, 8, 2843.

47,499-1 3-Bromo-4-methylthiophene, 95%

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

It is interesting how customers see us and our commitment to service; for example, we recently received the following e-mail:

I am in receipt of Volume 30, Number 1, 1997 of your *Aldrichimica Acta* magazine.

This issue's cover, Sir Edwin Henry Landseer's "Attachment", struck me as particularly interesting. The picture depicts a "faithful terrier's long vigil beside the lifeless body." This cover generated a lot of interest in our laboratory.

My question to you is this: Does the cover have a secondary meaning?

One of the most interesting possibilities might be that the faithful terrier's vigil could be interpreted as Aldrich's long-standing commitment to its customers.

What do you think?

I look forward to more interesting choices of fine artwork on the covers of your publications.

Michael L. Valentine
Washington College
Chestertown, MD

Asymmetric Synthesis Using Rhodium-Stabilized Vinylcarbenoid Intermediates

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Abstract

Rhodium(II) carboxylate-catalyzed decomposition of 2-diazobutenoates in the presence of alkenes or dienes results in highly diastereoselective cyclopropanations. Furthermore, these cyclopropanations occur with high asymmetric induction when using either α -hydroxy esters as chiral auxiliaries on the carbenoid, or chiral catalysts containing *N*-arylsulfonylprolinates ligands. These transformations can be used in general methods for the asymmetric synthesis of vinylcyclopropanes, cyclopropaneamino acids, 4,4-diarylbutanoates, cycloheptadienes, bicyclo[3.2.1]octadienes, 8-oxabicyclo[3.2.1]octan-3-ones, tropanes and other polycyclic compounds.

Introduction

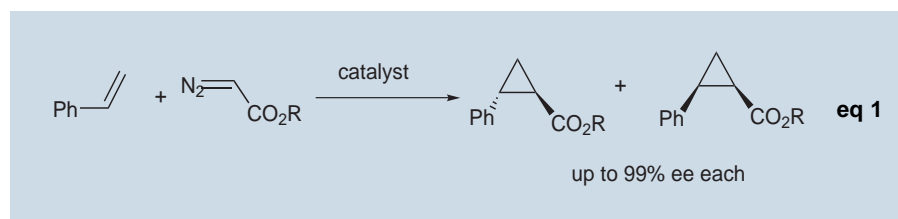
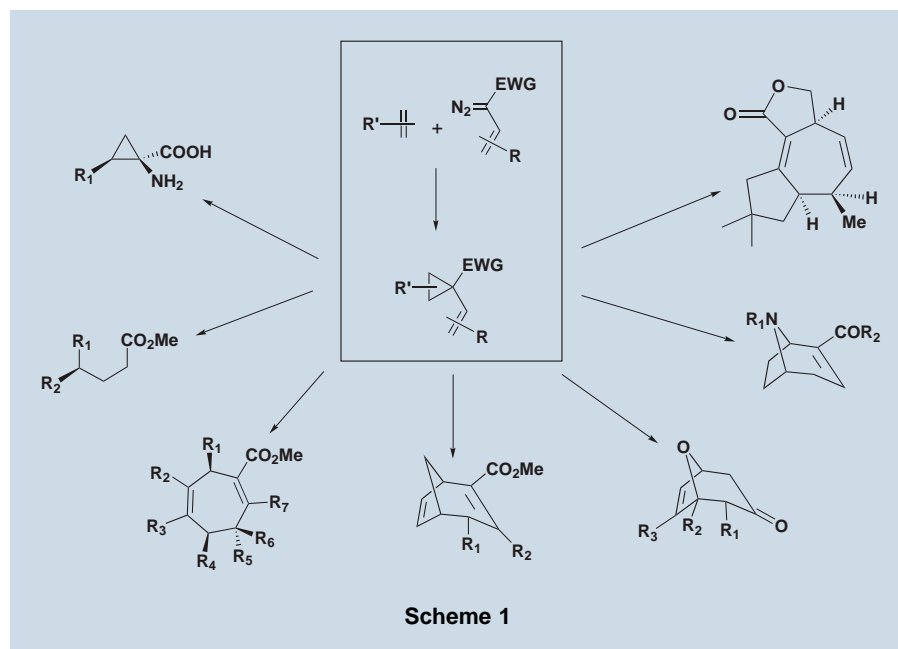
Enantiomerically pure cyclopropanes are very useful chiral building blocks since they may be converted to a variety of acyclic and cyclic products through stereochemically well-defined ring-opening reactions or rearrangements.¹ This article focuses on a new method for the highly diastereoselective and enantioselective synthesis of vinylcyclopropanes, and the utilization of these in the asymmetric synthesis of many types of ring systems as illustrated in **Scheme 1**.

A number of methods have been developed for the asymmetric synthesis of cyclopropanes. One of the most efficient methods has been the metal-catalyzed decomposition of diazoacetate derivatives in the presence of alkenes (**eq 1**).² In the last few years, a series of highly effective C-2 symmetric copper,³ ruthenium⁴ and rhodium(II) amide catalysts⁵ has been developed for this reaction. However, the reaction scope remains limited since diazoacetate cyclopropanations generally occur with poor control of diastereoselectivity unless very bulky ester groups are used;⁶ furthermore, these catalysts do not necessarily exhibit great utility in reactions with other types of carbenoids.⁷

The focus of our research program has been on the cyclopropanation chemistry of 2-diazobutenoate derivatives.⁸ Prior to our

studies, the chemistry of metal-stabilized vinylcarbenoids had met with fairly limited success.⁹ Intermolecular cyclopropanations occurred in poor to moderate yield and stereoselectivity (**eq 2 and 3**).^{9a-c} One notable early example was reported by Corey and involved an intramolecular cyclopropanation that was used in the synthesis of sirenin (**eq 4**),^{9f,g} and has since been achieved asymmetrically using a chiral copper catalyst.¹⁰ In general, not only are the vinylcarbenoid transformations ineffective, but the vinyl diazomethane precursors are difficult to handle as they are prone to rearrangement to 3*H*-pyrazoles.¹¹

When we initiated our program on vinylcarbenoid chemistry, we discovered that vinyl diazomethane **1a** was indefinitely stable at ambient temperature but underwent



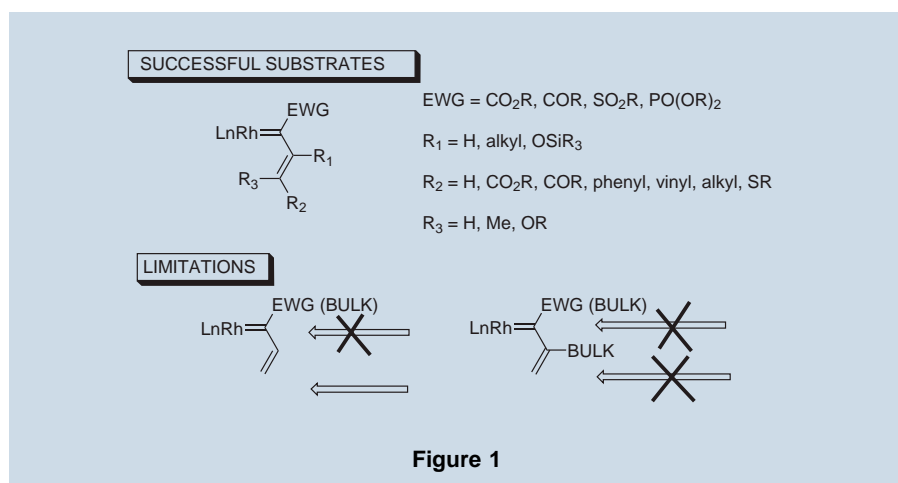
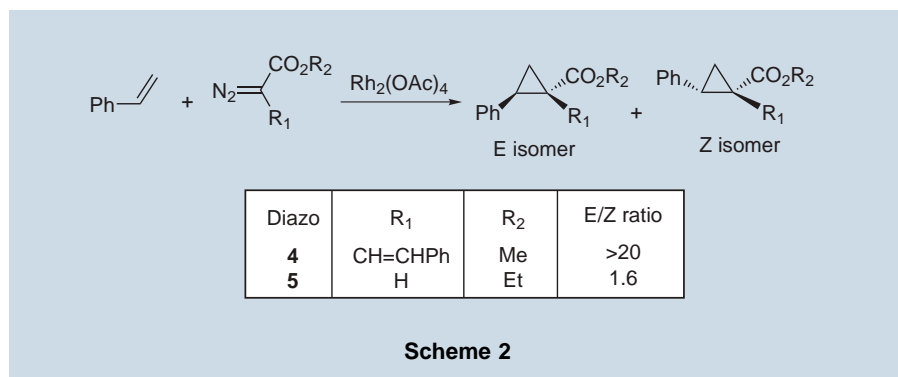
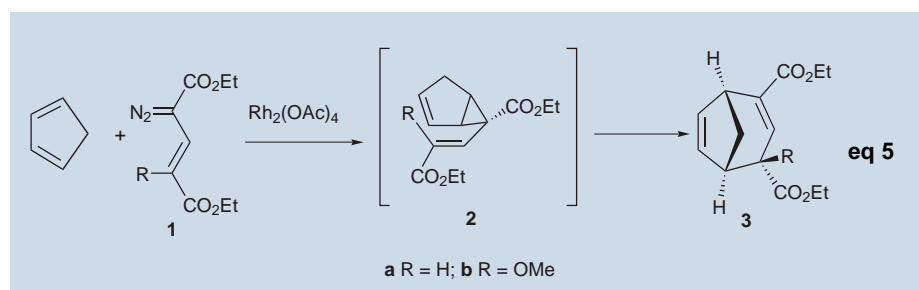
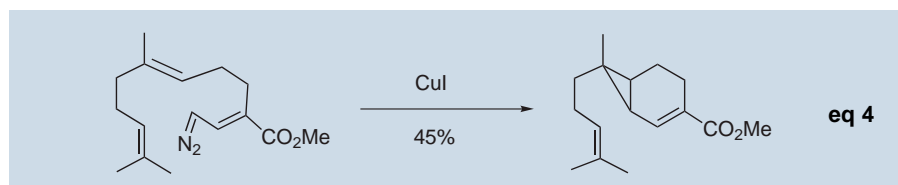
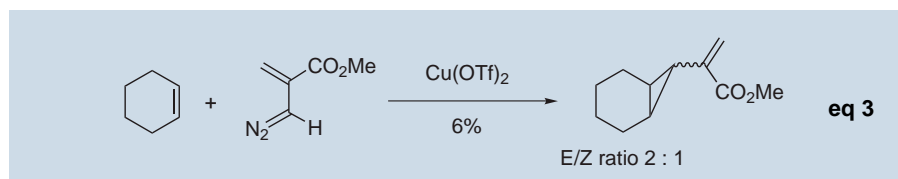
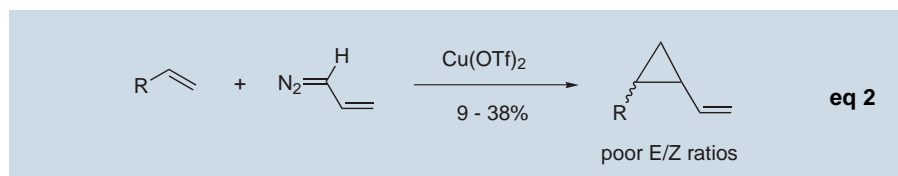
rhodium(II) acetate catalyzed decomposition in the presence of cyclopentadiene to give the endo product **3a** exclusively in 98% yield (eq 5).¹² This remarkable stereochemical result was considered to be due to a two-step reaction process, a cyclopropanation followed by a Cope rearrangement of the divinylcyclopropane intermediate. This mechanistic hypothesis was confirmed by using the bulkier vinyl diazomethane **1b**. With this substrate, divinylcyclopropane **2b** was isolated and its slow rearrangement to **3b** was followed.

The formation of **3a** in such high yield meant that the vinylcarbenoid cyclopropanation with **1a** had proceeded with very high diastereoselectivity, as only cis divinylcyclopropanes would be expected to undergo a Cope rearrangement under moderate conditions.¹⁴ This was confirmed in the model cyclopropanation reaction with styrene (Scheme 2) in which the diastereoselectivity seen with vinyl diazomethane **4** (>20 : 1)¹³ was in stark contrast to the low levels observed with the traditional diazoacetate system **5** (1.6 : 1).¹⁴

The ability of vinylcarbenoids to generate vinylcyclopropanes of defined stereochemistry offers numerous synthetic opportunities. This review will first describe the range of vinyl diazomethanes that may be used in this chemistry. This will be followed by an account of two methods for the asymmetric synthesis of the vinylcyclopropanes. The final section will describe the elaboration of the highly enantioenriched cyclopropanes into a variety of other ring systems.

Synthesis of Vinyl diazomethanes

The vinyl diazomethanes that have been commonly used in our studies contain an electron-withdrawing group adjacent to the diazo functionality.⁸ This electron-withdrawing functionality not only inhibits the tendency of vinyl diazomethanes to rearrange to 3*H*-pyrazoles, but is also necessary to achieve highly diastereoselective cyclopropanations. The types of vinyl diazomethanes that have been successfully used are shown in Figure 1. A range of functionality can be tolerated in the vinyl portion, including electron-withdrawing and electron-donating groups, and even cyclic systems. The major limitation for the vinylcarbenoid structure is the presence of excessive bulk around the carbenoid site. Bulky electron-withdrawing groups can cause the vinylogous portion of the vinylcarbenoid to become the active electrophilic site, but usually the use of nonpolar solvents can minimize this type of reactivity.¹⁵ If bulky functionality is flanking both sides of the

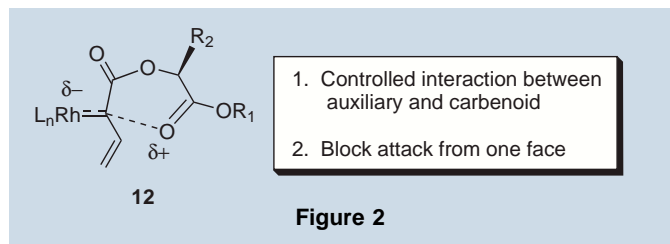
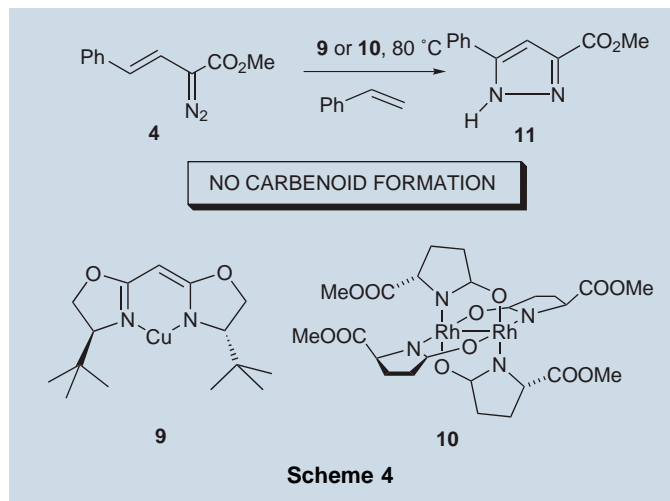
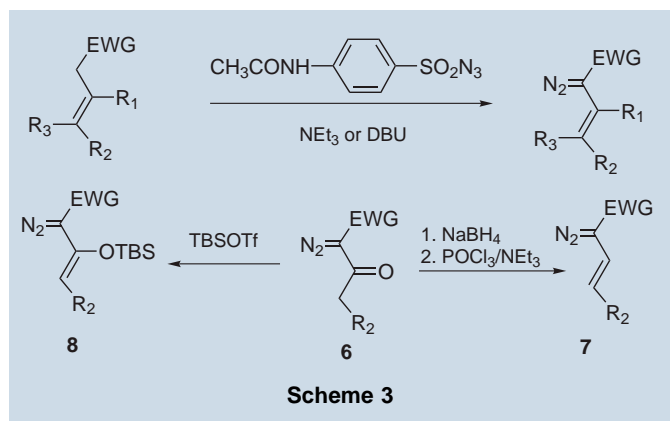


carbenoid, intermolecular reactivity can be seriously inhibited and the vinylcarbenoid will simply rearrange to a cyclopropene.¹⁶

Vinyldiazomethanes with two electron-withdrawing groups are readily prepared by diazo transfer reactions using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and triethylamine as the base (Scheme 3).¹⁷ Vinyldiazomethanes with a single electron-withdrawing group may be prepared by a diazo transfer reaction using DBU as the base. Alternatively, vinyldiazomethanes with a single electron-withdrawing group may be prepared from diazoacetate 6 either by reduction followed by dehydration to form 7,¹⁸ or by *O*-silylation to form 8.¹⁹ Vinyldiazomethanes with two electron-withdrawing groups tend to be indefinitely stable at ambient temperature, while most vinyldiazomethanes containing a single electron-withdrawing group may be stored for weeks in solution at -20 °C.

Asymmetric Vinylcarbenoid Cyclopropanations

Considering the range of chiral catalysts that are available for diazoacetate decomposition, the development of reaction conditions for asymmetric vinylcarbenoid cyclopropanations had initially been

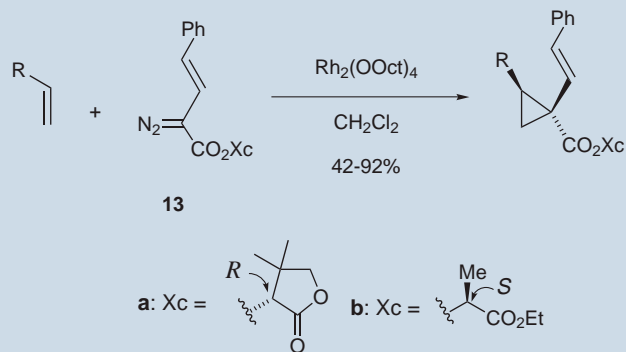


considered to be relatively straightforward. Unfortunately, this was not the case because vinyldiazomethanes require a kinetically active catalyst such as rhodium(II) carboxylates to avoid their competing rearrangement to 3*H*-pyrazoles. As can be seen in Scheme 4, Masamune's copper complex 9^{3a,b} or Doyle's rhodium(II) amide complex 10⁵ failed to catalyze carbene formation from vinyldiazomethane 4 at room temperature.²⁰ Under more forcing conditions, 4 rearranged to pyrazole 11. Consequently, two alternative strategies were developed to achieve asymmetric cyclopropanations by vinylcarbenoids. The first utilizes α -hydroxy esters as chiral auxiliaries on the vinylcarbenoid, while the second is based on a chiral rhodium(II) carboxylate catalyst.

A. α -Hydroxy Esters as Chiral Auxiliaries on the Vinylcarbenoid

From preliminary studies, it became abundantly clear that traditional strategies for designing chiral auxiliaries such as the use of menthol or borneol derivatives²¹ would not be practical for intermolecular vinylcarbenoid transformations. Any auxiliary that would have been effective at blocking one face of the carbenoid was also likely to react with the highly reactive carbenoid. Therefore, an alternate approach was explored in which a deliberate interaction between the carbenoid and auxiliary was employed as illustrated in Figure 2.²⁰ The extent of the neighboring group participation would be limited, allowing structure 12 still to exhibit carbenoid rather than ylide reactivity,²² while the rigid arrangement would permit the chiral influence to dictate which face of the carbenoid would be accessible. This led to the development of (*R*)-pantolactone and (*S*)-lactate as viable chiral auxiliaries for vinylcarbenoid cyclopropanations (Table 1).²⁰ Rhodium(II) octanoate catalyzed decomposition of (*R*)-pantolactone derivative 13a in the presence of alkenes resulted in cyclopropanation with up to 97% de. Alternatively, cyclopropanation with the (*S*)-lactate derivative 13b occurred in 67% de.

Table 1. Asymmetric cyclopropanation using chiral auxiliaries.



R	Diazo	Temp, °C	de, %	Abs. config.
Ph	13a	25	89	(1 <i>R</i> ,2 <i>R</i>)
Ph	13a	0	97	(1 <i>R</i> ,2 <i>R</i>)
<i>p</i> ClC ₆ H ₄	13a	0	>95	(1 <i>R</i> ,2 <i>R</i>)
<i>p</i> MeOC ₆ H ₄	13a	0	>95	(1 <i>R</i> ,2 <i>R</i>)
AcO	13a	0	90	
EtO	13a	0	92	
Ph	13b	25	67	(1 <i>S</i> ,2 <i>S</i>)

B. Rhodium(II) Prolinates as Chiral Catalysts

Even though the chiral auxiliary method resulted in cyclopropanation with impressive levels of diastereoselectivity, still it was felt that the optimum method for asymmetric vinylcarbenoid cyclopropanations would use an appropriate chiral catalyst instead. Rhodium(II) carboxylates are kinetically very active at decomposing diazo compounds, but the literature precedence for asymmetric intermolecular cyclopropanations using rhodium(II) carboxylates was not encouraging.²³ However, both McKervy²⁴ and Ikegami²⁵ had achieved notable successes in asymmetric intramolecular C-H insertions using proline and phenylalanine derivatives as chiral ligands.

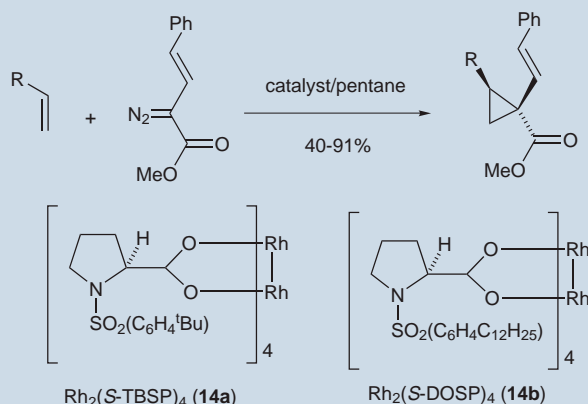
Even though rhodium(II) proline derivatives are not effective at asymmetric cyclopropanation using the traditional diazoacetates as substrates, these catalysts give spectacular results with the vinyl diazomethane system. The optimum catalysts are the (*S*)-*N*-(4-*tert*-butylphenylsulfonyl)proline derivative, Rh₂(*S*-TBSP)₄ (**14a**), and the (*S*)-*N*-(4-dodecylphenylsulfonyl)proline derivative, Rh₂(*S*-DOSP)₄ (**14b**), since the highest enantioselectivity occurred in hydrocarbon solvents in which these catalysts are soluble. Examples of the asymmetric intermolecular cyclopropanation are shown in **Table 2**.²⁶ The catalysts are so active that when the reactions are carried out at -78 °C virtually all substrates result in cyclopropanations with greater than 90% ee. The reaction is applicable to 1-substituted, 1,1-disubstituted, and *cis*-1,2-disubstituted alkenes. *trans*-1,2-Disubstituted alkenes, however, do not react intermolecularly with vinylcarbenoids.

The combination of an electron-withdrawing (EWG) and an electron-donating substituent (EDG) on the carbenoid appears to be the crucial requirement for high diastereoselectivity and enantioselectivity when the rhodium(II) proline system is used. Carbenoids containing only an EWG, only an EDG, or two EWG's result in cyclopropanations with very poor diastereo- and enantioselectivities.²⁷ This has led to the discovery of methyl phenyldiazoacetate **15** as an excellent substrate for asymmetric cyclopropanation.²⁷ A range of alkene substrates can be used and the results are summarized in **Table 3**.^{27,28} Doyle has compared the efficiency of Rh₂(*S*-TBSP)₄ with some of the chiral rhodium amide and copper catalysts and found that Rh₂(*S*-TBSP)₄ is by far the superior catalyst for asymmetric induction in the phenyldiazoacetate system.²⁸

Models for Vinylcarbenoid Stereoselectivity

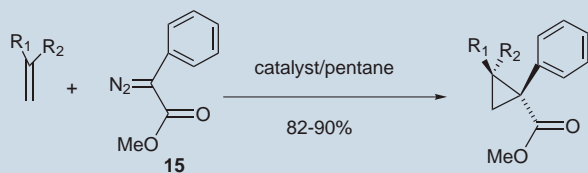
Reasonable models to explain the stereoselectivity in these reactions are shown in **Scheme 5**.^{22,26} Model **16** accounts for the remarkable *E/Z* stereoselectivity exhibited in vinylcarbenoid cyclopropanations: Due to the fact that vinylcarbenoids do not react with *trans* alkenes, the alkene is considered to approach the carbenoid in a side-on mode with bulky substituents pointing away from the "wall" of the catalyst. The cyclopropanation is believed to be nonsynchronous with the alkene approaching preferentially on the side of the EWG. This general model is very similar to that proposed by Doyle for the stereoselectivity of diazoacetate cyclopropanations.¹⁴ Structure **17** represents the model for the asymmetric induction using the (*R*)-pantolactone auxiliary.²⁰ The lactone carbonyl preferentially blocks the Si face of the carbenoid as this would limit unfavorable steric interactions between the auxiliary and the wall of the catalyst. Using the same trajectory for the alkene approach to the carbenoid as was considered above, structure **17** would lead to the preferential formation of the (1*R*,2*R*)-cyclopropane. Structure **18** represents the working hypothesis for the asymmetric induction using the proline catalysts.²⁶ In this predictive model, the catalyst behaves as if it had D₂ symmetry with the arylsulfonyl groups (marked as a thickened line) aligned

Table 2. Asymmetric cyclopropanation using chiral catalysts.



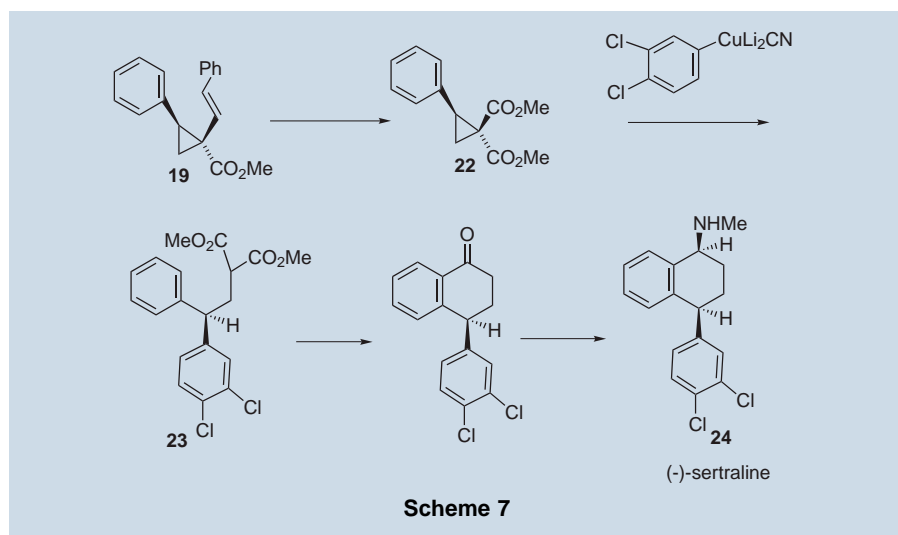
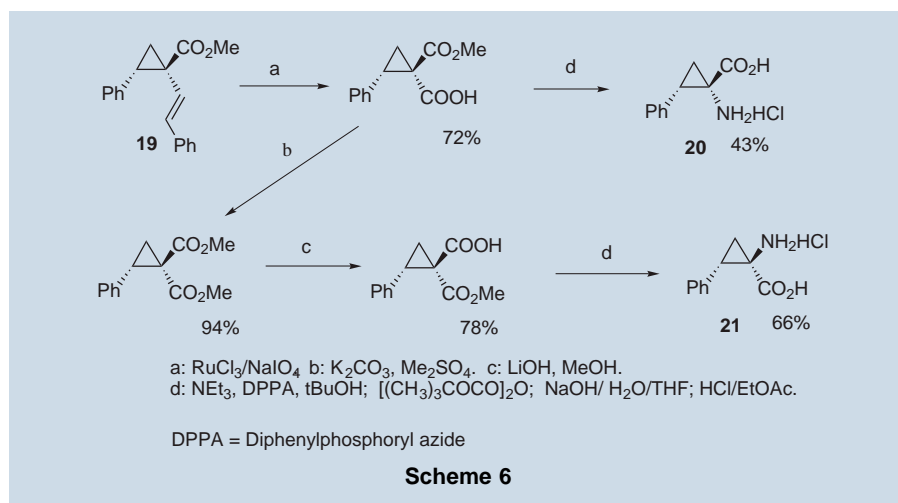
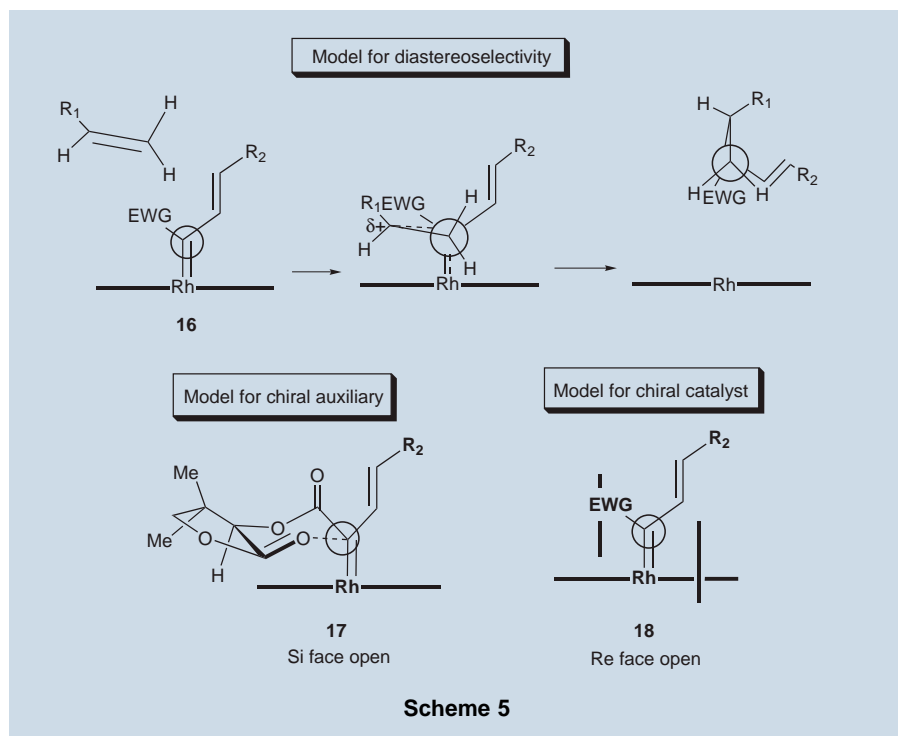
R	ee, % at 25 °C (with Rh ₂ (<i>S</i> -TBSP) ₄)	ee, % at -78 °C (with Rh ₂ (<i>S</i> -DOSP) ₄)
Ph	90	98
pClC ₆ H ₄	89	>97
pMeOC ₆ H ₄	83	90
AcO	76	95
EtO	59	93
nBu	>90	-
Et	>95	-
iPr	95	-

Table 3. Asymmetric cyclopropanation using methyl phenyldiazoacetate.



R ₁	R ₂	Catalyst	ee of Z, % at 25 °C
Ph	H	Rh ₂ (<i>S</i> -TBSP) ₄ ²⁷	87
pClC ₆ H ₄	H	Rh ₂ (<i>S</i> -TBSP) ₄ ²⁷	85
pMeOC ₆ H ₄	H	Rh ₂ (<i>S</i> -TBSP) ₄ ²⁷	88
EtO	H	Rh ₂ (<i>S</i> -DOSP) ₄ ²⁷	66
nBuO	H	Rh ₂ (<i>S</i> -DOSP) ₄ ²⁷	64
nBu	H	Rh ₂ (<i>S</i> -DOSP) ₄ ²⁷	77
Ph	Ph	Rh ₂ (<i>S</i> -TBSP) ₄ ²⁸	97
Ph	Me	Rh ₂ (<i>S</i> -TBSP) ₄ ²⁸	85(<i>E</i>), 81(<i>Z</i>)

in an "up-down-up-down" arrangement. Due to the D₂ symmetry, only one face of the catalyst needs to be considered. As can be seen in structure **18**, assuming a similar alkene approach as in structure **16**, the Re face of the carbenoid is blocked, leading to the formation of the (1*S*,2*S*)-cyclopropane.



Applications

Vinylcyclopropanes with up to three stereogenic centers are readily formed in the reaction between vinylcarbenoids and alkenes.⁷ The vinyl functionality that exists in the resulting cyclopropane offers numerous opportunities for further transformations. A generally useful application of vinylcyclopropanes is as chiral auxiliaries for the stereoselective synthesis of cyclopropaneamino acids as illustrated for **19** (Scheme 6).²⁶ By an appropriate sequence of oxidative alkene cleavage followed by a Curtius rearrangement either diastereomer of phenylcyclopropaneamino acid (**20** and **21**) can be formed in enantiomerically pure form.

Vinylcyclopropane **19** is readily converted to diester **22** by oxidative cleavage followed by esterification.^{20,26,29} Corey has demonstrated that **22**, on aryl cuprate induced ring opening, readily forms **23** with complete inversion of stereochemistry (Scheme 7).²⁹ This methodology was elegantly applied to the asymmetric synthesis of the 5-HT reuptake inhibitor (-)-sertraline (**24**).

The extension of the asymmetric vinylcarbenoid cyclopropanation to dienes results in an extremely general method for the construction of seven-membered rings (**26**) with excellent control of stereochemistry (Scheme 8).³⁰ The stereoselectivity that occurs in these vinylcarbenoid cyclopropanations results in a strong preference for the formation of *cis*-divinylcyclopropanes **25**. Furthermore, the Cope rearrangement of the divinylcyclopropane takes place through a boat transition state such that seven-membered rings with up to three stereocenters (e.g. **26**) are formed in a predictable manner.

The stereocontrol that is possible with this type of chemistry is illustrated in the case of *cis*- and *trans*-piperylene (Scheme 9).³⁰ Decomposition of **4** in the presence of *cis*-piperylene at room temperature results in the stereocontrolled formation of *trans*-cycloheptadiene **27** in 90% ee (96% ee at -78°C).³¹ Alternatively, the reaction with *trans*-piperylene results in the formation of *cis*-cycloheptadiene **28** in 90% ee (99% ee at -78°C).³¹

The reaction between cyclopentadiene and a series of vinylcarbenoids illustrates the range of functionality that can be accommodated on the carbenoid while maintaining a high degree of asymmetric induction (Table 4).^{30,31} Bicyclo[3.2.1]octadienes **29** are formed with complete control of relative stereochemistry. The ideal vinylcarbenoid substrates for asymmetric induction contain either an alkyl, vinyl, or phenyl group at the vinyl terminus, while the presence of an electron-deficient group at this position or

a large substituent at the central carbon is detrimental to the asymmetric induction.

The reaction between vinylcarbenoids and furans is an efficient method for the asymmetric

synthesis of 8-oxabicyclo[3.2.1]octan-3-ones (**Scheme 10**).³² These oxabicyclic systems are very versatile intermediates in organic synthesis and have been prepared

typically in racemic form by the [3 + 4] annulation between allyl cations and furans.³³ The chiral auxiliary approach is best suited for high asymmetric induction with the siloxyvinyl diazomethane **30**. The reaction of **30** with furans generates 8-oxabicyclo[3.2.1]octadienes **31** in good yield and diastereoselectivity (75-95% de).³² The utility of this methodology was demonstrated by the synthesis of oxabicycles **32-34**, which had been previously used in racemic form as crucial building blocks in diastereoselective syntheses.

The reaction between vinylcarbenoids and pyrroles is a general method for the stereoselective construction of tropanes (**Table 5**).^{34,35} Asymmetric induction using the rhodium prolinolate catalyst is not effective in this case because the pyrrole is too electron rich and leads to products derived from zwitterionic intermediates.³⁵ On the other hand, the subtle advantage of the chiral auxiliary approach is demonstrated in the tropane series because the neighboring group interaction between the auxiliary and the carbenoid not only results in diastereocontrol but also enhances the chemoselectivity of the carbenoid.³⁶ Using the reactions of the *S*-lactate derivatives **35** with *N*-BOC-pyrroles, the asymmetric synthesis of tropanes **36** was achieved in respectable yields and diastereoselectivity.³⁵ The utility of this methodology has been demonstrated by the synthesis of a series of 2β-acyl-3β-aryltropanes **37**.³⁷ These compounds are of considerable current interest because they are useful as molecular probes and potential medications for the treatment of cocaine addiction.

In principle, the asymmetric reaction between vinylcarbenoids and dienes has very broad applications. An illustration of this

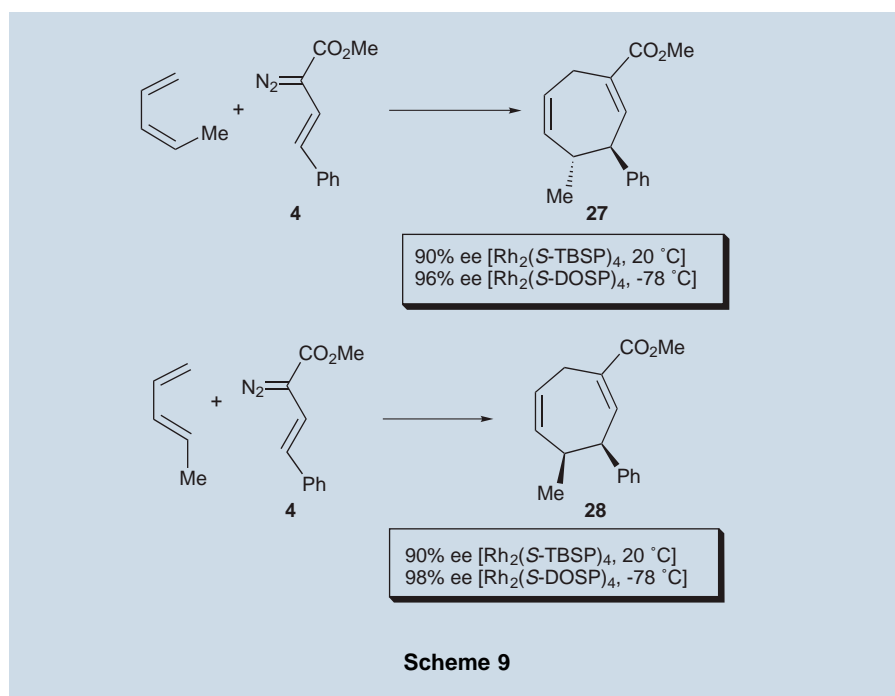
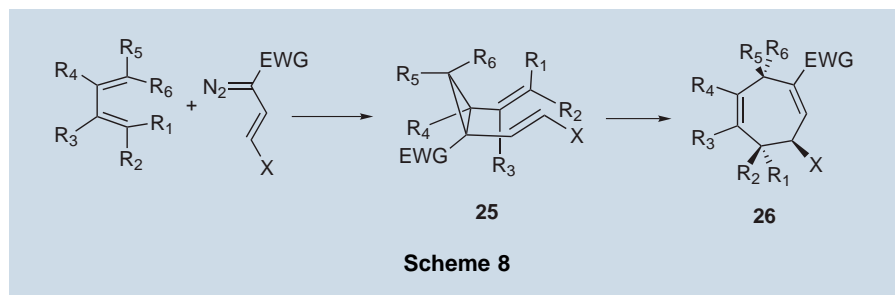
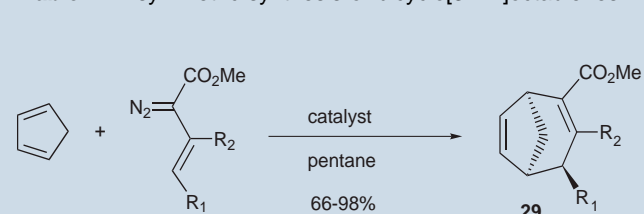


Table 4. Asymmetric synthesis of bicyclo[3.2.1]octadienes.



R ₁	R ₂	ee at 25 °C, % [with Rh ₂ (<i>S</i> -TBSP) ₄]	ee at -78 °C, % [with Rh ₂ (<i>S</i> -DOSP) ₄]
Ph	H	75	93
Me	H	83	92
CH=CH ₂	H	91	93
H	H	63	-
CO ₂ Et	H	10	-
H	Me	64	-
H	OTBS	42	-

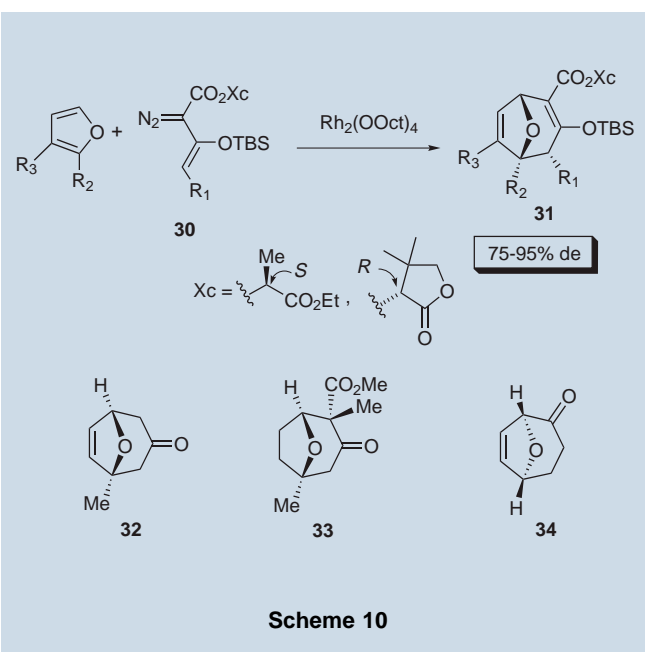
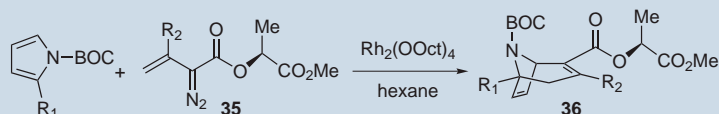
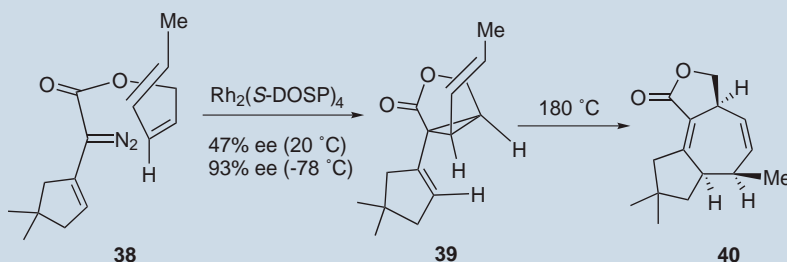
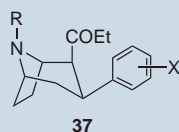
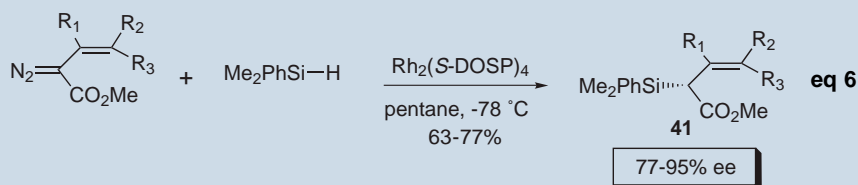


Table 5. Asymmetric synthesis of tropanes.

R ₁	R ₂	Yield, %	de, %
H	H	82	66
Me	H	54	59
Ph	H	64	53
CH ₂ OTBS	H	62	70
Ac	H	30	67
H	OTBS	64	66
Me	OTBS	55	58
Ph	OTBS	74	52
Ac	OTBS	58	79

**Scheme 11**

point is seen in the intramolecular reaction used in the synthesis of 5-epitremulenolide (**Scheme 11**).³⁸ Rh₂(S-DOSP)₄-catalyzed decomposition of vinyl diazomethane **38** at -78 °C resulted in the formation of *trans*-divinylcyclopropane **39** in 65% yield. Under forcing conditions, **39** underwent a Cope rearrangement to form the tricyclic product **40** (absolute stereochemistry has not been determined) in 85% yield and 93% ee with full control of the relative stereochemistry at the three stereogenic centers.

The focus of this account has been on the asymmetric cyclopropanation chemistry of vinylcarbenoids, but in principle other asymmetric vinylcarbenoid transformations should be equally feasible. An illustration of this point is the asymmetric Si-H insertion reaction (**eq 6**).³⁹ A series of allyl silanes **41** was prepared with high enantioselectivity using Rh₂(S-DOSP)₄ as catalyst at -78 °C.

Conclusion

In summary, the cyclopropanation reaction of rhodium-stabilized vinylcarbenoids has great utility since it is highly diastereoselective, and the resulting vinylcyclopropanes are versatile synthetic intermediates. In combination with the two complementary methods that have been developed for asymmetric vinylcarbenoid cyclopropanations, the chemistry is applicable to the enantioselective synthesis of a wide variety of acyclic, cyclic, and polycyclic systems.

Acknowledgment

The author thanks the members of his group, both past and present, who have contributed to much of the work described in this report. These studies were generously supported by the National Science Foundation

(CHE 9024248 and CHE 9421649) and by PHS grants DA-06301 and DA-06634.

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About the Author

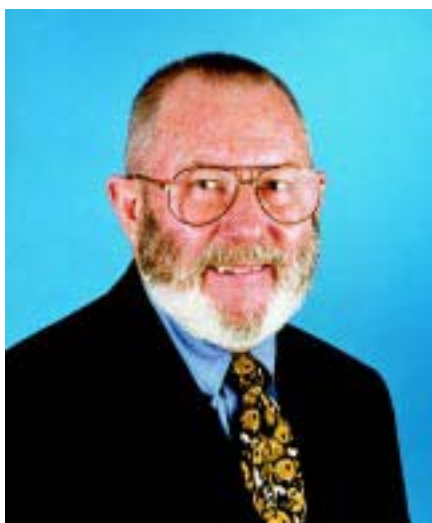
Huw M.L. Davies was born in Aberystwyth, Wales. He received his B.Sc. degree from University College Cardiff, Wales in 1977 and his Ph. D. degree (A. McKillop) from the University of East Anglia, England in 1980. After a postdoctoral position with E.C. Taylor at Princeton University, he was appointed Assistant Professor of Chemistry at Wake Forest University in 1983. In 1995, he moved to the State University of New York at Buffalo, where he currently holds the rank of Professor of Chemistry. His research interests include new synthetic methodology based on carbenoid intermediates, total synthesis of biologically active natural products, and molecular probes for neurochemical studies.

Dimethyl tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3,4-dicarboxylate: A Versatile Ambident Dienophile

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Outline

1. Introduction
2. Preparation of Smith's Diene and its 7,8-Dihydro Derivative
3. Diels-Alder Cycloadditions
 - 3.1. Reactions at the Cyclobutene-1,2-diesters π -Bond
 - 3.1.1. Quadricyclanes: Routes to Binanes and Molracs
 - 3.1.2. Cyclopentadiene, Furan, and Pyrroles
 - 3.1.3. Fulvenes: Carriers of Functionality
 - 3.1.4. Cyclobutadiene: Entry to [n]Ladderanes
 - 3.1.5. Cyclones: Entry to Fused 1,10-Phenanthrolines
 - 3.1.6. Isobenzofurans and their Crown Ethers
 - 3.1.7. Photochemical Cycloaddition Reactions
 - 3.2. Reactions at the Norbornene π -Bond
 - 3.2.1. *s*-Tetrazines: Route to Fused DPP Ligands
 - 3.2.2. 1,2,4-Triazines
 - 3.2.3. 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles
 - 3.2.4. 1,3-Diazaanthracenes: Uracil Delivery Agents
 - 3.2.5. β -Lactam Products
 - 3.2.6. Aryl Sulfinylamine Cycloadditions
4. 1,3-Dipolar Cycloadditions
 - 4.1. Diazoalkanes: Spiro-Fused Diazafluorene Ligands
 - 4.2. Azides
 - 4.3. Epoxycyclobutane, Alkene Cycloadditions
5. Summary of Cycloadditions in Flow Sheet Form
6. Acknowledgements
7. References



1. Introduction

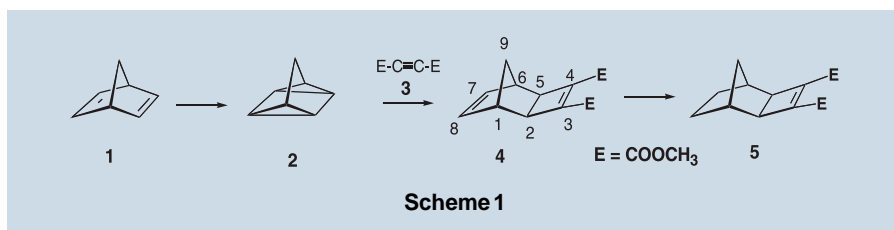
Our interest in the title compound, dimethyl tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3,4-dicarboxylate (Smith's diene) (**4**, **Scheme 1**), commenced in the early 1980s and stemmed from the fact that it was an easily obtained cyclobutene which we required as a transfer reagent¹⁻³ for cyclobutene-1,2-diesters. It became more important, however, when we realized its potential for preparing spacer molecules. Indeed, diene **4** was the starting point in our original report on the synthesis of binanes (Section 3.1.1)⁴ as typified by the production of 6 σ -binane **8** from the reaction of quadricyclane **2** with diene **4** (**Scheme 2**).

As part of our program for building rigid alicyclic architectures,⁵ we have used Smith's diene (**4**) as a model system for evaluating cycloaddition reagent reactivities as well as

site- and stereoselectivities. This role played by Smith's diene (**4**) is the theme of this review.

2. Preparation of Smith's Diene and its 7,8-Dihydro Derivative

Dimethyl tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3,4-dicarboxylate (**4**) was first described by Claibourne D. Smith in 1966.⁶ Referred to as Smith's diene by our research group (and in this review), **4** is made by the bishomo Diels-Alder cycloaddition of dimethyl acetylenedicarboxylate (DMAD, **3**) with quadricyclane (**2**) (**Scheme 1**). As quadricyclane (**2**) is produced⁷ by the photoinduced $[2\pi + 2\pi]$ intramolecular cycloaddition of norbornadiene **1**—itself a Diels-Alder product of acetylene and cyclopentadiene⁸—so the strong Diels-Alder influence commenced from the very beginning of **4**.



Preparation of Dimethyl (1 α ,2 β ,5 β ,6 α)-tricyclo[4.2.1.0^{2,5}]-nona-3,7-diene-3,4-dicarboxylate "Smith's Diene" (4)⁶

A mixture of quadricyclane (2) (36.8 g, 0.40 mol) and dimethyl acetylene dicarboxylate (3) (56.8 g, 0.40 mol) in carbon tetrachloride (100 mL) was heated under reflux for 5 hours. The solvent was removed to give crude 4 as a yellow oil. Vacuum distillation afforded the product as a colorless, viscous liquid (77.5 g, 83%), bp 82–88 °C at 3 x 10⁻² torr (lit. bp 94 °C at 5 x 10⁻¹ torr).⁶ ¹H NMR (CDCl₃) δ 1.37 (m, 2H, H9a,b), 2.56 (s, 2H, H2, H5), 2.61 (m, 2H, H1, H6), 3.80 (s, 6H, 2 CH₃'s), 6.18 (m, 2H, H7, H8). ¹³C NMR (CDCl₃) δ 38.16, 39.45, 44.13, 51.69, 135.88, 144.94, 161.65.

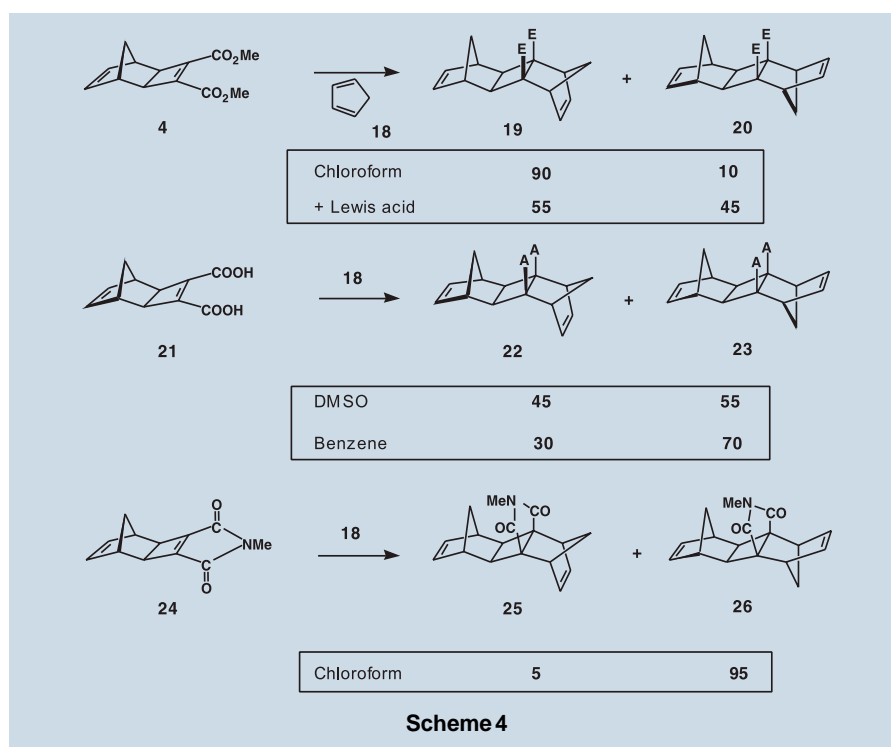
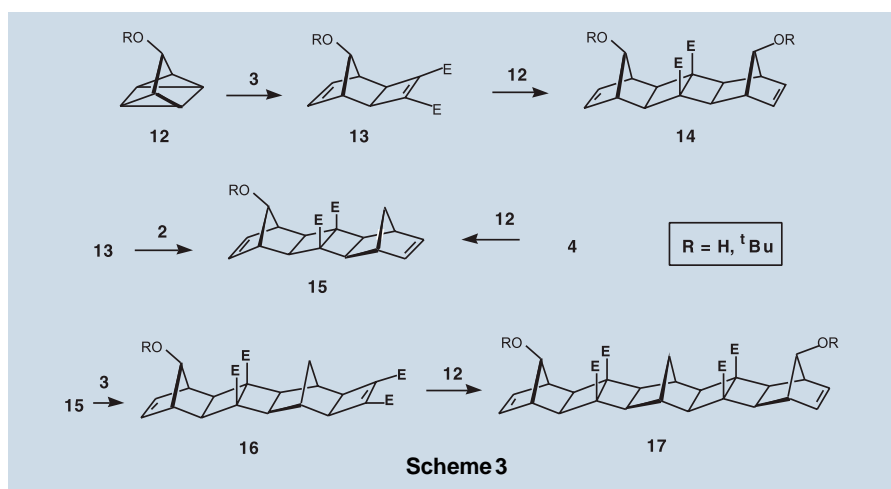
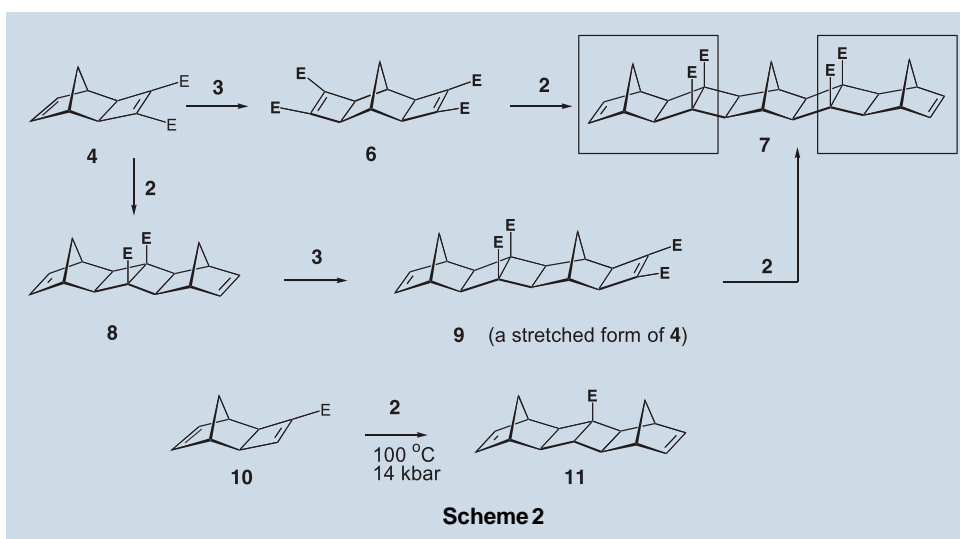
The 7,8-dihydro derivative 5 serves as a model cyclobutene-1,2-diester in many cycloaddition reactions. It can be formed by controlled hydrogenation (Pd/C) of 4 in ethyl acetate at atmospheric pressure, or by ruthenium-catalyzed [2 π +2 π] addition of dimethyl acetylenedicarboxylate (DMAD) onto norbornene.⁹ Cycloaddition results obtained with alkene 5 are a better guide to reactivity than those obtained from Smith's diene (4), as it is the dihydro subunit in 5 which is present in those other polycyclic systems produced by catalyzed cycloaddition of DMAD onto norbornene end groups (see later).

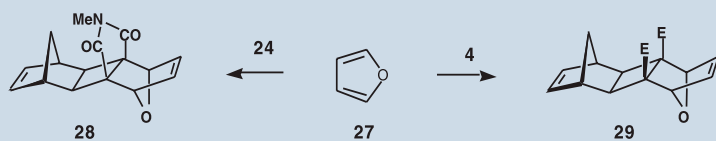
3. Diels-Alder Cycloadditions

3.1. Reactions at the Cyclobutene-1,2-diester π -Bond

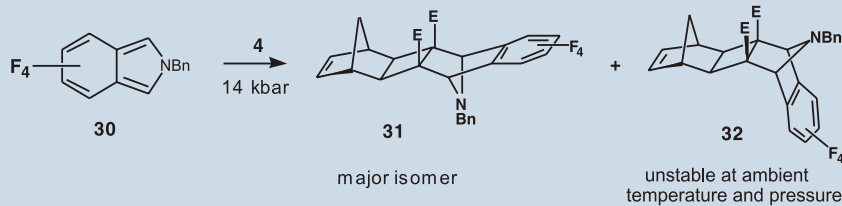
3.1.1. Quadricyclanes: Routes to Binanes and Molracs

As mentioned in the introduction, we used Smith's diene (4) as the starting point for molrac construction. This happened as a result of our curiosity about why 4 didn't react further with quadricyclane in Smith's original reaction. Subsequent experiments revealed that the reaction did occur at higher temperatures. Quadricyclane (2) reacted at the cyclobutene-1,2-diester π -bond of 4 to form the hexacyclic molrac 8,⁴ in which high stereospecificity accompanied the cycloaddition process (Scheme 2). This observation was the first step in the development of a rigid polycyclic framework and became a driving force when it was coupled with the observations reported by Mitsudo and his group in Japan.⁹ They had found some years earlier, that dimethyl acetylenedicarboxylate (DMAD) reacted with norbornenes under the influence of certain ruthenium catalysts to produce exo-fused cyclobutene-1,2-diesters. Application of these two reactions in tandem allowed the stereospecific

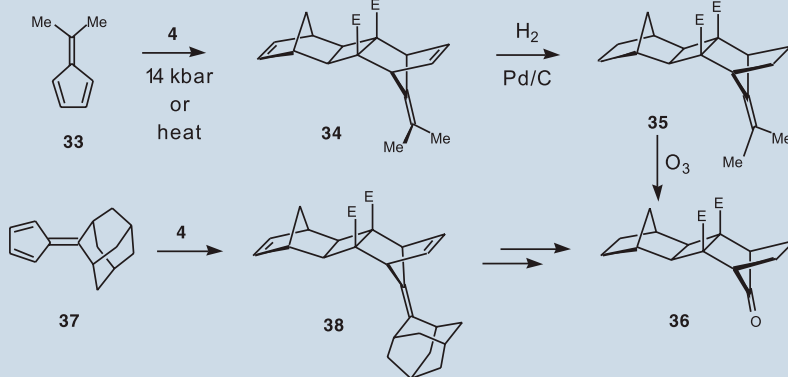




Scheme 5



Scheme 6



Scheme 7

formation of extended molecular structures comprised entirely of fused norbornanes and cyclobutanes (Scheme 2). At that time they were termed binanes and are now recognized as a subclass of molecular racks (molracs)—renamed to accommodate a larger selection of alicyclic and aromatic fusion partners.

Reaction of quadricyclane with Smith's diene produces the hexacyclic structure **8**, while controlled Mitsunobu cycloaddition of DMAD onto **8** can be used to form the heptacyclic system **9**. Since molracs of type **9** have both norbornene and cyclobutene-1,2-diester groups at the termini, they can be viewed as stretched Smith's dienes. Further reaction of quadricyclane with the cyclobutene-1,2-diester system of **9** produces the decacyclic system **7**, in which each terminus contains a 3,4-dihydro variant of Smith's diene (boxed).

More recently, Jenner¹⁰ has shown that quadricyclane reacts with **10**, the monoester equivalent of Smith's diene, to produce the hexacyclic system **11**. In this case the reaction was achieved using a combination of heat (100 °C) and high pressure (14 kbar). We have found that only trace amounts of adduct are formed from the high pressure (10–15 kbar, several days) treatment of quadricyclane with

Smith's diene when conducted at room temperature, leading to the conclusion that both heat and pressure are apparently required to effect quadricyclane cycloadditions in these systems.

This same construction method can be used to produce spacer molecules with built-in hydroxyl groups suitable for the attachment of functionality (Scheme 3). The substituted quadricyclane **12**, readily produced by photoisomerization of the corresponding norbornadiene, reacts with DMAD to produce the derivatized Smith's diene **13**.¹¹ Further reaction between **12** and **13** yields the symmetrical product **14** where the two alkoxy groups are outward-facing. These transformations are conducted on the *tert*-butyl ethers which can be transformed into the corresponding alcohols by treatment with trifluoroacetic acid.

Spacer molecule **17** is a stretched variant of **14** and is produced from the mixed cycloadduct **15**. Starting *bis*-alkene **15** can be prepared either by reaction of quadricyclane with functionalized Smith's diene **13**, or by reaction of substituted quadricyclane **12** with Smith's diene **4**. The alkoxy substituent in **15** has the *syn* configuration relative to the norbornene π -bond and protects it from *exo* attack. Consequently, ruthenium-catalyzed

cycloaddition of DMAD onto **15** occurs only at the exposed norbornene π -center and provides monocyclobutene-1,2-diester **16** in high yield. Reaction of quadricyclane **12** with **16** produces the symmetrical product **17** in which each alkoxy group is outward-facing.

3.1.2. Cyclopentadiene, Furan, and Pyrroles

Smith's diene (**4**) is quite a reactive dienophile, reacting with cyclopentadiene (Cp, **18**) in refluxing chloroform to furnish a mixture of stereoisomeric adducts, **19** and **20**, by exclusive reaction at the β -face of the cyclobutene π -center (Scheme 4).⁴ Adduct **19**, with a bent frame, is the dominant product, with only small amounts of the extended isomer **20** produced. The proportion of **20** can be improved by conducting the reaction in the presence of a Lewis acid (e.g., AlCl₃). The best way of producing **20**, however, is *via* cyclopentadiene addition to the dicarboxylic acid derivative **21** (formed by base hydrolysis of **4**) in benzene, yielding the extended adduct **23** as the major product (70%). Adduct **23** can be transformed into the diester **20** by controlled reaction with diazomethane (excess diazomethane yields a new cycloaddition adduct, see Section 4). The fused cyclobutenomaleimide **24**¹² is much more reactive than Smith's diene; it reacts with cyclopentadiene exothermically at room temperature to yield the extended isomer **26** as the major cycloaddition product.

While furan **27** reacted with the fused maleimide **24** at room temperature to form the extended stereoisomer **28** (Scheme 5), it reacted only sluggishly with Smith's diene (**4**) and only produced adduct **29** under the influence of a Lewis acid (ZnCl₂, AlCl₃, LiClO₄ are all effective) or high pressure; exclusive formation of the extended isomer was observed in all cases.

N-substituted pyrroles are much less reactive than the other 5-membered 1,3-dienes; no reaction was observed between *N*-(trimethylsilyl)pyrrole or *N*-benzylpyrrole with Smith's diene (**4**) under thermal or high pressure (4 days at 14 kbar) conditions, even in the presence of Lewis acids.¹³

Isoindoles, however, do react with **4** under high-pressure conditions; for example, *N*-benzyltetrafluoroisoidole **30** forms a mixture comprised of the extended adduct **31** and its bent isomer **32** (Scheme 6). The bent isomer is not stable, however, and reverts to the starting materials soon after exposing it to ambient temperature and pressure.¹³

3.1.3. Fulvenes: Carriers of Functionality

Fulvenes react with Smith's diene (**4**) under thermal conditions; typically, 6,6-dimethylfulvene **33** yields the extended isomer **34** as the exclusive product (Scheme 7).¹⁴ X-ray

structural data obtained for **34** established conclusively the stereoselectivity of the reaction.¹⁵ Using adamantylidenylfulvene (**37**), a similar adduct, **38**, was obtained where the adamantyl group is positioned rigidly onto the molecular framework by virtue of the olefinic linkage originating from the fulvene. Conversion of **34** and **38** (hydrogenation/ozonolysis) to the common ketone **36** confirmed the stereochemistry of **38** (Scheme 7).¹⁴

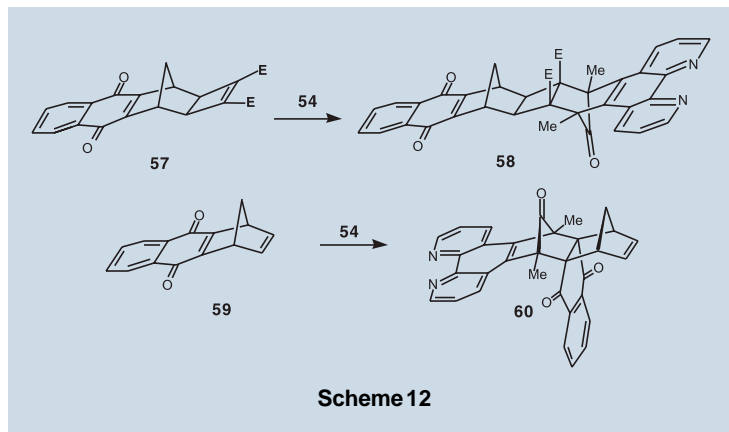
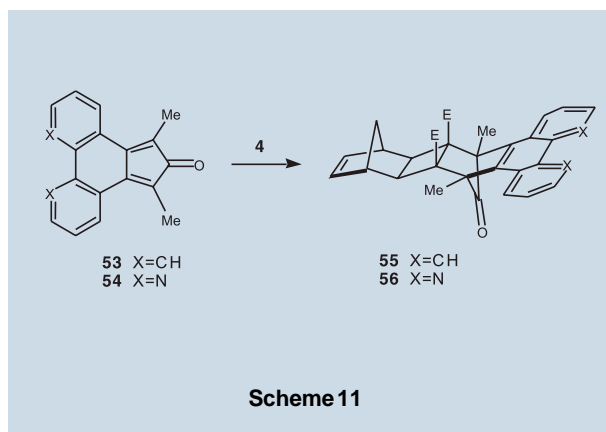
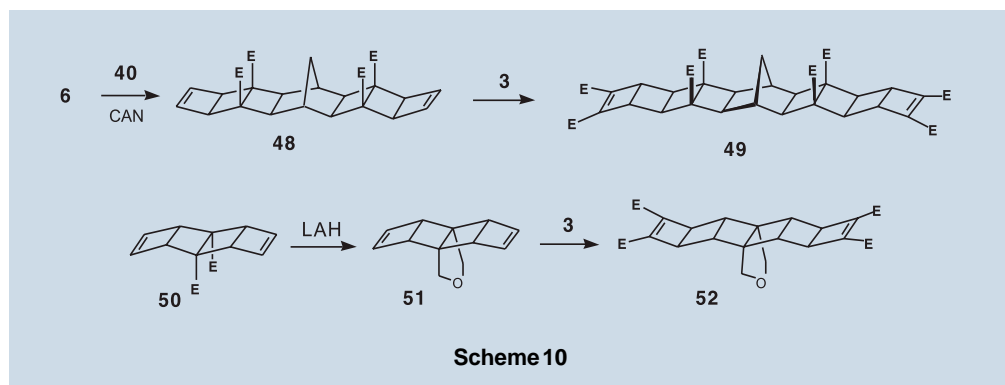
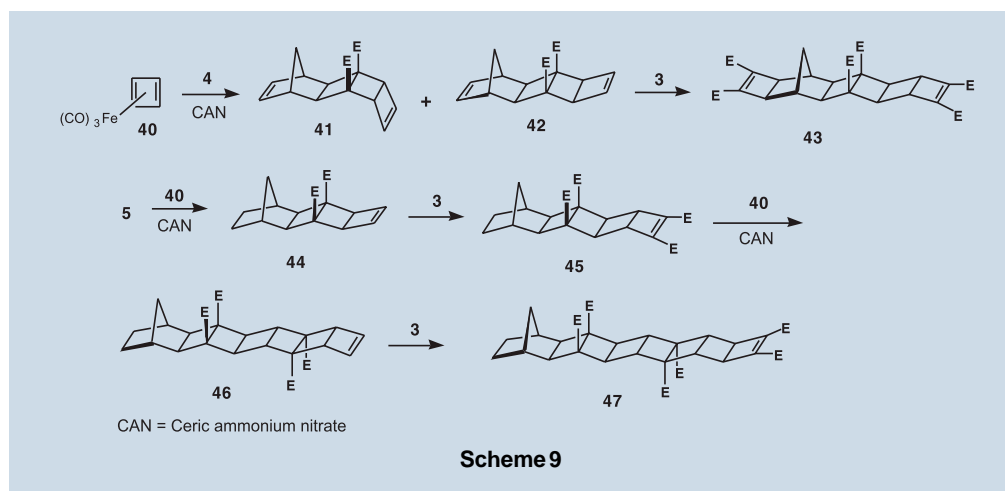
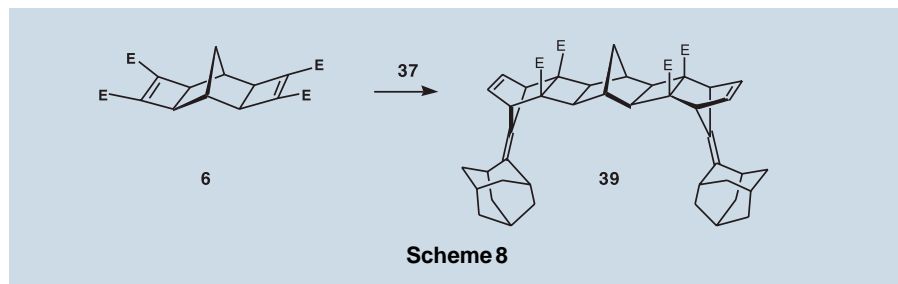
These reactions, which are improved by conducting the experiments under high-pressure conditions, can be extended to the formation of bisadducts by using the biscyclobutene **6**; e.g., adamantylidenylfulvene **37** affords the symmetrical product **39** as outlined in Scheme 8.¹⁴

3.1.4. Cyclobutadiene: Entry to [n]Ladderanes

Smith's diene (**4**) reacts efficiently with cyclobutadiene (liberated from its iron tricarbonyl complex **40** with CAN) to form Diels-Alder adducts **41** and **42** by selective reaction at the cyclobutene π -bond of **4** (Scheme 9). The extended isomer **42** dominates 10:1 over the bent isomer **41**. Both π -bonds in **42** react with DMAD in the presence of a Ru-catalyst to produce bisadduct **43**; this is the first example of a cyclobutene π -bond reacting in this fashion. This process has been developed into an [n]ladderane synthesis by starting with the dihydro derivative **5** of Smith's diene and working in tandem.¹⁶ In this way, the extended [n]ladderanes **46** and **47**, where $n=6, 7$, were produced (Scheme 9). This tandem process can be applied to other cyclobutenes and provides the most versatile route to [n]ladderanes currently available.

Bis(cyclobutene-1,2-diester) **6** reacted with two equivalents of cyclobutadiene to form the homo[8]ladderane **48** as the major bisadduct. This was shown to undergo

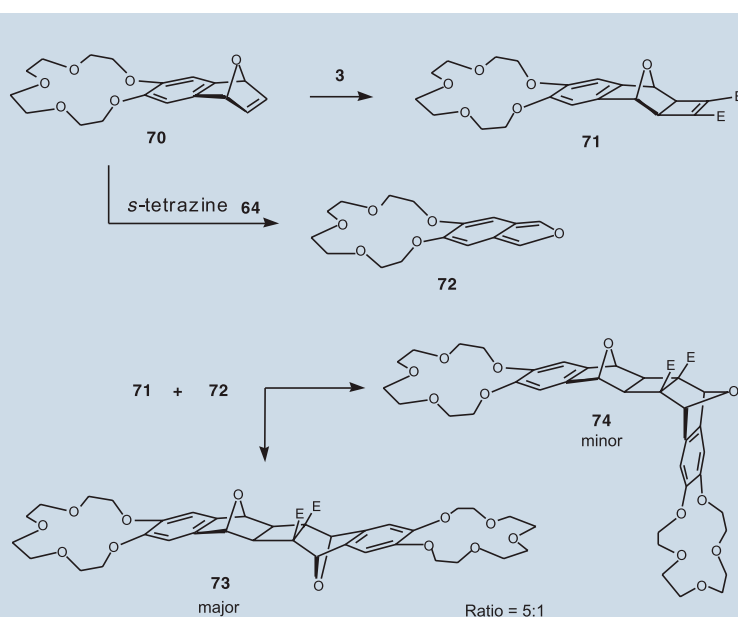
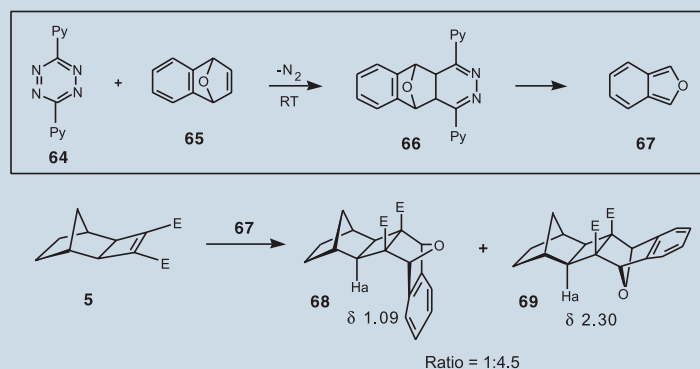
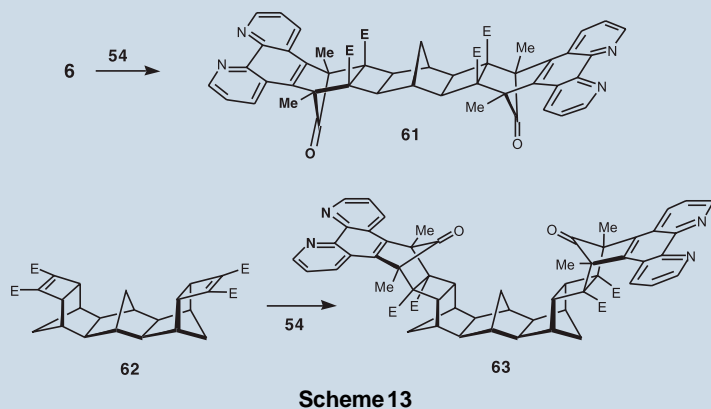
further extension by treatment with DMAD/Ru-catalyst to produce the homo[10]-ladderane **49** (Scheme 10).¹⁷ Such systems dwarf the pterodactylane **50**^{18,19} and must



surely originate from the pterodactylane *grandis* species! Indeed, [6]ladderane **52** is a direct offspring of **50**. The reactions of substituted cyclobutadienes in this context have also been reported.²⁰

3.1.5. Cyclones: Entry to Fused 1,10-Phenanthrolines

Cyclopentadienones (cyclones) readily react with Smith's diene (**4**) to form exclusively a single 1:1 adduct having the extended stere-



isomeric structure; e.g., phencyclone **53** yielded adduct **55** (**Scheme 11**).²¹ The specificity was conclusively established on the basis of ¹H NMR spectroscopy: the site selectivity by the retention of the norbornenyl resonances, and the stereospecificity by the upfield shift of the ester methyl resonances (δ 3.20).

The availability of diazaphencyclone (DAPC) **54** has allowed the cyclopentadienone methodology to be used for attaching the 1,10-phenanthroline ligand onto molracs.²² Reaction of DAPC **54** with **4** again occurred stereoselectively at the cyclobutene-1,2-diester moiety to produce **56** (**Scheme 11**); this has opened up the stereospecific production of mono- and bisligands fused to rigid spacer systems.²³ Ambident dienophile **57** reacts with DAPC **54** at the cyclobutene π -bond to produce ligand **58**; in contrast, the related ambident dienophile **59** reacts with DAPC **54** at the naphthoquinone π -center to produce adduct **60** (lack of shielding of the methylene protons supports the stereochemical assignment) (**Scheme 12**).

The presence of the dihydro-Smith subunit is exploited in the preparation of bisligand systems **61** and **63** by reaction of DAPC **54** with *bis*-alkene **6** or "U"-shaped **62**, respectively (**Scheme 13**).²⁴

3.1.6. Isobenzofurans and their Crown Ethers

A complex mixture of adducts arose from the reaction of isobenzofuran **67** with Smith's diene (**4**) as addition occurred nonstereospecifically at both π -centers of **4**. This mixture was examined by NMR spectroscopy, but individual components were not separated.²⁵ The stereospecificity of the reaction at the cyclobutene π -center was established using dihydro-Smith's alkene **5**, which was converted to adducts **68** and **69** (**Scheme 14**). Adducts **68** and **69** were easily distinguished by ¹H NMR spectroscopy using the ring-current effect of the aromatic ring: the norbornane protons Ha are shielded in **68** (δ =1.09) relative to **69** (δ =2.30), while the ester methyl groups in **69** (δ =3.54) are partially shielded relative to the corresponding ones in **68** (δ =3.80).²⁶

Isobenzofuran **67** was generated in situ by reaction of 1,4-dihydro-1,4-epoxynaphthalene (**65**) with 3,6-di(2-pyridyl)-*s*-tetrazine (**64**) in chloroform solution.²⁷ The intermediate dihydropyridazine **66** can be isolated as a crystalline product if the reaction is performed in DMSO, and **66** can be used as a source of isobenzofuran in reactions where the substrate itself reacts with *s*-tetrazine **64**.

The use of isobenzofurans as delivery agents for the crown ether ionophore has formed a part of our host/guest study program.²⁸ Ruthenium-catalyzed addition of DMAD to the dihydroepoxynaphthalene **70**—having the

15-crown-5 subunit attached to the 6,7-position of the aromatic ring—gave oxa-Smith's derivative **71**. Compounds **70** and **71** are versatile starting materials for polycyclics containing crown ethers; their potential is illustrated by the generation of crown ether-isobenzofuran **72** by the *s*-tetrazine method, and its addition to the cyclobutene-1,2-diester component of **71** (Scheme 15). Two stereoisomeric adducts are observed: the extended product **73** and the bent isomer **74**; the former being the dominant one.

In the case of cavity bisalkene **75**, a single isomer was obtained with two equivalents of isobenzofuran **72**, each reacting stereospecifically with a cyclobutene-1,2-diester group to produce the symmetrical product **76** (Scheme 16). The "arms-outstretched" configuration of this product, together with the lining of the cavity's interior with bridging oxygen atoms, makes this material an enticing substrate for supramolecular studies.

3.1.7. Photochemical Cycloaddition Reactions

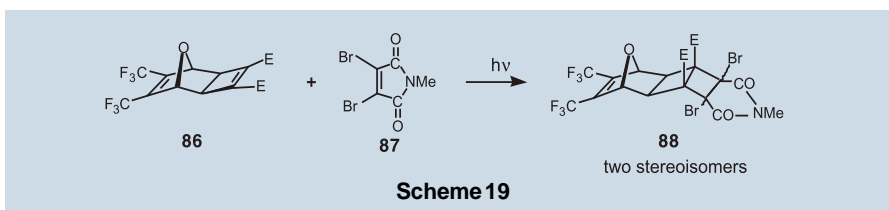
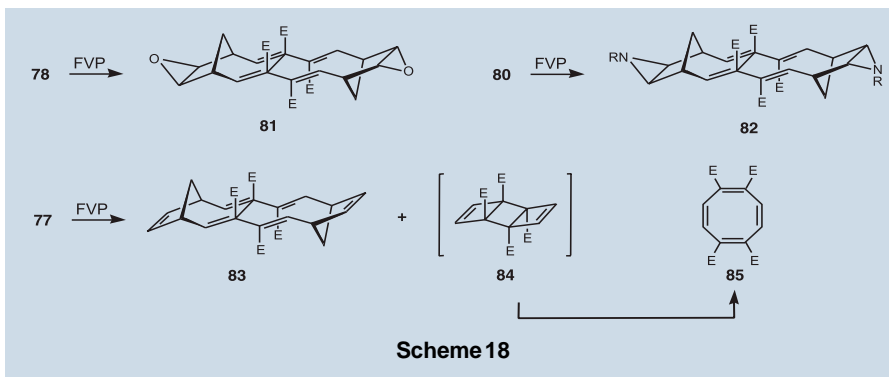
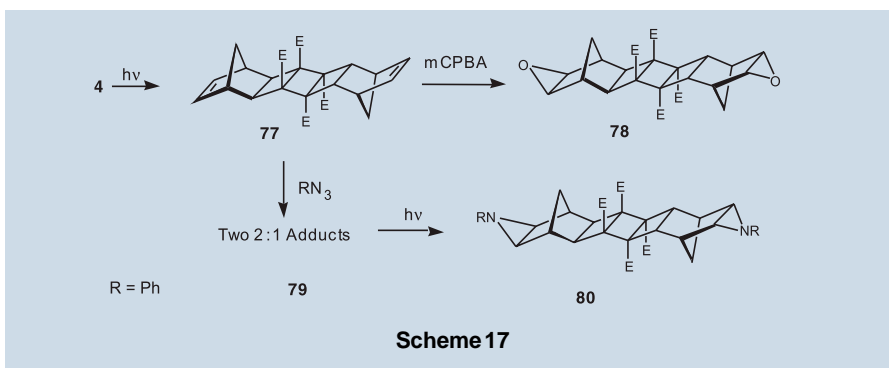
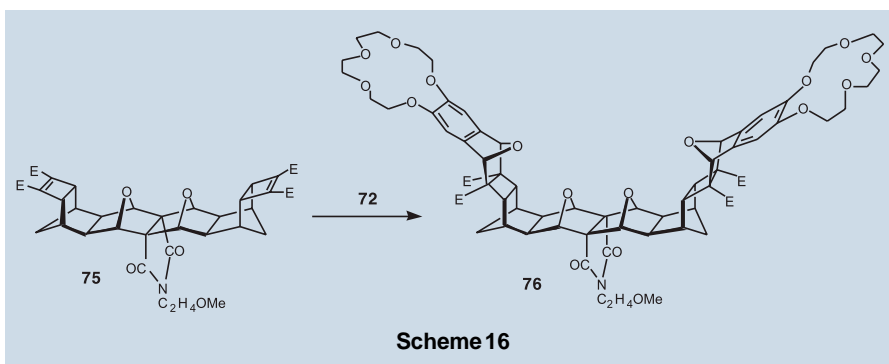
Eberbach reported that UV irradiation of Smith's diene (**4**) yielded the exo, anti dimer **77** (Scheme 17) where cycloaddition occurred specifically at the cyclobutene-1,2-diester chromophores.²⁹ We have shown that the norbornene π -bonds in **77** reacted with azides to produce a diastereomeric pair of 2:1 adducts **79** that were converted photochemically to a single bisaziridine **80**. Formation of the oxygen analog **78** was achieved by direct mCPBA epoxidation of **77**.³

The value of products **78** and **80** was that they could be converted to a special type of rigid polyene structure (Scheme 18). Thus, thermally induced ring-opening of the cyclobutane rings was achieved under flash vacuum pyrolysis (FVP) conditions (500 °C, 5×10^{-3} torr), and led to the formation of rigid macrocyclic polyenes **81** and **82**, respectively. FVP of bisalkene **77** was also conducted, and produced the cyclic hexaene **83**. The lower yield (11%) of **83** reflects the operation of a competing retro Diels-Alder pathway open to **77**, where loss of cyclopentadiene yields cyclooctatetraene-1,2,5,6-tetraester **85**, possibly formed from intermediate **84**.

Mixed photocycloadditions have been conducted with norbornenes or cyclobutenes and, while Smith's diene (**4**) has not been involved in the study directly, the oxa-bridged relative **86** has (Scheme 19). Thus, irradiation of **86** with *N*-methyl-3,4-dibromomaleimide (**87**) produced a mixture of stereoisomeric cycloadducts **88** by exclusive reaction at the cyclobutene π -bond.¹²

3.2. Reactions at the Norbornene π -Bond

Almost all the reactions discussed up to this point involve site-selective attack at the



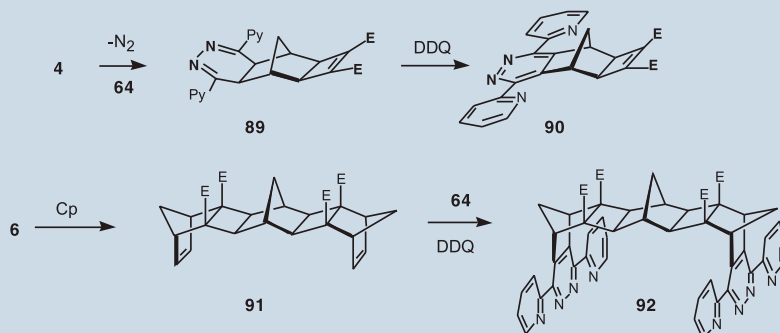
cyclobutene π -bond (at least initially). It would be remiss, however, to think that the norbornene π -bond was without its own character. Indeed, it is the preferred site of attack for many reagents, especially reverse-electron-demand dienes.

3.2.1. *s*-Tetrazines: Route to Fused DPP Ligands

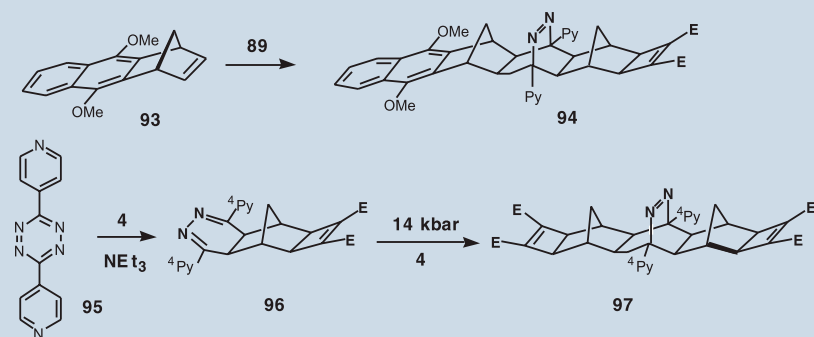
Smith's diene (**4**) reacts with *s*-tetrazines at the norbornene π -bond to produce dihydropyridazines; e.g., 3,6-di(2-pyridyl)-*s*-tetrazine (**64**) reacts with **4** to furnish

4,5-dihydropyridazine **89** (Scheme 20).³⁰ This intermediate is moderately stable in the absence of acid, and either it, or its rearranged product, can be oxidized (DDQ) to the fused pyridazine **90**. The X-ray structure shows the conformation of each pyridine substituent almost coplanar with the pyridazine ring, and the nitrogen atom of each pyridine ring anti-related to an *N*-atom in the pyridazine ring.

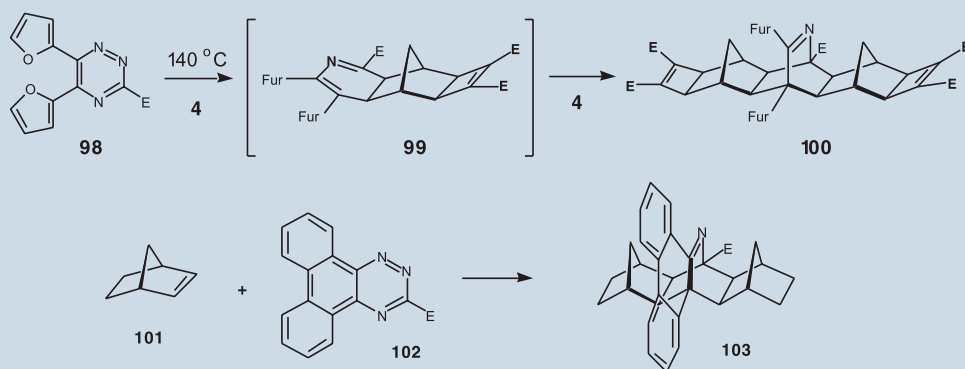
This reaction sequence of cycloaddition/DDQ dehydrogenation has been used to prepare a whole range of fused mono- and bisligands containing a fused 3,6-dipyridylpyridazine



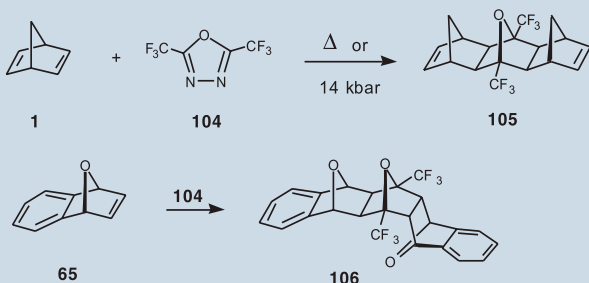
Scheme 20



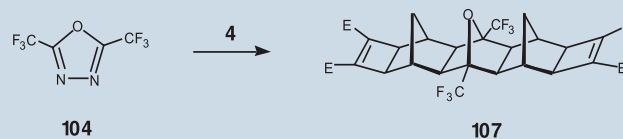
Scheme 21



Scheme 22



Scheme 23



Scheme 24

(dpp) component. Treatment of bisalkene **91**, readily obtained by cyclopentadiene addition to **6**, under these conditions produced the cavity-shaped system **92** containing two dpp subunits, where the ligand systems are roughly coplanar. Many other examples of such bisligands are reported in the original papers.^{30,31}

The dihydropyridazines described above (e.g., **89**) are reactive 1,3-dienes and can be coupled with ring-strained dienophiles. Thus, reaction of **89** with naphthalenonorbomadiene **93** produces the coupled product **94** (Scheme 21). In a similar fashion, 3,6-di(4-pyridyl)-*s*-tetrazine **95** has been used to couple with Smith's diene (**4**) to produce the fully symmetrical aza-bridged product **97**; the intermediate dihydropyridazine **96** is not isolated, and the second step is achieved using high pressure (14 kbar).

3.2.2. 1,2,4-Triazines

1,2,4-Triazines are also active reverse-electron-demand dienes that react with ring-strained olefins to yield dihydropyridines. The triazine can be used as a carrier of functionality; thus, difuryltriazine **98** reacts with Smith's diene (**4**) exclusively at the norbornene π -bond to produce the 2:1 product **100** (Scheme 22). Dihydropyridine **99** is the presumed intermediate but is not isolated under the high-pressure conditions used to achieve coupling. In a similar fashion the fused triazine **102** can be used to couple norbornene to furnish the symmetrical product **103**.

3.2.3. 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles

2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole (**104**) has been reported by several groups^{32,33} to react with ring-strained alkenes under forcing thermal conditions to produce coupled products; e.g., norbornadiene produced the symmetrical tetracyclic system **105** (Scheme 23). More recently, we have found that similar conversions can be promoted by high pressure (8–14 kbar) even at room temperature. 1,4-Dihydro-1,4-epoxynaphthalene (**65**) can also be

coupled with oxadiazole **104**, although this time the coupled product **106** has a bent frame.³⁴

Reaction of Smith's diene (**4**) with oxadiazole **104** yields the coupled product **107** (Scheme 24) in which two dihydro-Smith's units are fused stereospecifically to the central 7-oxanorbornane.

The corresponding 1,3,4-thiadiazole **108** produces the thia-bridged hexacycle **109** on treatment with norbornadiene **1** either thermally³⁵ or under high pressure.³⁶ (Scheme 25). In this and the oxa-related cycloadditions (above), a diaza-alicycle related to **110** is considered to be an intermediate that decomposes to a 1,3-dipolar species **111**—the active intermediate for the second coupling step; other evidence rules out epoxide **112** (X=O) as an intermediate.

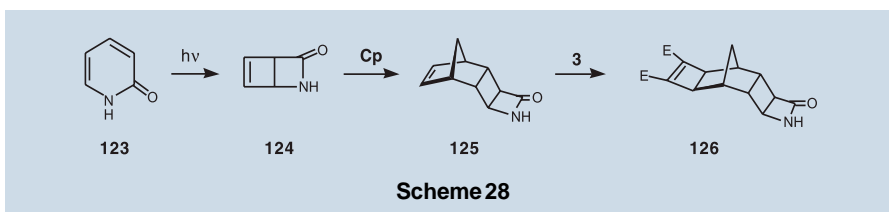
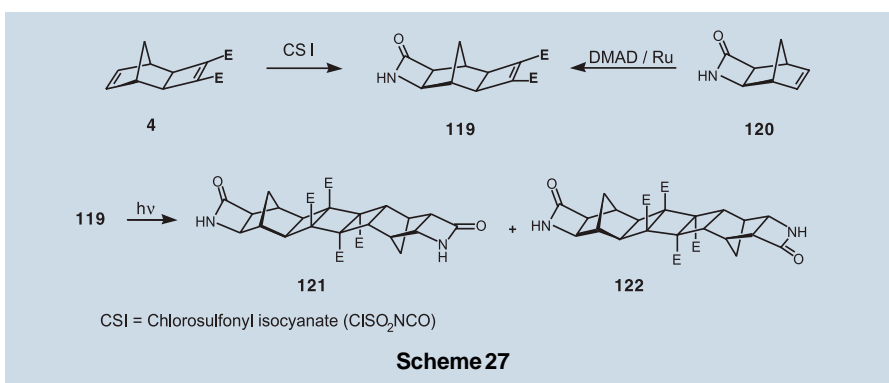
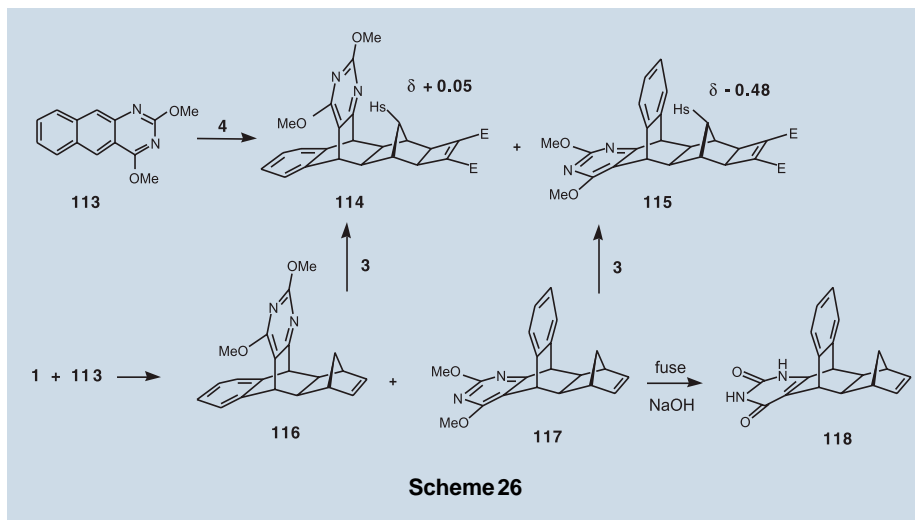
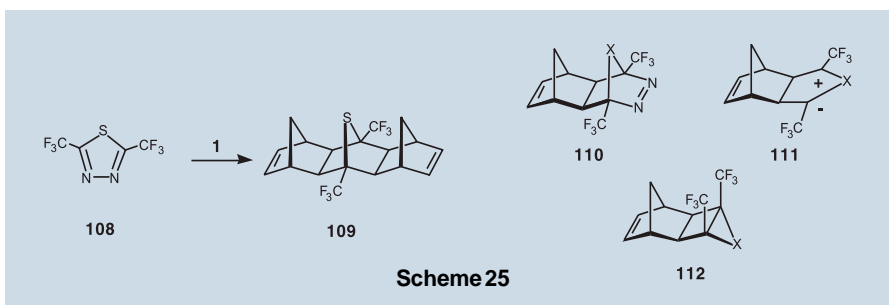
3.2.4. 1,3-Diazaanthracenes: Uracil Delivery Agents

The annellation of the pyrimidine ring onto alicyclic alkenes has been achieved using Diels-Alder chemistry. 2,4-Dimethoxy-1,3-diazaanthracene (DDA) (**113**) reacts with Smith's diene (**4**) under forcing thermal conditions (sealed tube at 180 °C) to form a mixture of stereoisomeric adducts **114** and **115** which can be separated by fractional crystallization (Scheme 26).³⁷ The stereochemical assignments are made on the basis of ¹H NMR chemical shift data where the benzenoid ring is more shielding than the pyrimidine ring, a fact reflected in the chemical shift of the proximate methylene bridge proton (Hs), which occurs at δ -0.48 and +0.05, respectively.

An alternative route to adducts **114** and **115** is the synthetically preferred method and involves cycloaddition of DDA (**113**) with norbornadiene **1** to produce a 2:3 ratio of adducts **116** and **117**, and in this respect follows on our earlier work³⁸ with anthracene (Scheme 26). These adducts, which can be separated by HPLC, are assigned their structures using the previously described shielding criteria. Ruthenium-catalyzed cycloaddition of DMAD onto **116** and **117** yields the corresponding cyclobutenes **114** and **115**. Conversion of this type of product to the uracil derivative is illustrated by the hydrolysis (NaOH fusion) of **117** to uracil **118**.

3.2.5. β -Lactam Products

β -Lactams fused to Smith's diene are available by chlorosulfonyl isocyanate cycloaddition.³⁹⁻⁴² Addition occurs site selectively at the norbornene π -bond to furnish the azahomo[4]ladderane **119** (also available by ruthenium-catalyzed cycloaddition of DMAD onto the lactam **120**). Photo-dimerization of **119** produced the bislactams



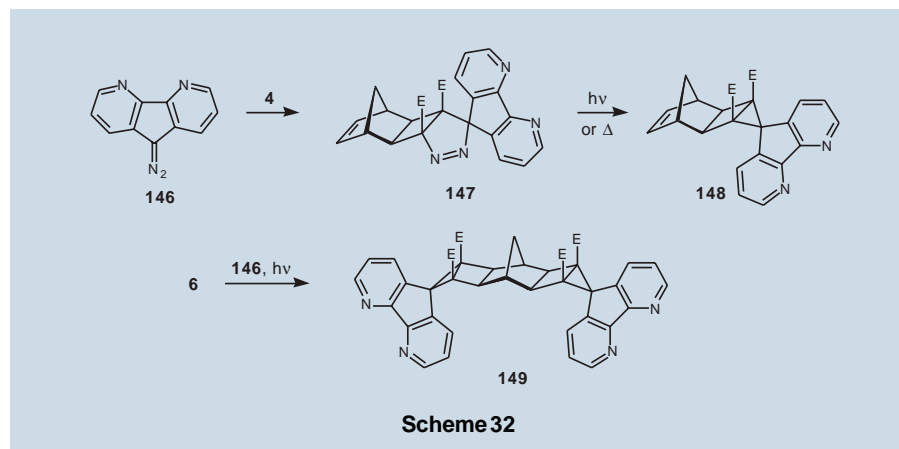
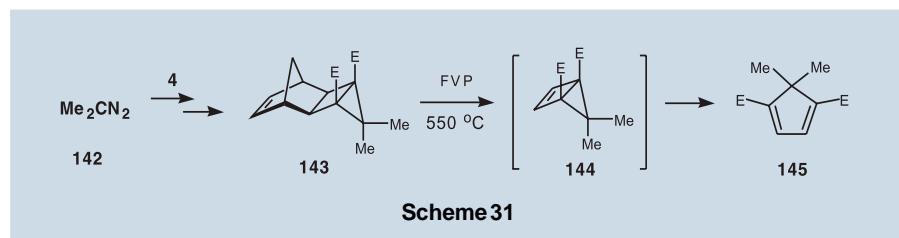
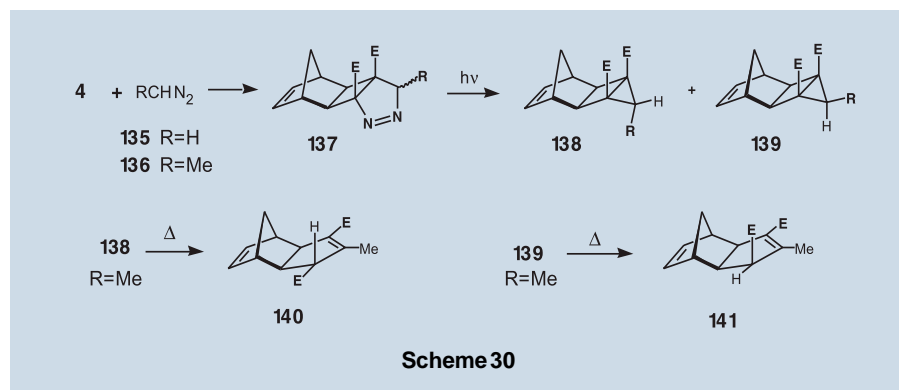
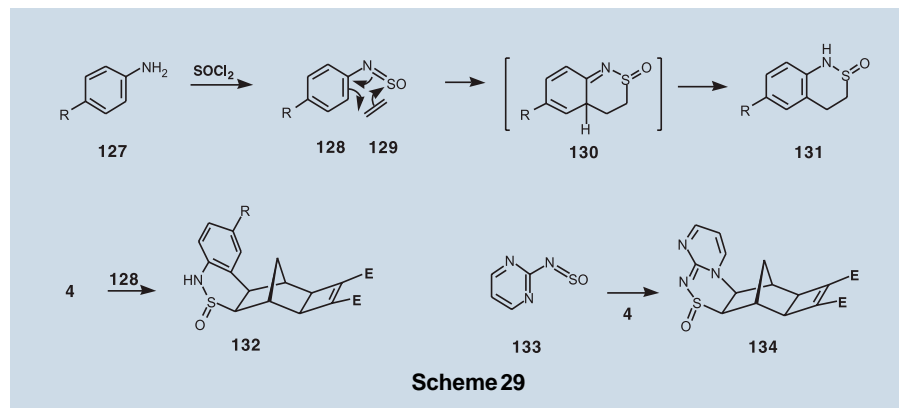
121 and **122** (Scheme 27). These diastereomers open the way for the production of space-separated β -amino acids by ring-opening of the β -lactam ring. Isomer **121** would produce a spacer where the peptides formed from the amino acids at its ends would extend in the same direction (i.e., syn), whereas from isomer **122** they would extend in opposite directions (i.e., anti) with respect to the vertical planes of the spacers.

Formal fusion of a β -lactam component into the norbornene end of Smith's diene can also be achieved indirectly (Scheme 28). In this method, **124**, a photoisomer of **123**, is reacted with cyclopentadiene to yield exclusively **125**. Catalyzed addition of DMAD to the norbornene π -bond of **125** introduces the cyclobutene-1,2-diesther component and completes production of the dihydro-Smith product **126**.⁴³

3.2.6. Arylsulfinylamine Cycloadditions

Arylsulfinylamines **128**, readily prepared by treatment of arylamines **127** with thionyl chloride, act as heterodienes with ring-strained dienophiles to form fused products **131** (Scheme 29).^{44,45} We have exploited this characteristic to attach

functionality to Smith's diene. Reaction of *N*-sulfinylanilines **128** with Smith's diene (**4**) occurred site selectively at the norbornene π -bond to produce the fused tetrahydro-1,2-azathianaphthalenes **132**. Extension of this procedure to *N*-sulfinylaminopyrimidine **133** provided access to the fused pyrimidine **134**.⁴⁶



4. 1,3-Dipolar Cycloadditions

4.1. Diazoalkanes: Spiro-Fused Diazafluorene Ligands

Diazomethane **135** reacts rapidly with Smith's diene (**4**) to produce pyrazoline **137** (R = H) by exclusive reaction at the cyclobutene π -bond (Scheme 30); diazoethane **136** and 2-diazopropane **142** produce analogous products.⁴⁷ Photochemical ejection of dinitrogen yields the bicyclo[2.1.0]pentane derivatives **138**, **139**, and **143**, respectively. Since reaction occurs specifically at the cyclobutene π -bond, the opportunity to effect a retrodiene loss of cyclopentadiene becomes an option. However, it is again apparent that cyclopentadiene is a reluctant dienofuge since rearrangement of the strained bicyclo[2.1.0]pentane moiety occurs preferentially. In the case where diazoethane is involved, both cyclopropane stereoisomers **138** (R=Me) and **139** (R=Me) are available, allowing for the evaluation of the stereochemistry of the bicyclo[2.1.0]pentane rearrangement since **138** selectively forms **140** and **139** selectively forms **141**.

Flash vacuum pyrolysis of the dimethyl-diazomethane adduct **143** caused fragmentation to cyclopentadiene and the substituted cyclopentadiene **145** (Scheme 31). In this example, no evidence for the intermediate bicyclopentene **144** was observed, and it might be that *direct* formation of the cyclopentadiene occurred as a result of the cyclopropane σ -bond participation in the fragmentation process.

Another ligand delivery reagent (see Section 3.1.6), this time for the introduction of the 1,8-diazafluorene ligand, has been developed using diazo chemistry (Scheme 32). Diazodifluorene⁴⁸ (DADAF) **146** is an active 1,3-dipolar reagent which reacted with Smith's diene (**4**) to produce the 1:1 cycloadduct **147** under the influence of heat (benzene at reflux) or high pressure (CH_2Cl_2 , 14 kbar, room temperature). Ejection of dinitrogen thermally (toluene at reflux) or photochemically (350 nm) produced the spiro compound **148**. This opened the way for the preparation of molracs containing the 1,8-diazafluorene ligand.^{23,49} In particular, the dual ligand **149** was produced in two steps from **6**.

4.2. Azides

Reaction of azides occurred preferentially at the norbornene π -center of Smith's diene to produce the corresponding triazoles **150** and subsequent photochemically induced loss of dinitrogen formed aziridines **151** (Scheme 33).⁵⁰ While there is evidence of dual adduct formation from continued reaction of monoadduct **150** with azides, no discrete products were isolated. With benzo-Smith's diene **152** as a substrate, reaction was achieved at the cyclobutene-1,2-diester π -bond to form

a triazoline adduct **153**, which was transformed to the aziridine **154** by UV irradiation.

4.3. Epoxycyclobutane-Alkene Cycloadditions

The cyclobutene-1,2-diester component of the 7,8-dihydro derivative of Smith's diene **5** can be epoxidized (MeLi, ^tBuO₂H) to form epoxycyclobutane **155** (Scheme 34).⁵¹ Heating **155** with norbornene **101** generates a single product **157** in a stereospecific cycloaddition involving ring-opening of the epoxide to the 1,3-dipolar intermediate **156**. Smith's diene forms a similar epoxide **158**, and it too undergoes similar cycloadditions.

This process can be employed as a coupling reaction for the production of large, rigid structures containing complex functionality (Scheme 35). This is illustrated using the methoxynaphthalene-functionalized epoxycyclobutane **160**, which is reacted with functionalized norbornenes **93**, **56**, and **148** to produce polyalicyclic structures **161-163**, respectively, as examples of space-separated bi-chromophoric systems.

5. Summary of Cycloadditions in Flow Sheet Form

Flow Sheet 1: Reactions at the cyclobutene-1,2-diester π -bond of Smith's diene (**4**).

Flow Sheet 2: Reactions at the norbornene π -bond of Smith's diene (**4**).

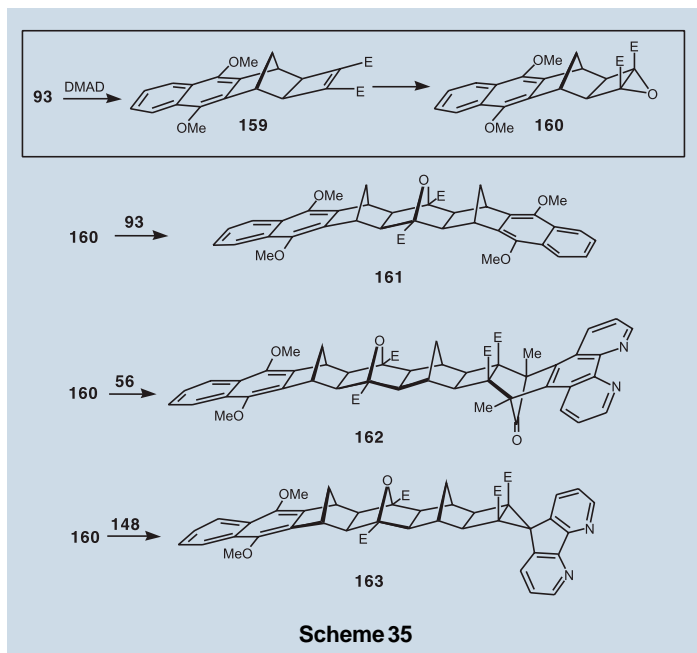
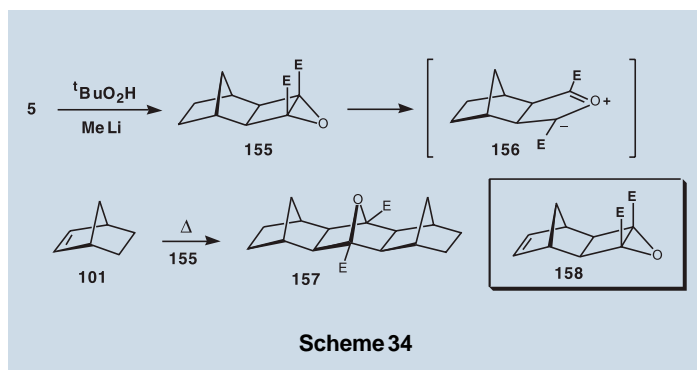
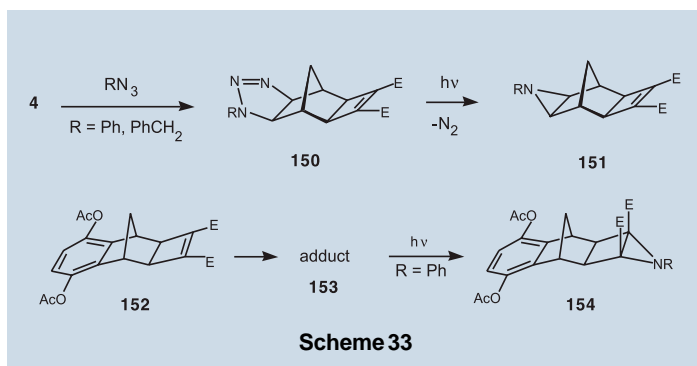
6. Acknowledgements

In concluding, it would be remiss not to mention the sterling contributions made by our many co-workers during the course of our love affair with Smith's diene. Much of this occurred in the course of preparing other targets, and it is only when combined in an account of this sort that one appreciates the central role Smith's diene has played in much of our research.

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Ronald (Ron) N. Warrener studied chemistry at Sydney University (B.Sc., M.Sc.) and the University of New South Wales (Ph.D.). This was followed by a Postdoctoral Fellowship at Princeton (with E.C. Taylor), and academic appointments at the Australian National University (Professor and Head of Department 1979-1988), Bond University (Dean of Science and Technology 1988-1991), and Central Queensland University (Director, Centre for Molecular Architecture, 1992 to present). He has published extensively (200+ papers) in synthetic organic chemistry with special interest in photochemistry and cycloaddition chemistry. Also a noted researcher in Forensic Science, he directed centers in this specialty at ANU and Bond Universities. Since 1992 he has held an ARC Senior Research Fellowship, during which time he worked full-time in research and set up the CMA at Central

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