ORGANIC SYNTHESIS
THEORY AND APPLICATIONS

A Research Annual

Editor: TOMAS HUDLICKY

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Department of Chemistry
Virginia Polytechnic Institute
and State University

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INTRODUCTION TO THE SERIES: AN EDITOR'S FOREWORD

The field of organic chemistry has developed dramatically during the past forty years. Thus it appears to be an opportune time to publish a series of essays on various relevant themes in the 80s written by workers who are active in the discipline. This collection includes many of the important areas of current research interest. To cover such a broad area a very substantial effort is needed, as was the cooperation of a large number of colleagues and friends who have agreed to act as series editors. I have been gratified by the favorable response of research workers in the field to the invitation to contribute chapters in their own specialities. Each contributor has written a critical, lively and up-to-date description of his field of interest and competence, so that the chapters are not merely literature surveys. It is hoped that this new and continuing series will prove valuable to active researchers, and that many new ideas will be generated for future theoretical and experimental research. The wide coverage of material should be of interest to graduate students, postdoctoral fellows and those teaching specialized topics to graduate students.

Department of Chemistry
Emory University
Atlanta, Georgia

Albert Padwa
Consulting Editor

PREFACE

The series entitled *Organic Synthesis: Theory and Applications* will provide a summary of the state of the art synthetic methodology of the 1980s. This first volume is intended as an introduction to some of the topics that enjoyed widespread popularity during the past decade. The developments associated with, for example, the use of the Diels–Alder reaction are truly astonishing and leave only fine details to be worked out in this field. Similarly, the carbocyclic silane-mediated cyclizations are at the point today where precise physical organic parameters need to be identified and established to render these processes permanent and reliable tools of the synthetic chemist. The chapter on nonconventional methods of synthesis mirrors the trend of the last 15 years in which organic chemists ventured to other areas of science in search of novel means of energizing the reactions pathways.

The development of organic synthesis in the post-Woodward years (1960–present) has traveled a path that diverged from the total synthesis focus of the 1960s on to the details of the processes involved in total synthesis. Indeed while an astonishing amount of progress has been reached in the area of especially the enantioselective methodology, very little has changed in the way of design of complex molecules other than what the Woodward legacy left us. The daily use of MM2 calculation by the organic community is perhaps the only improvement in the way molecular architects guide their approach to complex targets. Furthermore, the advances in such procedures as aldol condensation and Diels–Alder cycloaddition still fall short of achieving the fundamental ability of chemists to predict as well as explain the pathways of organic reaction.

While every trained chemist can readily justify the outcome of a known experiment using the principles of mechanistic organic chemistry, the same chemist with a pencil, a chalk, or a computer terminal runs a little better than 50% chance of predicting the outcome of a reaction yet to be performed. Clearly then, the theoretical foundation that we use is inadequate and incomplete if such discrepancies are possible. What is the

solution? Amendments or complete overhaul of mechanistic rationalizations in the days to come to achieve better powers of prediction.

The next volumes will examine some of the mathematical concepts emerging in organic synthesis today as well as some applications of novel design elements to the synthesis of complex molecules. The bioorganic and polymer subsets of our discipline are increasingly making their influence on the preparation and management of organic compounds. The next decade will undoubtedly witness a marriage between all of these disciplines as greater understanding of the fundamentals of organic chemistry will bring about the much needed departure from the way we currently do business. It is hoped that this first volume will start the reader thinking about such changes.

Tomas Hudlicky
Series Editor

CONTENTS

ASYMMETRIC DIELS–ALDER REACTIONS

Michael J. Taschner

OUTLINE

Organic Synthesis: Theory and Application, Vol. 1, pages 1–101.

ISBN: 0-89232-865-7

I. INTRODUCTION

The Diels–Alder reaction has evolved into one of the most effective weapons in the arsenal of the organic chemist since the first such reaction was reported by Diels and Alder in 1928.[1] Its remarkable regioselectivity,[2] relatively predictable endo selectivity,[3] syn stereospecificity,[4] and capacity to control the relative stereochemistry at up to four of the newly created chiral centers render the Diels–Alder reaction unequalled in terms of elegance and efficiency in the construction of six-membered rings. As organic synthesis matured, the ability to control the relative stereochemistry was no longer sufficient. Organic chemists had become increasingly concerned with the control of absolute stereochemistry.[5] Therefore, it was only natural that during the course of this development, both the intermolecular Diels–Alder reaction[6] and its intramolecular counterpart[7] would be proded and probed with the hope they would be capable of inducing asymmetry in the bond-forming process in a controllable and predictable manner.[8]

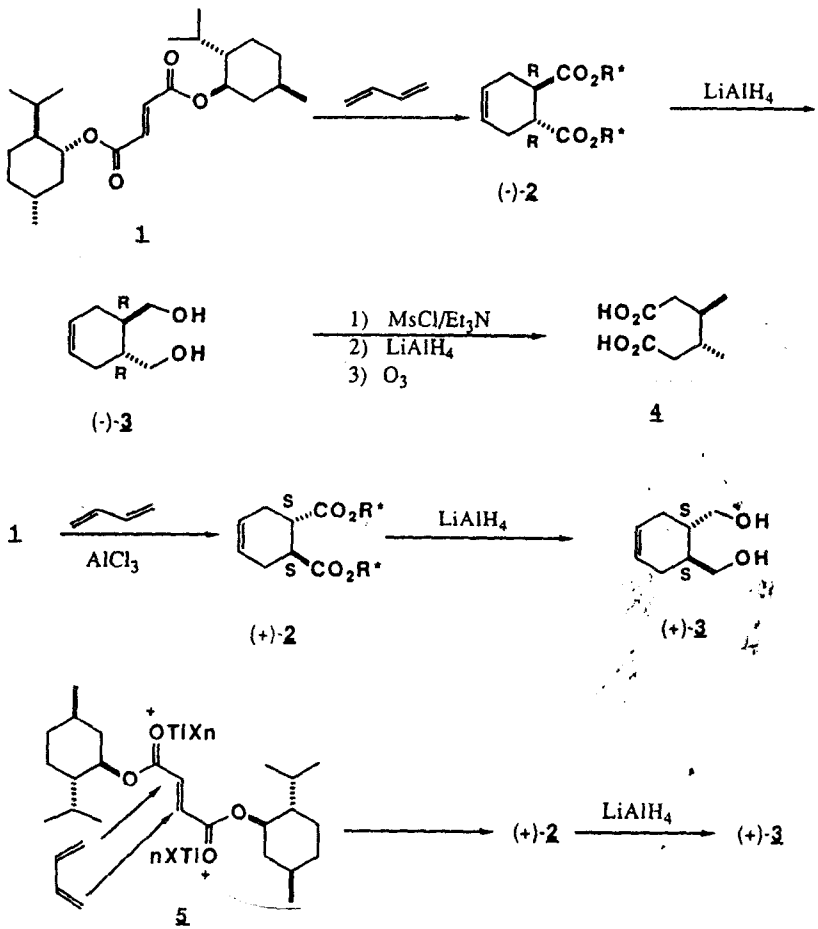
The development of the strategies to attain absolute stereochemical control in the intermolecular and intramolecular [4 + 2] cycloaddition processes will be presented within the individual sections in as chronological an order as coherently possible. When appropriate, mechanistic interpretations concerning potential diastereomeric transition states of a particular transformation will be advanced in an effort to furnish a better understanding and appreciation of the overall process. The application of particular tactics in the context of enantioselective total syntheses of a number of natural and a few unnatural products will be interspersed within the sections. An effort was made to be as thorough as possible in the coverage of the pertinent literature to date. However, it is inevitable that a number of articles will have been inadvertently and unintentionally omitted. Apologies are extended in advance to the authors of any of the articles that may have been overlooked.

II. CHIRAL DIENOPHILES

A preliminary communication from Walborsky in 1961 reported the inaugural investigation[9] directed at the induction of asymmetry in the Diels–Alder process.[10] The reaction between (−)-dimenthyl fumarate **1** and 1,3-butadiene under thermal conditions produced the cyclohexenyl diester **2**. In order to avoid any possibility for resolution, the diester was immediately reduced with $LiAlH_4$ to afford diol **3** with the (1*R*,2*R*)-configuration in 2.4% enantiomeric excess (ee). The absolute configuration was established by chemical conversion of **3** to (−)-*threo*-3,4-dimethyladipic acid (**4**), whose absolute configuration was known. In the presence of $AlCl_3$, the reaction of

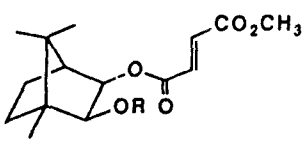
1 and butadiene produced the same product **2**, but was of opposite sign and configuration. Reduction of this diester with $LiAlH_4$ yielded diol **3** in 57% ee which possessed the (1*S*,2*S*)-configuration.

Two years later, Walborsky published the full details of the study that showed the results to be dependent on solvent, temperature, and catalyst. In the thermal reaction, the optical purity of the (*R*)-(−)-isomer was found to increase with increasing temperature (3% ee at 180°C). However, this minimal increase in optical yield was more than offset by the decrease in chemical yield. The best results were obtained using Lewis acid conditions with 1 equivalent of $TiCl_4$ in toluene at 25°C. After reduction of the diester, diol **3** was isolated in 78% optical purity and 80% yield. The results have been explained by means of a modified Prelog model in which the conformation of the fumarate resembles that shown in **5**.[11]

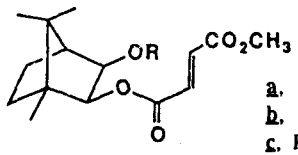


Although the cycloadditions of **1** were dependent on solvent and temperature, their effect was minimal. The use of Lewis acid catalysis greatly enhanced the induction, but the adducts were of opposite absolute configuration to those obtained under thermal conditions. This prompted Jurczak to investigate the use of high pressure in this asymmetric Diels–Alder reaction. There was a modest increase in the diastereoselectivity (12.8%); however, the absolute configuration was the same as that observed in the Lewis acid-catalyzed reactions and remained unchanged over the range of pressures examined.[12]

In the quest for new alcohol reagents capable of imparting some diastereofacial differentiation, the mixed fumarate esters of the isoborneols **6** and **7** were prepared. The reactions with anthracene as the diene were examined to determine the efficiency of these dienophiles to induce asymmetry in the Diels–Alder reaction. As evidenced in Table 1, the uncatalyzed reaction of **6c** with anthracene and subsequent $LiAlH_4$ reduction results in the formation of the (11*S*,12*S*)-diastereomer **8** in 90% yield [60% diastereomeric excess (de)]. The uncatalyzed reaction of **7c** produces the adduct with the expected opposite (11*R*,12*R*)-configuration, but in reduced yield (68%) and diastereoselectivity (34%). In combination with $AlCl_3$, the dienophiles exhibit increased reactivity and better diastereofacial selectivity. The reaction of **6a** in the presence of $AlCl_3$ provides the (11*S*,12*S*)-diastereomer in 96% yield with a diastereomeric excess of 99%. The Lewis acid-mediated reaction of **7c** affords a quantitative yield of the (11*R*,12*R*)-diastereomer with a diastereomeric excess of 92%.[13]

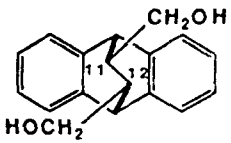


6

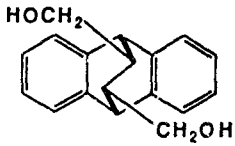


7

a. R= CH_2Ph
b. R= $CHPh_2$
c. R= CONHPh



(11S, 12S)-8



(11R, 12R)-8

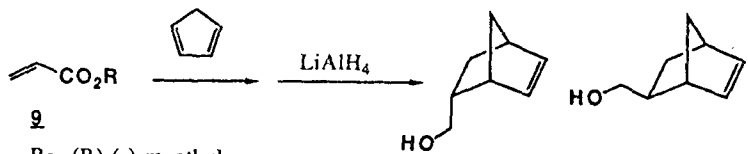
The catalyzed and uncatalyzed reactions of mono- and dibornyl fumarates with diphenylisobenzofuran have been used in an analysis of the transition state geometry of the cycloaddition. Tolbert found the amount of asymmetric induction provides a useful probe of transition state geometry.

Table 1. Cycloadditions of **6** and **7** with Anthracene

Dienophile	*Catalyst*	*Temperature (°C)*	*% Yield*	*% de*
6a	—	110	30	< 10
6b	—	110	68	< 10
6c	—	110	90	60
7c	—	110	68	34
6a	$AlCl_3$	−30	96	> 99
6c	$AlCl_3$	−30	100	99
7c	$AlCl_3$	0	100	92

He concluded the Diels–Alder reaction was synchronous only when a catalyst was not available to polarize the transition state and the effect of the Lewis acid in enhancing asymmetric induction was to increase the steric interaction at the end furthest away from the complexed catalyst.[14]

Two groups have reported the cycloadditions of chiral acrylates **9a–9e** with cyclopentadiene. The results were consistent with the Prelog model hypothesized by Walborsky. However, as can be seen in Table 2, the enantiomeric excesses for the uncatalyzed reactions were low, and those for the Lewis acid-catalyzed processes were moderate to good.[15]



9

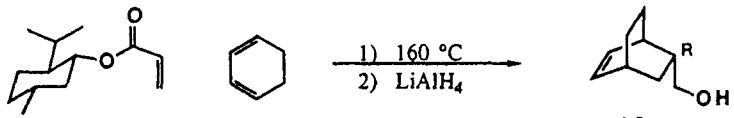
a, R= (R)-(-)-menthyl
b, R= (R)-(-)-2-octyl
c, R= (S)-(+)-2-octyl
d, R= (S)-(+)-2-(3,3-dimethyl)butyl
e, R= (S)-(+)-2-butyl

(+)-**10** (+)-**11**

Table 2. Reactions of Acrylates **9** with Cyclopentadiene

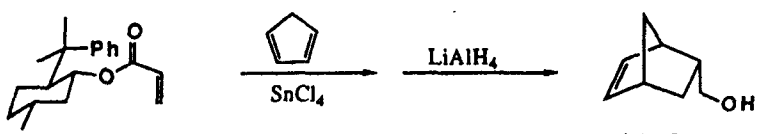
Acrylate	*Temperature (°C)*	*Catalyst*	**10** *(% ee)*		**11** *(% ee)*		*Reference*
9a	0	—	(+)	9.1	—	—	15a
9a	−70	$AlCl_3 \cdot Et_2O$	(+)	67	—	—	15a
9a	−70	$BF_3 \cdot Et_2O$	(+)	82	—	—	15a
9a	4	$SnCl_4$	(+)	41	—	—	15b
9b	35	—	(+)	4.1	(+)	3	15a
9b	−70	$BF_3 \cdot Et_2O$	(+)	27	—	—	15a
9c	35	—	(−)	4.1	—	—	15a
9c	−70	$BF_3 \cdot Et_2O$	(−)	28	—	—	15a
9c	4	$SnCl_4$	(−)	15	—	—	15b
9d	35	—	(−)	11	—	—	15a
9d	−70	$BF_3 \cdot Et_2O$	(−)	88	—	—	15a
9e	4	$SnCl_4$	(−)	24	—	—	15b

An isolated study of acrylate **9a** with 1,3-cyclohexadiene under thermal conditions was reported to produce predominantly the (*R*)-(+)-*endo*-isomer **12** in 60% ee after $LiAlH_4$ reduction.[16]

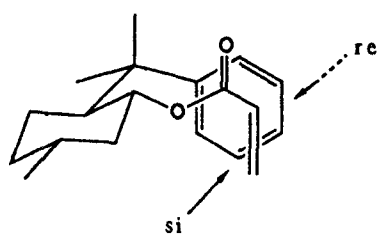


9a **12**

The turning point in the development of asymmetric induction in the Diels–Alder reaction came when Corey and Ensley reported the preparation of an optically active intermediate for the synthesis of prostaglandins via an asymmetric Diels–Alder reaction, which utilized the 8-phenylmenthyl auxiliary in combination with the acrylate dienophile.[17] They found the 8-phenylmenthyl group to be more effective at differentiating between the diastereotopic faces of the acrylate. The $SnCl_4$-catalyzed reaction of **13** with cyclopentadiene and subsequent $LiAlH_4$ reduction was originally reported to provide (+)-**10** in 99% ee. A reinvestigation of this reaction by Oppolzer corrected the value to 89% ee.[18] The improvement in diastereoselection has been attributed to the reactive conformation being similar to the one shown below. The acrylate is assumed to have the antiplanar arrangement of the olefin and the carbonyl which results in the shielding of the *re*-face of the acrylate by the phenyl substituent, as well as allowing for π-stacking interactions between the acrylate and the aromatic ring. It is believed the combination of these steric and electronic effects are responsible for the heightened selectivity.

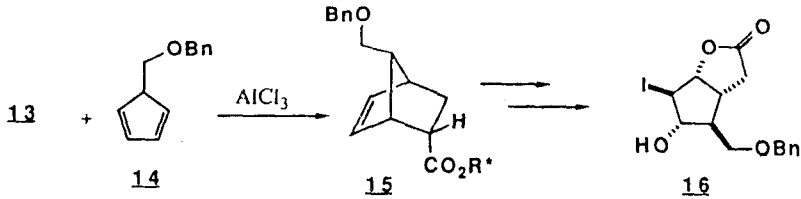


13 (+)-**10**

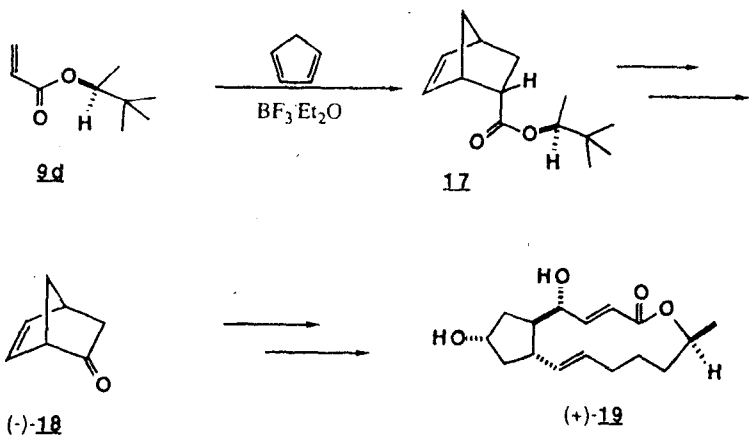


For the prostaglandin work, **13** was reacted with cyclopentadiene **14** in the presence of $AlCl_3$ to furnish an 89% yield of the (−)-*endo*-adduct **15**. This

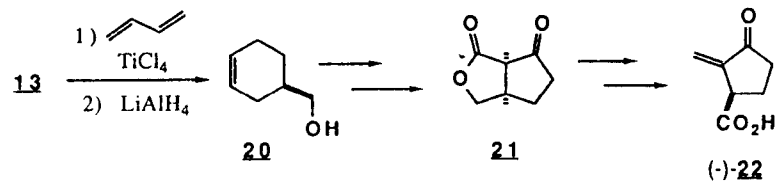
was transformed by a series of reactions into the known, optically active iodolactone **16**, which had previously been employed in the preparation of a number of prostaglandins. The preparation of **16** also proved the absolute configuration of **15** is as shown.[17]



Green used the $BF_3{\cdot}Et_2O$-catalyzed cycloaddition of the enantiomer of **9d** with cyclopentadiene in a total synthesis of (+)-brefeldin-A (**19**). The adduct **17**, obtained in 75% yield, was transformed into norbornenone (−)-**18** (80–85% ee). This was converted into (+)-**19** by previously established procedures.[19]



In 1980, Boeckman reported an efficient enantioselective synthesis of the antitumor agent sarkomycin from the 8-phenylmenthyl acrylate **13**.[20] Walborsky's model predicted the cycloaddition of **13** with butadiene would produce the required (*R*)-configuration in the cyclohexenyl ester for the ultimate conversion to (*R*)-(−)-sarkomycin (**22**). The reaction between acrylate **13** and butadiene in the presence of $TiCl_4$ produced the desired cycloadduct. Other Lewis acids were reported to be inferior in terms of chemical or optical yields. The ester was then reduced with $LiAlH_4$ to provide (*R*)-(+)-**20** in 70% chemical yield and 86–91% ee. The alcohol was converted to the bicyclic keto lactone **21**, which was further transmuted in a series of reactions to (*R*)-(−)-**22**.



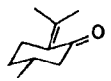
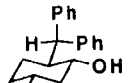
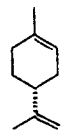
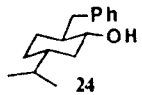
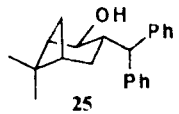
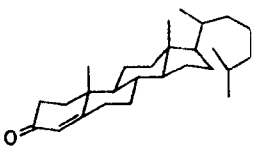
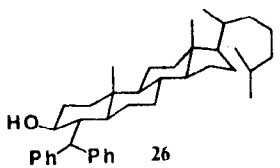
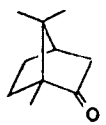
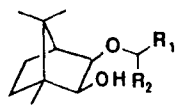
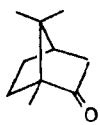
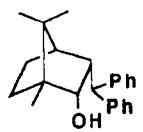
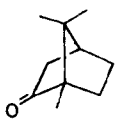
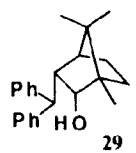
The degree of asymmetric induction in all the Diels–Alder reactions of **9a** and **13** prior to 1981 was determined entirely by chiroptic measurements of the $LiAlH_4$ product **10**. Because this method was not reliable, Oppolzer undertook a reinvestigation of the Diels–Alder reaction of these two dienophiles under a variety of conditions. The extent of asymmetric induction was measured using ^{19}F-NMR spectroscopy of the Mosher esters derived from alcohol **10**. This method was found to be a more reliable technique for the determination of the enantiomeric purity of the products as well as a useful check of the enantiomeric purity of the chiral auxiliary. Shown in Table 3 is a summary of the results obtained in the systematic studies of the reactions of **9a** and **13** in which the solvent, temperature, and Lewis acid were varied.[18]

Table 3. Systematic Study of the Cycloadditions of **9a** and **13**

Acrylate	*Equivalent Lewis acid*	*Solvent*	*Temperature (°C)*	*Time (h)*	*% Yield*	*endo/exo*	*% ee of 2-(R)-10*
9a	1.0 $SnCl_4$	$PhCH_3$	0	0.5	–	–	51
13	1.5 $SnCl_4$	$PhCH_3$	0	3.5	95	84:16	89
9a	0.7 $AlCl_3$	CH_2Cl_2[23]	−55	—	—	—	48
13	0.7 $AlCl_3$	CH_2Cl_2	−20	3.5	89	91:9	65
13	0.7 $AlCl_3$	$PhCH_3$	−20	3.5	96	92:8	52
9a	1.5 Me_2AlCl	CH_2Cl_2	0	3.5	73	92:8	47
13	1.5 Me_2AlCl	CH_2Cl_2	0	3.5	95	89:11	64
13	1.5 Me_2AlCl	$PhCH_3$	0	3.5	81	88:12	55
9a	1.5 $TiCl_4$	CH_2Cl_2	−20	3.5	65	92:8	62
13	1.5 $TiCl_4$	CH_2Cl_2	−20	3.5	83	89:11	90

The table shows that the most useful conditions involve the use of either 1.5 equivalents of $SnCl_4$ in toluene at 0°C (89% ee) or 1.5 equivalents of $TiCl_4$ in CH_2Cl_2 (90% ee). Under all conditions studied, the predominant product, as demonstrated previously, proved to be the 2-(*R*)-enantiomer. Also corroborating previous work, the 8-phenylmenthyl group was found to be superior to the menthyl group for the induction of chirality into the cycloadducts.

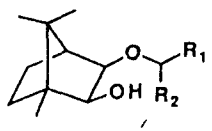
Table 4. Cycloadditions of Acrylates Derived from **23–29** with Cyclopentadiene

Starting material	*Alcohol*	*Adduct configuration*	*% ee*
 (+)-Pulegone	 **23**	*R*	88
 (+)-Limonene	 **24**	*R*	63
 (−)-β-Pinene	 **25**	*R*	85
 (+)-4-Cholesten-3-one	 **26**	*S*	84
 (+)-Camphor	 **27a**, R_1 = Ph; R_2 = H	*S*	88
 (+)-Camphor	 **28**	*R*	81.5
 (−)-Camphor	 **29**	*S*	82.7

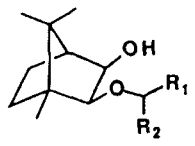
Although the chiral inductions with the 8-phenylmenthyl group were very good, there were still some shortcomings with the overall implementation of the asymmetric Diels–Alder strategy using this auxiliary. The two major limitations are the need to purify the (−)-8-phenylmenthol by careful medium pressure chromatography and the relative inaccessibility of its *re*-face directing optical antipode. To overcome these problems, Oppolzer initiated a program designed to prepare more effective and versatile chiral auxiliaries. Utilizing the insight obtained from the 8-phenylmenthyl studies concerning the shielding of one acrylate face via the π-stacking interactions, investigations concentrated on the preparation and use of the *si*-face and *re* face directing auxiliaries **23**–**29**. These were transformed into their acrylate esters and then condensed with cyclopentadiene in the presence of $TiCl_4$ to afford the cycloadducts. The adducts were reduced to either (+)-(*R*)-**10** or (−)-(*S*)-**10** with $LiAlH_4$ for the determination of chiral induction. Shown in Table 4 are the results of this study.[21]

Examination of the results reveals a number of important findings. The acrylates derived from alcohols **26**, **27a**, and **29** were the first readily available *re*-face directing acrylates developed which gave excellent chiral inductions. The alcohols **27a** and **29** have the additional advantages in that both are crystalline and both enenatiomeric forms of the precursors are readily available. Also worth noting is the result from alcohol **25**. This produces an absolute configuration and enantiomeric excess comparable to that obtained with **13**. It also is crystalline and both enantiomeric precursors are readily available.

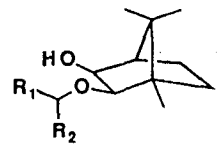
Encouraged by the results obtained with alcohol **27a**, the acrylates derived from the *cis*-3-hydroxyisobornyl ethers **27**, **30**, and **31** were prepared to examine how important a role the hypothetical aryl/acrylate π-stacking played in the asymmetric Diels–Alder reaction with cyclopentadiene (Table 5). With most of these acrylates, $TiCl_4$ proved to be too harsh a Lewis acid and usually caused rapid ether cleavage. This problem was overcome by the use of the milder Lewis acid $TiCl_2(O\text{-}i\text{-}Pr)_2$ [$TiCl_4$/$Ti(O\text{-}i\text{-}Pr)_4$, 1:1]. The milder conditions afforded the adducts in excellent chemical yields and produced diastereomeric excesses of up to 92%.



27



30



31

In light of these results, there appears to be no particular advantage to increasing the aromatic surface of the appendant ether. This seems to imply