Chalcogenides as Organocatalysts

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1. Introduction

In this review, we describe the many roles chalcogenides play as organocatalysts. Chalcogens, or the oxygen family,

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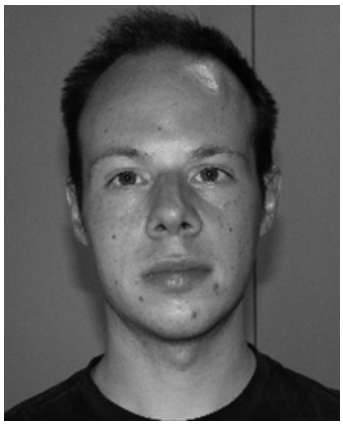
Eoghan M. McGarrigle was born in Dublin, Ireland. He studied chemistry at University College Dublin, where he obtained his B.Sc. degree in 1998. He carried out his doctoral studies under the supervision of Dr. Declan Gilheany and was awarded his Ph.D. for his thesis on metal(salen) chemistry in 2003. He then worked as a postdoctoral fellow in the group of Dr. Gilheany, researching novel routes to *P*-stereogenic compounds. Since 2005, he has been the research officer in the group of Prof. Aggarwal in the University of Bristol.



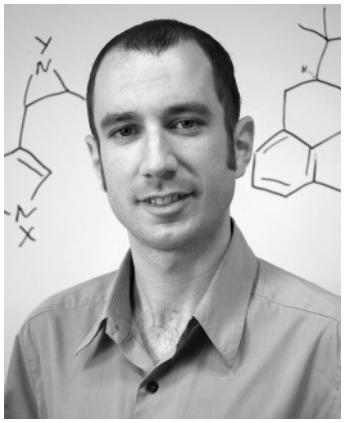
Eddie L. Myers graduated with a B.A. (Natural Science) from Trinity College Dublin in 2000. Under the supervision of Dr. Youla Tsantrizos, he received a M.Sc. (Chemistry) from McGill University, Canada, in 2003, working on peptide nucleic acid (PNA) analogs. Under the supervision of Prof. Varinder Aggarwal, he earned a Ph.D. from University of Bristol in 2007, working on the development of novel Morita–Baylis–Hillman-type reactions. He is currently pursuing postdoctoral research in the laboratory of Prof. Ronald Raines at the University of Wisconsin–Madison.

consist of the elements O, S, Se, and Te. The name is generally considered to mean "ore former", from the Greek chalcos (ore) and −gen (formation). The review is organized according to reaction classes, rather than a discussion of each of the elements in turn, as this tends to be how chemists think. Furthermore, this allows us, where appropriate, to compare the reactivity/selectivity of different chalcogenides in a particular reaction. Our own interest in this area started with the exploration of sulfides as catalysts in ylide-mediated epoxidations. Many of the reactions described herein involve catalysis of ylide-mediated reactions, and it is with these reactions we begin.

1.1. Scope

Within this review, we have taken the broad definition of a catalyst to be a compound that takes part in the reaction but is regenerated during the course of the reaction. Instances where stoichiometric amounts of catalyst are used are described, but the focus is on the use of substoichiometric

Ona Illa was born and educated in Barcelona, Spain. She obtained her first degree from the Universitat Autònoma de Barcelona in 2000. She then undertook her Ph.D. studies with Professors Rosa Maria Ortuño and Vicenç Branchadell in the same university, working on the synthesis of phosphino(silyl)carbenes and diazocompounds and their reactivity with carbonyl groups and olefins. In 2006, she was a visiting postdoctoral fellow for 6 months with Professor Antoine Baceiredo in Toulouse, France, working with phosphorous and sulfur bisylides. In June 2006, she was awarded a Beatriu de Pinós Fellowship for 2 years in the group of Professor Aggarwal, where she works on the synthesis and applications of new chiral sulfides.



Michael A. Shaw was born in Glasgow, in the west of Scotland, U.K. During his undergraduate degree, he spent a year working with Millennium Pharmaceuticals and an ERASMUS placement at the University of Alicante, Spain. He then graduated with an M.Sci. from the University of Strathclyde in 2004. Thereafter, he spent a further year working with Professor John Murphy at Strathclyde on the synthesis of novel chalcogenide-based electron-transfer reagents, before moving to the University of Bristol to undertake his Ph.D. research with Professor Varinder Aggarwal. His work there is focused on the ylide-mediated synthesis of enantioenriched aziridines and their application in the asymmetric synthesis of indole alkaloids.

loadings. The catalysts consist of compounds with two single carbon−chalcogen bonds only (e.g., a sulfide), where the chalcogen atom is vital for the catalytic activity. To the best of our knowledge, we have described all instances where a chalcogenide has been used as a catalyst until June 2007. It should be noted that there are many related publications where a chalcogenide salt is used in substoichiometric amounts in ylide reactions and generates the corresponding chalcogenide in situ. We will provide leading references only for these chemistries.

2. Epoxidation

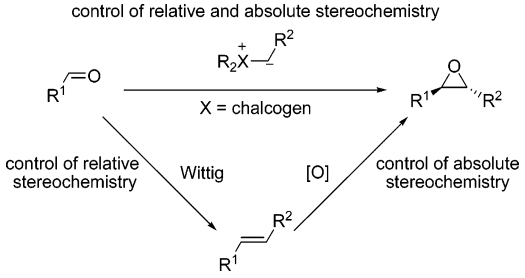
Epoxides are important building blocks and versatile substrates in organic synthesis. The synthesis of epoxides

Samantha L. Riches was born in Exeter in the United Kingdom. She studied chemistry at the University of Bristol, obtaining her M.Sci. in 2004. She then went on to undertake her Ph.D. research under the supervision of Professor Varinder Aggarwal. Her current research focuses on the application of asymmetric sulfur ylide cyclopropanation reactions towards the total synthesis of marine natural products.

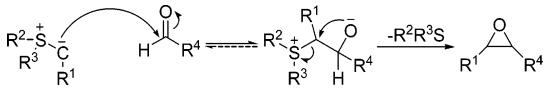
Varinder K. Aggarwal was born in Kalianpur in North India in 1961 and emigrated to the United Kingdom in 1963. He received his B.A. (1983) and Ph.D. (1986) from Cambridge University, the latter under the guidance of Dr. Stuart Warren. He was subsequently awarded a Harkness fellowship to carry out postdoctoral work with Professor Gilbert Stork at Columbia University, NY (1986–1988). He returned to a lectureship at Bath University and in 1991 moved to Sheffield University, where in 1997, he was promoted to Professor of Organic Chemistry. In 2000, he moved to the University of Bristol to take up the Chair of Synthetic Chemistry. He is the recipient of the AstraZeneca Award (1996), Pfizer Awards (1996, 1998), GlaxoWelcome Award (1998), RSC Hickinbottom Fellowship (1997), Novartis Lectureship (1999), Nuffield Fellowship (1997), RSC Corday Morgan Medal (1999), GDCh Liebigs Lecturship (1999), RSC Green Chemistry Award (2003), Zeneca Senior Academic Award (2004), RSC Reaction Mechanism Award (2004), Royal Society Wolfson Merit Award (2006), RSC/GDCh–Alexander Todd–Hans Krebs Lectureship (2007), EPSRC Senior Research Fellowship (2007), and RSC Tilden Lecturer (2008).

continues to attract interest, especially because of the possibility of regio- and stereoselectively ring-opening epoxides with a nucleophile to afford bifunctional compounds. The main methods employed to prepare epoxides can be divided into two groups: those that involve the oxidation of an alkene, which in turn can be obtained from a carbonyl compound by a Wittig-type reaction, and those that involve the alkylidenation of a carbonyl compound, either by using an ylide (Scheme 1), a carbene, or a Darzens' reaction. If the starting material is a carbonyl compound, then the latter class of reactions represents a potentially more efficient way of synthesizing the desired epoxide, but with the significant challenge of controlling both relative and absolute stereochemistries in one step. Chalcogenide-catalyzed ylide epoxidations shall be described below.

Scheme 1. Comparison of Ways to Synthesize an Epoxide from a Carbonyl Compound



Scheme 2. Epoxidation Reaction Using a Sulfur Ylide



2.1. Sulfide-Catalyzed Epoxidations

Stoichiometric sulfur ylide-mediated epoxidations were first reported in 1958 by Johnson and LaCount.[1] Since then, and after the establishment of the well-known method of Corey and Chaykovsky,[2] many improvements have been made to these reactions.[3] The reaction involves the attack of an ylide on a carbonyl group, which yields a betaine intermediate that collapses to give an epoxide and a sulfide (which can be recovered) (Scheme 2).

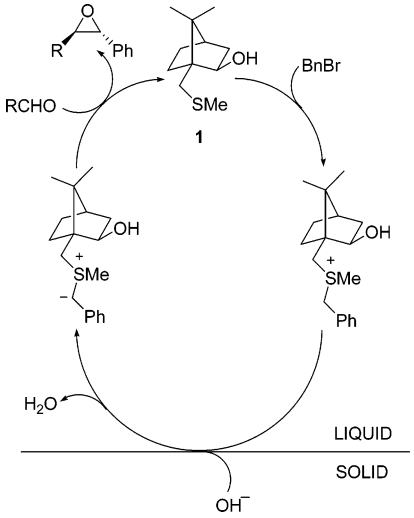
It is important to note that there are two main ways of carrying out the ylide-mediated epoxidation reaction; one involves the preformation and isolation of a sulfonium salt from a sulfide, which then is deprotonated to give an ylide that can then react with the carbonyl group.[4−10] The other method, on which we will focus, is the formation of an ylide from a sulfide followed by reaction with the carbonyl group in the same pot.[4,6,10−13] The reaction returns the starting sulfide, and so the sulfide is a catalyst and can be used in substoichiometric amounts. Two different approaches to forming the sulfur ylide in situ have been used: (1) the alkylation of the sulfide followed by deprotonation with a base, and (2) the direct reaction of the sulfide with a carbene or carbenoid. These are described in detail below.

2.1.1. Catalysis via Sulfide Alkylation/Deprotonation

The first catalytic sulfur ylide epoxidation was reported by Furukawa et al. in 1987.[14] The first example of an enantioselective reaction of this type was described by the same authors 2 years later.[15] Substituted benzyl bromides were used to alkylate chiral sulfide **1**, among others, and in situ deprotonation of the resulting sulfonium salt by powdered potassium hydroxide yielded a sulfur ylide that epoxidized benzaldehyde and *p*-chlorobenzaldehyde and regenerated the sulfide (Scheme 3).

The best results were obtained in acetonitrile using benzyl bromide (2 equiv) and benzaldehyde (2 equiv), resulting in *trans*-stilbene oxide being obtained in 100% yield (based on sulfide) and 47% ee after stirring at room temperature for 36 h. Furukawa et al. also demonstrated turnover numbers of up to 2.3 using 10 mol % of sulfide relative to benzaldehyde and benzyl bromide. Since that pioneering work, a number of research groups have worked on the same catalytic cycle, trying to improve different aspects of the

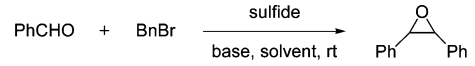
Scheme 3. Catalytic Cycle for Epoxidation Reactions via Sulfide Alkylation/Deprotonation

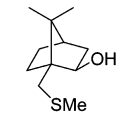


reaction: the scope of aldehydes and alkyl halides that can be used and the amount and nature of the sulfide necessary to achieve the transformation with good yields and enantiomeric excesses.[16−25] Representative examples of sulfides tested and results in the epoxidation of benzaldehyde are shown in Chart 1.

Optimally, these reactions are carried out open to air at room temperature, using a mixture of ^{t}BuOH/water (9:1) or MeCN/water (9:1) as solvent and with sodium or potassium hydroxide as base. These conditions suppress undesired side reactions (e.g., Cannizzaro reaction, benzyl bromide solvolysis and Williamson alkylation, and solvent reactivity). Benzyl bromide is the most commonly reported halide component in the reaction. The presence of water has an effect on diastereoselectivity as well as on enantioselectivity (see sections 2.1.5 and 2.1.6). Sulfide loadings range from 100% to 10%, although low yields or long reaction times are reported at low loadings of some sulfides. Reported reaction times vary from 1 day to 1 month, depending on the sulfide and reaction conditions chosen. The rates are often

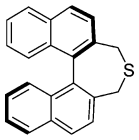
Chart 1. Selected Chiral Sulfides and Results Obtained for Epoxidation Reactions Using the Alkylation/Deprotonation Methodology (Solvent and Additives Vary); dr = trans/cis





Furukawa

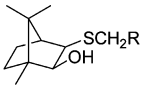
1[15]
36 h, 50 mol%
50%
dr = 100:0
ee = 47% (*R,R*)



Uemura

7[22a]
2 d, 10 mol%
96%
no *cis* reported
ee = 32% (*S,S*)

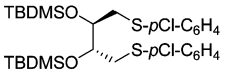
7[22a]
1 d, 100 mol%
66%
no *cis* reported
ee = 54% (*S,S*)



a: R = H
b: R = Ph
Dai

2a[16]
15 h, 20 mol%
97%
dr = 100:0
ee = 42% (*R,R*)

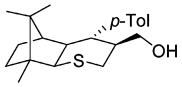
2b[16]
30 h, 100 mol%
87%
dr = 100:0
ee = 74% (*R,R*)



Ishizaki

8[22b]
1-4 d, 10 mol%
11%
dr = 78:22
ee = 68% (*R,R*)

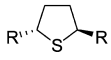
8[22b]
1-4 d, 100 mol%
59%
dr = 78:22
ee = 69% (*R,R*)



Saito

3[20]
4 d, 10 mol%
35%
dr = 91:9
ee = 44% (*S,S*)

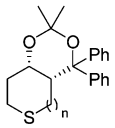
3[20]
4 d, 100 mol%
72%
dr = 94:6
ee = 56% (*S,S*)



a R = Me
b R = Et
Metzner

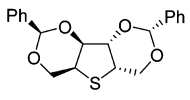
9a/b[18]
4/6 d, 10 mol%
82/90%
dr = 92:8
ee = 85/92% (*S,S*)

9a/b[17,18]
2/4 d, 100 mol%
92/97%
dr = 94:6
ee = 84/93% (*S,S*)



a n = 0
b n = 1
Shimizu

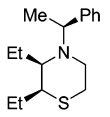
4a/b[19]
23/20 h, 50 mol%
53/32%
no *cis* reported
ee = 78/7% (*R,R*)



Goodman

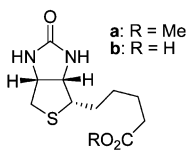
10[21]
4 d, 10 mol%
41%
dr = 90:10
ee = 97% (*R,R*)

10[21]
7 d, 100 mol%
59%
dr = 93:7
ee = 97% (*R,R*)



Aggarwal

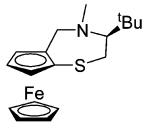
5[25]
19 h, 100 mol%
97%
dr = 87:13
ee = 90% (*S,S*)



a: R = Me
b: R = H
Metzner

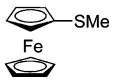
11a[22d]
7 d, 10 mol%
50%
dr = 70:30
ee = 70% (*S,S*)

11b[22d]
1 d, 100 mol%
50%
dr = 67:33
ee = 50% (*S,S*)



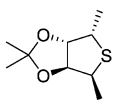
Metzner

6[23]
14 d, 20 mol%
66%
dr = 76:24
ee = 83% (*R,R*)



Metzner

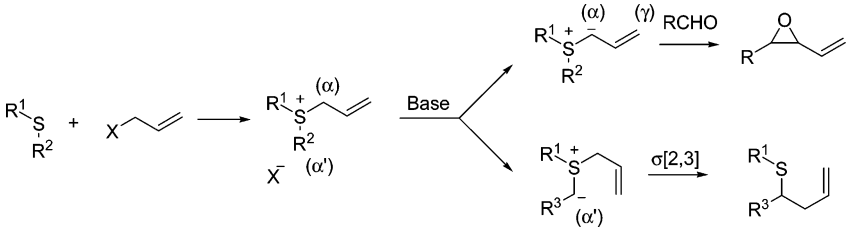
12[22c]
7 d, 100 mol%
92%
dr = 81:19



Metzner

13[24]
1 d, 20 mol%
88%
dr = 83:17
ee = 96% (*R,R*)

Scheme 4. Epoxidation Reaction and Possible Side Reactions Occurring when the Base Deprotonates the Sulfonium Salt



improved by increasing the concentration, but it must be noted that then side reactions can compete, so, in those cases, a balance must be found.

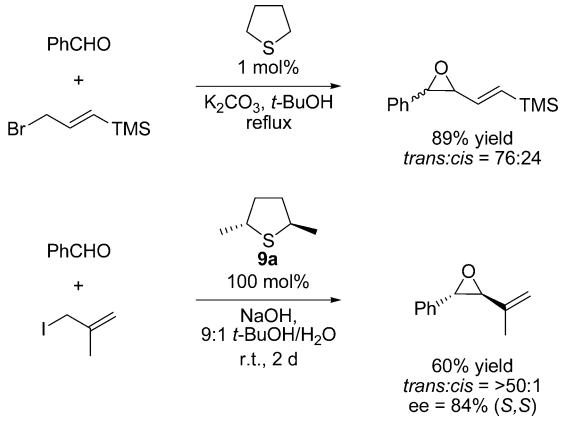
The alkylation step is slow and reversible.[26] In the presence of excess alkyl halide, most of the catalyst is in the form of sulfonium salt. In protic solvents, the deprotonation by base is rapid and reversible, and the equilibrium between the ylide and the salt lies largely on the side of the salt. Additives such as Bu_4NI and NaI have been used to activate the benzyl bromide through halogen exchange and to speed up the alkylation step.[18] Other additives such as catechol (0.5 mol %) and Bu_4NHSO_4 can also have positive effects.[24] It has been proposed that the ammonium cation might act as a phase-transfer catalyst, helping the extraction of the hydroxide anion into the organic phase to effect deprotonation of the sulfonium salt.[24] Increasing the bulk of the sulfide sometimes improves the selectivity but generally slows the alkylation step.

The scope of the reaction is limited because of the use of basic conditions, which generally limit the reaction to aldehydes with nonenolizable protons. The epoxidation of aromatic aldehydes with benzyl ylides can be achieved with high yields and high diastereo- and enantioselectivity. Cinnamaldehyde and heteroaromatic aldehydes generally react well, too. It is noteworthy that, with Metzner's sulfide, **9a**, when aliphatic aldehydes were used, low diastereoisomeric ratios were found but high enantiomeric excesses for the *cis*- and *trans*-epoxides were achieved.[17,18,27] The C_2-symmetric sulfides of Goodman and co-workers[21] give the highest enantioselectivities, but reaction times of 4−7 days are required for moderate yields. The C_2-symmetric sulfides of Metzner and co-workers produce the best combination of yield and selectivity. The diastereo- and enantioselectivities are discussed in sections 2.1.5 and 2.1.6.

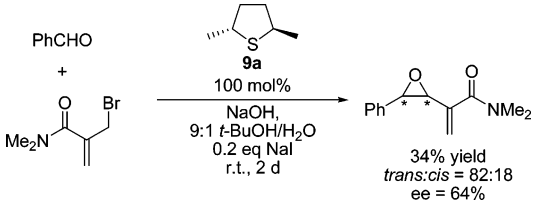
Sulfide **4b** gives significantly lower ees than **4a**. This is probably due to the distance of the stereogenic center in **4b** to the reacting center.[19] Cyclic sulfides with 5-, 6-, and 7-membered rings have been synthesized, but no general trend exists. While the groups of Metzner, Goodman, and Shimizu have reported good to excellent results with 5-membered rings, results with 6-membered rings from the groups of Saito, Shimizu, and Aggarwal vary from poor to excellent.

In some cases, authors have reported recovery of the sulfides. Saito and co-workers could recover enantiopure sulfide **3** in essentially quantitative yield, and they could reuse it repeatedly.[20,28] Goodman and co-workers recovered sulfide **10** in yields of 70−96%.[21] Similar yields of recovery were achieved by Metzner and co-workers with sulfide **6**,[23] while for sulfides similar to **12**, recovery was only possible in some cases, with yields varying from 60 to 95%.[29] Wang and Huang reported recovery of their ferrocenyl-derived sulfide with yields from 92 to 98%.[30] Aggarwal and co-workers reported that **5** could be recovered in good yield without recourse to chromatography through an acid/base extraction.[25]

Scheme 5. Synthesis of Vinylic Oxiranes[31−33]



Scheme 6. Synthesis of a Vinyl Epoxide Bearing a Morita−Baylis−Hillman Backbone



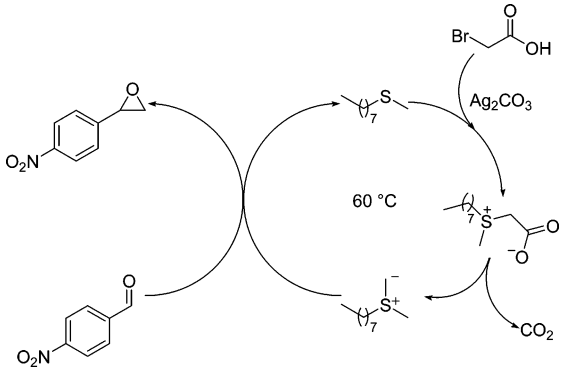
With regard to substrate scope, there are extra complications in the synthesis of vinyl epoxides using sulfur ylides. Alkylation with an allyl halide followed by deprotonation of the resulting sulfonium salt can lead to more than one reaction pathway unless the reaction conditions are controlled (Scheme 4). Deprotonation at the α′-position rather than the α-position can result in a [2,3]-sigmatropic rearrangement, while attack on the aldehyde from the γ-position of the ylide is also a possibility. Sulfides can be designed so that deprotonation at the α′-position is hindered by substitution.[31]

When non-β-substituted allyl halides are used, low diastereoselectivities are obtained. The best results using benzaldehyde are shown in Scheme 5.[32] Good results have been obtained in terms of diastereo- and enantioselectivity when β-substituted allyl halides have been used together with chiral sulfides.[31,33]

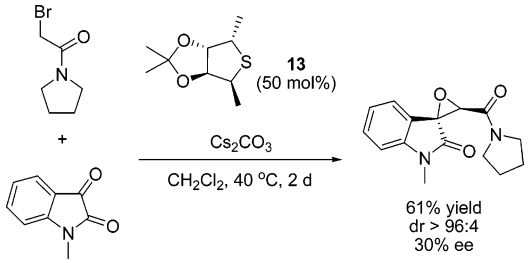
The recent work of Metzner and co-workers using α-(bromomethyl)acrylamide is noteworthy because it gives rise to functionalized vinyl epoxides bearing a Morita−Baylis−Hillman backbone, which are present in pharmacologically important molecules as well as being important building blocks.[34] Scheme 6 shows an example using chiral sulfide **9a**.

Forbes et al. have reported epoxidations using ylides generated by decarboxylation of preformed carboxymethylsulfonium salt.[35] They also report one example of sulfide

Scheme 7. Catalytic Cycle Using Ylide Generation by Decarboxylation



Scheme 8. Enantioselective Synthesis of a Glycidic Amide through the in situ Alkylation/Deprotonation Catalytic Cycle



being used to generate the carboxylate intermediate in situ (Scheme 7). *p*-Nitrobenzaldehyde gave 40% conversion to epoxide in an unoptimized procedure using 200 mol % of methyloctylsulfide.

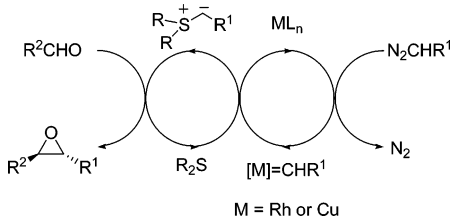
2.1.1.1. Synthesis of Glycidic Amides via Sulfide Alkylation/Deprotonation. Glycidic amides are important molecules in organic synthesis because they are key intermediates in various syntheses of pharmaceutical products. Their synthesis starting from an aldehyde and a sulfonium salt was reported in 1966.[36] Recently, Metzner and co-workers have shown that the alkylation/deprotonation methodology works well for building spiroepoxyoxindoles from various isatins.[37] These kinds of glycidic amides are obtained in this work starting from a ketone and an α-bromoacetamide, whereas usually these structures are obtained either by using a stoichiometric amount of preformed amide sulfonium salt reacting with an aldehyde[38] or by an α-diazoacetamide through the carbene route (see section 2.1.2.1). The epoxidation proceeds with very high diastereoselectivity, and when sulfide **13** was used, a 30% ee was obtained (Scheme 8).

2.1.2. Catalysis via Ylide Formation from a Carbene Source I: Diazo Compounds

The use of a metal to decompose a diazo compound and generate a metal carbene that can further react with a sulfide is another very important method for generating ylides. Aggarwal et al. first reported the application of this method in a catalytic cycle in 1994.[39] They proposed a catalytic cycle (Scheme 9) that broadens the scope of the reaction, not only because the use of neutral conditions permits the use of base-sensitive aldehydes but also because less reactive sulfides and aldehydes can be used.[40,41]

This first study revealed some important factors that need to be taken into account. The rate of addition of the diazo compound to the reaction mixture needs to be slow to minimize the amount of carbene dimerization (Scheme 10).[39,41−43] The choice of sulfide is also important because

Scheme 9. Catalytic Cycle for Ylide Epoxidation via the Carbene Route



Scheme 10. Main Side Reaction in the Catalytic Cycle of the Carbene Route

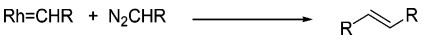
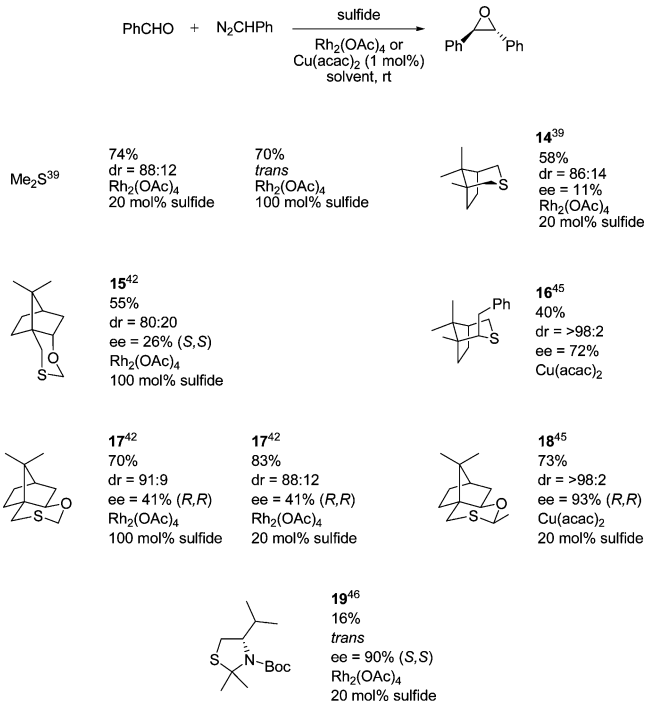


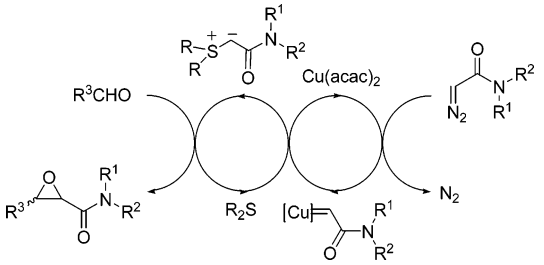
Chart 2. Selected Chiral Sulfides and Results Obtained for Epoxidation Reactions Using the Carbene Route (dr = trans/cis)



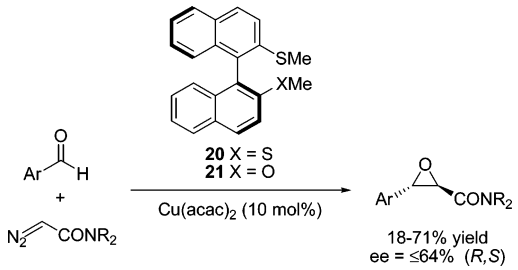
the reaction of the metallocarbene with the sulfide has to be faster than that of the diazo compound with the metallocarbene, so that dimerization products are again avoided.[41] Nevertheless, it is important to note that the metal carbene species is much more reactive than alkyl halides, so less-reactive sulfides can be used with this method.

Two further issues are important to note. First, the amount and concentration of the sulfide affected the yield. Using substoichiometric amounts of sulfide, but at similar concentrations to those in the stoichiometric reaction, gave similar yields. With substoichiometric amounts of sulfide, further improvements in yield were achieved by slower addition of the diazo compound.[39,42] Second, the process could be rendered asymmetric by the use of enantiopure sulfide **14**, obtaining similar enantioselectivities to those obtained by Breau and Durst using the same sulfide under standard stoichiometric sulfonium salt epoxidation reactions.[44] The challenge was then to design new chiral sulfides that permitted higher enantioselectivities in these reactions. Some of the best results are summarized in Chart 2.[42,45−47] $Cu(acac)_2$ gave much better results than $Rh_2(OAc)_4$ when the bulk of the sulfide was increased. This is believed to be

Scheme 11. Catalytic Cycle for the Synthesis of Glycidic Amides



Scheme 12. Sulfide-Catalyzed Asymmetric Synthesis of Glycidic Amides



due to the fact that the copper carbenoid is less sterically hindered than the rhodium carbenoid.[45] Zhu and co-workers have described epoxidations using pentafluorophenyldiazomethane with $Rh_2(OAc)_4$ as the metal catalyst and tetrahydrothiophene (THT) as the sulfide. The sulfur ylide generated was only reactive enough to react with *para*-substituted benzaldehydes bearing electron-withdrawing groups, achieving yields of 64−100% and very high diastereoselectivities (>99:1 trans/cis).[48]

The main problems with this methodology are the inherent hazards associated with working with diazo compounds. For this reason, a new catalytic cycle was devised in which the diazo compound was generated in situ from less hazardous materials (see section 2.1.3).

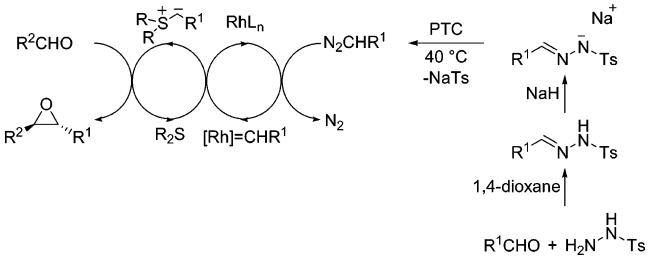
2.1.2.1. Synthesis of Glycidic Amides via Ylide Formation from Diazo Compounds. Aggarwal et al. reported in 1998 that their catalytic cycle starting from a diazo compound could also be applied to the synthesis of glycidic amides.[49] Diazoacetamides were used as the diazo compounds, but reaction temperatures needed to be raised to promote formation of the metal carbenoid (Scheme 11). The best conditions found for the achiral version of the reaction were to use $Cu(acac)_2$ and THT in highly concentrated acetonitrile solutions. A wide variety of aldehydes could be used: electron-rich, neutral, and electron-poor aromatic aldehydes, as well as aliphatic aldehydes. The reaction also tolerated the use of a variety of *N*-substituted diazoacetamides.

An asymmetric version of the same reaction was reported by Seki and co-workers in 1999.[50] A variety of substituted aromatic aldehydes gave epoxides in yields ranging from 18 to 71% and ees up to 64% when 20 mol % of chiral sulfides **20** or **21** were used (Scheme 12). Sulfide **20** was recovered in 76% yield by column chromatography. High enantioselectivities with this class of ylides can be obtained using stoichiometric amounts of a camphor-based sulfonium salt related to **2**.[38]

2.1.3. Ylide Formation from a Carbene Source II: N-Tosylhydrazone Salts

In a modified procedure, tosylhydrazone salts are used as the source of a diazo compound.[51] Tosylhydrazones can be

Scheme 13. In situ Generation of Diazo Compound and Resulting Catalytic Epoxidation Cycle

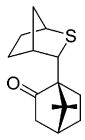


generated in situ from an aldehyde and tosylhydrazine; treatment with base gives the hydrazone salt. This salt decomposes to the diazo compound with the aid of a phase-transfer catalyst in acetonitrile at 30−40 °C. $Rh_2(OAc)_4$ was found to be better than $Cu(acac)_2$ as the metal catalyst under these conditions (Scheme 13).[52,53]

This procedure, employing the tosylhydrazone salt, was shown to work well with low sulfide loadings (even down to 5 mol %) and has been scaled up to 20 mmol.[43] Furthermore, yields and diastereoselectivities were higher using this method than when a preformed diazo compound was used. Another important point is that some epoxides that could not be synthesized using the previous catalytic cycle because of the instability of the parent diazo compound could be accessed easily through this route. For example, the *p*-methoxybenzaldehyde-derived hydrazone salt worked well, but the corresponding diazo compound decomposes at −80 °C and can detonate when isolated.[53]

An extensive study was carried out to establish the scope of the reaction.[53] Tetrahydrothiophene (THT) was chosen as the sulfide, and changes in the metal catalyst, the tosylhydrazone salt counterion and substituents, and the substituents of the aldehyde were considered. A variety of tosylhydrazone counterions can be used (Na, K, Li, NBu_4), although lithium tends to give lower diastereoselectivities and sodium gives the best results. Electron-rich, neutral, electron-poor, and even hindered aromatic aldehydes yield epoxides with very high yields and *trans*-diastereoselectivities. Heteroaromatic aldehydes give moderate to very good yields (33−90%) and good to excellent *trans*-diastereoselectivity (87:13 to 98:2). Aliphatic and propargylic aldehydes can also be employed, as well as some α,β-unsaturated aldehydes. Ketones were also tested, but although small amounts of epoxides were obtained, substantial amounts of a side product were obtained, probably coming from Sommelet−Hauser rearrangements of the sulfur ylides due to lower reactivity with ketones (see also section 4.1.2). Table 1 summarizes some of these results. A variety of substituted tosylhydrazone salts can be employed. A study of the scope was carried out using benzaldehyde as a model aldehyde.[53] It is important to note that the reproducibility of the reaction depends on the quality of the tosylhydrazone salt used.[43] Good yields were obtained with both electron-deficient and electron-rich aryl diazo precursors. Electron-deficient diazo compound precursors furnish the diazo compounds more readily, so lower temperatures can be employed. Most heteroaromatic diazo precursors can be used, resulting in epoxides being obtained with moderate to good yields. Finally, an acetophenone-derived hydrazone salt gave good yields but was somewhat capricious. Table 2 shows some of these results.

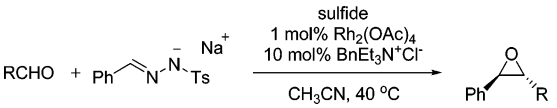
Although several different chiral nonracemic sulfides have been tested in these reactions,[54] sulfide **22**[52] (Figure 1) has



22

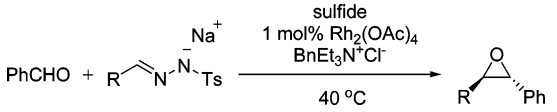
Figure 1. Sulfide **22**.

Table 1. Selected Epoxides Obtained from the Reaction of PhCHNNTsNa with Different Aldehydes Using 22 or THT as Catalyst



entry	R	sulfide (mol %)	time (h)	yield (%)	trans/cis	ee (%)
1	Ph	**22** (5)	48	82	>98:2	94
2	Ph	THT (20)	24	95	>98:2	
3	*p*-MeOC$_6$H$_4$	**22** (5)	48	68	>98:2	92
4	*p*-MeOC$_6$H$_4$	THT (20)	24	98	>98:2	
5	*p*-ClC$_6$H$_4$	**22** (5)	48	80	>98:2	91
6	*p*-ClC$_6$H$_4$	THT (20)	24	86	>98:2	
7	3-furyl	**22** (5)	48	77	>98:2	92
8	3-furyl	THT (20)	24	85	90:10	
9	*c*-hexyl	**22** (5)	48	58	88:12	90
10	*c*-hexyl	THT (20)	24	70	65:35	

Table 2. Selected Epoxides Obtained from the Reaction of Benzaldehyde with Substituted Tosylhydrazone Salts Using 22 or THT as Catalyst



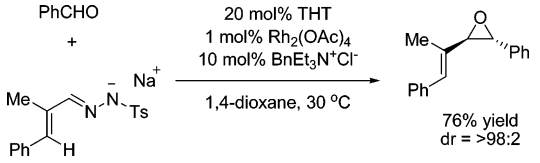
entry	R	sulfide (mol %)	equiv of PTC[a]	solvent	yield (%)	trans/cis	ee (%)
1	*p*-MeC$_6$H$_4$	**22** (5)	0.05	CH$_3$CN	74	95:5	93
2	*p*-MeC$_6$H$_4$	THT (20)	0.05	CH$_3$CN	87	87:13	
3[b]	*o*-MeOC$_6$H$_4$	**22** (5)	0.05	CH$_3$CN	70	>98:2	93
4	*o*-MeOC$_6$H$_4$	THT (20)	0.05	CF$_3$C$_6$H$_5$	92	>98:2	
5	*p*-CNC$_6$H$_4$	**22** (20)		1,4-dioxane	70	>98:2	73
6	*p*-CNC$_6$H$_4$	THT (20)		1,4-dioxane	90	>98:2	
7	2-furyl	**22** (20)	0.1	CH$_3$CN	53	90:10	61
8	2-furyl	THT (20)	0.05	CF$_3$C$_6$H$_5$	96	80:20	

[a] PTC = BnEt$_3$NCl. [b] 30 °C.

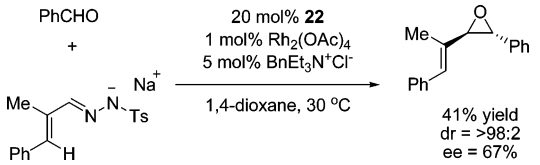
proven to be the best in terms of yields and enantio- and diastereoselectivities. It is stable to the reaction conditions, can be synthesized on a 20 g scale in four steps from camphor sulfonyl chloride, can be reisolated by chromatography after the reaction in quantitative yields, and is available in both enantiomeric forms.[52,55]

The effect of the solvent on the enantioselectivity was studied, and toluene, 1,4-dioxane, acetonitrile, and trifluorotoluene were found to give the best yields and enantioselectivities. In general, the other trends found when an achiral sulfide was used were reproducible when using sulfide **22**.[53] Aromatic aldehydes gave good ees (90−94%) and yields (68−84%) and excellent trans/cis diastereoselectivities (>98:2). The only case in which the yield was lower was when mesitaldehyde was used, probably due to steric hindrance. Heteroaromatic aldehydes, with the exception of pyridine carboxaldehydes,[8] gave moderate to good yields and high enantiomeric excesses (89−93%) and diastereomeric ratios (>98:2). Aliphatic aldehydes gave moderate yields, moderate to good drs, and high ees. A limited number of α,β-unsaturated aldehydes could also be employed, for example, cinnamaldehyde. Representative examples using both THT and **22** are given in Table 1.

Scheme 14. Synthesis of a Vinyl Oxirane Starting from a Vinyl Tosylhydrazone Salt in a Catalytic Epoxidation Cycle Using THT as the Sulfide Catalyst



Scheme 15. Asymmetric Synthesis of a Vinyl Oxirane Starting from a Vinyl Tosylhydrazone Salt in a Catalytic Epoxidation Cycle Using Chiral Sulfide 22



Substituted tosylhydrazone salts were also tested. Electron-rich aromatic diazo precursors generally gave good yields and very high drs and ees (83−94%). Electron-deficient aromatic diazo precursors gave good yields and high diastereoselectivities, but enantioselectivities (64−93% ee) were found to be more variable and solvent-dependent. Heteroaromatic precursors could also be employed, but yields and enantioselectivities were only moderate. A selection of the best examples using THT and sulfide **22** is given in Table 2.

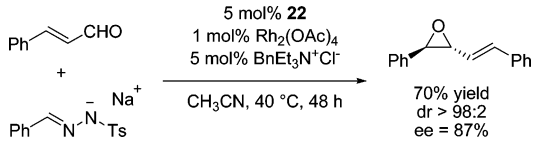
Tables 1 and 2 show the broad scope of the reaction, clearly showing that it is much wider than the alkylation/deprotonation protocol and that some products can only be obtained through this route.

Vinyl oxiranes have also been obtained using this catalytic cycle. It is important to note that most of the vinyl epoxides obtained are hydrolytically sensitive and have to be purified on basic alumina. When using THT as the sulfide catalyst, yields and diastereoselectivities were highly dependent on the structure of the tosylhydrazone salt. The best results were obtained when both the α- and β-positions are substituted. One of the best results is shown in Scheme 14. When sulfide **22** was used yields, enantio- and diastereoselectivities were generally low to moderate. The best results were obtained if the α-position was substituted and the β-position was unsubstituted or monosubstituted (Scheme 15).[53] Use of preformed sulfonium salts derived from **22** gave better results.[8]

An alternative way to synthesize vinyl epoxides is to start with an unsaturated aldehyde. When sulfide **22** was used in the reaction of *trans*-cinnamaldehyde and the tosylhydrazone salt derived from benzaldehyde, the yields and enantioselectivities were good, and the diastereoselectivities observed were excellent (>98:2 trans/cis) (Scheme 16).[53]

As a summary for this section, Scheme 17 shows a retrosynthetic analysis for the synthesis of differently substituted epoxides when achiral unhindered sulfides (e.g., THT) are used as catalysts.[53] Scheme 18 shows the analogous analysis for the enantioselective synthesis of various epoxides using **22**.

Scheme 16. Asymmetric Synthesis of a Vinyl Oxirane Starting from a Tosylhydrazone Salt in a Catalytic Epoxidation Cycle Using Chiral Sulfide 22 and *trans*-Cinnamaldehyde



2.1.4. Ylide Formation from a Carbene Source III: Simmons–Smith Reagent

Because diazomethane cannot be employed in the catalytic cycle shown in Scheme 9 (it is believed to form ethylene very easily), an alternative catalytic cycle based on the use of the Simmons−Smith reagent as a source of carbene has been developed (Scheme 19). The process proved to be useful for aromatic, aliphatic, unsaturated, and α-alkoxy and α-amino aldehydes,[56] furnishing terminal epoxides in yields ranging from 58 to 85% with THT (100 mol %) as sulfide. When aldehydes bearing a chiral center were used, no racemization of this chiral center was observed, although mixtures of diastereoisomers were obtained.

An asymmetric version of this reaction was reported using sulfide **23** that incorporated a ligand capable of binding to the metal ion (Figure 2).[57] In this case, it was demonstrated that the zinc ion was intimately involved in the epoxidation

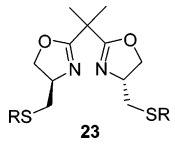


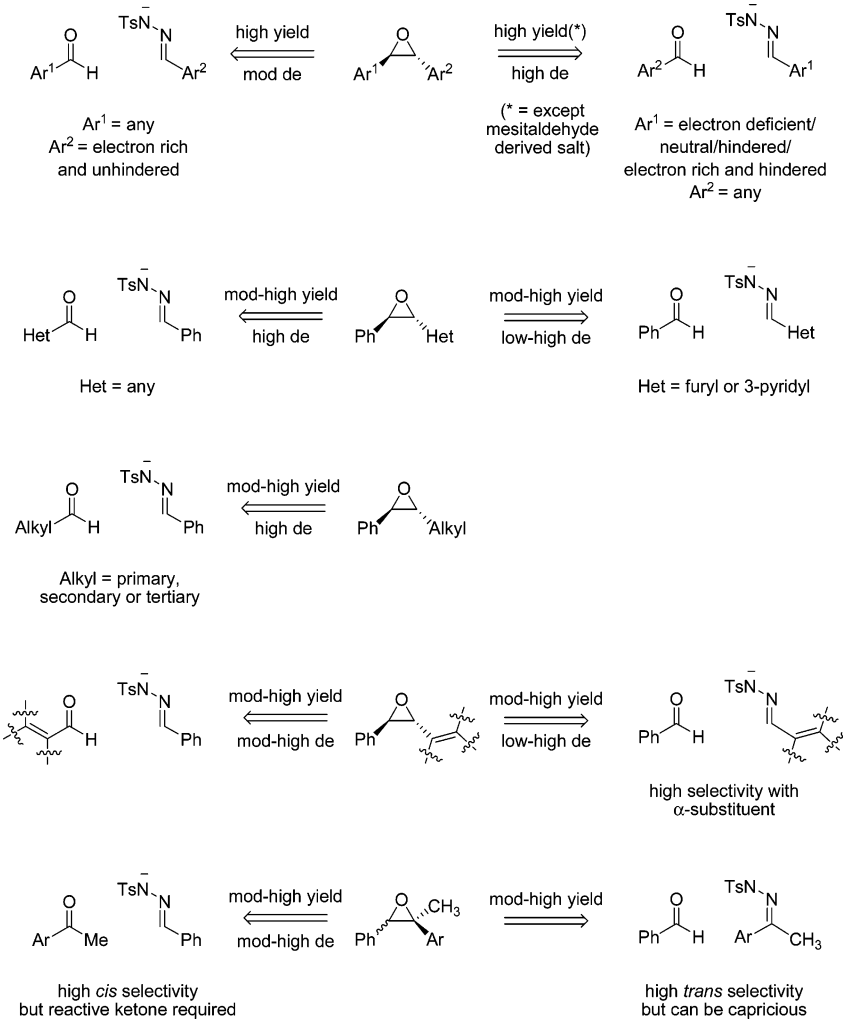
Figure 2. Sulfide **23**.

step, so, in this example, the organocatalyst and the metal catalyst were working cooperatively. Enantiomeric excesses of up to 54% were obtained. In 2004, Bellenie and Goodman showed that epoxides could be obtained in up to 76% enantiomeric excess and 96% yield when using 2 equiv of sulfide **10**.[58]

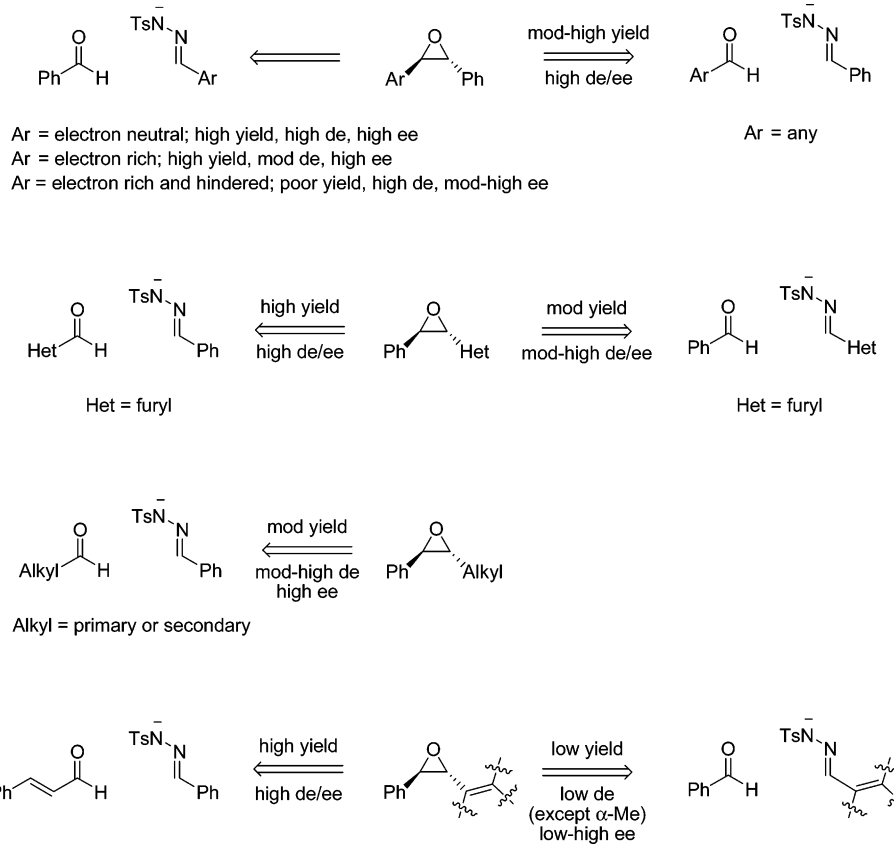
2.1.5. Origin of Diastereoselectivity in S-Ylide Epoxidations

The diastereoselectivity obtained in *S*-ylide epoxidations depends on the degree of reversibility of the formation of the betaine intermediates arising from the attack of the sulfur ylide on the carbonyl group of the aldehyde.[59] Scheme 20 shows the individual steps for the reaction. The addition of the ylide to the aldehyde occurs in a "cisoid" manner, which is preferred due to favorable Coulombic interactions, and two rotamers of the *anti*- and *syn*-betaines are formed (**24a** and **26a**).[60] Calculations suggest that the barriers for formation of these two rotamers from an aldehyde are very similar

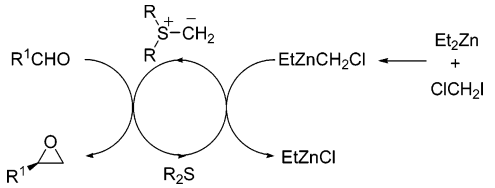
Scheme 17. Retrosynthetic Analysis of Epoxide Formation Using Achiral Unhindered Sulfides; mod = moderate. (Reprinted with permission from Aggarwal et al. *J. Am. Chem. Soc.* 2003, *125*, 10926. Copyright 2003 American Chemical Society.)



Scheme 18. Retrosynthetic Analysis of Epoxide Formation Using Chiral Sulfide 22; mod = moderate. (Reprinted with permission from Aggarwal et al. *J. Am. Chem. Soc.* 2003, *125*, 10926. Copyright 2003 American Chemical Society.)



Scheme 19. Catalytic Cycle for Ylide Epoxidation Reactions Using the Simmons−Smith Reagent



in energy, so if both these steps were nonreversible, only a low trans/cis ratio would be observed. When aryl-stabilized sulfur ylides are used, high diastereoselectivities are observed due to the reversible, and largely nonproductive, formation of the *syn*-betaine **26a**. Experimentally, it was demonstrated that, in reactions with benzaldehyde and dimethylsulfonium benzylide, *anti*-betaine **24a** forms nonreversibly and yields *trans*-epoxide **25**, while *syn*-betaine **26a** formation is reversible.[59] Calculations predict that, for the *syn*-betaine **26a**, the energy necessary for C−C bond rotation to lead to rotamer **26b**, which can ring-close, is higher than the energy necessary to revert to starting materials.[60] In contrast, the formation of the *anti*-betaine **24a** is nonreversible and, after C−C bond rotation, leads to the formation of *trans*-epoxide **25**. Finally, the ring-closure step from the *anti*-periplanar rotamers (**24b**, **26b**) is rapid (Scheme 20). It has recently been shown that equilibration of intermediate betaines can also occur by deprotonation of a benzylic carbon α to sulfur under basic conditions.[61]

The degree of reversibility of the *syn*-betaine formation is influenced by a number of factors:[62]

(i) *syn*-Betaine formation is more reversible when the thermodynamic stability of the starting materials is increased. Aromatic aldehydes, for example, give better *trans*-selectivity than aliphatic aldehydes. Electron-deficient benzylides also yield better diastereoselectivities than other semistabilized ylides because of their greater stability.

(ii) Increased reversibility also results when the steric hindrance of the ylide and/or the aldehyde is increased, which leads to an increase in the torsional rotation barrier. With chiral aldehydes and sulfides, match/mismatch effects arise and affect the ease of rotation and thus, the degree of reversibility.[63]

(iii) Reversibility is decreased if there is improved solvation of the betaine alkoxide by a metal or a protic solvent, which lowers the torsional rotation barrier.[62]

It is important to note that, while all these factors can also have an effect on the reversibility of *anti*-betaine formation, the effects on *syn*-betaine formation normally dominate the diastereoselectivity. Consideration of all these factors allows the rationalization of the different diastereoselectivities observed in sulfur ylide-mediated epoxidations.

2.1.6. Origin of Enantioselectivity in Sulfide-Catalyzed Asymmetric Epoxidations

Enantioselectivity is governed by four main factors:[62]

(i) The selectivity for the alkylation of only one of the lone pairs on sulfur, so that only a single diastereomeric sulfonium salt and/or ylide is formed;

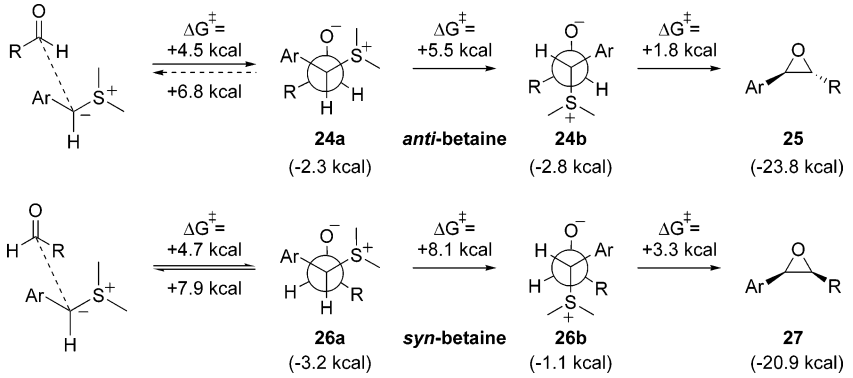
(ii) The ylide conformation;

(iii) The facial selectivity of the ylide reaction with the carbonyl; and

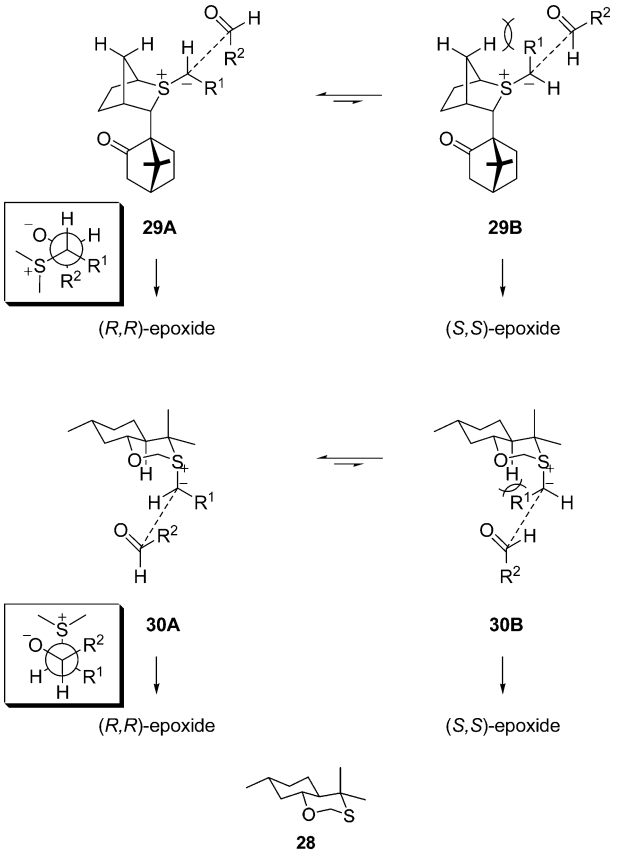
(iv) The degree of reversibility of the betaine formation.

Sulfides **22** and **28** control all of these factors well and give high enantioselectivities in all cases.[53,64] Solladié-Cavallo

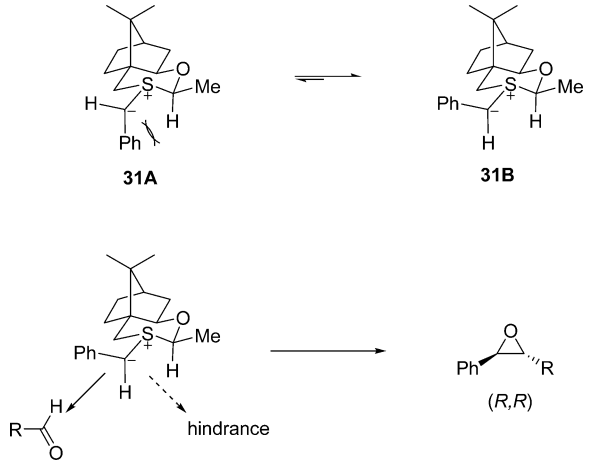
Scheme 20. Individual Steps Involved in Epoxide Formation with Energies from DFT Calculations[60]



Scheme 21. Equilibrium of Ylide Conformers 29 and 30 and Aldehyde Approach



Scheme 22. Equilibrium of Ylide Conformers 31 and Aldehyde Approach to 31B

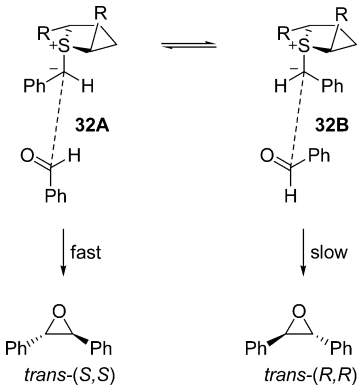


and Adib have reported the synthesis of epoxides with good-to-excellent yields and diastereoselectivities and with excellent enantioselectivities using stoichiometric amounts of preformed sulfonium salt derived from **28**.[64,65] In both cases, a single sulfonium ylide diastereomer is formed. This is due to steric effects in the case of sulfide **22**. In the case of **28**, the alkylation of the axial lone pair can be explained by a combination of steric effects and the 1,3-anomeric effect (the equatorial lone pair may overlap with the σ^*-orbital of the C−O bond and so be less nucleophilic than the axial lone pair).[66] There is a preference for the lone pair on sulfur to be orthogonal to the lone pair on the ylidic carbon,[67] and therefore, there are two potentially important conformers of the resulting ylides, **29A/B** and **30A/B** (Scheme 21). Conformers **29A** and **30A** are much more favored, due to reduced steric interactions.[66,67] In the case of ylide **29A**, facial selectivity is ensured because of the presence of a bulky group on the *Si* face of the ylide, which forces the aldehyde to approach from the *Re* face. In the case of ylide **30A**, facial selectivity arises from the presence of a *gem*-dimethyl group, forcing the aldehyde to approach from the opposite face. Nevertheless, it is important to note that a compromise needs to be found when designing a chiral sulfide because too much steric hindrance around the sulfur atom leads to a decrease in the rate of reaction with the alkylating agent or metal carbenoid.

Another example of a rigid structure that leads to good enantioselectivities is sulfide **18**, which has been used in the carbene route. Once the ylide is formed, one of the conformations is highly favored, **31B** (Scheme 22), and the methyl substituent on the carbon α to sulfur hinders the *Si* face from attack by aldehydes, thus leaving only one main approach, and so enantiomeric excesses as high as 93% are obtained.[45,47] The facial selectivity with sulfur ylide **31** is also believed to benefit from electronic effects.[47] The anomeric effect should give rise to a lengthened C−S bond in the oxathiane moiety, making it more electron rich. This should increase the tendency of the incoming aldehyde to attack from the face opposite the oxathiane moiety due to a Cieplak effect (nucleophilic attacks on π-systems occur on the face opposite the better donor).

Control of lone-pair alkylation, ylide conformation, and facial selectivity should lead to the formation of one preferred *anti*-betaine intermediate. If *anti*-betaine formation is nonreversible, control of these factors gives highly enantioselective epoxide formation. It is believed that, in many cases, the minor enantiomer of epoxide observed is formed from the aldehyde reacting with the minor ylide conformer.[53,68] However, if the *anti*-betaine is formed (partially) reversibly,

Scheme 23. Equilibrium of Ylide Conformers 32 and Aldehyde Approaches to 32



the bond-rotation and/or ring-closure steps can become enantiodifferentiating, and lower enantioselectivities can result because of differences in the reversibility of betaine formation and subsequent steps for the pathways starting from, e.g., **29A** and **29B**.[62,68] This has been used to explain the slightly lower ee values observed in reactions of benzaldehyde with ylides derived from electron-poor aromatic tosylhydrazone salts (Table 2, entry 5).

When low enantioselectivities are observed, it is most often due to either poor control of either ylide conformation or the reversibility of the betaine formation. To deduce which of the two factors is responsible for reduced ees in any given case, a simple test was designed for reactions using the carbene catalytic cycle.[53,62] As mentioned above, the use of protic solvents reduces the reversibility of the betaine formation. The same reaction can be carried out using neat MeCN and using a mixture of MeCN/H_2O. If the ee value is higher when the aqueous mixture is used, it shows that reversibility of the betaine formation is a problem. This method is a valuable test to determine the origin of low enantioselectivities but does not constitute a practical way of improving them when reversibility is a problem because, usually, lower yields are observed via the carbene route in the presence of water. The presence of water in the in situ alkylation/deprotonation catalytic cycle has the effect of lowering the diastereomeric ratio because of the reduced reversibility of the betaine formation (see section 2.1.5) but also has a positive effect on enantioselectivity: under these conditions, *anti*-betaine formation can become nonreversible, and then the four criteria for obtaining high levels of enantiocontrol can be achieved.

Another strategy for controlling enantioselectivity is the use of C_2-symmetry in the structure of a chiral sulfide, e.g., **9a**, **9b**, and **10**. These sulfides have been used in the in situ alkylation/deprotonation catalytic cycle. In these cases, a single sulfonium salt is formed (lone-pair alkylation selectivity is not an issue here). Julienne and Metzner originally suggested that the conformation of the resulting ylide is well-controlled by the group on the carbon α to sulfur, which would prevent the phenyl moiety from sitting near it.[17] However, calculations by Goodman and co-workers suggest that the conformation of the ylide is not very well-controlled and that both conformers are in a rapid equilibrium. High enantioselectivities are still obtained with these sulfides because conformer **32A** reacts more rapidly with aldehydes than conformer **32B** (Scheme 23).[69]

Finally, Dai and co-workers showed in their in situ alkylation/deprotonation catalytic cycle that, by using sulfide

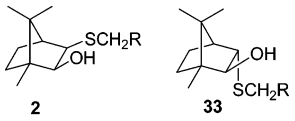
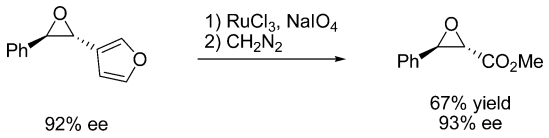
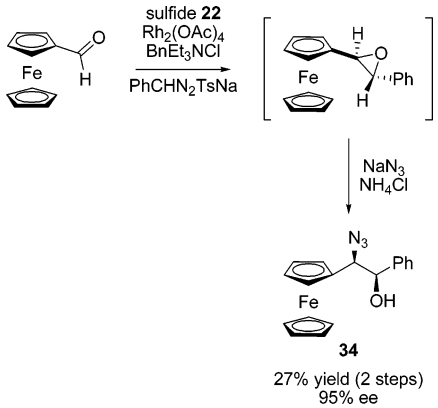


Figure 3. Sulfide **2** and its *endo*-benzylthio analogue **33**, used in preparing epoxides with the opposite sense of asymmetric induction.

Scheme 24. Synthesis of Glycidic Esters



Scheme 25. Synthesis of a Ferrocenyl Epoxide and Derivative



2 and its *endo*-benzylthio analogue **33**, there is the possibility to prepare epoxides with the opposite sense of asymmetric induction (Figure 3). It was postulated that the free hydroxyl group on the sulfide improves the facial-selectivity significantly due to nonbonding interactions between the hydroxyl group and the carbonyl group of the aldehyde.[16]

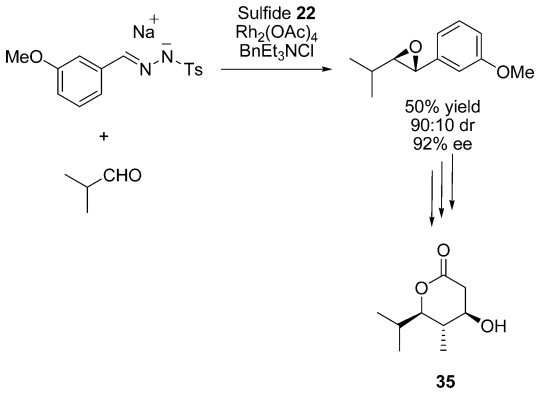
2.1.7. Applications in Synthesis

Although much of the effort in the epoxidation field using *S*-ylides has been focused on the establishment of the methodology, there are some examples of synthetic applications. Glycidic esters are important intermediates in synthesis and have found widespread use. Furaldehyde-derived epoxides, obtained by catalytic epoxidation using sulfur−ylide chemistry, can be easily converted to glycidic esters by oxidation followed by esterification (Scheme 24).[52] The methodology proved useful in the preparation of the first α-ferrocenyl epoxide, which is not only important in itself but also reinforces the potential of the methodology for the synthesis of sensitive molecules that are not accessible by olefin oxidation.[70] The reaction was also carried out asymmetrically using sulfide **22**. Because of its instability, the epoxide was not isolated but was ring-opened with sodium azide to give **34** in very good enantioselectivity, albeit in low yield (Scheme 25). Sulfide **22** was also used in a key epoxidation reaction in the synthesis of prelactone B, **35**, which is an early metabolite in the biosynthesis of polyketide antibiotics (Scheme 26).[71] This methodology will undoubtedly find further applications in the future.

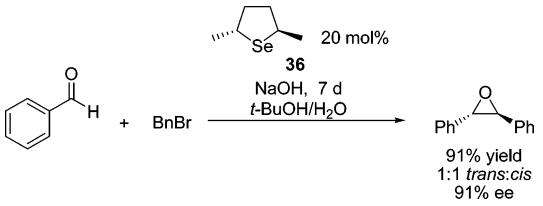
2.2. Selenide-Catalyzed Epoxidations

There are very few examples of epoxidation reactions using selenides in a catalytic manner.[72,73] Metzner and co-

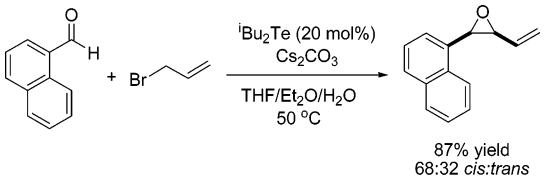
Scheme 26. Catalytic Asymmetric Ylide Epoxidation in the Synthesis of Prelactone B



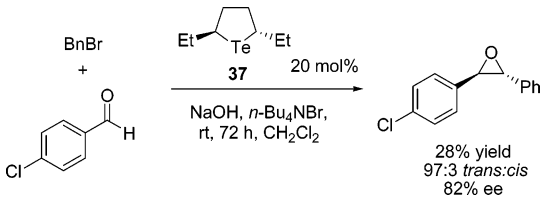
Scheme 27. Selenium Ylide-Catalyzed Asymmetric Epoxidation



Scheme 28. Telluride-Catalyzed Epoxidation Reaction



Scheme 29. Telluride-Catalyzed Asymmetric Epoxidation Reaction



workers described the use of selenide **36**, analogous to sulfide **9a**. One of the best results is shown in Scheme 27. In contrast to reactions using sulfides, no diastereoselectivity was observed when using selenide **36**.

2.3. Telluride-Catalyzed Epoxidations

Tellurium ylides react with carbonyl compounds to yield either epoxides or olefins (see section 6 for a discussion of the latter class of reactions). Examples of the use of tellurides in catalytic epoxidation reactions are scarce. The first example using a telluride catalytically was reported by Huang and co-workers in 1990.[74] Diisobutyl telluride was used as the catalyst and Cs_2CO_3 as the base using the in situ alkylation/deprotonation catalytic cycle (see section 2.1.1). The reaction was carried out using allyl bromide and worked well with a range of aromatic, heteroaromatic, and nonprimary aliphatic aldehydes. An example is shown in Scheme 28.

Scheme 29 shows an example of the first telluride-catalyzed asymmetric epoxidation. Telluride **37**, the Te-analogue to sulfide **9b**, was reported to give very good *trans*-diastereoselectivities and good enantioselectivities, but low yields.[73] It is worth noting that the *trans*-epoxide was favored in this case, but no rationalization for this has been put forward yet. Traces of olefination product were also observed (see section 6.1).

Finally, Tang and co-workers reported the synthesis of vinyl epoxides using a slightly modified procedure.[75] Their synthesis involved the use of 2−20 mol % of a telluronium salt, as well as an allyl halide, aldehyde, and base. The telluronium salt was used to start the epoxidation, liberating the telluride, which then entered the catalytic cycle. Good yields but low diastereoselectivities were obtained for a range of vinyl epoxides.

2.4. Summary of Chalcogenide-Catalyzed Epoxidations

Chalcogenides catalyze the epoxidations of carbonyl compounds via ylide-mediated pathways. There are a variety of ways of generating the ylide in situ. The use of *N*-tosylhydrazone salts to generate diazo compounds in situ allows a particularly broad substrate scope. Using sulfide-catalyzed methods, high yields and diastereoselectivities can be obtained for a range of *trans*-epoxides. Chiral nonracemic sulfides provide good to excellent enantioselectivities. Selenide and telluride-catalyzed methodologies are less well-developed but show some promise.

3. Aziridination

Aziridines can be prepared from imines by addition of (i) a metal carbenoid or (ii) a carbanion bearing a leaving group.[4,76] In this section, we will discuss the reactions of ylides, where again sulfur ylides have enjoyed most success.[77] The ylide is often synthesized by deprotonation of a preformed salt, and useful stoichiometric asymmetric protocols have been developed by various groups.[4,7,78−80] Similarly, tellurium[5,81] and arsonium ylides[81,82] have been generated from the corresponding salts and employed in ylide-mediated aziridinations. Methods that use the chalcogenide as a catalyst are less common and confined to sulfides.[4,11] As with epoxidation, there are two ways of accessing the ylide: (a) sulfonium salt formation from alkyl halide followed by deprotonation[83,84] and (b) sulfide reaction with a metallocarbene.[10−12,51,57,85−92] These two approaches are discussed in turn, followed by a discussion of the factors that control diastereoselectivity and, where applicable, enantioselectivity in these reactions. Finally, successful applications of these procedures in synthesis are described.

3.1. Sulfide-Catalyzed Aziridinations

3.1.1. Catalysis via Sulfide Alkylation/Deprotonation

Dai and co-workers were the first to report sulfide-catalyzed aziridinations (Scheme 30), based on the reaction in acetonitrile of a sulfide with cinnamyl bromide, followed by deprotonation of the resulting sulfonium salt and reaction of the ylide with an imine to yield an aziridine (cf. Scheme 3).[83] Cinnamyl bromide was the only halide that could be used in this system (Table 3); the reactions with other allyl halides proved unsuccessful. Potassium carbonate was found to be the most effective base, and reaction times were generally of the order of 1.5 h.

Dimethyl sulfide was found to be the best catalyst, although Et_2S and chiral sulfide **2a** were also demonstrated

Scheme 30. Sulfide-Catalyzed Aziridination via Alkylation/Deprotonation Cycle

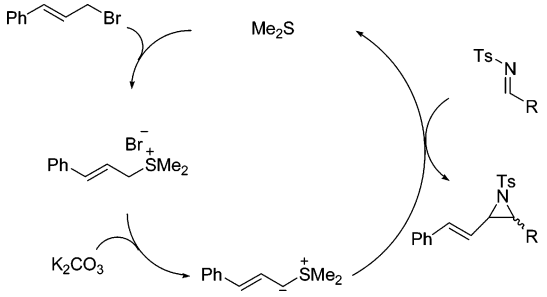
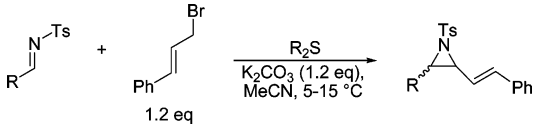


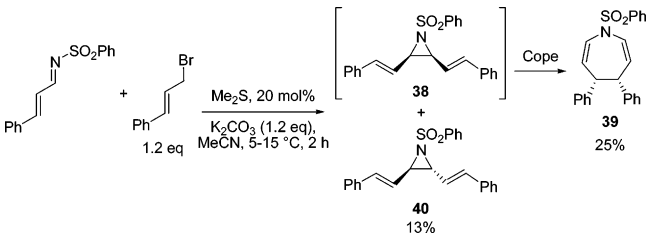
Table 3. Dai and co-workers' Catalytic Styryl Aziridine Synthesis[83]



entry	R	sulfide	mol %	time (h)	yield (%)	trans/cis
1	*p*-ClC_6H_4	Me_2S	100	0.75	72	31:69
2	*p*-ClC_6H_4	Me_2S	20	1.5	43	43:57
3[a]	*p*-ClC_6H_4	Me_2S	20	1.5	49	53:47
4	*p*-$NO_2C_6H_4$	Me_2S	20	1.5	30	35:65
5	Ph	Me_2S	20	2.0	49	38:62
6	*o*-$MeOC_6H_4$	Me_2S	20	3.5	45	29:71
7	*p*-ClC_6H_4	Et_2S	20	4.0	20	45:55
8	*p*-ClC_6H_4	**2a**	20	1.5	23	49:51

[a] 1.2 equiv of KI were also added.

Scheme 31. Formation of *cis*-Azepine 39 by Cope Rearrangement of Bisstyryl *cis*-Aziridine 38[83]

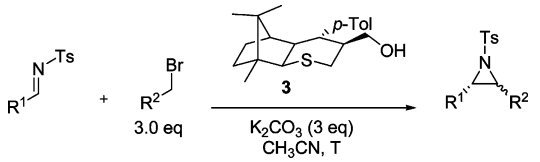


to catalyze the reaction successfully, albeit in lower yield (Table 3, entries 7 and 8). No ee was reported for the reaction of **2a**. Loadings of 20 mol % of Me_2S gave yields of up to 49%, although higher loadings resulted in significantly improved yields (entry 1). The addition of KI resulted in a small increase in yield attributed to faster salt formation with cinnamyl iodide generated in situ (entry 3).

The diastereomeric ratios varied from very poor in favor of the *trans*-aziridine, to 29:71 in favor of the *cis*-isomer. Both toluenesulfonyl and benzenesulfonyl were found to be suitable *N*-activating groups. Benzaldimines bearing both electron-withdrawing groups and electron-donating groups were tolerated to varying degrees. *N*-Benzenesulfonyl cinnamaldimine gave a mixture of the *trans*-aziridine **40** and *cis*-azepine **39**, believed to arise from the Cope rearrangement of the unisolated *cis*-aziridine **38** (Scheme 31).

Saito et al. reported an asymmetric variant of the alkylation/deprotonation cycle (Table 4).[84] Reaction of chiral sulfide **3** with excess benzyl bromide (3 equiv) and potassium carbonate in *anhydrous* acetonitrile gave aziridines in moderate to excellent yields. Use of this more hindered sulfide required longer reaction times (1−4 days), even with 1 equiv

Table 4. Saito et al.'s Catalytic Asymmetric Aryl Aziridine Synthesis[84]



entry	R^1	R^2	mol % **3**	*T*	time	yield (%)	trans/cis	ee[a] (%)
1	Ph	Ph	100	rt	2 d	99	75:25	92
2	Ph	Ph	20	rt	4 d	61	75:25	90
3	Ph	Ph	100	82 °C	2 h	94	72:28	84
4	*p*-MeC_6H_4	Ph	100	rt	2 d	99	79:21	89
5	*p*-$MeOC_6H_4$	Ph	100	rt	2 d	94	63:37	86
6	*p*-ClC_6H_4	Ph	100	rt	2 d	86	78:22	92
7	Ph	*p*-MeC_6H_4	100	rt	2 d	87	74:26	89
8	Ph	*p*-$NO_2C_6H_4$	100	rt	2 d	99	65:35	98
9	Ph	*E*-PhCHCH	100	rt	2 d	99	54:46	42
10	*E*-PhCHCH	Ph	100	rt	2 d	99	75:25	94

[a] ee of *trans*-product.

of **3**, but yields were improved and the previously competitive hydrolysis of the imine was wholly eliminated under the dry conditions employed. Very good to excellent ees were obtained (86−98%, Table 4). Increasing the temperature shortened the reaction time significantly at a small cost to ee (entry 3). However, in all cases the drs were poor, ∼2:1−3:1 in favor of the *trans*-isomer. In addition to benzyl bromides, yields of up to 99% were also obtained with cinnamyl bromide, but ees were significantly lower for these cases (entry 9). However, the same vinyl aziridine product was synthesized with excellent enantioselectivity and yield using the same sulfide **3** to transfer a benzylidene group from a benzyl bromide to a cinnamaldimine (entry 10).

3.1.2. Catalysis via Ylide Formation from a Carbene Source I: Diazo Compounds

Aggarwal and co-workers have also developed a method for the catalytic asymmetric aziridination of imines via sulfur ylides generated by the reaction of a metallocarbene with a sulfide (Scheme 32),[12,85−88,91] closely related to their epoxidation system described above (sections 2.1.2 and 2.1.3). The carbenoid was generated by the decomposition of phenyl diazomethane in the presence of a suitable transition metal salt, usually $Rh_2(OAc)_4$. To avoid reaction of the metallocarbene with excess phenyl diazomethane, the latter reagent was added slowly over the course of the reaction.

A range of imines could be aziridinated via semistabilized ylides in moderate to excellent yield using 0.2−1.0 equiv of sulfide (Table 5). Using (trimethylsilyl)ethanesulfonyl (SES), which was most frequently employed as the imine-activating group because of its ease of removal,[86,88] the diastereomeric ratios obtained were moderate at best (∼3:1

Scheme 32. Catalytic Cycle for Aggarwal's Sulfide-Catalyzed Aziridination[85,88]

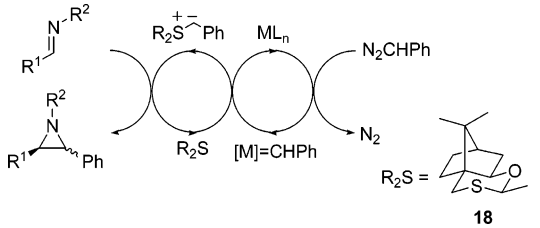
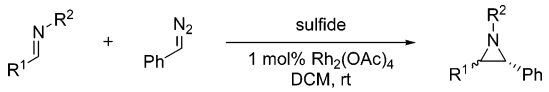


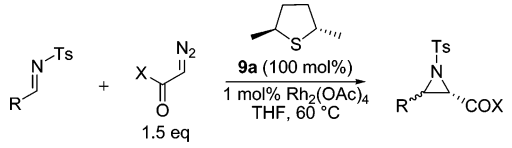
Table 5. Aggarwal and co-workers' Sulfide-Catalyzed Asymmetric Aziridination Using Phenyldiazomethane[87,88]



entry	R^1	R^2	sulfide	mol %	yield (%)	trans/cis	ee[a] (%)
1	Ph	SES	Me_2S	20	92	3:1	
2	Ph	SES	**18**	20	47	3:1	95
3	Ph	SES	**18**	100	84	3:1	95
4	*p*-MeC_6H_4	SES	**18**	20	91	3:1	93
5	*p*-ClC_6H_4	SES	**18**	20	58	3:1	88
6	(*E*)-PhCHCH	SES	**18**	20	62	5:1	93
7	C_6H_{11}	SES	**18**	100	72	1:1	89
8	Ph	Ts	**18**	100	71	3:1	92
9	Ph	$P(O)Ph_2$	Me_2S	100	86	3:1	
10	Ph	CO_2Me	**18**	100	75	6:1	92
11	Ph	CO_2Bn	**18**	100	58	6:1	90
12	Ph	$CO_2(CH_2)_2TMS$	**18**	100	55	9:1	91
13	Ph	$CO_2{}^tBu$	**18**	100	60	9:1	92
14	Ph	$CO_2CMe_2CCl_3$	**18**	100	58	>10:1	92

[a] ee of *trans*-product.

Table 6. Aggarwal et al.'s Catalytic Asymmetric Aziridine Synthesis with Stabilized Ylides[88]



entry	R	X	yield (%)	trans/cis	ee[a] (%)
1	*p*-$MeOC_6H_4$	OEt	53	2:3	45
2[b]	Ph	OEt	80	1:3	58
3	*p*-ClC_6H_4	OEt	72	1:5	54
4	*p*-$NO_2C_6H_4$	OEt	83	1:12	56
5	C_6H_{11}	OEt	76	1:11	44
6	Ph	NEt_2	98	1:1	30

[a] ee of *cis*-product. [b] 20 mol % of sulfide used.

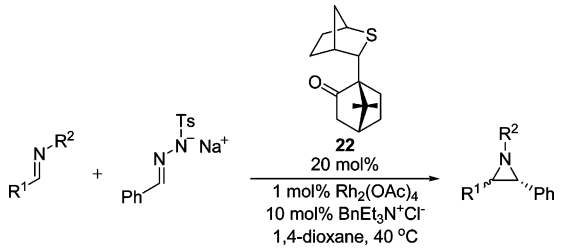
in favor of the *trans*-isomer), but the enantiomeric excesses achieved with sulfide **18** were very good to excellent (88−95%). Crucially, Aggarwal et al. also demonstrated that this chemistry was not limited to *N*-SES imines; Ts, $POPh_2$, and a range of alkoxycarbonyl groups were also successfully deployed as *N*-activating groups (Table 5).[88] Higher drs were obtained in some of these cases, and the ees remained very high.

Aggarwal et al. have also reported that diazoesters and diazoacetamides can be used in this catalytic procedure to synthesize ester- and amide-bearing aziridines (Table 6).[88] Higher temperatures were required to effect diazo decomposition of the more stable diazo-precursors. Sulfide **9a** gave moderate to excellent yields and moderate ees at 60 °C in THF. The diastereoselectivities with ester-derived ylides were variable and favored the more stable *cis*-aziridines. More electron-poor imines led to higher levels of *cis*-selectivity. The reasons for this change in selectivity compared with semistabilized ylides are discussed in section 3.1.5.

3.1.3. Ylide Formation from a Carbene Source II: N-Tosylhydrazone Salts

Aggarwal and co-workers reported that phenyl *N*-tosylhydrazone salts can be used as the carbene source in reactions employing chiral sulfide **22**.[51,91] As explained in section 2.1.3,

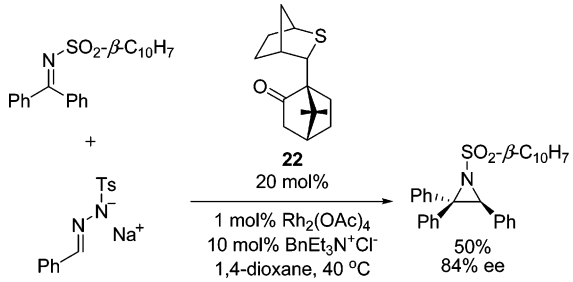
Table 7. Aggarwal et al.'s Catalytic Asymmetric Aziridination Using *N*-Tosylhydrazone Salts[91]



entry	R^1	R^2	yield (%)	trans/cis	ee[a] (%)
1	*p*-$MeOC_6H_4$	SES	60	2.5:1	92 (78)
2	Ph	SES	75	2.5:1	94
3[b]	Ph	SES	66	2.5:1	95
4	*p*-ClC_6H_4	SES	82	2:1	98 (81)
5	C_6H_{11}	SES	50	2.5:1	98 (89)
6	(*E*)-PhCH=CH	SES	59	8:1	94
7	3-furfuryl	Ts	72	8:1	95
8	*t*-Bu	Ts	53	2:1	73 (95)
9	Ph	Ts	68	2.5:1	98
10	Ph	SO_2-*β*-$C_{10}H_7$	70	3:1	97
11	Ph	Cl_3COCO-	71	6:1	90

[a] ee of *trans*-aziridine (ee of *cis*-aziridine). [b] 5 mol % of sulfide used.

Scheme 33. Use of an *N*-Tosylhydrazone Salt in the Synthesis of a Trisubstituted Aziridine[91]



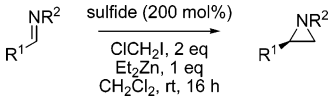
this protocol avoids the need to handle the potentially hazardous diazo compounds by generating them slowly in situ by decomposition of the hydrazone salts at 40 °C. Results employing sulfide **22** with the sodium salt of phenyl *N*-tosylhydrazone and a range of imines are summarized in Table 7. Excellent ees and moderate to good yields of the favored *trans*-aziridine were obtained in all cases, and the drs varied from poor to good.

Good yields could still be obtained with sulfide loadings as low as 5 mol % (entry 3), with no diminution of ee. In addition to examples of aryl, heteroaryl, cinnamyl, and aliphatic imines as substrates, this system has also allowed for the extension of this methodology to the synthesis of trisubstituted aziridines for the first time, employing an imine generated from a symmetrical ketone (Scheme 33).

3.1.4. Ylide Formation from a Carbene Source III: Simmons−Smith Reagent

Aggarwal and co-workers have extended their sulfide-catalyzed system for the formation of terminal epoxides (section 2.1.4) to the synthesis of terminal aziridines (Table 8).[57,90] Imines derived from aromatic and aliphatic aldehydes were suitable substrates. Interestingly, the usual requirement in ylide aziridination for an activating electron-withdrawing group on the imine nitrogen was not found, *provided the N-substituent had at least one possible coordinating site*

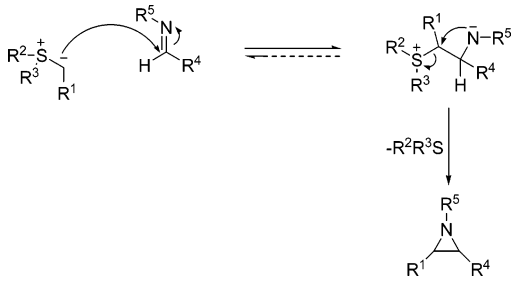
Table 8. Aggarwal and co-workers' Sulfide-Catalyzed Terminal Aziridine Synthesis[57,90]



entry	R^1	R^2	sulfide	yield (%)	ee (%)
1	Ph	Ts	THT	68	
2[a]	*p*-$NO_2C_6H_4$	Ts	THT	66	
3	*p*-$AcOC_6H_4$	Ts	THT	68	
4	C_6H_{11}	Ts	THT	72	
5	Ph	SES	THT	72	
6	Ph	*p*-$MeOC_6H_4$	THT	<3	
7	Ph	*o*-$MeOC_6H_4$	THT	79	
8	Ph	*o*-$MeOC_6H_4$	**9a**	70	19

[a] 2.5 equiv of $ClCH_2I$ were used.

Scheme 34. Generalized Mechanism for Sulfur Ylide-Mediated Aziridination

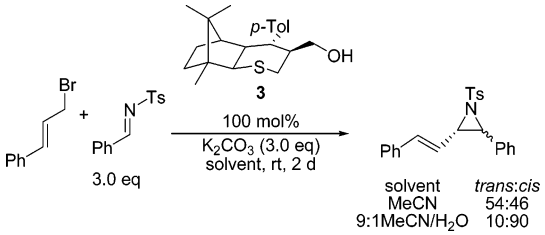


(compare entries 6 and 7 in Table 8).[90] It was postulated that these imines were activated through chelation of zinc. Although some investigations were undertaken into rendering this process asymmetric, the best ee obtained to date is 19%, employing sulfide **9a** (entry 8).[57]

3.1.5. Origin of Diastereoselectivity in Sulfide-Catalyzed Aziridinations

With different ylides, the diastereoselectivity-determining step in the reaction mechanism varies (Scheme 34). Using crossover experiments (generation of the betaine intermediate in the presence of a more reactive imine), Aggarwal et al. showed that the addition of semistabilized ylides to *N*-sulfonylimines forming intermediate betaines was nonreversible.[93] Therefore, in these cases, the product distribution is determined by the initial facial selectivity of the attack of the ylide on the imine. Stabilization of the anion of the betaine by the electron-withdrawing *N*-sulfonyl group might partly explain the difference compared with the related epoxidation case. In the case of stabilized ylides, however, the analogous crossover experiments demonstrated that the addition of the ylide was reversible. The rate of ring-closure of the betaines is the rate-determining and diastereodifferentiating step for stabilized ylides. A computational study on *N*-sulfonylimines by Robiette has supported these findings,[94] also shedding great light on the nature of the transition states involved (see below).

Scheme 35. Effect of Water on the Stereochemical Outcome of Sulfide-Catalyzed Aziridinations Observed by Saito et al.[84]



On the basis of calculations on the reaction of *N*-sulfonylimines with semistabilized ylides, Robiette predicted that, for *anti*-betaine formation, the ylide approaches the imine in a cisoid fashion analogous to the transition state found for epoxides (see section 2.1.5), but unlike epoxides, for *syn*-betaines a transoid approach is favored (see Figure 4, TS-*anti*-A and TS-*syn*-B). For the *anti*-betaine, both steric and Coulombic interactions favor the cisoid approach. In addition, a C−H···O hydrogen bond between an oxygen of the sulfonyl moiety and a sulfide methyl hydrogen also stabilizes TS-*anti*-A. For the *syn*-betaine, steric factors outweigh the Coulombic interactions and the transoid approach is favored. In addition, solvation lowers the energy of the transoid structures (TS-B) relative to the cisoid TS (TS-A and TS-C, due to better access to the polar groups) and competes with Coulombic stabilization. Thus, more polar protic solvents give more *cis*-aziridine (see Scheme 35).[84] In both cases, the steric clashes with the *N*-sulfonyl group are the dominant steric interactions. The calculated energy

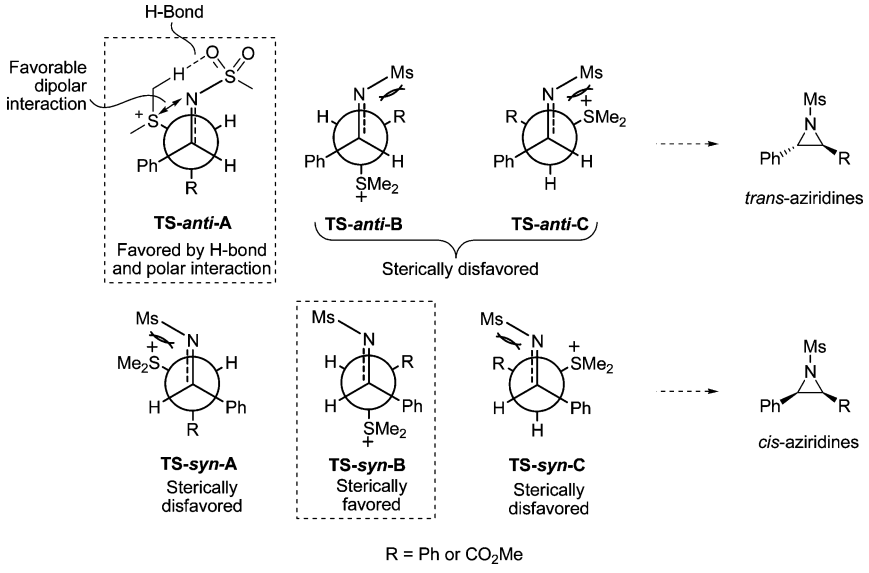


Figure 4. Six possible staggered transition states leading to *syn*- and *anti*-betaines.

differences between the transition states for *syn*- and *anti*-betaines predict that *trans*-aziridines will be favored but only just, leading to low stereoselectivity, as is generally observed experimentally (see Tables 4, 5, and 7).

For stabilized ylides, Robiette's calculations predict that the ring-closing step from betaine to aziridine is the rate- and selectivity-determining step. The *cis*-aziridine transition state is favored over the *trans*-aziridine transition state by decreased steric interactions around the *N*-sulfonyl group. The relative energies of the transition states for ring-closure of the betaines to *cis*- and *trans*-aziridines predict a small preference for the *cis*-isomer, as is observed experimentally (Table 6). Amide-stabilized ylides show intermediate reactivity (between ester- and aryl-stabilized ylides) and show intermediate selectivity, i.e., essentially a 1:1 ratio of *cis*- and *trans*-aziridines.

The substantial effect of the imine *N*-substituent on the diastereoselectivity in the reaction of semistabilized ylides has not been fully explained. Clearly, the substituent can affect whether transoid or cisoid approaches are favored and affect the relative energy differences of the transition states for *syn*- and *anti*-betaine. In addition, the degree of reversibility might be affected by the steric bulk and the electron-withdrawing ability of the substituent. In the reaction of ylides generated from preformed sulfonium salts, Hou and co-workers have also shown that the imine *N*-substituent can influence the diastereoselectivity in the reactions of amide-stabilized ylides and imines.[80] In their system, betaine formation could change from reversible to nonreversible by changing the *N*-substituent (and indeed other variables). Future studies may delineate the influence of each of these factors more clearly.

3.1.6. Origin of Enantioselectivity in Sulfide-Catalyzed Asymmetric Aziridinations

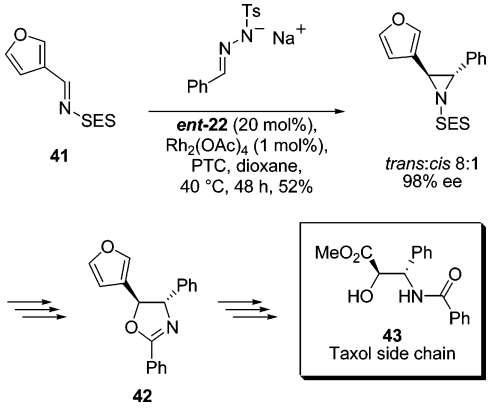
As in the related epoxidation reactions, four main factors affect the enantioselectivity in ylide-mediated aziridinations with semistabilized ylides.[62] These are discussed in section 2.1.6. Again, the enantioselectivity is controlled in the nonreversible betaine formation step. A single diastereomer of ylide must be formed, and the ylide conformation must be well-controlled. Finally, the ylide must exhibit high facial selectivity in the approach to the imine.[79,95] In aziridinations with sulfides such as **22**, these factors are well-controlled and high enantioselectivities are observed (especially for *anti*-betaines and, thus, *trans*-aziridines). In the case of stabilized ylides, betaine formation is reversible and the ee is determined in the ring-closure step, and poor to moderate enantioselectivities are observed (Table 6). The restriction to semistabilized ylides is the main limitation of this asymmetric methodology, and it is likely that new sulfides will have to be designed to achieve high enantioselectivities with stabilized ylides.

3.1.7. Applications in Synthesis

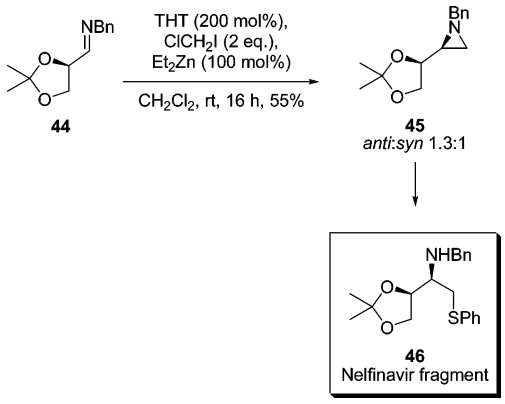
Sulfide-catalyzed aziridination methodologies have been applied to the synthesis of the Taxol side chain (**43**)[92] and a fragment of the HIV-protease inhibitor Nelfinavir.[90] The key steps of both of these syntheses are outlined below.

Aggarwal and Vasse sought to synthesize the Taxol side chain through catalytic aziridination of the *N*-SES-protected imine **41** (Scheme 36).[92] Deprotection of the SES group, followed by benzoylation and rearrangement, then afforded

Scheme 36. Synthesis of the Taxol Side Chain Using Sulfide-Catalyzed Aziridination[92]



Scheme 37. Synthesis of a Fragment of Nelfinavir Using Sulfide-Catalyzed Aziridination[90]



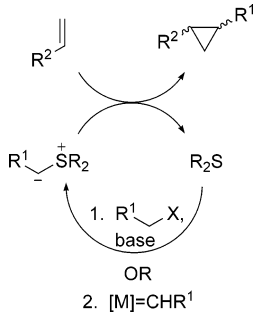
oxazoline **42**. Further transformations then furnished the Taxol side chain in 20% yield over seven steps from commercially available starting materials.

Aggarwal et al. have also demonstrated the utility of their sulfide-catalyzed terminal aziridine synthesis.[90] Aziridination of the *N*-benzylimine **44** derived from glyceraldehyde yielded aziridine **45**, which readily underwent ring-opening with thiophenol to afford a fragment of the protease inhibitor Nelfinavir (see Scheme 37).

3.1.8. Summary of Chalcogenide-Catalyzed Aziridinations

A range of aziridines are accessible through sulfide-catalyzed chemistry. Some systems employ alkyl halides, but the best results are obtained with metallocarbenes as the alkylidene source. The use of diazo compounds to this end has been largely superseded by the application of the safer *N*-tosylhydrazone salts. As aziridines bearing a range of nitrogen substituents can be synthesized, this method allows access to compounds that could not be reached readily by olefin aziridination.[4,76] Furthermore, it is possible to synthesize vinyl aziridines through ylide chemistry, which is difficult through olefin aziridination. The main drawback with sulfide-mediated imine aziridination is that the drs are low in many cases. Excellent enantioselectivities and good yields have been consistently obtained in the synthesis of vinyl and aryl aziridines. Ester- and amide-bearing aziridines can also be accessed in good yield, but ees are moderate at best. A separate process also allows for the synthesis of terminal aziridines in good yields, but only with low enantioselectivity.

Scheme 38. Standard Methods for Sulfide-Catalyzed Ylide-Mediated Cyclopropanation



4. Cyclopropanation

Cyclopropanes are commonly prepared by reaction of metal carbenoids with nucleophilic alkenes or by addition of carbanions bearing potential leaving groups to electrophilic alkenes.[11,96] Within the latter process, reports of organocatalytic chalcogenide-catalyzed cyclopropanation reactions are somewhat limited. As with epoxidation and aziridination reactions, these reports have centered on the in situ generation of an ylide from a chalcogenide, which is regenerated in the reaction.[11] There are two principal methods by which this may be achieved: (i) through alkylation of the chalcogen heteroatom with an alkyl halide followed by deprotonation, and (ii) by reaction of the chalcogen with a metal carbene (Scheme 38). The most studied, sulfide-catalyzed cyclopropanation will be discussed first, followed by the use of selenides and tellurides as cyclopropanation catalysts.

4.1. Sulfide-Catalyzed Cyclopropanations

4.1.1. Catalysis via Sulfide Alkylation/Deprotonation

The most traditional method for the formation of a sulfonium ylide is through the alkylation of a sulfide with an alkyl halide followed by deprotonation of the resulting sulfonium salt.[6] The alkylation is often carried out in a separate step with isolation of the salt, which may then be either deprotonated in the presence of a Michael acceptor for cyclopropanation or, in cases where the ylide is highly stabilized, deprotonated in a separate step to form the ylide, which may then be isolated and stored for several weeks.[97] However, it has recently been shown that it is possible to carry out this alkylation/deprotonation sequence in the presence of non-base-sensitive Michael acceptors, thus allowing a one-pot reaction, and, since the sulfide is regenerated in the reaction, substoichiometric amounts as low as 20 mol % of sulfide can be used.[98]

This methodology has been demonstrated by Tang and co-workers, who have extended the stoichiometric use of their sulfide **2a** in asymmetric cyclopropanations[5] to a catalytic version of this chemistry (Scheme 39).[98] In this case, only 20 mol % of the preformed sulfonium salt is required, and in the presence of 1.5 equiv of cinnamyl bromide, a number of β-aryl enones have been cyclopropanated. High yields and diastereoselectivities were achieved using this catalytic cycle with moderate to high enantioselectivities, although prolonged reaction times were required (Table 9). It is also worth noting that it is possible to obtain the other enantiomer of the product by using the diastereomeric sulfide in which the hydroxyl and thioether occupy the endo positions. Most of the examples reported by Tang and co-workers for this reaction were conducted through the addition

Scheme 39. Catalytic Cycle for Cyclopropanation Proposed by Tang and co-workers[98]

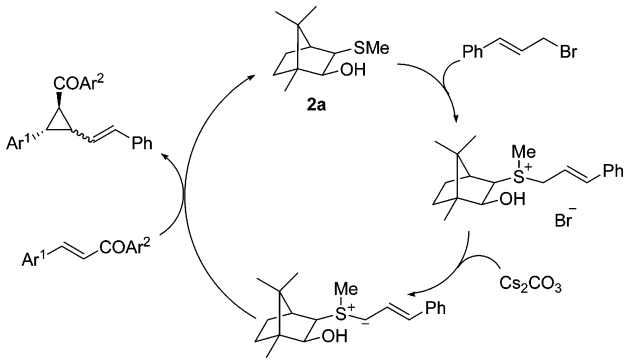
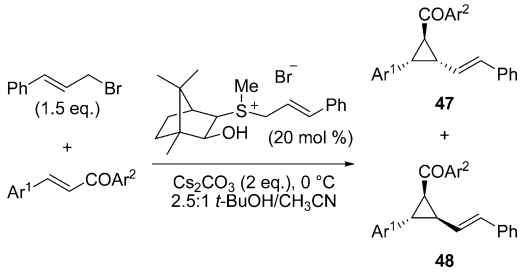
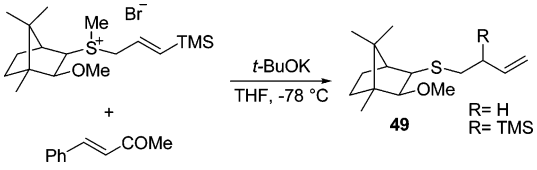


Table 9. Tang and co-workers' Sulfide-Catalyzed Cyclopropanation using Alkylation/Deprotonation Ylide-Mediated Protocol



entry	Ar^1	Ar^2	time (h)	yield (%)	**47**/**48**	ee (%)
1	Ph	Ph	36	92	86:14	82
2	Ph	*p*-MeC_6H_4	57	87	87:13	81
3	*o*-BrC_6H_4	Ph	20	90	77:23	88
4	*p*-BrC_6H_4	Ph	30	89	75:25	77
5	*p*-$MeOC_6H_4$	Ph	80	66	86:14	80

Scheme 40. Attempted Cyclopropanation Reaction with Sulfonium Salt Derived from *O*-Methylated Chiral Sulfide

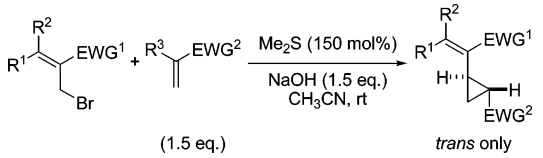


of a substoichiometric amount of the preformed sulfonium salt, although addition of an equivalent amount of sulfide was reported to yield similar results.

Unlike the reaction in which a stoichiometric amount of the sulfonium salt is deprotonated, this reaction does not tolerate sulfonium salts bearing a β-trimethylsilyl substituent. The cyclopropanations of α,β-unsaturated esters and amides have also proven to be problematic. Furthermore, the higher temperatures required for the catalytic reaction mean that, although the diastereo- and enantioselectivities are high, they are occasionally not as good as those obtained in the stoichiometric reaction.

The presence of the hydroxyl group on the sulfide was reported to be critical to the reaction as it is proposed to serve as a hydrogen-bond donor to the Michael acceptor.[98] Methylation of this oxygen was shown to prevent the desired reaction from occuring, with only products (**49**) resulting from rearrangement of the ylide (Scheme 40). It is believed that the hydroxy sidearm helps to organize the transition state, leading to excellent face-selectivity. This, in combination

Table 10. Kim and co-workers' Dimethyl Sulfide-Catalyzed Cyclopropanation[99]

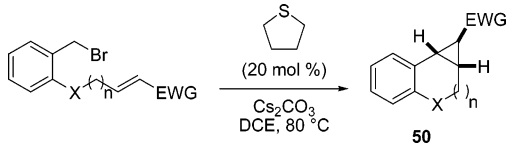


(1.5 eq.) *trans* only

entry	R^1	R^2	EWG^1	R^3	EWG^2	time (h)	yield (%)
1	Ph	H	CO_2Me	H	COMe	12	45
2	*p*-MeC_6H_4	H	CO_2Me	H	COMe	12	47
3	*p*-ClC_6H_4	H	CO_2Me	H	COMe	13	49
4	*p*-MeC_6H_4	H	CO_2Me	Cl	CN	20	57[a]
5	H	Ph	CN	H	COMe	12	48

[a] Two stereoisomers were obtained in a ratio of 3:2.

Table 11. Sulfide-Catalyzed Intramolecular Cyclopropanation



50

entry	X	*n*	EWG	yield (%)
1	O	1	CO_2Me	76
2	CH_2	0	CO_2Me	53[a]
3	CH_2	1	CO_2Et	63
4	CH_2	1	CHO	64
5	CH_2	1	COPh	64[a]

[a] At 45 °C.

with the well controlled ylide geometry (see section 2.1.6), results in good diastereo- and enantioselectivities in the products. Furthermore, the use of dimethyl sulfide or THT in place of this sulfide under the same conditions gave only trace amounts of the cyclopropanation products.

In contrast, under different conditions, Kim and co-workers employed dimethyl sulfide in a catalytic cyclopropanation using allylic bromides derived from Baylis−Hillman adducts (Table 10).[99] In these cases, although the sulfide is regenerated in the reaction, 150 mol % of sulfide was used to obtain the cyclopropanation products with moderate yield and excellent *trans*-selectivity. Acyclic enones were reported to work well with this chemistry, but reactions with cyclic enones, acrylates, and acrylonitrile were unsuccessful. Interestingly, 2-chloroacrylonitrile could be employed in this reaction, giving the product in 57% yield. A range of substituted allylic bromides was also used.

More recently, Tang and co-workers have extended this chemistry to a catalytic intramolecular cyclopropanation reaction to obtain benzobicyclic compounds **50** (Table 11).[100] The use of 20 mol % of THT in these reactions, in the presence of Cs_2CO_3 and 1,2-dichloroethane at 80 °C, afforded the desired compounds as single diastereomers in moderate to good yields. The reaction could be applied to α,β-unsaturated esters, ketones, and aldehydes, and both *E*- and *Z*-alkenes were found to give the same diastereomer of the product.

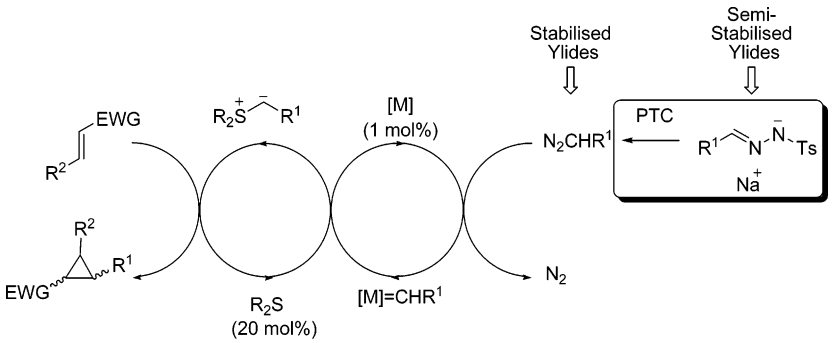
4.1.2. Catalysis via Ylide Formation from a Carbene Source

Several reports have dealt with the generation of an ylide in situ via reaction of a sulfide with a metal carbene.[41,91,101] Unlike the more traditional method in which a sulfide is reacted with an alkyl halide followed by deprotonation, this reaction is conducted under neutral conditions and thus tolerates base-sensitive substrates. Furthermore, the long reaction times associated with some of the above methods may also be avoided in many cases as ylide formation via this method is often much faster.

To this end, the catalytic cycle developed by Aggarwal et al. for epoxidation and aziridination (see sections 2.1.2 and 3.1.2) has also been applied to cyclopropanation, and allows substoichiometric amounts of sulfide to be employed (Scheme 41). Using this process, both semistabilized and stabilized ylides can be generated. Stabilized ylides may be generated directly from the diazo compound. In this case, slow addition of the diazo compound via syringe pump is required in order to minimize its concentration in solution and thus prevent side reactions between the metal carbenoid and the diazo compound.[101] Semistabilized ylides,[91] however, should be generated from the *N*-tosylhydrazone salts, which allows a much safer in situ generation of the less stable diazo compounds in the presence of a phase-transfer catalyst.[51] In this case, slow addition via a syringe pump is not required because diazo compound generation can be easily regulated by controlling the temperature of the reaction (typically 30−40 °C).[91]

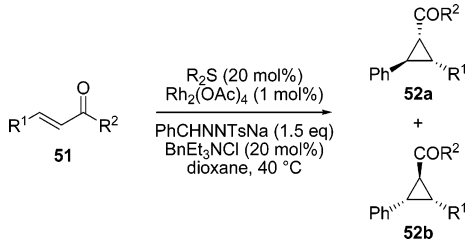
For semistabilized ylides, the reaction has been shown to work well for a number of acyclic enones, giving high yields and moderate diastereoselectivities in many cases (Table 12).[91,101] Six-membered-ring sulfides such as pentamethylene sulfides **53** and **54** gave better yields than five-membered-ring sulfides (see Figure 5). The cyclopropanation reactions are slower than the corresponding epoxidation and aziridination reactions. As a result, ylide equilibration can become competitive and it has been noted that products resulting from Sommelet−Hauser rearrangements have been obtained in reactions employing THT as the ylide precursor (Scheme

Scheme 41. Aggarwal and co-workers' Sulfide-Catalyzed Cyclopropanation Using Metal Carbenes as the Ylide Precursor



M = $Rh_2(OAc)_4$, $Cu(acac)_2$, PTC = $BnEt_3NCl$ (20 mol%)

Table 12. Aggarwal and co-workers' Sulfide-Catalyzed Cyclopropanation Using Diazo Compounds



entry	R^1	R^2	R_2S	dr (**52a**/**52b**)	ee (%)	yield (%)
1	Ph	Ph	**53**	4:1		92[a,b]
2	Ph	Ph	THT	1:1		40[a,b]
3	Ph	Ph	**18**	4:1	97	38[a]
4	Ph	Ph	**22**	5:1	89	30[c]
5	Ph	Ph	**54**	4:1	91	73
6	Ph	Me	**54**			5
7	Me	Ph	**54**	4:1	90	50
8	H	OEt	**54**	7:1		10

[a] Conditions: $Rh_2(OAc)_4$ (1 mol %), $PhCHN_2$ (1 equiv), toluene, rt, 12 h. [b] 100 mol % R_2S. [c] 50% starting material recovered.

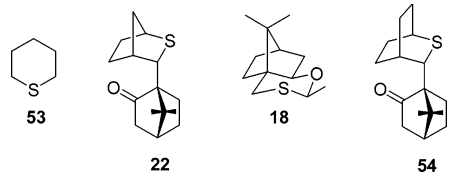
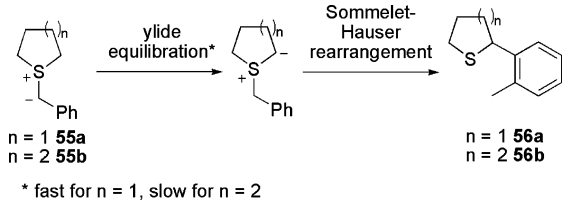


Figure 5. Compounds **53**, **22**, **18**, and **54**.

Scheme 42. Sommelet−Hauser Rearrangement of Five- and Six-Membered Ring Sulfur Ylides

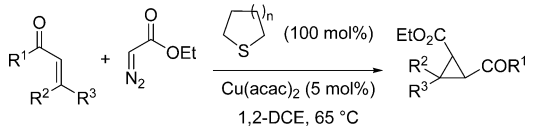


42).[101,102] However, six-membered-ring ylides do not allow such rapid equilibration to occur[103] and thus give improved yields.

A number of chiral sulfides have also been developed for this chemistry.[91,101,102] Because of the propensity of ylides containing five-membered rings to undergo rapid isomerization under these conditions, the reactions using semistabilized ylides have been conducted with the [2,2,2]-sulfide **54** as catalyst to give optimum yields and enantiomeric excesses (Table 12).[91] To explain the observed selectivities, the same factors must be considered as for sulfur ylide-mediated epoxidations (sections 2.1.5 and 2.1.6). Betaine formation is nonreversible and so this step is also the enantioselectivity-determining step. As before, a single diastereomer of ylide should be formed and its conformation and face selectivity should be well controlled. The diastereoselectivity is controlled by nonbonding interactions between the ylide and the Michael acceptor substituents.

In many cases the reactivity of substrates in this carbene-based catalytic cycle for sulfur ylide cyclopropanation is not mirrored by the equivalent reaction where the ylide is formed through deprotonation of the salt. In some cases this can be attributed to the increased reaction temperature required for the catalytic reaction; however, this is not always the case.

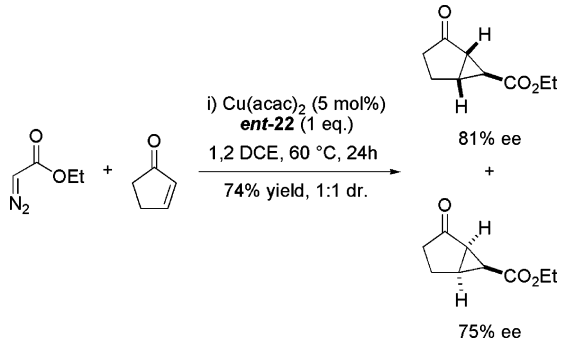
Table 13. Use of Different Michael Acceptors in the Sulfide-Catalyzed Cyclopropanation Using Stabilized Ylides[101,104]



entry	R^1	R^2	R^3	n	yield (%)	dr
1[a]	Ph	H	Ph	2	72	4:2:1
2[a]	Me	H	H	2	64	>95:5
3[a]	OEt	H	CO_2Et	2	68	>95:5
4[a]	Me	Me	Me	2	5	>95:5
5[b]	$-(CH_2)_2-$		H	1	81	1:1

[a] Ref 101. [b] Ref 104.

Scheme 43. Catalytic Asymmetric Cyclopropanation Using Stabilized Ylides Derived from *ent*-22



It can sometimes be difficult to predict which substrates will work well with this chemistry.[101]

The catalytic reaction with stabilized ylides works well with both cyclic and acyclic enones to give high yields and, in some cases, high diastereoselectivities (Table 13). However, acrylates, enals, and nitrostyrene have proven to be problematic.

Sulfide **ent-22** has been used catalytically in the synthesis of cyclopropanes with stabilized sulfur ylides (Scheme 43). In this case it was possible to obtain high enantioselectivities in the reaction although the diastereoselectivity was poor.[104] Contrastingly, however, the equivalent reaction using the stoichiometric sulfonium salt deprotonation method of generating the ylide was shown to provide high diastereoselectivity but low enantioselectivity in one of the products (**57**, 14% ee) (Scheme 44). The difference between the catalytic reaction and the preformed salt reaction has been attributed to one of the diastereomeric betaines ring-closing slowly due to nonbonded steric interactions in the TS and, thus, undergoing competitive base- and/or ylide-mediated equilibration under these conditions. This base/ylide-mediated proton transfer does not occur in the catalytic reaction because of the neutral conditions and the low concentration of ylide intermediates in these reactions (Scheme 43).

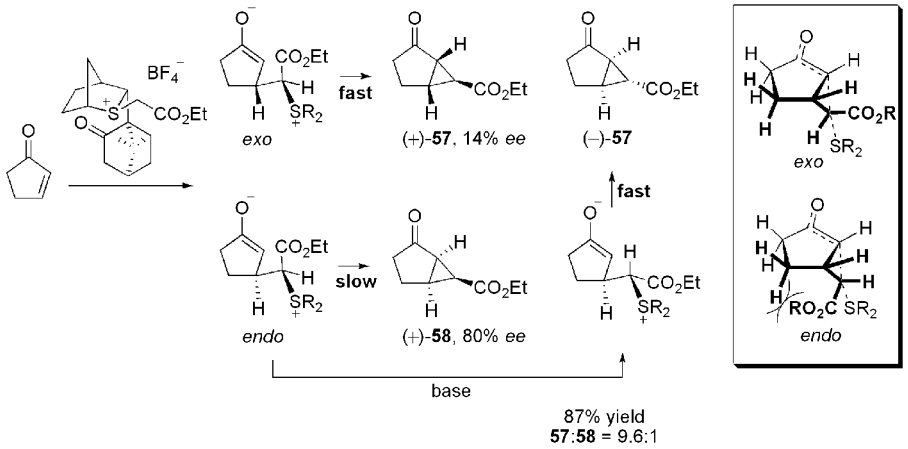
4.1.3. Applications in Synthesis

Sulfide **54** has also been used in the synthesis of conformationally constrained cyclopropyl amino acids (Scheme 45). Using the conditions shown, the product was obtained with complete cis diastereoselectivity and, following recrystallization, was also obtained with high enantiomeric purity.[91]

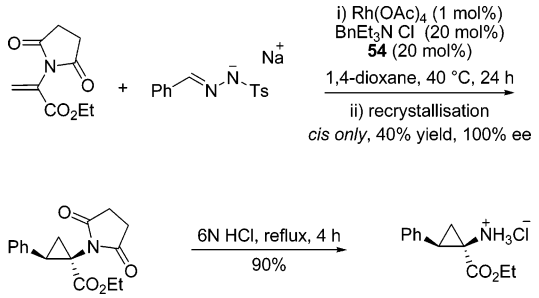
4.2. Selenide-Catalyzed Cyclopropanations

One account has been reported of a cyclopropanation reaction that uses a selenide catalyst (Scheme 46).[105] In this

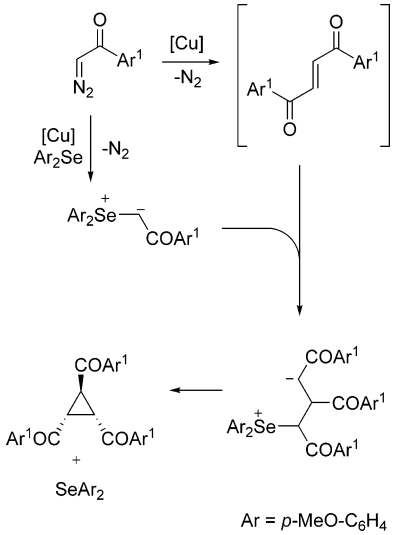
Scheme 44. Mechanism of Base- and Ylide-Mediated Epimerization of the Intermediate Betaine in Cyclopropanation Leading to High Diastereoselectivity and Low Enantioselectivity in One of the Diastereomers (57)[104]



Scheme 45. Application of Sulfide 54 in Catalytic Asymmetric Cyclopropanation toward the Synthesis of Cyclopropyl Amino Acids



Scheme 46. Trimerization of Diazoketones Catalyzed by Selenides



case, as little as 5.5 mol % of selenide was used as a catalyst in the trimerization of a number of aromatic diazoketones to form the cyclopropanes in moderate to good yields (Table 14).

4.3. Telluride-Catalyzed Cyclopropanations

There are a number of reports of catalytic telluride-mediated cyclopropanation reactions. In particular, Huang and co-workers have extended their catalytic cyclopropanation through the in situ alkylation of sulfides with an allyl bromide (section 4.1.1) to the use of tellurides.[5,106,107] The reaction is believed to proceed through a similar mechanism as that described for the formation of sulfur ylides, and under these conditions a number of β-aryl enones have been cyclopropanated to give high yields and excellent diastereoselectivities (Table 15).

Table 14. Yields Obtained in Selenide-Catalyzed Cyclopropanation (According to Scheme 46)

entry	Ar^1	selenide (mol %)	yield (%)
1	Ph	100	59
2	*p*-ClC_6H_4	100	54
3	*m*-ClC_6H_4	100	49
4	*p*-$MeOC_6H_4$	100	55
5	*p*-CNC_6H_4	100	41
6	*p*-MeC_6H_4	100	68
7	*p*-MeC_6H_4	5.5	44

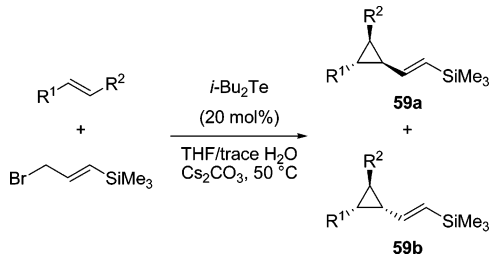
It has also been shown that substituted benzyl bromides make good substrates for this reaction.[108] In this case, a number of β-aryl heteroaromatic enones have been cyclopropanated to give the products in good to excellent yields (Scheme 47).

An asymmetric version of the above reaction has also been developed by Tang.[109] The replacement of diisobutyl telluride with a C_2-symmetric telluride to make salt **60** has been shown to yield the product vinyl cyclopropane with high yield, diastereoselectivity, and enantioselectivity with some β-aryl enones (Scheme 48).

4.4. Summary of Chalcogenide-Catalyzed Cyclopropanations

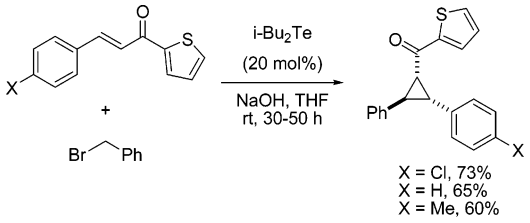
In summary, there are limited reports of catalytic chalcogenide-mediated cyclopropanation reactions. Methodologies are based on the in situ generation of an ylide from a chalcogenide, either through alkylation of the heteroatom with an alkyl halide followed by deprotonation or by reaction of the heteroatom with a metal carbene. The majority of examples that exist are catalyzed by a sulfide, and the groups of both Tang and Aggarwal have developed chiral sulfides that allow the generation of the product cyclopropanes with high yield, diastereoselectivity, and enantioselectivity being obtained in many cases. Tang and co-workers have also extended their work to incorporate tellurium ylide cyclopropanations, and the use of a chiral telluride allows the synthesis of cyclopropanes in good enantiomeric excesses. To date, there is only one report of a selenide-catalyzed cyclopropanation.

Table 15. Telluride-Catalyzed Ylide-Mediated Cyclopropanation

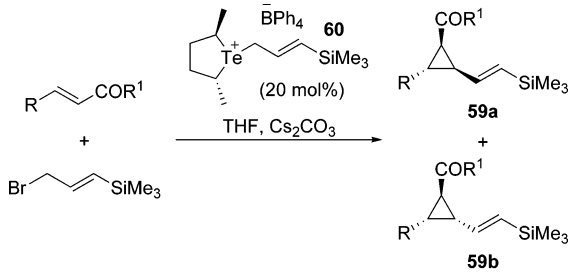


entry	R^1	R^2	**59a**/**59b**	yield (%)
1	Ph	COPh	>98:2	70
2	*p*-ClC_6H_4	COPh	>99:1	64
3	*p*-$NO_2C_6H_4$	COPh	>99:1	83
4	*p*-MeC_6H_4	COPh	>98:2	70
5	Ph	COCH=CHPh	>99:1	58

Scheme 47. Use of Benzyl Bromide in Telluride-Catalyzed Cyclopropanation Reactions



Scheme 48. Application of a Chiral Tellurium Salt in Tang and co-workers' Organocatalytic Cyclopropanation Reaction



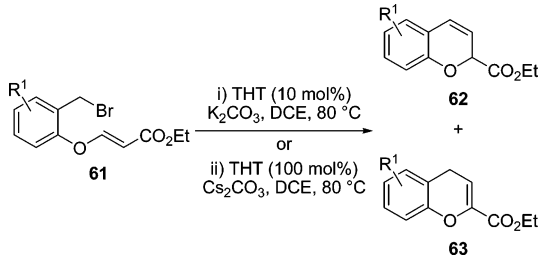
R = R^1 = Ph: 86% ee, 91% yield, **59a**/**59b** = 90/10
R = *p*-Cl-C_6H_4, R^1 = Ph: 89% ee, 94% yield, **59a**/**59b** = 91/9

5. Sulfide-Catalyzed Chromene Synthesis

While investigating sulfide-catalyzed cyclopropanations (see section 4.1), Tang discovered that THT could catalyze the formation of chromenes **62** and **63** from appropriately substituted benzyl bromides (Table 16).[100,110] Either *2H*- or *4H*-chromenes could be obtained selectively depending on the choice of base employed: potassium carbonate or cesium carbonate. Optimal sulfide loadings varied from 1−100 mol % depending on the substrate and the desired outcome. Good to excellent yields were achieved with a variety of α,*β*-unsaturated esters using this simple and mild protocol.

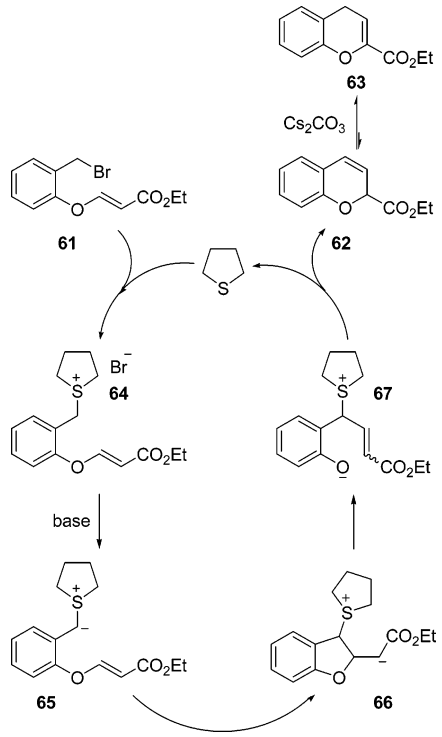
The proposed mechanism is shown in Scheme 49. Tetrahydrothiophene reacts with benzylic bromide **61** and deprotonation leads to ylide **65**. However, conjugate addition is not followed by the expected cyclopropane formation; rather, phenolate is eliminated, and S_N2' attack leads to expulsion of THT and formation of **62**. If Cs_2CO_3 is used, **62** isomerizes to **63**.

Table 16. Sulfide-Catalyzed Chromene Synthesis



entry	R^1	conditions	**62**/**63**	yield (%)
1	H	i	33:1	85
2	1-naphthyl	i	37:1	88
3	6-^{t}Bu	i	>99:1	99
4	4-Me	i	20:1	85
5	H	ii	1:20	83
6	1-naphthyl	ii	1:>99	85
7	6-^{t}Bu	ii	1:20	87
8	4-Me	ii	1:25	85

Scheme 49. Proposed Mechanism for Sulfide-Catalyzed Chromene Synthesis

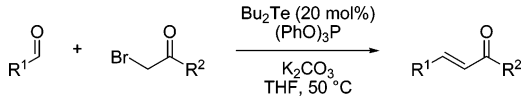


6. Telluride-Catalyzed Olefin Synthesis

6.1. Te-ylide Olefination and Related Reactions

In the early 1980s, it was reported that stabilized telluronium ylides react with aldehydes to yield alkenes.[5,107,111] Later, Huang et al. reported that the corresponding telluronium salts react with aldehydes in the absence of base to give *E*-α,*β*-unsaturated alkenes in excellent yields.[112] The salts could be generated in situ from the reaction of dibutyltelluride with α-haloesters, α-halonitriles, and α-haloketones to give a one-pot telluride-mediated olefination process. Subsequently, Huang et al. reported a method for using the telluride as a catalyst with triphenyl phosphite as a stoichiometric reductant.[113,114] Thus, reaction of dibutyl telluride (20 mol %) with an α-haloester or an α-haloketone, potassium carbonate, triphenyl phosphite, and aldehyde in THF afforded

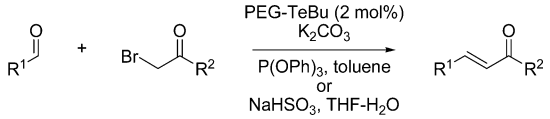
Table 17. First Telluride-Catalyzed Olefination of Aldehydes



entry	R^1	R^2	time (h)	yield[a] (%)
1	*p*-Cl-C_6H_4	OMe	13	89
2	*p*-Cl-C_6H_4	OMe	20	79[b]
3	Ph	OMe	13	98
4	*p*-Me-C_6H_4	OMe	18	95
5	2-furyl	OMe	7	76
6	(*E*)-PhCH=CH	OMe	17	80
7	$Me(CH_2)_8$	OMe	17	83
8	cyclohexyl	OMe	12	74
9	*p*-Cl-C_6H_4	Ph	17	89
10	Ph	*i*-Pr	14.5	98

[a] No *Z*-isomer found in any case. [b] $NaHSO_3$ and a trace of water were used in place of $(PhO)_3P$.

Table 18. Tang and co-workers' PEG-TeBu-Catalyzed Olefination of Aldehydes

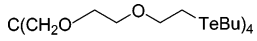


entry	R^1	R^2	reductant	time (h)	*E*/*Z*	yield (%)
1	*p*-Cl-C_6H_4	OEt	$P(OPh)_3$	7	>99:1	98
2	*p*-Cl-C_6H_4	O*t*Bu	$NaHSO_3$	48	>99:1	93
3	Ph	OEt	$P(OPh)_3$	18	>99:1	98
4	Ph	O*t*Bu	$NaHSO_3$	11	>99:1	92
5	*p*-Me-C_6H_4	OEt	$P(OPh)_3$	23	90:10	93
6	*p*-Me-C_6H_4	O*t*Bu	$NaHSO_3$	24	94:6	96
7	2-furyl	OEt	$P(OPh)_3$	12	>99:1	96
8	2-furyl	O*t*Bu	$NaHSO_3$	11	>99:1	88
9	*trans*-PhCH=CH	OEt	$P(OPh)_3$	48	>99:1	74
10	*trans*-PhCH=CH	O*t*Bu	$NaHSO_3$	23	>99:1	88
11	$Me(CH_2)_8$	OEt	$P(OPh)_3$	48	86:14	74
12	$Me(CH_2)_8$	O*t*Bu	$NaHSO_3$	72	95:5	84
13	cyclohexyl	OEt	$P(OPh)_3$	48	>99:1	70
14	cyclohexyl	O*t*Bu	$NaHSO_3$	48	>99:1	76

alkenes in good to excellent yield and with excellent *E*-selectivity (see Table 17). Use of inorganic reducing agents in place of triphenyl phosphite gave lower yields under their reaction conditions (entry 2).

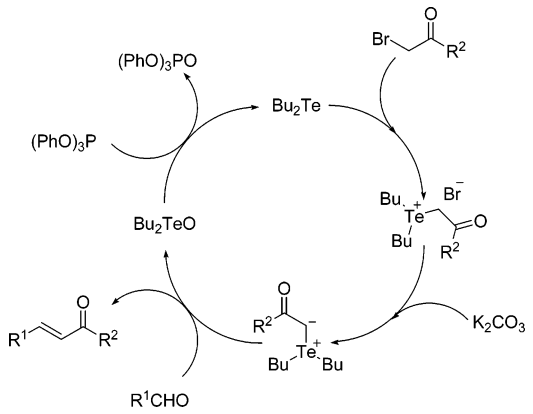
In 2001, Tang and co-workers reported that catalyst loading could be reduced to 2 mol % using a more active poly(ethylene glycol) (PEG)-supported telluride, PEG-TeBu (Table 18).[115,116] Changes to the order of addition reduced side products and were crucial to obtaining optimum yields at low catalyst loadings. In addition to the lower catalyst loading, under these conditions the use of $NaHSO_3$ as reducing agent in THF/water (4:0.07) gave comparable yields to those obtained with triphenylphosphite. This gave a more practical method and also simplified the purification of the products. Use of *tert*-butyl α-bromoacetate as the α-haloester gave the best yields by reducing formation of side products due to ester hydrolysis in the $NaHSO_3$ system. Excellent *E*-selectivities and good to excellent yields were obtained (Table 18). Use of the $NaHSO_3$ system led to improved selectivities in cases where lower selectivities had been observed using $P(OPh)_3$ in toluene.

It was proposed that the PEG could interact with the potassium ions in a similar manner to crown ethers and, therefore, act as a phase-transfer catalyst and increase the basicity of the potassium carbonate. This would, in turn, increase the rate of telluronium ylide formation and improve the catalyst turnover. This proposal was supported by the fact that, with $P(OPh)_3$ as reductant, the use of 4 mol %

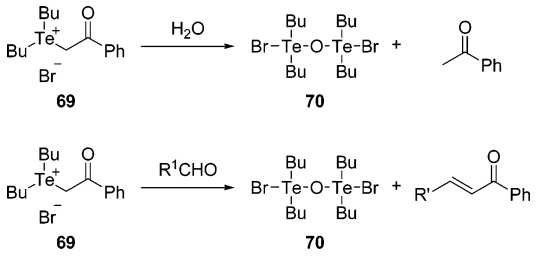


68

Scheme 50. Proposed Major Catalytic Cycle for Telluride-Catalyzed Olefination



Scheme 51. Routes for Formation of 70

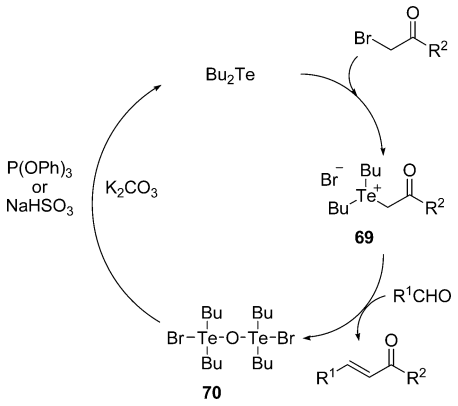


Bu_2Te in combination with 18-crown-6 gave a 69% yield of ethyl (*E*)-*p*-chlorocinnamate (cf. trace amounts in the absence of the crown ether). Additionally, it was proposed that the oxygens in the PEG could help stabilize the telluronium salts, improve efficiency, and decrease catalyst degradation. The PEG-supported telluride was synthesized in two steps from PEG in 82% yield. The catalyst could be recovered by precipitation with diethyl ether but gave reduced yields in subsequent reactions. To improve the tellurium loading on the carrier, a telluride-functionalized oligoglycol **68** and related telluronium salts were used in place of PEG-TeBu.[117] Excellent yields and selectivities were obtained with 2−5 mol % of the salts. Trisubstituted olefins were formed with good to excellent *E*/*Z*-selectivities (70:30 to 99:1) using the salt derived from the reaction of ethyl α-bromopropionate with **68** as catalyst.

Recently, Zhu et al. reported telluride-mediated olefinations using perfluorophenyl diazomethane to form a rhodium carbenoid, which in turn reacted with stoichiometric amounts of Bu_2Te to give the corresponding tellurium ylide.[48] Excellent yields and *trans*-selectivities were obtained; however, the tellurium oxide byproducts were not recycled.

The catalytic cycle proposed for telluride-catalyzed olefinations is shown in Scheme 50 and is similar to that proposed for other chalcogenide-catalyzed ylide reactions (see section 2.1.1).[113] Mechanistic investigations revealed that telluronium salt **69** reacted with water to give acetophenone and compound **70** (Scheme 51) (see section 6.2).[116,118] Initially it was thought that this was a catalyst deactivation pathway; however, it was later shown that **70** could be converted to Bu_2Te in the presence of $P(OPh)_3$ and K_2CO_3. Compound **70** can in fact be used as an effective catalyst for olefination of α-halocarbonyl compounds.[118] Tang and co-workers also confirmed earlier reports that the olefination

Scheme 52. Proposed Minor Pathway for Telluride-Catalyzed Olefination



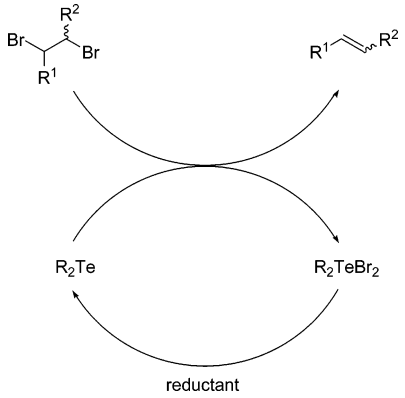
reaction could be carried out in the absence of base to give low yields of the desired alkenes and showed that compound **70** was produced under these conditions (Scheme 51). Therefore, two pathways for olefination may be operating (Schemes 50 and 52). It is believed that the major pathway involves the telluronium ylide.

6.2. Telluride-Catalyzed Dehalogenation and Related Reactions

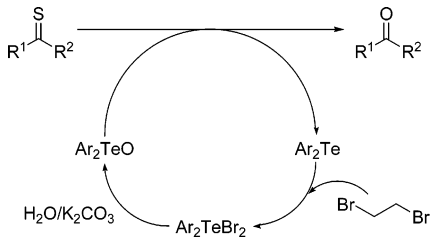
Vicinal dibromides can be dehalogenated to form olefins using tellurides as catalysts (Table 19).[119] Suzuki et al. reported that (*p*-$MeOC_6H_4)_2Te$ was an effective catalyst using potassium disulfite as a stoichiometric reductant under biphasic conditions. The reaction exhibited excellent stereoselectivity, e.g., only *trans*-stilbene was obtained from the corresponding (*1R*,2S**)-dibromide (entry 1) whilst *cis*-stilbene was formed with very high dr (6:94) from the alternative diastereomeric dibromide (entry 2). Detty and coworkers found that, with more electron-rich tellurides such as $(Me_2NC_6H_4)_2Te$, the scope could be extended to less reactive nonbenzylic bromides and could give terminal and trisubstituted olefins, although these reactions were very slow.[120] Either glutathione (GSH) or sodium ascorbate (SA) was used as the stoichiometric reductant in these cases. Scheme 53 shows the proposed catalytic cycle. Complex **70** has also been used as a source of Bu_2Te in the catalytic dehalogenation of α-halocarbonyl compounds.[118]

Ley et al. have reported a related reaction using 1,2-dibromoethane as a sacrificial reductant. Reaction of a telluride with the dibromide in the presence of water gives a telluroxide, which is a mild oxidant for the conversion of thiocarbonyl compounds to carbonyl compounds (Scheme

Scheme 53. Proposed Catalytic Cycle for Telluride-Catalyzed Debrominations



Scheme 54. Telluride-Catalyzed Transformation of Thiocarbonyls to Carbonyl Compounds with Proposed Catalytic Cycle



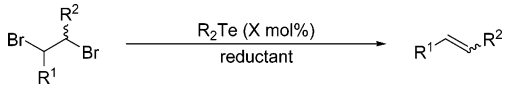
54).[121] Using (*p*-$MeOC_6H_4)_2Te$ as the catalyst, good to excellent yields were obtained with catalysts loadings as low as 1.5 mol %, e.g., *t*-$Bu_2C{=}S$ gave a quantitative yield of *t*-$Bu_2C{=}O$ in 15 h.

7. Morita–Baylis–Hillman-type Reactions

7.1. Introduction

Scheme 55 shows a Morita−Baylis−Hillman (MBH) reaction, which effects an α-functionalization of alkenes activated with an electron-withdrawing group. Traditionally these reactions use tertiary amine (e.g., DABCO)[122] or tertiary phosphine[123] catalysts, and typically involve an aldehyde or activated ketone as the terminal electrophile, thus leading to hydroxyalkylated substrates **71**. Alternatively, the employment of an oxophilic Lewis acid and a weaker Lewis base, such as chloride,[124,125] bromide,[125] iodide,[126] or chalcogenide (the subject of this review), species which are unable to effect the transformation alone, is useful (Scheme 55, conditions b). These conditions allow more reactive Michael acceptors

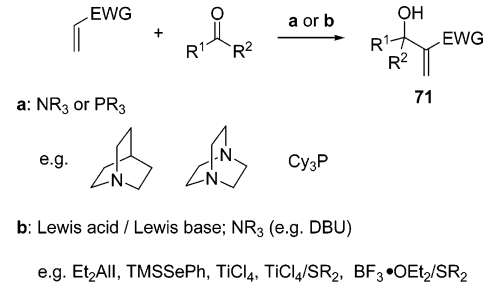
Table 19. Telluride-Catalyzed Debromination of *vic*-Dibromides



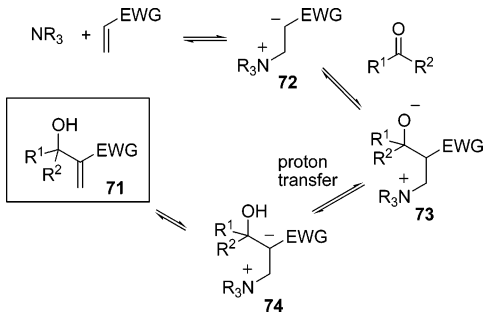
entry	*X*	R	reductant[a]	geometry	R^1	R^2	time (h)	E/Z	yield (%)
1	5	*p*-$MeOC_6H_4$	$K_2S_2O_5$	(*1R*,2S**)	Ph	Ph	24	*E* only	92
2	5	*p*-$MeOC_6H_4$	$K_2S_2O_5$	(*1R*,2R**)	Ph	Ph	24	6:94	88
3	25	*n*-C_6H_{13}	GSH	(*1R*,2S**)	Ph	Ph	135	*E* only	97
4	25	*n*-C_6H_{13}	SA	(*1R*,2S**)	Ph	Me	42	*E* only	87
5	25	*p*-$Me_2NC_6H_4$	GSH		C_8H_{17}	H	536		79
6	25	*p*-$Me_2NC_6H_4$	GSH	(*1R*,2R**)	Et	Me	96[b]	*Z* only	96
7	25	*p*-$Me_2NC_6H_4$	SA		Ph	Me_2	116		85

[a] GSH = glutathione and SA = sodium ascorbate. [b] Bu_4NI used as additive.

Scheme 55. Morita−Baylis−Hillman Reaction: General Methods



Scheme 56. Mechanism for a Traditional Morita−Baylis−Hillman Reaction



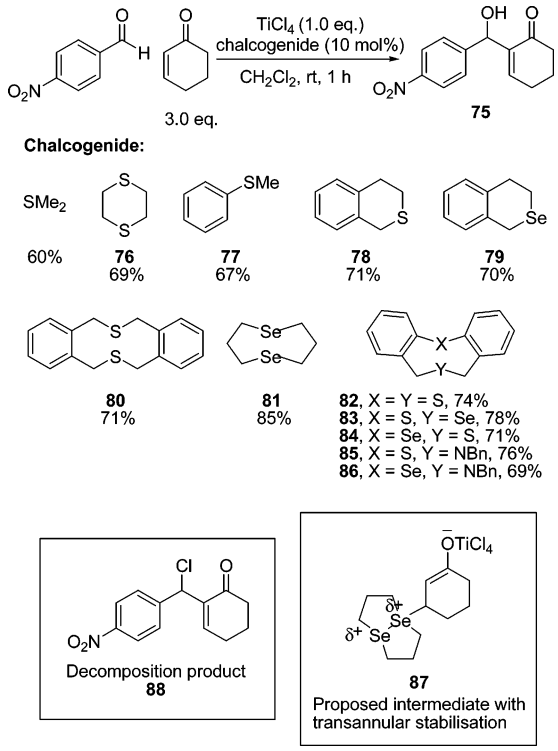
such as enones and enals to participate without complications involving their dimerization (the Rauhut−Currier reaction[127]) or polymerization[128,129] and enable terminal electrophiles other than aldehydes and activated ketones to be used, such as oxonium[130,131] or iminium ions.[132] Using traditional catalysis, the ensuing basic environment facilitates in situ enolization/proton transfer of the intermediate **73** with subsequent expulsion of catalyst from **74** (mechanism outlined in Scheme 56).[133] On the other hand, transformations conducted under Lewis acidic conditions usually require stoichiometric amounts of Lewis base since the analog of intermediate **73**, now stabilized by coordination to the Lewis acid, is unable to undergo efficient enolization or the resultant Lewis acid-stabilized enolate **74** is kinetically stable at ambient conditions. However, release of the Lewis base becomes facile during workup/purification or by treatment of the β-substituted aldol-type precursor with an amine base, typically DBU. Moreover, in many cases where in situ enolization is apparent, dehydration rather than catalyst turnover is the observed consequence, especially when the reaction is conducted at elevated temperatures (>0 °C).[125,128,134,135] The MBH reaction and its Lewis base/Lewis acid variants have been extensively reviewed.[136] This section will focus on those MBH-type transformations involving neutral chalcogenide-centered Lewis bases, but other transformations will be discussed briefly where important comparisons need to be drawn.

7.2. Aldehydes and Activated Ketones as Terminal Electrophiles

7.2.1. $TiCl_4$ and Chalcogenide

In 1998, Kataoka and co-workers reported that substoichiometric amounts of a chalcogenide in the presence of a stoichiometric amount of $TiCl_4$ effected a MBH reaction between a Michael acceptor and an aldehyde; the reactions were conducted at room temperature, and following a saturated aqueous $NaHCO_3$ quench, the MBH adducts were

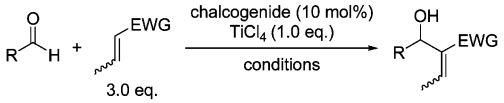
Scheme 57. MBH Reaction Using $TiCl_4$/Chalcogenide as Reagents by Kataoka and co-workers

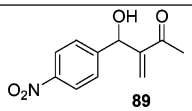
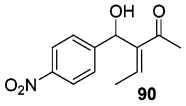
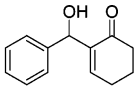
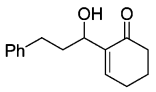
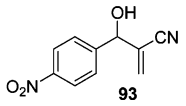
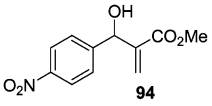
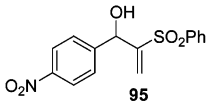


isolated by preparative thin-layer chromatography (TLC).[137,138] The methodology was developed using *p*-nitrobenzaldehyde and 2-cyclohexen-1-one as reactants. When using SMe_2 as the chalcogenide, no reaction was observed in the absence of Lewis acid or even in the presence of BF_3•OEt_2, $SnCl_4$, $ScCl_3$, $Sc(OTf)_3$, $LaCl_3$, $La(OTf)_3$, $SmCl_3$, $Sm(OTf)_3$, $LuCl_3$, $Lu(OTf)_3$, $YbCl_3$, $Yb(OTf)_3$ or $Mg(ClO_4)_2$. MBH adduct **75** was isolated in the presence of a substoichiometric amount of SMe_2 (0.1 equiv) and stoichiometric amounts of $TiCl_4$ (60% yield), $AlCl_3$ (30% yield), $EtAlCl_2$ (13% yield), Et_2AlCl (11% yield), or $HfCl_4$ (15% yield) (Scheme 57). Using $Hf(OTf)_4$, an aldol reaction involving the saturated α-carbon of 2-cyclohexen-1-one was predominant (47% yield). Using substoichiometric amounts of $TiCl_4$ (0.1 equiv) and SMe_2 (0.1 equiv), the yield dropped to 17%; using stoichiometric amounts of both reagents, the yield remained essentially unchanged (62% yield). A library of 11 sulfides and selenides was screened in the reaction between *p*-nitrobenzaldehyde and cyclohexen-1-one, and the yields after 1 h ranged from 60% (SMe_2) to 85% (bisselenide **81**) (Scheme 57). The authors attributed the superiority of **81** to a transannular stabilization of the cationic trivalent selenium center by the second selenium atom (intermediate **87**). The effect of time on the yield of MBH adduct was also examined using SMe_2; the optimum reaction time was found to be ~15 min (70% yield). If the reaction was allowed to proceed further, the yield steadily dropped to ~45% after 12 h. In order to determine the origin of the apparent decomposition, MBH adduct **75** was treated with $TiCl_4$ (3.0 equiv) at room temperature for 1 h. A significant amount (57% conversion) was converted to chloride **88** (Scheme 57).

Kataoka and co-workers also explored the scope of the reaction with respect to Michael acceptor and aldehyde using SMe_2 and bisselenide **81** as Lewis bases. Electron-deficient aldehydes were converted in moderate to good yields (Table 20, entries 1 and 2), while more electron-rich aromatic

Table 20. Scope of Achiral Chalcogenide/$TiCl_4$-Mediated MBH Reaction

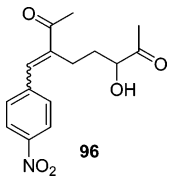


Entry	Chalcogenide	Aldehyde	Alkene	Conditions	Product	%
1	SMe_2	*p*-$NO_2C_6H_4CHO$		rt, 1 h	 **89**	68[a]
2	**81**					70
3	SMe_2	*p*-$NO_2C_6H_4CHO$		rt, 1 h	 **90**	30
4	**81**					29
5	SMe_2	PhCHO		rt, 1 h	 **91**	25
6	**81**					52
7	SMe_2	$PhCH_2CH_2CHO$		reflux, 10 min	 **92**	42
8	**81**					55
9	SMe_2	*p*-$NO_2C_6H_4CHO$		reflux, 24 h	 **93**	88
10	SMe_2	*p*-$NO_2C_6H_4CHO$		rt, 2 min	 **94**	49
11	**81**					14
12	SMe_2	*p*-$NO_2C_6H_4CHO$		rt, 50 h	 **95**	28

[a] A small amount of side product **96** was also isolated.

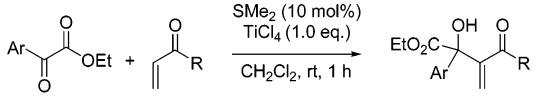
[a] A small amount of side product **96** was also isolated.

aldehydes resulted in poor isolated yields (Table 20, entries 5 and 6). A single example of an enolizable aliphatic aldehyde gave a moderate yield of its corresponding MBH adduct **92** (Table 20, entries 7 and 8). With respect to the Michael acceptor, enones gave good yields (Table 20, entries 1−8), with the exception being the acyclic β-substituted enone, (*E*)-3-penten-2-one (Table 20, entries 3 and 4), which gave a ~30% yield of the desired adduct **90**. Additionally, in the reaction of methyl vinyl ketone (MVK), a side product **96** was also isolated in 11−15% yield; the authors proposed that it resulted from a sequence of transformations beginning with an acid-catalyzed hetero-Diels−Alder reaction between the MBH-adduct of methyl vinyl ketone **89** and MVK. With further optimization of conditions, they were able to achieve the coupling of *p*-nitrobenzaldehyde with more demanding Michael acceptors (Table 20, entries 9−12), such as acrylonitrile, methyl acrylate and phenyl vinyl sulfone. The optimum chalcogenide varied with substrate.



96

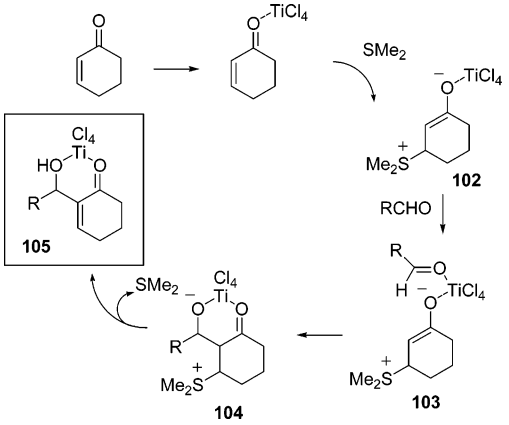
Scheme 58. α-Ketoesters as Terminal Electrophiles Using the Reagents $TiCl_4/SMe_2$



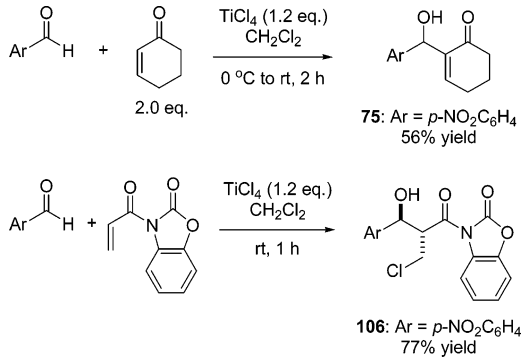
97: R = Me, Ar = C_6H_5, 73%
98: R = Me, Ar = $C_{10}H_7$, 43%
99: R = Et, Ar = C_6H_5, 40%
100: R = Me, Ar = *p*-$MeOC_6H_4$, 64%
101: R = Me, Ar = *p*-MeC_6H_4, 51%

Basavaiah and co-workers used Kataoka and co-workers' conditions ($TiCl_4/SMe_2$) to access MBH adducts **97**−**101** using nonenolizable α-ketoesters as terminal electrophiles and methyl vinyl ketone or ethyl vinyl ketone as Michael acceptors (Scheme 58).[139] Yields ranged from 40−73%, but attempts to expand the methodology to enolizable α-ketoesters such as ethyl pyruvate were unsuccessful. Using Kataoka and co-workers' conditions, Bauer and Tarasiuk obtained moderate yields of the MBH adducts of 2-cyclo-

Scheme 59. Proposed Mechanism for the $TiCl_4$/Chalcogenide-Mediated MBH Reaction



Scheme 60. Li and co-workers' Synthesis of MBH Adducts Using $TiCl_4$ Alone



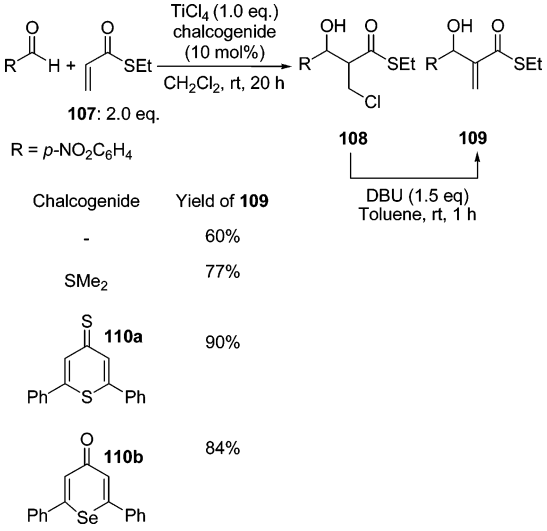
hexen-1-one and (−)-menthyl and (−)-8-phenylmenthyl glyoxylate in 54:45 and >97.5:2.5 dr, respectively.[140] Attempts to extend the methodology to methyl acrylate were unsuccessful.

Kataoka and co-workers proposed a mechanism (Scheme 59) that involved initial generation of a β-sulfonium-$TiCl_4$-stabilized enolate **102** by conjugate addition of SMe_2 to the $TiCl_4$-activated Michael acceptor.[137] Coordination of the aldehyde to the metal center of **102** is followed by C−C bond formation to give the $TiCl_4$-stabilized alkoxide **104**. They then proposed an in situ enolization and expulsion of the sulfide to form the MBH-adduct **105**, coordinated via its oxygen atoms to $TiCl_4$, the stability of which they assume accounts for the requirement of the stoichiometric amount of Lewis acid.

In 2000, the role and importance of chalcogenides in the conditions developed by Kataoka and co-workers was brought into question when Li and co-workers reported that treating a solution of a Michael acceptor, specifically a cyclic enone and an aldehyde with $TiCl_4$ alone, resulted in the isolation of MBH adducts (Scheme 60).[124] When *N*-acryloyloxazolidinones were employed as Michael acceptors, the β-chloroaldol adducts **106** were isolated after aqueous workup; a method to effect dehydrochlorination to the MBH adduct was not reported. The authors proposed a mechanism, similar to that outlined in Scheme 59, where a chloride ion acts as the nucleophilic catalyst.

Despite Li and co-workers' report, evidence for the chalcogenide's involvement in some way under Kataoka and co-workers' conditions is compelling. For example, Kataoka and co-workers have shown that acrylates and acrylonitrile can participate readily using the $TiCl_4$/sulfide methodology

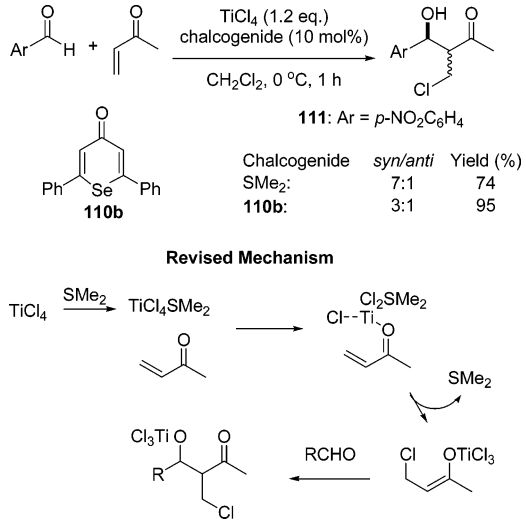
Scheme 61. α,β-Unsaturated Thioesters as Michael Acceptors in the $TiCl_4$/Chalcogenide MBH Reaction



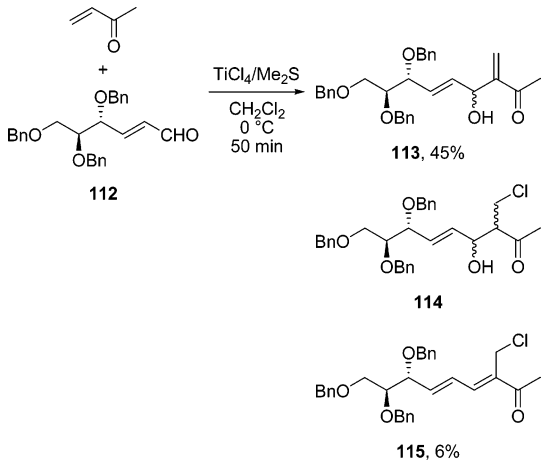
(Table 20).[137] Such relatively unreactive Michael acceptors have not been shown to participate using $TiCl_4$ alone. In a later publication, Kataoka and co-workers expanded the scope of the methodology to include α,β-unsaturated thioesters **107**.[141] Reactions in the presence of 10 mol % of SMe_2, sulfide **110a**, or selenide **110b** were superior to those without (Scheme 61). Other aldehydes, including more electron-rich aromatic aldehydes and enolizable aliphatic aldehydes, gave yields above 50%. The dehydrochlorination step was also examined in detail: Et_2NH was found to be as effective as DBU. Treatment with $Ti(OiPr)_4$ was effective and also brought about a transesterification to the isopropyl ester but with the added consequence of released thiolate recombining with product through 1,4-addition. However, in the presence of iodomethane, such 1,4-additions were suppressed, presumably through efficient methylation of thiolate.

Although it is clear that the addition of chalcogenide is important for the success of those reactions involving relatively unreactive Michael acceptors, its importance in those transformations involving enones is considerably less clear. However, Kataoka and co-workers provided evidence that the chalcogenide is not an innocent spectator in such transformations. In response to Li and co-workers' research, Kataoka and co-workers reported that the β-chloro derivatives of the MVK-derived MBH adduct **111** can be isolated using the conditions developed in their laboratory [$TiCl_4$ (1.0 equiv), chalcogenide (10 mol %)] and explained that previous failure to observe them was due to their method of purification where column chromatography, as used by Li and co-workers, allowed their isolation but preparative TLC did not (Scheme 62).[142] The diastereomeric composition (syn/anti) of β-chloro adducts **111** was dependent upon the chalcogenide used. For example, when SMe_2 or **110b** was used, **111** was isolated as a diastereomeric mixture favoring the *syn*-isomer, with the ratios being 7:1 and 3:1, respectively (the ratio in the absence of chalcogenide was not reported). Although they suggested that the chalcogenide may still function as a nucleophilic catalyst (with the resulting β-sulfonium aldol adducts undergoing in situ enolization, retro-Michael addition of chalcogenide, and subsequent hydrochlorination), their failure to isolate intermediates to support such a claim forced them to consider an alternative role for the Lewis base. They suggested that the chalcogenide may coordinate to the titanium center and alter its Lewis

Scheme 62. Kataoka and co-workers' Isolation of *β*-Chloroaldol Adducts Using $TiCl_4$ and Chalcogenide and Revised Mechanism



Scheme 63. MBH Reaction of an Acyclic Carbohydrate Derivative

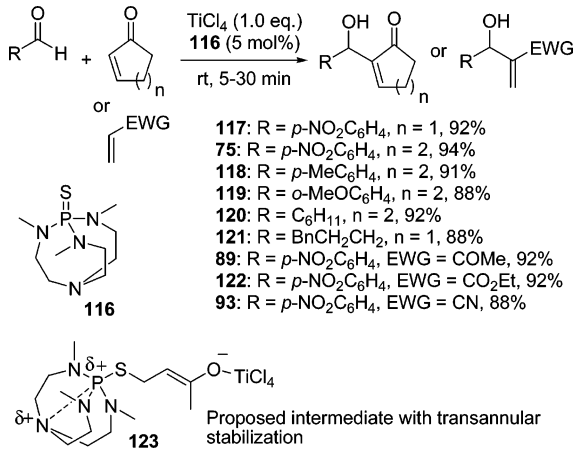


acidity and the availability of chloride for conjugate addition (Scheme 62). Solutions of $TiCl_4$ in $CDCl_3$ turned a reddish-brown color upon addition of chalcogenide; indeed, complexes of $TiCl_4$ and chalcogenides have been isolated and characterized.[143]

Shaw and co-workers used MVK and carbohydrate-derived α,*β*-unsaturated aldehydes such as **112** to obtain the MBH adduct **113** as well as small amounts of *β*-chloroaldol adducts such as **114** and **115** (Scheme 63); after 15 min, the major product was **114**, but after 50 min, **113** was isolated in 45% yield.[128] Dehydrochlorination of the *β*-chloroaldol adducts could be effected by DBU.

This chalcogenide-mediated enhancement of reactivity was emphasized further by a report from Verkade and co-workers, who described that $TiCl_4$ in the presence of a substoichiometric amount of proazaphosphatrane sulfide **116** were exceptional conditions, allowing the isolation of MBH adducts derived from methyl acrylate in short reaction times and in high yield (Scheme 64).[144] Interestingly, considering the fact that Kataoka and co-workers had demonstrated that *β*-chloro adducts derived from ketones were isolable by column chromatography, the assumed *β*-(chloro or sulfonium) aldol-type precursors to MBH adducts derived from methyl acrylate (akin to **111**, Scheme 62) were not detected

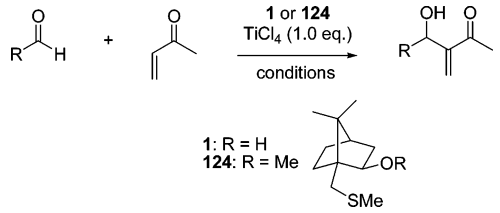
Scheme 64. Verkade and co-workers' Synthesis of MBH Adducts Using $TiCl_4$ and a Proazaphosphatrane Sulfide



in this case. One would expect such adducts to be less prone to enolization. The MBH adducts were isolated by column chromatography following an aqueous workup. Apparently, the presence of this particular Lewis base greatly facilitates the enolization of such precursors, a peculiarity not addressed by Verkade. Their discussion of mechanism was limited to the suggestion that the superiority of the Lewis base **116** over others originates from a transannular interaction between the tertiary amino group and the developing phosphonium ion, thus increasing the rate of formation of the *O*-titanium enolate (**123**, Scheme 64). Using $BF_3{\cdot}OEt_2$ as the Lewis acid (a reagent that is unable to effect a MBH reaction alone) and a substoichiometric amount of **116**, the MBH adduct **75** was obtained in 50% yield. Verkade and co-workers concluded that the apparent role of **116** as a nucleophilic catalyst under these conditions gave credence to an equivalent role in conditions with $TiCl_4$ as the Lewis acid.

Shi et al. reported that $TiCl_4$-catalyzed MBH reactions were superior in the presence of substoichiometric amounts of ethers and other Lewis basic oxygen additives such as alcohols, ketones, and triphenylphosphine oxide. They reported that while no MBH reaction (*p*-nitrobenzaldehyde and methyl vinyl ketone) occurred at −78 °C using $TiCl_4$ alone (1.4 equiv), a 30% yield of MBH adduct was obtained in the presence of 0.2 equiv of MeOH.[145] However, it should be noted that no such control experiments were conducted at higher temperatures, which encompasses most of the examples in Shi et al.'s work, and that Goodman and co-workers have reported that the same reaction devoid of any additive is facile even at −90 °C.[146] With some additives, *β*-chloro adducts analogous to **114** and **115** were also isolated. Shi et al. found that the preformed complexes $TiCl_4(THF)_2$ or $TiCl_4(OEt_2)_2$ were exceptional reagents, giving near quantitative yields of MBH adduct at −78 °C when using *p*-nitrobenzaldehyde and MVK as substrates. For more electron-rich aldehydes, dehydration rather than dehydrochlorination of the intermediate *β*-chloro-MBH adducts predominated. They proposed that association of the oxygen-based additives with the titanium metal facilitated a chloride ion displacement and subsequent Michael addition to the enone. The use of chiral oxygen-based additives gave MBH adducts of very low enantiopurity (<5%). They proposed that this was due to the chloroenolate being bound to the titanium center through a nonspecific ionic interaction and, thus, not being significantly influenced by the chiral environment in its reaction with aldehyde.

Table 21. Enantioselective MBH Reaction Using $TiCl_4$/Chiral Chalcogenide



entry	sulfide (mol %)	aldehyde	temp (°C) (time (h))	yield (%)	ee % (config.)
1	**1** (10)	*p*-nitrobenzaldehyde	−20 (1)	95	2 (*R*)
2	**124** (10)	*p*-nitrobenzaldehyde	−20 (1)	97	1 (*R*)
3	**1** (100)	*p*-nitrobenzaldehyde	−20 (1)	27	44 (*R*)
4	**124** (100)	*p*-nitrobenzaldehyde	−20 (1)	41	6 (*R*)
5	**1** (100)	*p*-nitrobenzaldehyde	−78 (1)	26	71 (*R*)
6	**1** (100)	*p*-nitrobenzaldehyde	−78 (24)	17	69 (*R*)
7	**1** (100)	*p*-chlorobenzaldehyde	−78 (1)	22	40
8	**1** (100)	3-pyridinecarboxaldehyde	−78 (1)	31	29
9	**1** (100)	4-pyridinecarboxaldehyde	−78 (1)	35	14
10	**1** (100)	3-phenylpropionaldehyde	−78 (1)	43	74

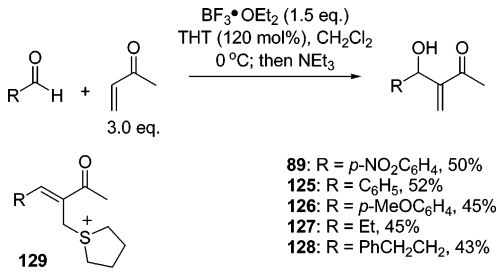
Kataoka and co-workers reported an enantioselective variant of the $TiCl_4$/chalcogenide-mediated MBH reaction using enantiomerically pure chiral hydroxy chalcogenides.[147] Using 10 mol % of **1** and conducting the reaction (*p*-nitrobenzaldehyde and MVK) at −20 °C, the MBH adduct **89** was isolated in 95% yield but was found to be essentially racemic (Table 21, entry 1). By using stoichiometric amounts of **1**, an ee of 44% was obtained, although the yield was dramatically reduced (Table 21, entry 3). The authors attributed the reduction in yield to the formation of titanium alkoxides with **1**, species of much lower Lewis acidity. However, the similar reduction in yield using the methyl ether derivative **124** suggests that other inhibitory processes are in operation (Table 21, entries 2 and 4). Conducting the reaction at −78 °C led to a further increase in ee (71%) but no improvement in yield (Table 21, entry 5); longer reaction times did not lead to an increase in yield either (Table 21, entry 6). Using the optimum conditions with respect to enantioselectivity (Table 21, entry 5), it was found that the ee was strongly dependent upon the nature of the aldehyde. For example, the use of *p*-chlorobenzaldehyde, 3-pyridinecarboxaldehyde, 4-pyridinecarboxaldehyde, and 3-phenylpropionaldehyde gave the corresponding adducts in 40%, 29%, 14% and 74% ee, respectively, but yields remained low (Table 21, entries 7−10). Although it is generally believed that the chalcogenide interacts with $TiCl_4$, thereby promoting the formation of the β-chlorotitanium enolate (Scheme 62), the mechanism involving **1** may be different. In this case, the alcohol is likely to bind to titanium and the tethered sulfide may perform the role of nucleophilic catalyst. The organized, cyclic intermediate could give rise to the high levels of selectivity observed.

7.2.2. BX_3 (X = F, Cl, Br) and Chalcogenide

In 2002, Goodman and co-workers reported that $BF_3{\cdot}OEt_2$ (1.5 equiv) in combination with tetrahydrothiophene (THT) (1.2 equiv) as the Lewis base represented moderately effective MBH conditions when MVK was employed as the Michael acceptor (Scheme 65).[146] The reaction was quenched with NEt_3 in order to effect enolization with concomitant release of sulfide. If, on the other hand, the reaction was quenched with aqueous acid, the allyl sulfonium salt **129** was isolated, thus providing compelling evidence to support the hypothesis that, in this case, sulfide functions as a nucleophilic catalyst; the reaction devoid of sulfide was unsuccessful. The use of the more challenging enone, cyclohexenone, as the Michael acceptor gave the corresponding MBH adduct in low yield (11%). In an earlier report, Kataoka and co-workers had shown that $BBr_3{\cdot}SMe_2$ or $BCl_3{\cdot}SMe_2$ could also effect MBH-type transformations.[125] Quenching the reactions with H_2O, rather than NMe_3 (which led to MBH adducts), allowed the isolation of β-bromo or β-chloro adducts akin to **129**, suggesting that, in these cases, chalcogenide may not function as a nucleophilic catalyst. Interestingly, in comparison to Goodman and co-workers' $BF_3{\cdot}OEt_2$/THT conditions, the scope of the Michael acceptor was much broader with $BCl_3{\cdot}SMe_2$ or $BBr_3{\cdot}SMe_2$, where MBH adducts derived from cyclic enones, methyl acrylate, and α,β-unsaturated thioesters could be isolated. Presumably, the increased reactivity has its origins in the superior Lewis acidity of BBr_3 and BCl_3 over BF_3,[148] and, in the latter case, the formation of enolate requires an entropically more demanding encounter of the BF_3-activated Michael acceptor with chalcogenide. For the former cases, intramolecular delivery of bromide or chloride following coordination of the respective Lewis acid to Michael acceptor may be faster than nucleophilic attack of sulfide. An intramolecular delivery of halide to an activated cyclic enone is difficult to envisage owing to its ring-constrained *s-trans* conformation, and an intermolecular delivery has been proposed.[124] It should be noted that for cyclic enones the presumed β-halogen aldol adducts have not been isolated or observed. Although not mentioned by the authors, it is also possible that SMe_2 undergoes conjugate addition to BBr_3 or BCl_3-activated enone, only to be displaced by bromide or chloride in a subsequent transformation.[128]

Using the C_2-symmetric sulfide **10** at −78 °C, Goodman and co-workers isolated MBH adducts with ees ranging from

Scheme 65. Goodman and co-workers' Synthesis of MBH Adducts Using $BF_3{\cdot}OEt_2$/THT



Scheme 66. Goodman and co-workers' Enantioselective Synthesis of MBH Adducts Using BF_3·OEt_2/Chiral Sulfide

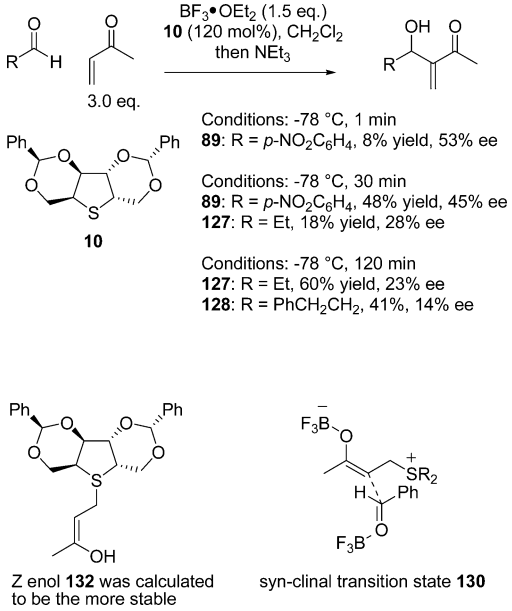
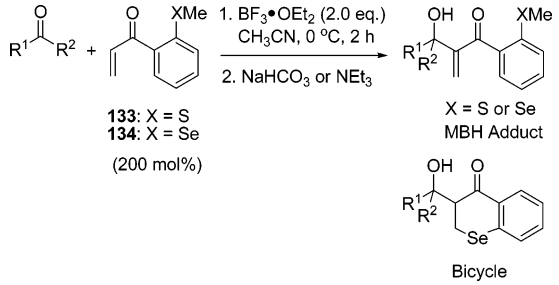


Table 22. Kataoka and co-workers' Synthesis of MBH Adducts Using Pendent Chalcogenides



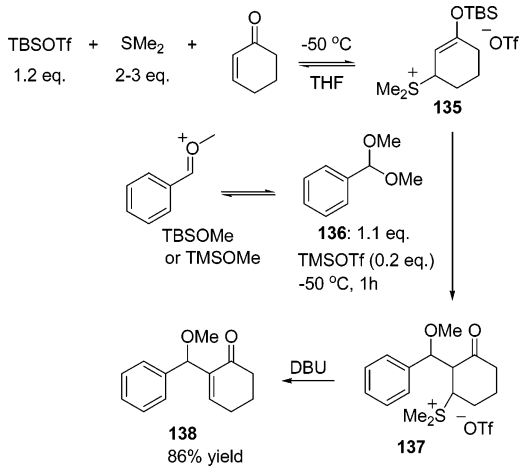
entry	Michael acceptor	terminal electrophile	yield % MBH adduct
1	**133**	*p*-nitrobenzaldehyde	75
2	**134**	*p*-nitrobenzaldehyde	75[a]
3	**133**	$R^1 = PhCH_2CH_2$, $R^2 = H$	70[b]
4	**133**	$R^1 = p\text{-}NO_2C_6H_4$, $R^2 = Me$	47
5	**134**	$R^1 = p\text{-}NO_2C_6H_4$, $R^2 = Me$	50
6	**133**	$R^1, R^2 = (CH_2)_5$	56
7	**133**	$R^1 = COPh$, $R^2 = Ph$	41
8	**134**	$R^1 = COPh$, $R^2 = Ph$	4
9	**133**	$R^1 = CO_2Et$, $R^2 = Me$	70[c]
10	**133**	$R^1 = CO_2Me$, $R^2 = Ph$	37[c]

[a] Selenobicycle (16%) also isolated. [b] Allowed to warm to rt (3 h). [c] rt, 2 h.

14 to 53% (Scheme 66).[146] With the support of computational data, the authors proposed that the major enantiomer originates from the open transition state **130**. Interestingly, there was a slight drop in ee at higher conversions (Scheme 66, see **89** isolated after 1 min and after 30 min reaction time) which suggests a slow racemization pathway.

In 2003, Kataoka reported a BF_3·OEt_2-catalyzed MBH reaction using phenyl vinyl ketones **133** or **134** as Michael acceptors and aldehydes, ketones, α-diketones, or α-ketoesters as terminal electrophiles. In these cases, the nucleophilic catalyst, either a sulfide or a selenide, was appended to the Michael acceptor, specifically on the phenyl substituent ortho to the keto substituent (Table 22).[149] NMR studies confirmed an intramolecular Michael addition of the sulfide

Scheme 67. Kim and co-workers' MBH-type Reaction with Oxonium Ions as Electrophiles Using TBSOTF/SMe_2



moiety in the presence of BF_3·OEt_2 to give a cyclic BF_2-stabilized enolate. It was proposed that the initial species formed was a BF_3-stabilized species, which subsequently transferred a fluoride ligand to a second equiv of BF_3. The use of **133** and an aldehyde in the presence of BF_3·OEt_2, followed by a NEt_3-based workup, gave good yields of the MBH adduct (Table 22, entries 1 and 3). If a neutral workup was employed, the intermediate sulfonium salt could be isolated as a 1:1 mixture of diastereomers. The use of the selenide substrate **134** gave a less clean reaction; although the MBH adduct was isolated in good yield, a product resulting from an apparent demethylation of the intermediate selenonium ion was also isolated (Table 22, entry 2). The use of acyclic or cyclic ketones (entries 4−6) or α-diketones (entries 7 and 8) as the terminal electrophile gave poor to moderate yields of the corresponding MBH adducts. The use of α-ketoesters gave poor to good yields; interestingly, enolizable rather than nonenolizable α-ketoesters were superior substrates (entries 9 vs 10).

7.3. Oxonium and Iminium Ions as Terminal Electrophiles

In 1993, Kim and co-workers reported that β-sulfonium silyl enol ethers could be generated at low temperature (−78 °C) by treating the corresponding enone or enal with TBSOTf and SMe_2 (Scheme 67).[130] It was found that SPh_2 was unable to undergo such a transformation, presumably because of its weaker nucleophilicity. Variable temperature NMR experiments in deuterated THF showed that, while the silyl enol ethers were thermodynamically stable at −40 °C, at higher temperatures (−20 °C) the position of the equilibrium lay predominantly on the side of starting material (i.e., enone, SMe_2, and TBSOTf).[131,150] A MBH-type reaction was performed by preforming the β-sulfonium silyl enol ether of cyclohexenone **135** at low temperature and then adding acetal **136** (a precursor to an oxonium species) and a substoichiometric amount of TMSOTf. The resulting β-sulfonium β-OMe-MBH adduct **137** was treated with DBU to give the *O*-methylated MBH-adduct **138** (Scheme 67). An earlier publication demonstrated that a similar transformation could be effected using pyridine as the Lewis base.[151]

In 2003, Kataoka and co-workers used phenyl vinyl ketones with pendent sulfide **133** or selenide **134** as Michael acceptors and acetals or ortho esters as the terminal electrophile in a BF_3·OEt_2-catalyzed synthesis of MBH-type

Scheme 68. Kataoka and co-workers' MBH Reaction of Acetals with Michael Acceptors Containing Pendent Chalcogenides

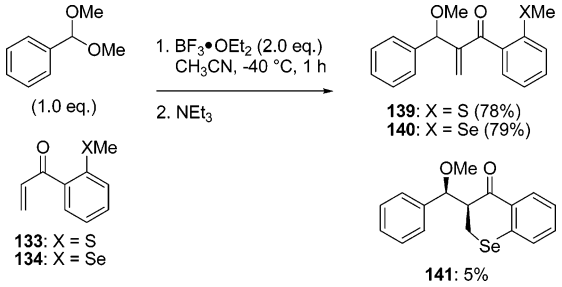
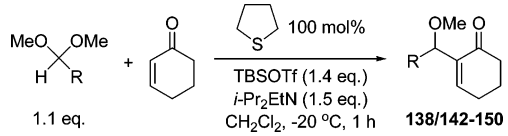


Table 23. Metzner and co-workers' MBH-Type Reaction with Oxonium Ions as Electrophiles Using TBSOTF/SMe$_2$



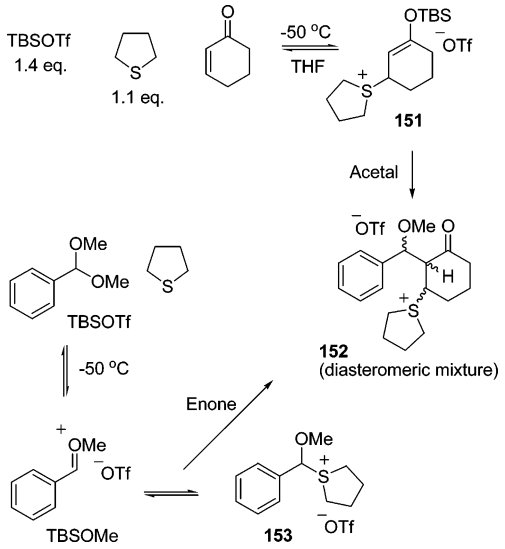
entry	R	product	yield (%)
1	Ph	**138**	80
2	4-MeC_6H_4	**142**	66
3	4-ClC_6H_4	**143**	66
4	4-FC_6H_4	**144**	83
5	4-$CF_3C_6H_4$	**145**	33 (65)[a]
6	4-MeOC_6H_4	**146**	26 (39)[a]
7	2-MeC_6H_4	**147**	45[a]
8	2-MeOC_6H_4	**148**	21[a]
9	(*E*)-PhCH=CH	**149**	64[a]
10	$PhCH_2CH_2$	**150**	none detected

[a] −50 °C for 6 h.

adducts (Scheme 68).[135] As described earlier in this review, Kataoka and co-workers published a similar work using carbonyl based terminal electrophiles (Table 22).[149] Treating **133**, benzaldehyde dimethyl acetal, in CH_3CN with BF_3•OEt_2 (2 equiv) at −40 °C for 1 h followed by a NEt_3-based workup, provided good yields of the methylated MBH adduct **139**. The seleno substrate **134** gave similarly good yields, but a product **141** derived from demethylation of the intermediate selenonium ion was also isolated. It should be noted that this chemistry and the aforementioned work of Kim and co-workers is reminiscent of earlier work by Noyori and co-workers, who generated neutral β-seleno silyl enol ethers by treating enones with TMSSePh and subsequently trapping them with oxonium ions; an oxidative workup provided MBH-type adducts of the type under discussion.[152]

In 2006, Metzner and co-workers reported a modification of Kim and co-workers' procedure, which allowed an in situ enolization of the β-sulfonium-β'-OMe intermediate akin to **137**, thus giving the MBH-type adducts directly following an aqueous quench.[131] They found that the treatment of close to equimolar amounts of enone and acetal (1.1 equiv) with TBSOTf (1.4 equiv), THT (1.1 equiv), and Hünig's base (1.5 equiv) in CH_2Cl_2 for 1 h at −20 °C gave optimum yields of the methylated MBH adduct (Table 23). The reaction could also be conducted at lower temperatures, −40 to −50 °C, but the lower rates required longer reaction times (∼6 h); no reaction was observed at −78 °C, and decomposition was observed if the reaction was conducted at 0 °C. It was also found that the success of the reaction was dependent upon the addition of Hünig's base as the final reagent to the reaction mixture. However, the authors confirmed that

Scheme 69. Metzner and co-workers' Investigation of Intermediates in a MBH-type Reaction Effected by TBSOTF/SMe$_2$

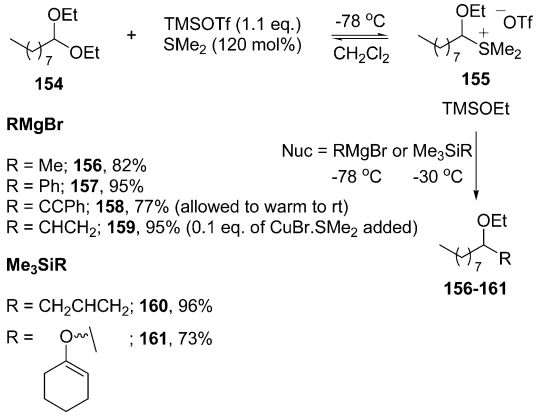


Hünig's base and TBSOTf were unable to effect a MBH-type transformation in the absence of THT. The yield was dependent upon the acetal. Generally, while electron-neutral and electron-poor aromatic acetals gave moderate to good yields (45−80%), the use of electron-rich substrates resulted in poor yields. Interestingly, the electron-poor (entry 5) and the electron-rich (entry 6) aromatic acetals gave poor yields using the optimized conditions (33% and 26%, respectively) but the yields were improved to 65% and 39%, respectively, by conducting the reactions at −50 °C for 6 h. Aliphatic acetals failed to undergo the MBH-type reaction; the propensity for the corresponding oxonium ions to undergo enolization may be an important consideration. Cyclic enones were better substrates than the acyclic substrate MVK: using benzaldehyde dimethyl acetal, the yields were 80% (cyclohexenone) and 55% (MVK).

In a further step toward the goal of an enantioselective variant using substoichiometric amounts of chiral sulfide, experiments using 20 mol % of THT were conducted in order to confirm catalyst turnover. However, when the reaction was conducted using the optimized conditions, the MBH adduct was isolated in 21% yield, suggesting no turnover of sulfide. When the reaction was conducted at −40 °C for 6 h with 1.0 equiv of Hünig's base (rather than 1.5 equiv), a 42% yield of MBH adduct was obtained, suggesting an apparent, albeit inefficient, turnover of catalyst. Although the lack of turnover at −20 °C was not commented upon, it may be that, at this temperature, the rate of enolization is too slow to compete with other processes consuming reactants.

The reaction (stoichiometric in sulfide) was also studied using ^{1}H NMR (Scheme 69). Similar to Kim et al.'s earlier findings,[130] Metzner and co-workers confirmed that a mixture of enone, THT, and TBSOTf in CD_2Cl_2 rapidly forms the β-sulfonium silyl enol ether **151** at low temperatures; the ratio of silyl enol ether to enone was 61:39 at −50 °C, while at −20 °C, only traces of silyl enol ether were detected. In a separate experiment, it was found that a mixture of acetal, THT, and TBSOTf rapidly forms the sulfonium species **153**. By adding the remaining reagent, acetal or enone, respectively, to the aforementioned NMR experiments, identical ^{1}H NMR spectra were produced, with signals corresponding

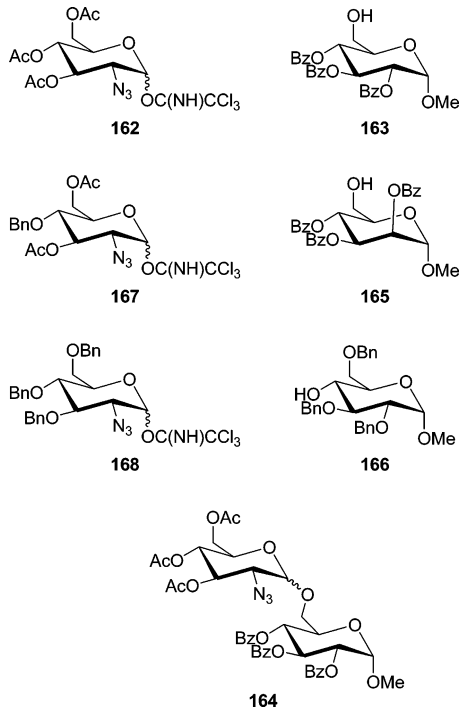
Scheme 70. Kim and co-workers' Generation of 1,2-Sulfonium Species and Their Reaction with Nucleophiles



to diastereomeric mixtures of β-sulfonium aldol adduct **152**. The importance of the 1,2-adduct **153** to the success of the reaction is unclear (Scheme 69).

In 1993, Kim and co-workers introduced, for the first time, 1,2-sulfonium adducts similar to **153** by treating aliphatic diethyl acetal **154** with TMSOTf and SMe_2 at −78 °C (Scheme 70).[153] The resulting solution was then treated with a range of Grignard and silicon-based reagents to give the adducts **156**−**161**. Although, the authors did not discuss mechanism, there are a number of possibilities: (a) direct displacement of sulfide with the nucleophile (i.e., an S_N2-type process); (b) the oxonium ion, in equilibrium with the 1,2 sulfonium adduct, is the pertinent electrophile (an S_N1-type process); or (c) a mechanism containing both S_N1 and S_N2 elements where Lewis acidic moieties on the nucleophile assist in the expulsion of sulfide. The authors did not report the results of the reaction in the absence of SMe_2.

Good evidence to support the importance of 1,2-sulfonium intermediates and their subsequent reaction in S_N2-type displacement reactions, as described previously, has recently come to light. Boons and co-workers demonstrated that the selectivity for the 1,2-cis product (or α-anomer) in glycosylation reactions between 2′-azido-2′-deoxyglucosyl trichloroacetimidate donors and a range of glucosyl acceptors was increased in the presence of a large excess of phenyl ethyl sulfide or thiophene (Table 24).[154] For example when the glycosylation reaction between donor **162** and acceptor **163** was conducted at −78 °C, in the presence of 10 mol % of TMSOTf, the disaccharide **164** was obtained in 91% yield with an α/β ratio of 2:1. In the presence of sulfide (10 equiv),



the anomeric ratio was improved to 5:1, but with a slight reduction in yield (83%). Interestingly, when the reactions (in the absence or presence of sulfide) were conducted at 0 °C, the selectivities were much improved, 8:1 (92%) and 20:1 (94%), respectively. Additionally, the replacement of phenyl ethyl sulfide with thiophene led to the exclusive formation of the α-anomer in 91% yield. A similar effect was observed with glycosyl acceptor **165**, with the conditions including a 10-fold excess of thiophene at an operating temperature of 0 °C being superior. As expected, the α/β ratio is highly dependent upon the glycosyl acceptor; for example, acceptor **166** gave only the α-anomer under all conditions, including those devoid of sulfide. Variation of the 2-azido donor was also important, while the use of 4′-*O*-benzyl donor **167** (remaining hydroxyl groups acetylated) gave significant improvements in α-selectivity in the presence of sulfide; the use of the per-*O*-benzylated donor **168** gave little or no improvement (Table 24). The authors did not provide examples using donors with other seemingly nonparticipatory substituents, besides the azido group, at the 2′-position.

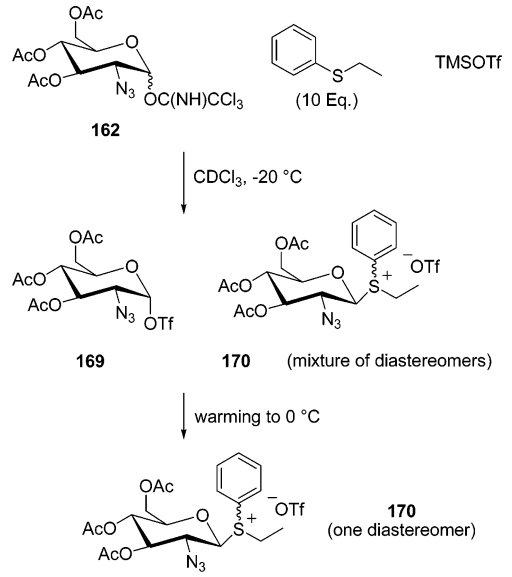
In order to understand the effect of sulfide, mixtures of donor **162** in the presence of TMSOTf (1 equiv) and phenyl ethyl sulfide (10 equiv) were analyzed by ^1H NMR spectroscopy (Scheme 71). At −20 °C, ionization of the trichloroacetimidate had occurred, resulting in the formation of three new species, the α-anomeric triflate **169** and two diastereomeric β-anomeric sulfonium species **170** (epimeric at sulfur). Upon warming to 0 °C, the triflate **169** and one of the diastereomeric sulfonium species were no longer detected, with the remaining β-anomeric sulfonium species now dominating the spectrum. Computational studies suggested that the absence of an α-sulfonium species was due to steric rather than stereoelectronic effects. The authors suggested that the selectivity for the α-anomeric disaccharide product originated from an S_N2 reaction between the β-anomeric sulfonium species **170** and the glycosyl acceptor.

Table 24. Boons and co-workers' Formation of Disaccharides with High α-Selectivities in the Presence of Sulfide

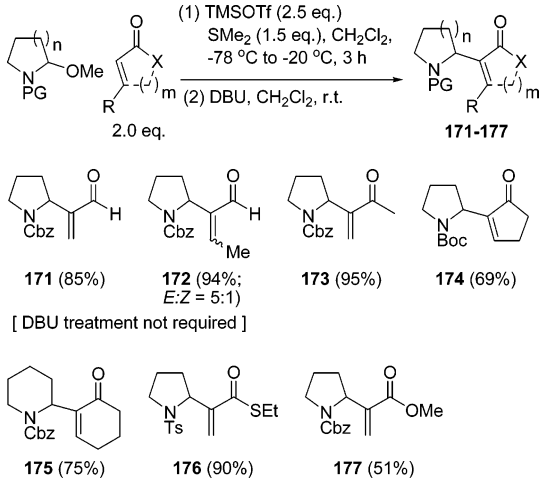
donor + acceptor —TMSOTf (0.1 eq.), sulfide (10 eq.), CH_2Cl_2, temp.→ disaccharide

entry	donor	acceptor	sufide	T (°C)	yield (%)	α/β
1	**162**	**163**	none	−78	91	2:1
2	**162**	**163**	PhSEt	−78	83	5:1
3	**162**	**163**	none	0	92	8:1
4	**162**	**163**	PhSEt	0	94	20:1
5	**162**	**163**	thiophene	0	91	α only
6	**162**	**165**	none	0	85	10:1
7	**162**	**165**	thiophene	0	95	18:1
8	**162**	**166**	none	0	40	α only
9	**162**	**166**	thiophene	0	43	α only
10	**167**	**163**	none	0	90	12:1
11	**167**	**163**	thiophene	0	93	20:1
12	**168**	**163**	none	0	80	3:1
13	**168**	**163**	thiophene	0	82	3:1

Scheme 71. Boons and co-worker's Detection of a β-Anomeric Sulfonium Salt 170



Scheme 72. Aggarwal and co-workers' MBH-type Reaction with Iminium Ions as Electrophiles Using TMSOTF/SMe_2



Recently, Aggarwal and co-workers showed that cyclic *N*-acyliminium ions, generated in situ from the corresponding *N*,*O*-acetals, are compatible terminal electrophiles in a TMSOTf/sulfide mediated MBH-type reaction (Scheme 72).[132] Pyrrolidine or piperidine based *N*,*O*-acetals were combined with a wide range of Michael acceptors, including enones (both cyclic and acyclic), enals (acrolein and crotonaldehyde), and α,β-unsaturated thioesters, to give the corresponding adducts **171**−**177** in good yield. The optimum conditions involved the treatment of a solution of the *N*,*O*-acetal and Michael acceptor (2 equiv) in CH_2Cl_2 with TMSOTf (2.5 equiv) and SMe_2 (1.5 equiv) at an initial temperature of −78 °C and a subsequent warming to −20 °C or room temperature (in the case of *N*-tosyl-*N*,*O*-acetals); following an aqueous quench, the crude material was treated with DBU in order to effect quantitative expulsion of sulfide from the β-sulfonium Mannich product; in the case of enals, the saturated $NaHCO_3$ quench was sufficient. The use of the more challenging Michael acceptor, methyl acrylate, required a longer reaction time at −20 °C and was only moderately successful, providing the MBH-type adduct in 50% yield; competitive dimerization of the *N*,*O*-acetal accounted for the fate of the remaining substrate. The superiority of sulfide as the Lewis base in these conditions compared to PPh_3 or pyridine was also demonstrated; the former led to the formation of a stable phosphine−iminium ion adduct, while the latter promoted formation of enamide, via deprotonation of the iminium ion. Presumably, the formation of a sulfide−iminium ion adduct is also occurring under these conditions but is kinetically unstable with respect to iminium ion at the operating temperature. Considering the previous discussion on such 1,2-sulfonium adducts, it cannot be ruled out that such an equilibrium contributes to the success of the reaction.

Scheme 73. Aggarwal and co-workers' Synthesis of (+)-Heliotridine Employing a Key MBH-type Cyclization

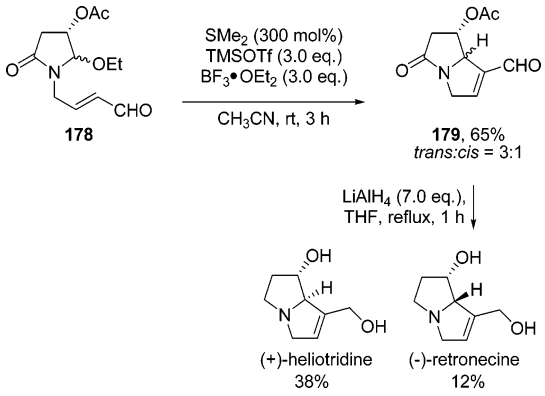
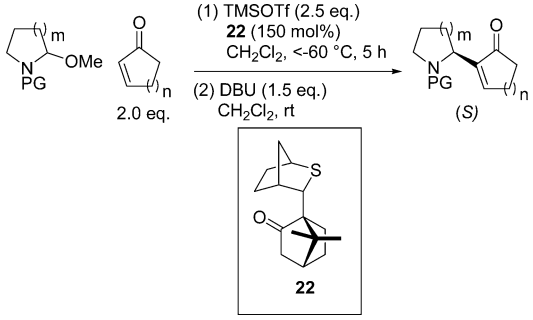


Table 25. Aggarwal and co-workers' Asymmetric MBH-Type Reaction with Iminium Ions Using TMSOTF/Chiral Sulfide 22

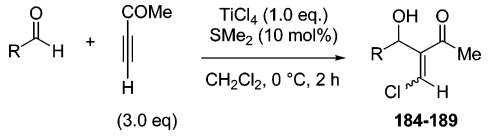


entry	acetal	enone	product	yield (%)	ee (%)
1	PG = Cbz, $m = 1$	$n = 1$	**180**	69	82
2	PG = Cbz, $m = 1$	$n = 2$	**181**	86	80
3	PG = Boc, $m = 1$	$n = 1$	**174**	75	88
4	PG = Boc, $m = 1$	$n = 2$	**182**	90	88
5	PG = Cbz, $m = 2$	$n = 1$	**183**	88	94
6	PG = Cbz, $m = 2$	$n = 2$	**175**	49	98

Aggarwal and co-workers applied the methodology to a short synthesis of (+)-heliotridine (Scheme 73). Intramolecular MBH-type reaction and global reduction of the resultant bicycle **179** gave a mixture of (+)-heliotridine and unnatural (−)-retronecine, with the source of the latter being the poor diastereoselectivity in the MBH-type ring closure.

Aggarwal and co-workers also reported an asymmetric variant of the MBH-type reaction for cyclic enones using the camphor−sulfonic acid-derived chiral sulfide **22** (Table 25).[132] The resulting MBH-type adducts were isolated with good to excellent enantioselectivity (80−98% ee) and in moderate to good yields (49−90%). Although stoichiometric amounts of sulfide were required (1.5 equiv), the sulfide was easily recovered by column chromatography. The use of an acyclic enone (MVK) led to the isolation of the adduct **173** in low enantioselectivity (8% ee).

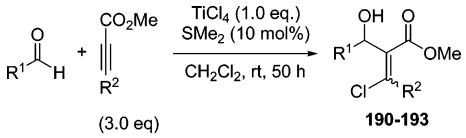
Table 26. Kataoka and co-workers' Halohydroxyalkylation of Acetylenic Ketones Using $TiCl_4$/Chalcogenide



entry	R	product	*E*/*Z* ratio	yield (%)
1	*p*-NO_2-C_6H_4	**184**	*E* only[a]	86
2	*p*-CF_3-C_6H_4	**185**	*E* only	73
3	*p*-F-C_6H_4	**186**	*E* only	89
4	C_6H_5	**187**	20:1	84
5	*p*-CH_3-C_6H_4	**188**	15:1	86
6	$PhCH_2CH_2$	**189**	20:1	84

[a] In the absence of sulfide, *E*/*Z* = 1:1 (84% yield).

Table 27. Kataoka and co-workers' Halohydroxyalkylation of Methyl Propiolates Using $TiCl_4$/Chalcogenide



entry	R^1	R^2	product	*E*/*Z* ratio	yield %
1	*p*-NO_2-C_6H_4	H	**190**	1:7	75[a]
2	*p*-NO_2-C_6H_4	Me	**191**	1:1	25
3	*p*-CF_3-C_6H_4	H	**192**	1:6	36
4	*p*-Cl−C_6H_4	H	**193**	1:7	47

[a] No reaction in the absence of sulfide.

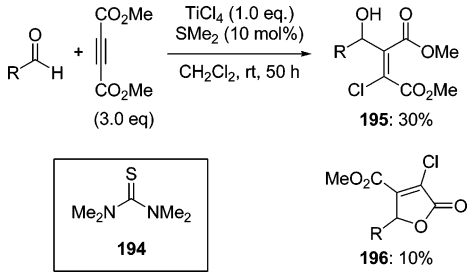
To summarize, conditions employing the combination of an oxophilic Lewis acid and a chalcogenide are useful for effecting Morita−Baylis−Hillman-type transformations. These conditions have an increased scope of the terminal electrophile (i.e., iminium ions and nonenolizable oxonium ions) over the tertiary amine/phosphine catalyzed reactions. With regard to the Michael acceptor, these conditions are superior for reactive substrates such as enones and enals but further development of the methodology is required to allow less-reactive substrates, such as acrylates, to participate as readily as they do using traditional catalysis. High levels of enantioinduction can be achieved by using enantiomerically pure chiral chalcogenides. There is strong evidence to suggest that, in reactions involving acetals in the presence of chalcogenides, specifically sulfides, the 1,2-sulfonium salts rather than oxonium ions are the pertinent electrophiles.

8. Miscellaneous Reactions Involving 1,4-Addition of Chalcogenide

8.1. Halohydroxyalkylation of Electron-Deficient Alkynes

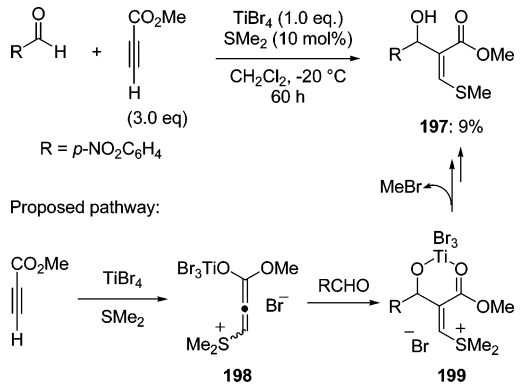
Kataoka and co-workers effected a chlorohydroxyalkylation of electron-deficient alkynes by treating them with $TiCl_4$, a substoichiometric amount of a chalcogenide, and the corresponding aldehyde (Tables 26 and 27).[155] Using acetylenic ketones, the products **184**−**189** (*β*-chloro-MBH adducts) were obtained in high diastereomeric purity in favor of the *E*-isomer; more electron-rich aldehydes gave lower *E*/*Z* ratios. They reported that the reaction in the absence of chalcogenide gave the adduct as a 1:1 mixture of *E*- and *Z*-isomers. However, it should be noted that Li and co-workers found that the reaction of $TiCl_4$, acetylenic ketone, and aldehyde gave >95% of the *E*-isomer, albeit at room temperature rather than 0 °C.[156] It has been shown by Taniguchi et al. in a similar reaction that, while the *E*-isomer is the thermodynamic product, the *Z*-isomer is kinetically favored, although the equilibration pathway has not been determined.[157] Kataoka and co-workers also reported that the *β*-bromo adducts were obtained in lower yield when $TiBr_4$ was used. The less reactive methyl propiolate required more forcing conditions (room temperature for 24−50 h) and the *β*-chloro-MBH adducts **190**−**193** were obtained in moderate yields in favor of the *Z*-isomer (Table 27). The reaction devoid of chalcogenide did not proceed, thus highlighting the importance of the chalcogenide additive. Selenide **110b** was also tested for all the aforementioned Michael acceptors but in all cases SMe_2 was superior. The reactions in the presence of selenide **110b** were slow, and in the case of methyl propiolate low yields of the corresponding adducts were obtained. Using dimethyl acetylenedicarboxylate (DMAD) and SMe_2 as additive, a mixture of the *E*-**195** (30% yield) and lactone **196** (10% yield) was formed, with the latter presumably being the result of transesterification of the *Z*-**195** (Scheme 74). Ultimately, for this substrate, thiourea **194** rather than SMe_2 was found to be the superior catalyst (40% of *E*-**195** and 40% of **196**).

Scheme 74. Kataoka and co-workers' Halohydroxyalkylation of DMAD Using $TiCl_4$/Chalcogenide



Although there was no evidence in the cases with acetylenic ketones as substrates to support a 1,4-addition role for the chalcogenide, in the case of methyl propiolate the isolation of small amounts (<10%) of thioether **197**, albeit only when $TiBr_4$ was used, suggests 1,4-addition may be involved (Scheme 75). The authors considered two mechanisms for the formation of **197**: (a) that mixtures of $TiBr_4$ and SMe_2 form a titanium thiolate species which subsequently catalyzes the formation of allenoate, which then reacts with aldehyde to give **197**, or (b) that SMe_2 catalyzes the formation of sulfonium allenoate **198**, which subsequently reacts with aldehyde to give sulfonium salt **199**, which in

Scheme 75. Kataoka and co-workers' Isolation of Thioether 197 and Proposed Mechanism of Formation



turn is converted to **197** via nucleophilic attack by bromide (Scheme 75). The former was ruled out as attempts to trap thiolate were unsuccessful. However, convincing evidence in support of the latter pathway was not obtained.

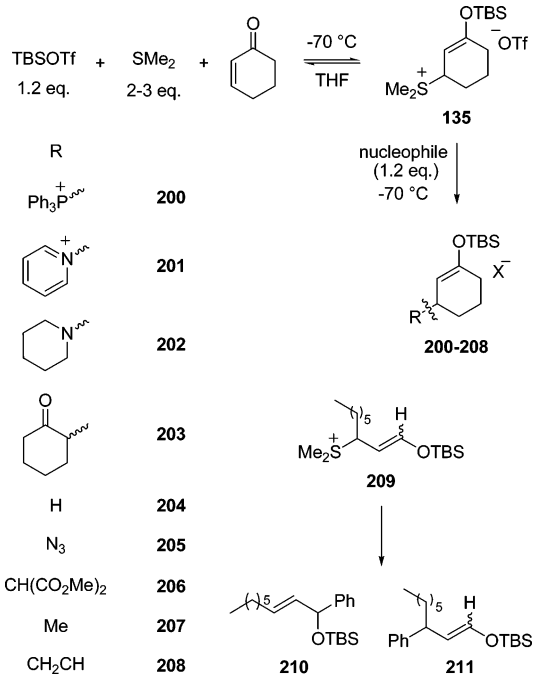
8.2. Synthesis of β-Substituted Silyl Enol Ethers

Kim and co-workers reported the reaction of in situ-generated β-sulfonium silyl enol ethers (Scheme 67) with various nucleophiles at −70 °C to give β-substituted silyl enol ethers (Scheme 76 and Table 28).[130] They suggested that the β-substituted silyl enol ether products **200**−**208** were formed via an S_N2 displacement of the sulfide by the nucleophiles. Using the β-sulfonium silyl enol ether **209** derived from a β-alkyl substituted acrolein, they reported that an apparent S_N2' displacement of sulfide to give **210** was observed in preference to S_N2 displacement to give **211**.

Lee and co-workers focused on the reaction of in situ-generated β-sulfonium silyl enol ethers with a variety of preformed organoindium reagents.[150,158] β-Alkyl, allyl (Table 29), β-propargylic and allenyl (Table 30) silyl enol ethers were isolated in good yield. When substituted allyl bromides were used (**212b** and **212c**), the new C−C bond was formed at the more substituted γ-position. When ethyl bromocrotonate was employed, a mixture of constitutional isomers was obtained via C−C bond formation at the α and γ (more-substituted) positions, with the latter being predominant (**221** and **222**). The use of terminal propargylic bromides led to exclusive formation of alkynyl products **230**−**235**, while the use of internal propargylic bromide **229c** gave the allenylated products **236**−**238**.

No product was obtained in the absence of sulfide, thus confirming that sulfide plays a crucial role in these transformations. The observation that β-sulfonium silyl enol ethers

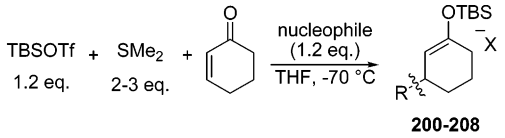
Scheme 76. Kim and co-workers' Synthesis of β-Substituted Silyl Enol Ethers



are formed quantitatively at the operating temperature led the authors to suggest a mechanism involving an S_N2 displacement of sulfide from these intermediates by the alkyl, allyl, propargylic, or allenyl ligand on indium. The formation of substitutionally crowded C−C bonds in some cases is noteworthy.

To summarize, the combination of a chalcogenide and a Lewis acid also allows activated alkynes to participate in

Table 28. Results from Kim and co-workers' Synthesis of β-Substituted Silyl Enol Ethers



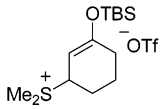
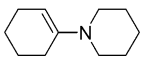
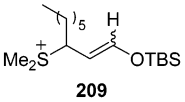
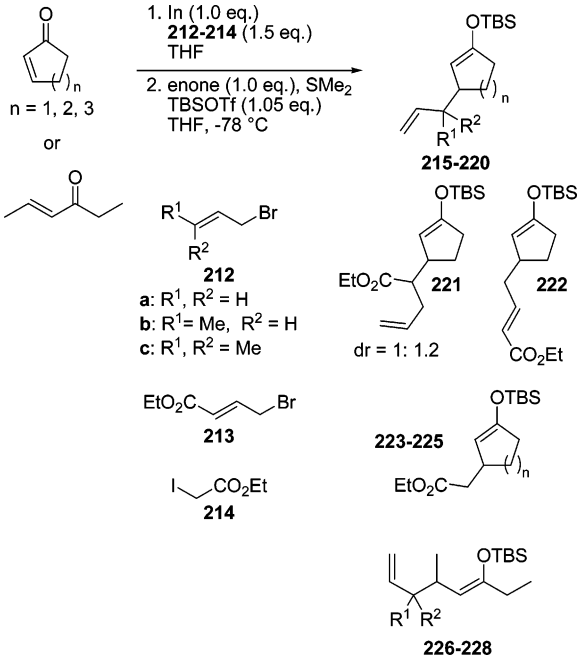
Entry	Proposed Intermediate	Nucleophile	Product	Yield (%)
1		PPh_3	**200**	nd
2		Pyridine	**201**	nd
3	**135**		**202**	76
4	"		**203**	75
5	"	Bu_3SnH	**204**	89
6	"	Bu_3SnN_3	**205**	82
7	"	$NaCH(CO_2Me)_2$	**206**	93
8	"	MeMgBr	**207**	94
9	"	$CH_2CHMgBr$	**208**	82
10	 **209**	PhMgBr	**210/211**	85/7

Table 29. Lee and co-workers' Synthesis of β-Allyl or β-Ethyl Acetate Silyl Enol Ethers



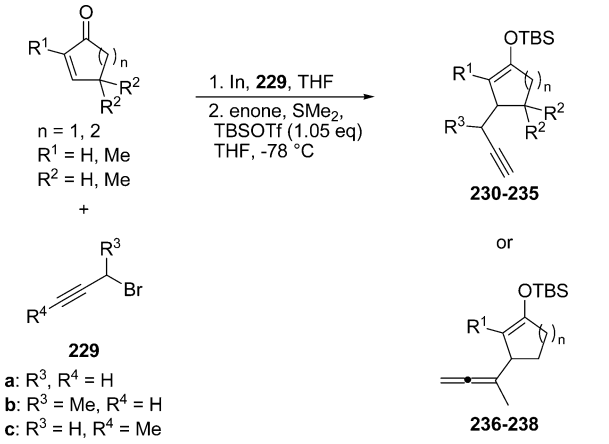
entry	RX	R^1	R^2	*n*	product	% yield (dr)
1	**212a**	H	H	1	**215**	62
2	**212b**	Me	H	1	**216**	64 (1:1)
3	**212a**	H	H	2	**217**	65
4	**212c**	Me	Me	2	**218**	61
5	**212a**	H	H	3	**219**	65
6	**212c**	Me	Me	3	**220**	66
7	**213**			1	**221:222** (3:1)	72
8	**214**			1	**223**	74
9	**214**			2	**224**	62
10	**214**			3	**225**	71
11	**212a**	H	H		**226**	65
12	**212b**	Me	H		**227**	69 (1:1.1)
13	**212c**	Me	Me		**228**	62

MBH-type processes. It is also apparent that β-sulfonium silyl enol ethers function as electrophiles in the presence of a variety of nucleophiles.

9. Radical-Polar Crossover Chemistry

Easily oxidized sulfides, such as tetrathiafulvalene (TTF, **239)**, can be used to reduce arene diazonium salts to aryl radicals, and in suitable cases, such species can then undergo conventional radical chemistry to convert to more stable, alkyl-centered radicals. These more stable radicals can thereafter couple with the sulfide's radical cation (formed on oxidation of the sulfide) to give sulfonium salts. Finally, the sulfide can then be displaced from the salt by a variety of nucleophiles, in a sequence that has become known as "radical-polar crossover chemistry" (see Scheme 77 for the catalytic cycle).[159,160] This process is catalytic in sulfide, and it is possible to use substoichiometric quantities of sulfide; however, the yields are generally superior if stoichiometric amounts are employed.[159,161,162] The two types of transformation which have been achieved by this chemistry, involving either radical cyclization or radical translocation, are described below.

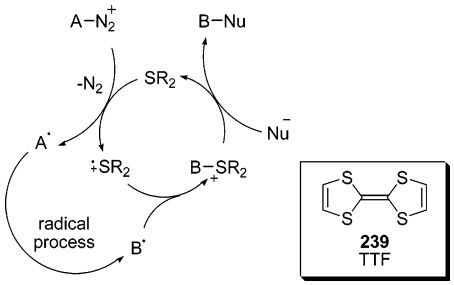
Table 30. Lee and co-workers' Synthesis of β-Propargylic and β-Allenyl Silyl Enol Ethers



entry	R^1	R^2	n	RX	product	% yield (dr)
1	H	H	1	**229a**	**230**	82
2	H	H	1	**229b**	**231**	71 (1:2.1)
3	Me	H	1	**229a**	**232**	81
4	H	H	2	**229a**	**233**	86
5	H	H	2	**229b**	**234**	81 (1:1.3)
6	H	Me	2	**229a**	**235**	48
7	H	H	1	**229c**	**236**	69[a]
8	Me	H	1	**229c**	**237**	73[a]
9	H	H	2	**229c**	**238**	64[a]

[a] LiI was used an additive with **229c**.

Scheme 77. General Scheme for Radical-Polar Crossover Reactions



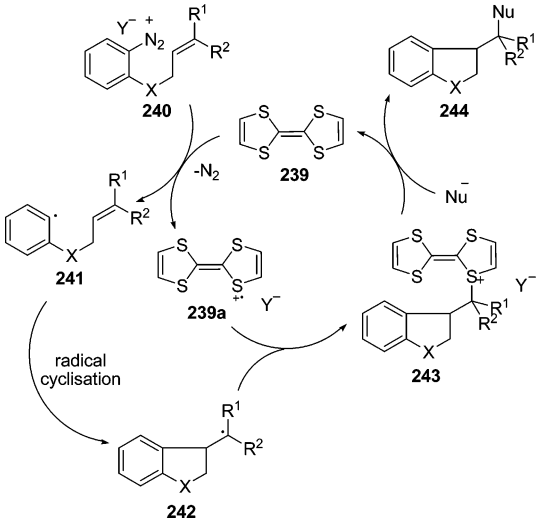
9.1. Radical Cyclization Followed by Oxidative Quench

The most-studied reaction in this field has been the cyclization of aryl radicals onto tethered olefins, which, after the coupling with the sulfide radical cation and displacement of the sulfide, gives rise to alcohols, ethers, or amides.[159,161] By far the most commonly used sulfide in this chemistry has been TTF, **239**, a sulfide often employed by materials chemists on account of its ease of oxidation.[163] Scheme 78 shows the application of TTF in the cyclization of a benzene diazonium salt, followed by oxidative quench.

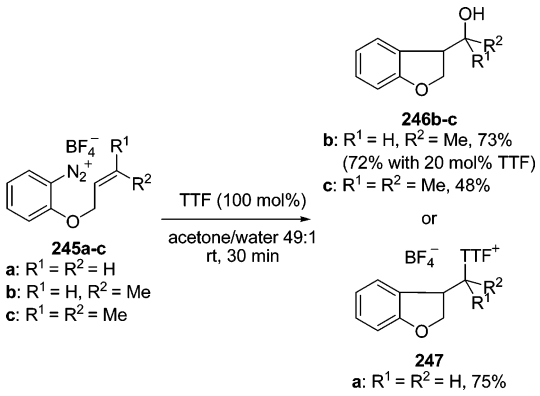
9.1.1. Reactions of 2-Allyloxy Benzene Diazonium Salts with TTF

The original substrates studied in this chemistry were allyl, crotyl, and prenyl ethers of benzene diazonium salts, **245a**−**c**.[159,161] The *O*-crotyl- and *O*-prenyldiazonium salts underwent smooth conversion to the desired alcohols, but in the case of the allyl ether, the reaction stopped at the sulfonium salt stage (Scheme 79). If dry acetone was used, all three sulfonium salts could be isolated, and the latter two

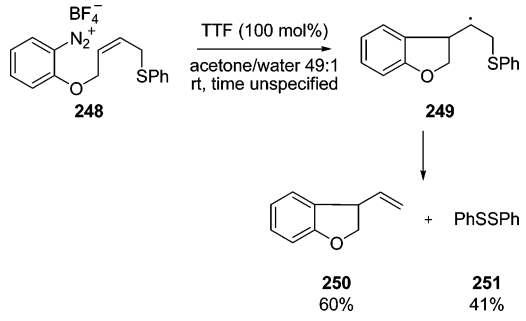
Scheme 78. Catalytic Cycle for Radical Cyclization of Arene Diazonium Salts



Scheme 79. Synthesis of Substituted Dihydrobenzofurans



Scheme 80. Evidence in Support of a Radical Mechanism

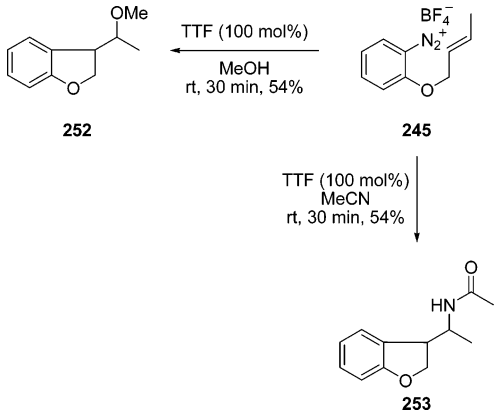


could subsequently be hydrolyzed to afford the alcohols. Subjection of sulfonium salt **247** to more vigorous hydrolysis conditions resulted only in decomposition of the tetrathiafulvalene moiety. This observation regarding the relative ease of hydrolysis of primary, secondary, and tertiary sulfonium salts has been found to be general, and the trend has been ascribed to a unimolecular reaction mechanism for the final displacement step.[159,161]

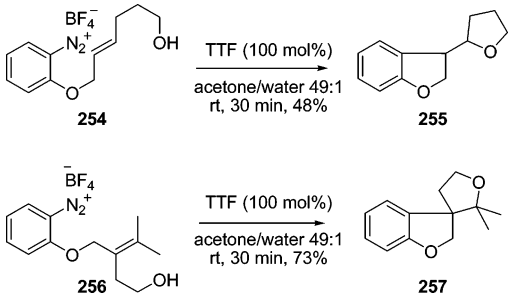
Support for the radical mechanism shown in Scheme 78 was found in the reaction of salt **248**, which, after cyclization, led to elimination product **250** (Scheme 80).[164] This elimination would not be expected to occur if the cyclization were to operate through a cationic mechanism.

Three external nucleophiles have been shown to displace TTF from its sulfonium salts. As well as water in acetone,

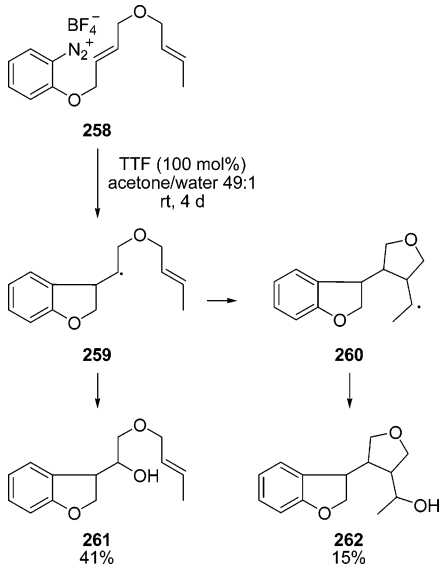
Scheme 81. External Nucleophiles Other than Water in Radical-Polar Cyclizations



Scheme 82. Internal Alcohols as Nucleophiles in Radical-Polar Cyclization Reactions



Scheme 83. Attempted Tandem Cyclization Reaction



as discussed above, the use of methanol or acetonitrile as solvent resulted in the formation of ethers and amides, respectively, although the yields were highest with water as the nucleophile (see Scheme 81).[159,161] Internal alcohols can also act as effective nucleophiles in the displacement of TTF from sulfonium salts (see Scheme 82).[165]

9.1.2. Tandem Cyclizations

Attempts to induce a second cyclization prior to trapping resulted in a significant degree of coupling between the TTF radical cation and the alkyl radical product of the first cyclization (Scheme 83).[161,166] This is presumably a consequence of the lower rate for the 5-*exo*-trig-cyclization of an

Scheme 84. Use of a Probe for Radical Involvement in Tandem Cyclizations

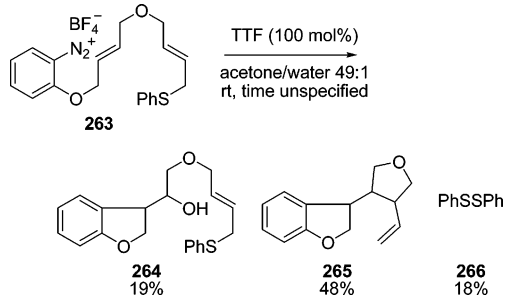
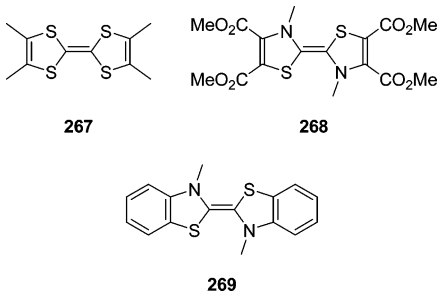
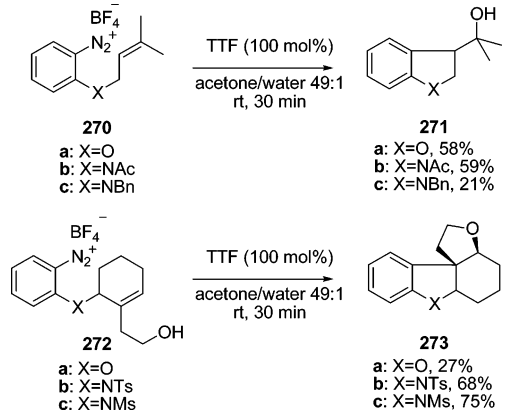


Chart 3. Bulkier Electron Donors



Scheme 85. Comparison of Oxygen and Nitrogen Linkers



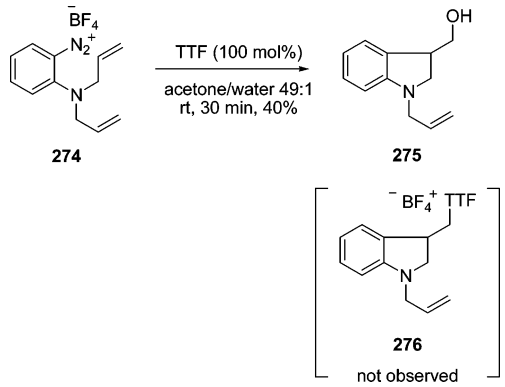
alkyl radical when compared with that of an aryl radical. The resulting sulfonium salt was hydrolyzed in situ to give **261** as the major product (41%), although some bicyclized product **262** (15%) was also obtained. The second cyclization was more effective in the presence of substrate **263** bearing a thioether (Scheme 84).[167]

The use of bulkier electron donors **267**−**269** (see Chart 3) appears to retard the coupling step and, thus, allow a second cyclization to occur more readily, allowing for even greater yields of **265** (67−73%) under the same conditions as above.[167] However, none of these reagents have been shown to undergo successful coupling and hydrolysis, giving instead either stable sulfonium salts or decomposition products.

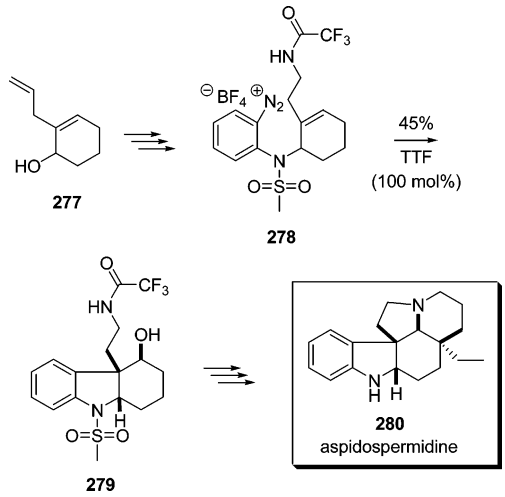
9.1.3. Extension to Indolines

Acetamide, benzene sulfonamide, and methyl sulfonamide linkers can be employed instead of ethers to tether the olefin to the arene, allowing for the synthesis of indolines through this chemistry (Scheme 85).[168] Acetamides gave yields comparable to ethers, while the more rigid sulfonamide systems gave significantly higher yields in reactions that do not proceed well with the analogous ethers. Benzamides were also examined, but radical attack on the phenyl ring of the linker proved to be a competitive reaction to the desired cyclization. Data for different linking groups is presented in Scheme 85.

Scheme 86. Radical-Polar Cyclization of an *N,N*-Diallyl-substituted Benzenediazonium Salt



Scheme 87. Use of Radical-Polar Crossover Chemistry as a Key Step in the Synthesis of Aspidospermidine



The analogous *N,N*-diallyl substrate afforded a 40% yield of the corresponding alcohol, rather than the expected primary sulfonium salt (Scheme 86).[166] It was proposed that this was because the slightly more electron-rich aromatic ring, relative to those of the ethers, acetamides, and sulfonamides, could act as a more effective participating neighboring group in this case, aiding the hydrolysis of the initially formed sulfonium salt.

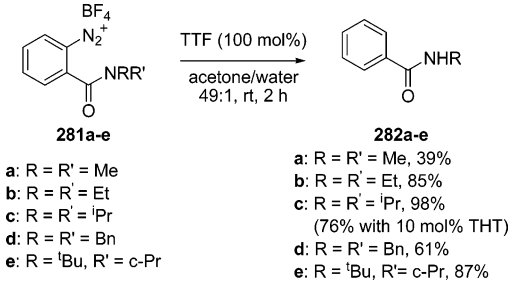
9.1.4. Application in Synthesis

The chemistry described above has been applied to the total synthesis of the pentacyclic alkaloid aspidospermidine, **280**.[169] The key step in this synthesis, the radical-polar reaction of **278** with TTF to give tricyclic alcohol **279**, proceeded in 45% yield (Scheme 87).

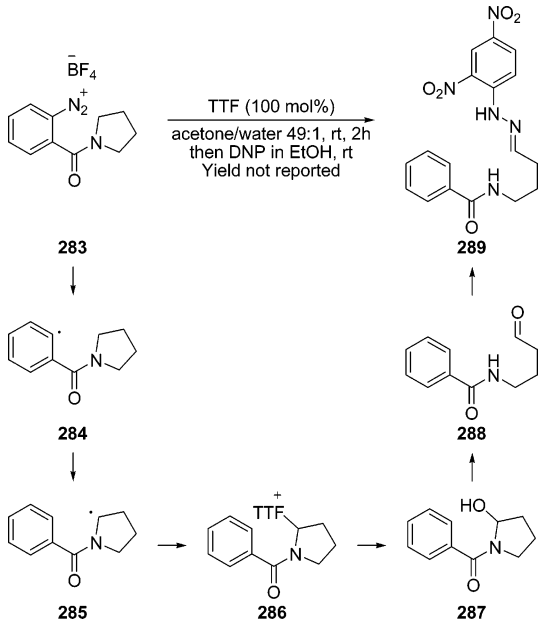
9.2. Radical Translocation

The second area of chemistry in which the radical-polar crossover catalyst TTF has been employed has been that of radical translocation.[162,166,170] Again, readily reduced benzene diazonium salts are employed as substrates, but no tethered olefin is present, so the most readily available reaction pathway for the aryl radical generated is hydrogen abstraction from a nearby C−H bond, to generate a more stable alkyl

Scheme 88. TTF-Catalyzed Transformation of Diazonium Dialkylbenzamide Salts to Monoalkylbenzamides



Scheme 89. Demonstration of Aldehyde Products in TTF-Catalyzed Monodealkylation of Dialkyl Amides: Reaction and Proposed Pathway (DNP = 2,4-Dinitrophenylhydrazine)



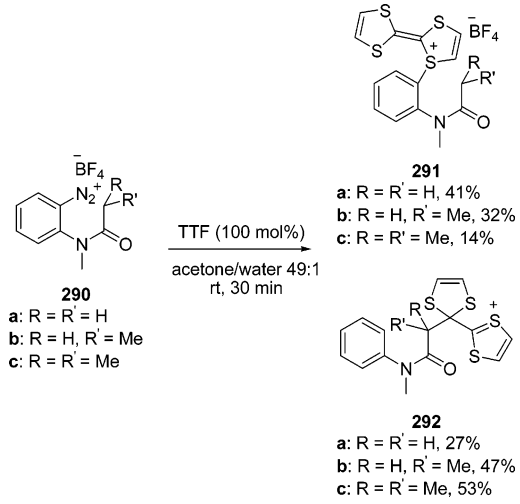
radical. This new radical can then couple with the TTF radical cation, and the resulting salt can be hydrolyzed or displaced by a nucleophile. This chemistry can thus allow selective functionalization at unactivated sites.

9.2.1. Benzamide Substrates

The most thoroughly studied system in which this type of chemistry has been examined is that of dialkylbenzamides **281a**−**e** (Scheme 88).[162,170] In all of these cases, successful translocation, trapping, and hydrolysis of the sulfonium salt to the *N*-benzoylhemiaminal resulted in overall oxidative monodealkylation. The proposed mechanism for these transformations is shown in detail for a similar substrate in Scheme 89. It can be clearly seen from Scheme 88 that the yield of dealkylated product is closely linked to the stability of the radical formed after translocation.

The catalytic nature of this chemistry was demonstrated with substrate **281c**, which afforded **282c** in good yield (76%) with only 0.1 equiv of TTF.[162] As the aldehydes presumed to result from this chemistry were of low molecular weight and were not isolated, the cyclic secondary amide **283** was examined; treatment on workup with 2,4-dinitrophenylhydrazine (DNP) resulted in hydrazone **289**, supporting the proposed mechanism of the oxidative dealkylations (Scheme 89).[162,170]

Scheme 90. Anilides as Substrates for TTF-Catalyzed Radical Translocation

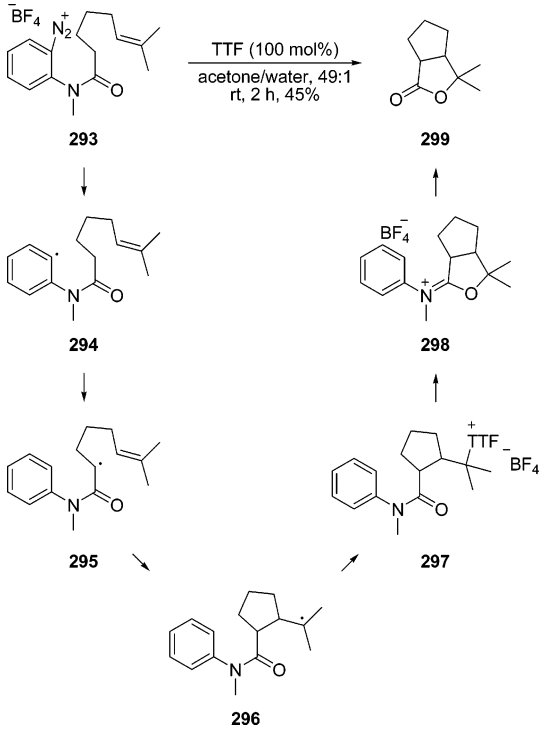


9.2.2. Anilide Substrates

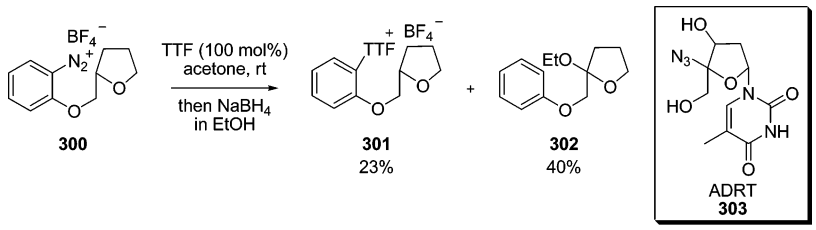
Anilides, the other substrates to have been studied in detail, have afforded substantially different results. All three anilides **290a**−**c** underwent a degree of translocation, but in all cases, significant trapping of the aryl radical by the TTF radical cation also occurred; in the acetamide case, it dominated (Scheme 90).[162,170] Furthermore, when radical translocation did occur, coupling of the resulting radical with the TTF radical cation occurred on carbon rather than on sulfur. Again, the yields of the products of translocation approximately matched the stabilities of the translocated radicals.

Such anilide substrates are the only reported instances in which the generation of sp^3 radicals under TTF-mediated radical-polar conditions has led to the formation of C-linked sulfonium salts (Scheme 90). It was suggested that the formation of an S-linked salt may be destabilized in these

Scheme 91. Lactone Synthesis Using TTF-Catalyzed Radical-Polar Cyclization: Reaction and Proposed Pathway



Scheme 92. TTF-Catalyzed Radical Translocation of Model Substrate for the Synthesis of ADRT



cases by the adjacent carbonyls. Such a destabilization could not only help to account for products **292a**−**c** but could also explain the successful translocation−cyclization sequence observed in substrate **293**. Ordinarily, an alkyl radical intermediate would be trapped by the TTF radical cation, but in the case of radical **294**, the rate of the trapping may be slowed by the adjacent carbonyl, hence allowing 5-*exo*-*trig*-radical cyclization to occur. The TTF radical cation would then intercept the new tertiary radical of **296** to give **297**, followed by intramolecular displacement by the amide oxygen, which, on hydrolysis, would produce lactone **299** (Scheme 91).

9.2.3. Ether Substrates

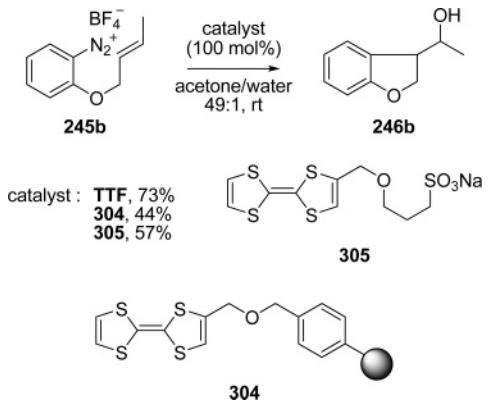
In a related example, with a potential application to the synthesis of anti-HIV ADRT, **303**, diazonium salt **300** gave acetal **302** in 40% yield together with sulfonium salt **301** (Scheme 92).[162,170]

9.3. TTF-Related Reagents

A number of variants of the standard radical-polar reagent have been developed, including one in which a TTF moiety is bound to a polymeric resin, **304**.[171] This polymer-bound reagent allows for easy separation from the product and recycling of the reagent, although, if the reaction is conducted under air, then the radical cation of the polymer bound reagent is isolated, necessitating a $NaBH_4$ reduction to regenerate the active species. The procedure has been tested in four consecutive radical cyclization cycles, with no diminution of yield observed (Scheme 93). Yields are, however, lower than in the solution phase (44% cf. 73% for salt **245b**).

Another TTF analogue, **305**, has been developed bearing a polar side chain that makes it water soluble.[172] This allows the products to be isolated by simple organic extraction. Yields in the radical-cyclization chemistry were only slightly lower than in the parent system (57% cf. 73% for salt **245b**).

Scheme 93. TTF Analogues Catalyzing a Radical-Polar Crossover Cyclization Reaction



Like the polymer-bound system, the reisolation of the reagent, by evaporation of the water after extraction, afforded the radical cation rather than the active species. In this case, though, reduction back to the donor reagent has not been reported. These reactions could also be conducted in pure water if the more soluble diazonium chlorides were used rather than the diazonium tetrafluoroborates, although the yields were found to be lower (20−37%).

9.4. Summary of Radical-Polar Crossover Chemistry

The radical-polar crossover chemistries of benzene diazonium salts represent two novel classes of reactions. Radical cyclization followed by oxidative quench allows for the synthesis of complex alcohols and polycycles, consisting primarily of dihydrobenzofurans and indolines. Most aspects of the mechanism of these reactions have been studied in detail and are well-understood. As well as hydrolysis with water, methanol, acetonitrile, and internal alcohol, nucleophiles can also be used to displace TTF from the initial sulfonium salt products. Tandem radical cyclizations are possible in some cases, but their general applicability is rather limited. Finally, the power of the radical-polar cyclization and oxidative quench has been successfully demonstrated in natural product synthesis.

Radical translocation followed by oxidative quench has less synthetic applicability than the radical cyclizations at present, with the monodealkylation of dialkylbenzamides being the most successful system studied. However, it has been shown that this chemistry can be used to functionalize tetrahydrofurans. Study of the translocation reactions has also engendered greater insight into the understanding of the mechanism of radical-polar crossover chemistry in general, showing that, while nucleophilic radicals couple to the TTF radical cation on sulfur, electrophilic radicals couple instead on carbon.

Although greater yields are generally obtained with stoichiometric amounts of catalyst, the cyclization followed by oxidative quench has been demonstrated to give good yields with as little as 20 mol % of sulfide, whereas the radical translocations can be conducted successfully with 10 mol %. The development of polymer-supported and water-soluble analogues of the prime catalyst, TTF, further increases the practicality of this chemistry.

10. Conclusions

Chalcogenide-catalyzed reactions provide a wide range of useful products. Sulfides are the most commonly used chalcogenide catalysts, but a growing number of useful reactions are being developed using the other members of the family. Chalcogenides can be involved in catalysis through a variety of distinctly different mechanisms. Most often, the first step of the catalytic cycle is nucleophilic attack

by the chalcogenide on one of the substrates. Subsequent or concurrent ylide formation then allows a range of reaction manifolds to occur. Alternatively, the initial step can be an electron transfer, with radical chemistry then ensuing. In either type of reaction, the chalcogen can then be regenerated, either by nucleophilic displacement (either intra- or intermolecular) or by elimination. Such cycles allow the catalytic synthesis of epoxides, aziridines, cyclopropanes, olefins, chromenes, MBH adducts, indolines, and a variety of other heterocycles.

11. Abbreviations

ADRT	4′-azidothymidine
c-Pr	cyclopropyl
Cy	cyclohexyl
DCM	dichloromethane
DNP	2,4-dinitrophenylhydrazine
EWG	electron-withdrawing group
GSH	glutathione
[M]	metal with unspecified ligands
MBH	Morita−Baylis−Hillman
MVK	methyl vinyl ketone
PEG	poly(ethylene glycol)
PTC	phase-transfer catalyst
SA	sodium ascorbate
SES	β-trimethylsilylethanesulfonyl
TcBoc	trichloro-*tert*-butoxycarbonyl
THT	tetrahydrothiophene
Tol	tolyl
TTF	tetrathiafulvalene

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