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Electrophilic Addition and Cyclization Reactions of Allenes

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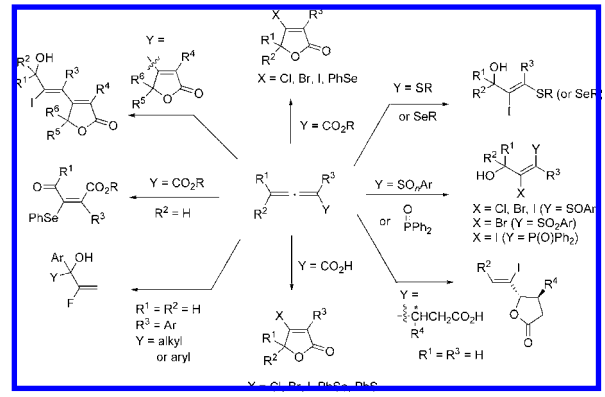
CONSPECTUS

Modern organic synthesis depends on the development of highly selective methods for the efficient construction of potentially useful target molecules. A primary goal in our laboratory is the discovery of new reactions that convert readily available starting materials to complex products with complete control of regio- and stereoselectivity. Allenes are one underused moiety in organic synthesis, because these groups are often thought to be highly reactive. However, many compounds containing the allene group, including natural products and pharmaceuticals, are fairly stable. The chemistry of allenes has been shown to have significant potential in organic synthesis.



Electrophilic additions to allenes have often been considered to be synthetically less attractive due to the lack of efficient control of the regio- and stereoselectivity. However, this Account describes electrophilic reactions of allenes with defined regio- and stereoselectivity developed in our laboratory. Many substituted allenes are readily available from propargylic alcohols. Our work has involved an exploration of the reactions of these allenes with many different electrophiles: the *E*- or *Z*-halo- or seleno-hydroxylations of allenyl sulfoxides, sulfones, phosphine oxides, carboxylates, sulfides or selenides, butenolides, and arenes, and the halo- or seleno-lactonization reactions of allenoic acids and allenoates.

These reactions have produced a host of new compounds such as stereodefined allylic alcohols, ethers, amides, thiiranes, and lactones. In all these reactions, water acts as a reactant and plays an important role in determining the reaction pathway and the stereoselectivity. The differing electronic properties of the two C=C bonds in these allenes determine the regioselectivity of these reactions. Through mechanistic studies of chirality transfer, isolation and reactivity of cyclic intermediates, ^{18}O-labeling, and substituent effects, we discovered that the *E*-stereoselectivity of some reactions results from the neighboring group participation of functional groups forming cyclic intermediates. We rationalize *Z*-stereoselectivity under other conditions by soft Lewis acid−base interactions and steric effects. These electrophilic reactions of allenes are efficient and useful methods for the synthesis of stereodefined alkenes and lactones, useful functionalities for synthesis.

Introduction

Allenes have two cumulated C=C bonds. Their history dates back to 1874, when Jacobus H. van't Hoff predicted the correct structure of this type of compound.[1] Because of their unique structure, for a long period of time they had been considered to be highly unstable. In fact, the first synthesis of pentadienoic acid was attempted with the purpose of proving the nonexistence of allenes.[1] However, many natural products and pharmaceuticals con-

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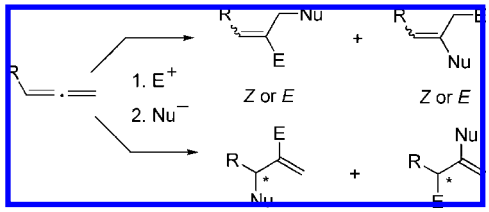
SCHEME 1. Possible Products of Electrophilic Additions to Allenes—Issues of Regio- And Stereoselectivity



tain the allene moiety.[1a] The reactivities of allenes are very different from those of alkenes and alkynes. During the last 10−15 years, many new reactions of allenes have been developed[1b−e,2] and some of these reactions had been successfully applied for the efficient synthesis of natural products.[2] The most recent notable advances are transition metal-catalyzed hydro-, carbo-, or heteroatom-metalations and cyclizations.[1c] It is obvious that the chemistry of allenes will further be extensively explored to show their potentials in organic chemistry.

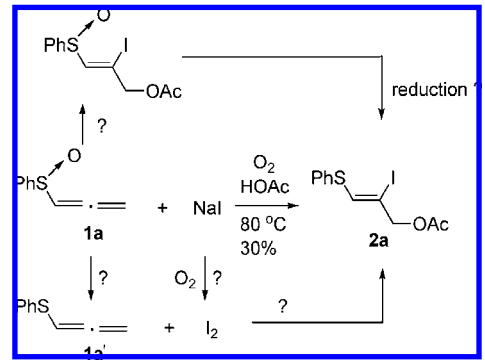
The rich abundance of electrophilic additions and cyclization reactions of alkenes and alkynes[3,4] suggests that allenes should also easily undergo electrophilic reactions.[5] Because of the presence of two C=C bonds in allenes, there are issues of regioselectivity (which C=C reacts and in which direction addition occurs) and stereoselectivity (Scheme 1).

After some trial and error, we observed that sulfoxide, sulfone, phosphine oxide, carboxylate, sulfide, selenide, and butenolide functionalities all may be used to control the regio- and stereochemistry of the halo-/seleno-hydroxylation or -amidation and thiiranation reactions. The mechanistic models to rationalize the products are different for different reagents. When there is a nucleophilic functional group in the allene, electrophilic cyclizations have been observed to afford the cyclic products with very high regio- and stereoselectivity. In this account, the electrophilic addition reactions of 1,2-allenyl sulfoxides, sulfones, phosphine oxides, sulfides, selenides, butenolides, and arenes, and the lactonization of allenoic acids and allenoates with electrophilic halogenation reagents or PhSeCl, are discussed.

Part 1. Electrophilic Addition Reactions with *E*-Stereoselectivity Controlled by the Formation of Cyclic Intermediates

1,2-Allenyl Sulfoxides. At the beginning of the research in this area, we studied the nucleophilic additions of inorganic halides to electron-deficient allenes,[6] specifically 1,2-allenyl sulfoxides.[7] The reaction of **1a** with NaI in HOAc gave a complicated mixture. Finally, one of the products in this mixture,

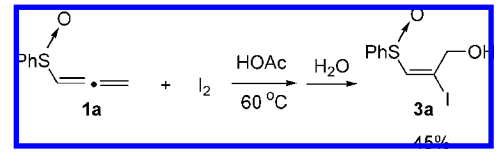
SCHEME 2. Reaction of Propadienyl Phenyl Sulfoxide **1a** with NaI in HOAc



i.e., 3-acetoxy-2-iodo-1(*Z*)-propenyl phenyl sulfide **2a**, was identified (Scheme 2).

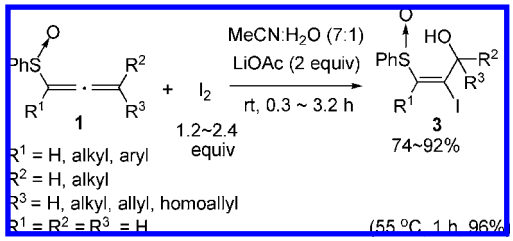
On the basis of the structure of this new product **2a**, we reasoned that this product may be formed by the electrophilic addition reaction of sulfoxide **1a** or sulfide **1a′** with the *in situ* generated I_2 by the oxidation of I^- with the aerobic oxygen.[8] We noted that (1) product **2a** has the *Z*-configuration; (2) the sulfoxide functionality has been reduced to form the sulfide; and (3) the acetoxyl group must come from HOAc. With these notions in mind, the direct electrophilic addition of propadienyl phenyl sulfoxide **1a** with I_2 in HOAc at 60 °C was tested. The reaction surprisingly afforded sulfoxide **3a** with exellent regio- and stereoselectivity albeit in a low yield.[9] Compound **3a** has the configuration of the C=C bond reversed and the acetoxyl group replaced by the hydroxyl group. This unexpected observation prompted us to further optimize the iodohydroxylation of 1,2-propadienyl phenyl sulfoxide **1a** (Scheme 3).

SCHEME 3. Reaction of 1,2-Propadienyl Sulfoxide **1a** with I_2 in HOAc



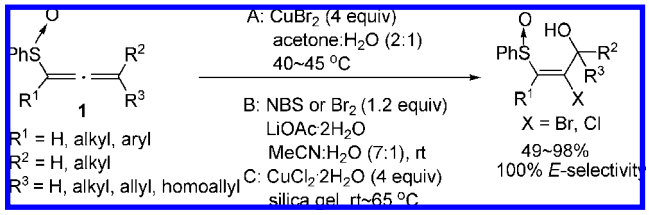
Eventually, we established the optimized reaction conditions for the high-yield formation of **3**: 1 equiv of 1,2-allenyl sulfoxide and 1.2−2.4 equiv of I_2 in MeCN−H_2O (7:1) in the presence of LiOAc (2 equiv) at room temperature (rt) (Scheme 4).[9] LiOAc acts as a base to remove the *in situ* generated HI to ensure high yields. Optimization of reaction conditions in such a case requires rather tedious testing of a variety of experimental conditions. While mechanistic insights may guide the experiments to be tested, there is really no substitute for the human labor required to identify optimum reaction conditions.

SCHEME 4. Regio- and Stereoselective *E*-Iodohydroxylation of 1,2-Allenyl Sulfoxides



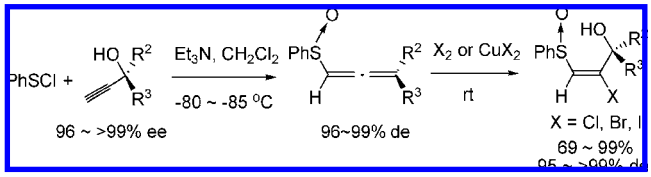
The reaction is faster with additional alkyl or aryl substitution, indicating the electrophilic nature of this reaction. No electrophilic addition reaction occurred to the more electron-deficient C═C bond of the allene. Even if there is an isolated C═C bond in the starting allenyl sulfoxide, the reaction occurs exclusively at the allene moiety. This reaction can be extended to bromohydroxylation[10] and chlorohydroxylation by using $CuBr_2$ (Br_2, NBS) or $CuCl_2$ (solvent free, mixing with silica gel), respectively (Scheme 5).[11a] The yields for chlorohydroxylations are usually lower.[11a] Conducting the reaction in MeCN in the presence of EtOH at 0 °C also afforded the *E*-iodohydroxylation product.[11b]

SCHEME 5. Bromo- or Chlorohydroxylation of 1,2-Allenyl Sulfoxides



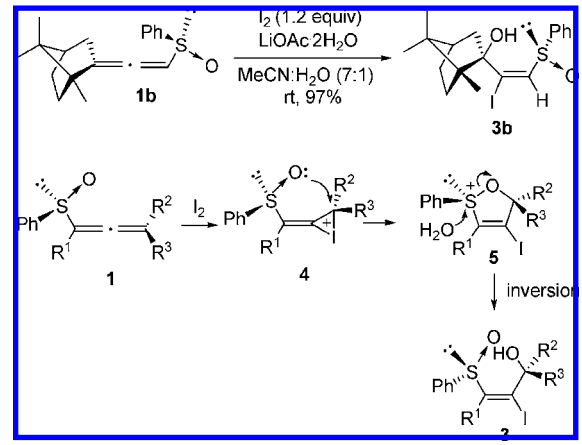
The corresponding reactions of optically active 1,2-allenyl sulfoxides, which are easily available from optically active propargylic alcohols,[12] afforded the expected *E*-halohydroxylation products with a new center of chirality at the 3-position in good-to-excellent yields without obvious racemization (Scheme 6).[11a]

SCHEME 6. Synthesis and Halohydroxylation of Optically Active 1,2-Allenyl Sulfoxides



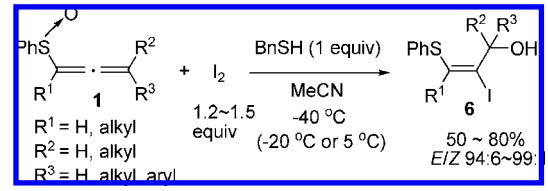
In order to obtain detailed steric information for this reaction via X-ray crystallographic structures of both the starting allene and product, many substrates were prepared, but all failed to yield solid products. It is lucky that the reaction of optically active **1b**, a solid, with I_2 under the optimized conditions afforded the crystalline product **3b**. X-ray diffraction studies on both the starting **1b** and the related product **3b** revealed that the axial chirality in the starting material was efficiently transferred to the center of chirality in the product (Scheme 7). The absolute configuration of the sulfur atom was inverted during the reaction. On the basis of these data, the following mechanism was proposed: The relatively electron-rich C═C bond at the 2-position of the starting 1,2-allenyl sulfoxides **1** reacts with I_2 to form the positively charged three-membered iodinonium intermediate **4**. Intramolecular attack of the sulfoxide oxygen at the carbon atom of the 3-position gives the five-membered intermediate **5**. Finally, attack of H_2O at sulfur gives **3** with the inverted configuration of the sulfur atom.[11a] This mechanism nicely explains the regio- and stereoselectivity.

SCHEME 7. Inversion of Chirality and Mechanism for Iodohydroxylation of 1,2-Allenyl Sulfoxides



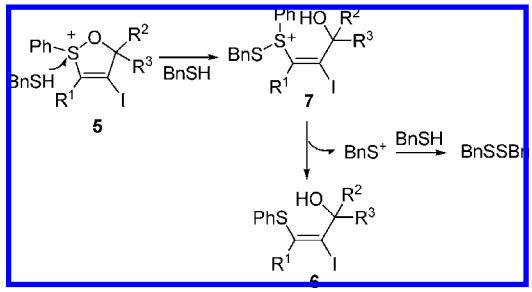
With this mechanism in mind, we envisioned that certain nucleophiles may attack the different locations of the five-membered heterocyclic intermediate **5**. However, we were surprised to observe that, when BnSH was added for such a purpose, the sulfoxide functionality was reduced to sulfide; the regio- and stereoselectivity are the same; and after the reaction, BnSH is converted to BnSSBn (Scheme 8).[13]

SCHEME 8. Iodohydroxylation and Sulfoxide-Reduction of 1,2-Allenyl Sulfoxides in the Presence of BnSH



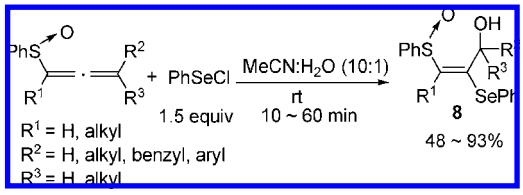
The mechanism in Scheme 9 accounts for the observations.[13]

SCHEME 9. Rationale for the Formation of *E*-2-Iodo-3-hydroxy-1-Alkenyl Sulfides



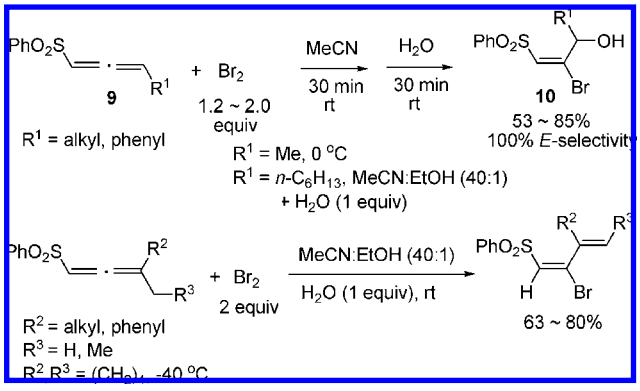
In addition, it has been observed that similar highly regio- and stereoselective selenohydroxylation of 1,2-allenylic sulfoxides with PhSeCl occurs (Scheme 10).[14]

SCHEME 10. Selenohydroxylation of 1,2-Allenyl Sulfoxides



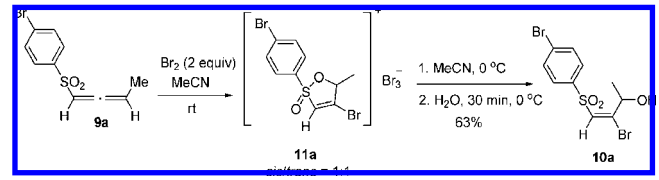
1,2-Allenyl Sulfones. Under the same reaction conditions for halohydroxylation of sulfoxides,[9,11] the halohydroxylation of 1,2-propadienyl phenyl sulfone failed to afford the expected product; 80% of the starting allene was recovered, most probably due to the fact that the relatively strong electron-withdrawing sulfone functionality makes the allene too electron-deficient. Thus, we reasoned that the interaction of 1,2-allenyl sulfones with Br_2 is the rate-determining step. For that reason, 3-monosubstituted 1,2-allenyl sulfones were mixed with Br_2 in MeCN at rt for 30 min, followed by the addition of H_2O. Luckily, the reaction afforded sulfones **10** (Scheme 11). With 3,3-disubstituted 1,2-allenyl sulfones, 2-bromo-1(*E*),3(*E*)-alkadienyl sulfones were formed.[15]

SCHEME 11. Electrophilic Reaction of 1,2-Allenyl Sulfones with Br_2



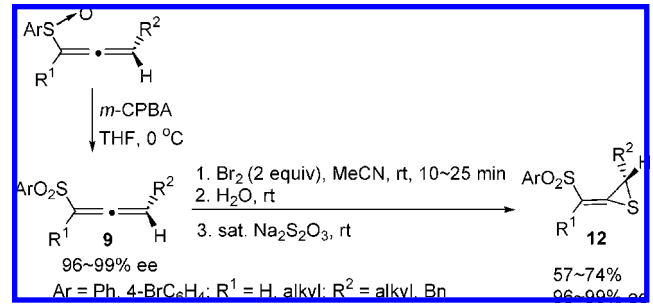
On the basis of these observations, we further reasoned that the five-membered **11**-type cyclic intermediate may be stable enough for isolation. Thus, in order to obtain a crystalline product, a *para*-bromine atom was introduced to the phenyl group. Indeed, a 1:1 *cis*/*trans* diastereoisomeric mixture **11a** was isolated by just mixing **9a** with Br_2 in MeCN at rt. Furthermore, the pure *cis*-isomer was obtained by recrystallization and characterized by X-ray diffraction (Scheme 12). In addition, this 1:1 diastereoisomeric mixture reacts with H_2O in MeCN at 0 °C to afford the *E*-bromohydroxylation product **10a** in 63% yield, proving the intermediacy of **11a** in this type of regio- and stereodefined transformation.

SCHEME 12. Isolation and X-ray Diffraction Study of Five-Membered Cyclic Intermediate **11a** and Its Reaction with Water



Since this type of cyclic intermediate is stable, we started to study its reactivity toward other nucleophiles. In the first place, when the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$, **12** was afforded unexpectedly.[16] By starting from the optically active 1,2-allenyl sulfones,[17,11a] the axial chirality was transferred into the center of chirality in **12** (Scheme 13).

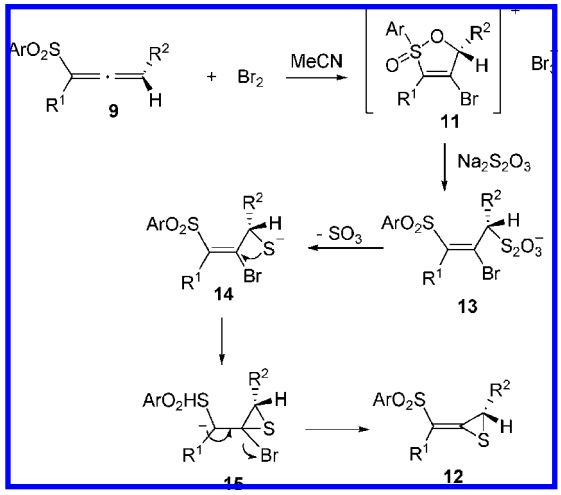
SCHEME 13. Formation of Optically Active Thiiranes



The reaction of **11a**-type compound under the same reaction conditions afforded the thiiranation product. We believe that $Na_2S_2O_3$ attacks the cyclic intermediate **11** to afford the ring-opened intermediate **13**, which eliminates one molecule of SO_3 to afford sulfide anion **14**. Conjugate addition and β-Br elimination affords the thiiranes **12** with high stereoselectivity (Scheme 14).[16]

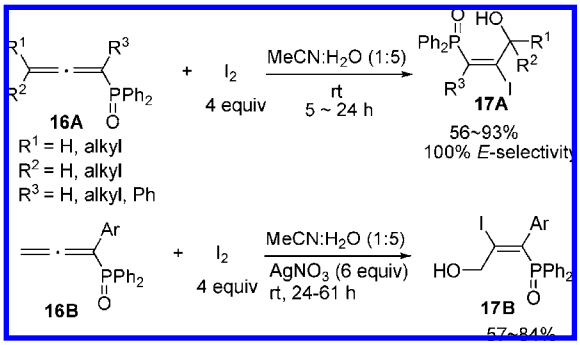
1,2-Allenyl Phosphine Oxides. Because of the similarity between sulfoxide/sulfone and phosphine oxide functionalities, we reasoned that 1,2-allenyl phosphine oxides may behave similarly. In fact, the reaction of 1,2-allenyl phosphine oxides **16A** with I_2 in aqueous MeCN afforded the *E*-iodohydroxylation products **17A**.[18] Four equiv of I_2 are required to ensure the high *E*-ste-

SCHEME 14. Mechanism for the Stereoselective Formation of Thiiranes



reoselectivity. The reaction of **16B** was conducted in the presence of $AgNO_3$ (6 equiv) to avoid the formation of the diiodides (Scheme 15).

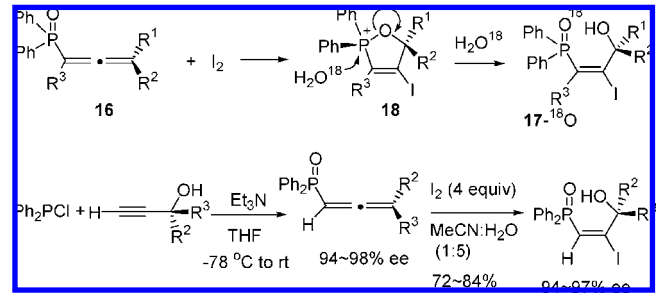
SCHEME 15. Iodohydroxylation of 1,2-Allenyl Phosphine Oxides



^{18}O-labeling experiments and reactions of optically active substrates[19] suggest that a similar type of mechanism involving the participation of the phosphine oxide functionality to form the five-membered intermediate **18** operates (Scheme 16). This is the first time that the neighboring group participation effect of the phosphine oxide functionality is observed.

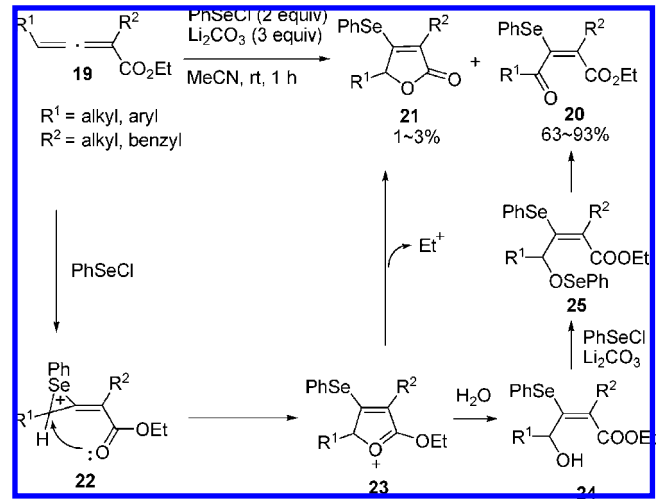
2,3-Allenoates. It is well-known that the alkoxycarbonyl group may act as a neighboring group.[20] However, when we tried to extend the iodohydroxylation to 2,3-allenoate, a complicated mixture was formed.[11a] Thus, we decided to try this type of reaction with other electrophiles and successfully observed the *E*-phenylselenohydroxylation of 2,3-allenoates with PhSeCl in MeCN. However, the alcohols **24** were immediately oxidized in the presence of PhSeCl and Li_2CO_3 to afford the corresponding ketones **20** as the final products, together with 1−3% of lactones **21**.

SCHEME 16. Chirality Transfer and Mechanism for Iodohydroxylation of 1,2-Allenyl Phosphine Oxides



The *E*-stereoselectivity is controlled by attack of the carbonyl oxygen to form **23** (Scheme 17).[21]

SCHEME 17. Reaction of 2,3-Allenoates with PhSeCl and the Mechanism for the Formation of Ketones **20**

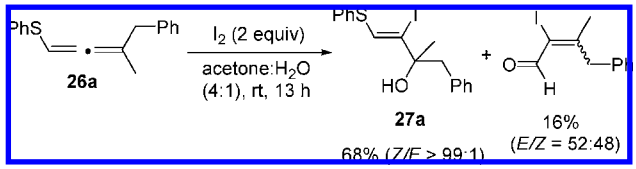


Part 2. Electrophilic Addition Reactions with *Z*-Stereoselectivity

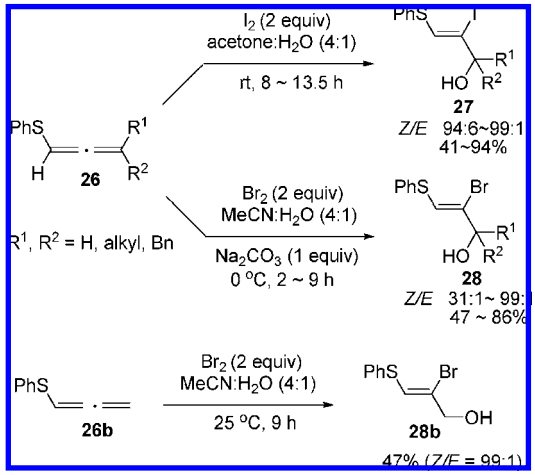
1,2-Allenyl Sulfides and Selenides. As shown in Scheme 2, we noted that the C=C bond in product **2** is in *Z*-configuration and the iodohydroxylation of 1,2-allenyl sulfoxides afforded the *E*-products (Scheme 4). We reasoned that the halohydroxylation of 1,2-allenyl sulfides may be sterically different. Indeed, the reaction of I_2 with **26a** in aqueous acetone afforded **27a** in 68% yield together with 2-iodo-3-methyl-4-phenyl-2-butenal in 16% yield (Scheme 18). In aqueous MeCN, the reaction afforded the aldehyde (*E*/*Z* = 0.32:1) as the only product in 16% yield.[22]

The aqueous acetone conditions are general for differently substituted 1,2-allenyl sulfides.[22] For bromohydroxylation, the related reaction in aqueous MeCN in the absence (for propadienyl sulfide) or presence of Na_2CO_3 (1 equiv) afforded **28b** or **28**, respectively (Scheme 19).

SCHEME 18. *Z*-Iodohydroxylation of 1,2-Allenyl Sulfide **26a**

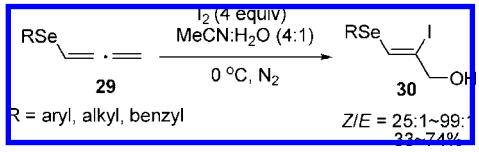


SCHEME 19. Halohydroxylation of 1,2-Allenyl Sulfides



This iodohydroxylation reaction may also be extended to 1,2-allenyl selenides, although the yields are relatively lower (Scheme 20).[22b]

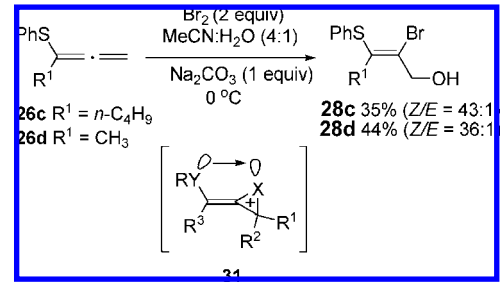
SCHEME 20. Iodohydroxylation of Propadienyl Selenides



The puzzle here is the reversed stereoselectivity. It has been noted in the literature that Br_2 reacts with an allene in the presence of MeOH to yield the methoxy-bromination *Z*-isomer as the major product (*Z*/*E* = 87:13); the selectivity was attributed to a steric effect of the substituent on the allene.[23] Thus, we introduced an extra alkyl group to the 1-position of 1,2-allenyl sulfides to see if this added alkyl group would change the stereoselectivity. However, the reaction of 1-alkyl substituted propadienyl sulfides **26c** and **26d** still afforded the *Z*-products **28c** and **28d**,[22b] indicating that the sulfide functionality is exclusively responsible for the stereoselectivity (Scheme 21). Thus, the *Z*-stereoselectivity was rationalized by the soft Lewis acid−base interaction between the sulfur or selenium atom and the positively charged X^+ as in intermediate **31** in Scheme 21.[22b]

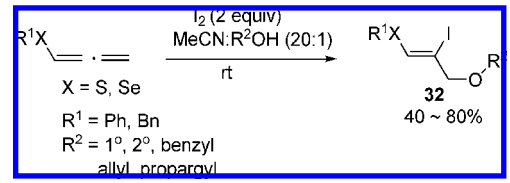
If **31** reacts with water, allylic alcohols **27** or **28** are formed. The reactivity of **31**-type intermediate was further demonstrated by conducting the reaction in the presence of alcohols to afford

SCHEME 21. Bromohydroxylation of 1-Alkyl-Substituted Propadienyl Sulfides and the Rationale for the Stereoselectivity



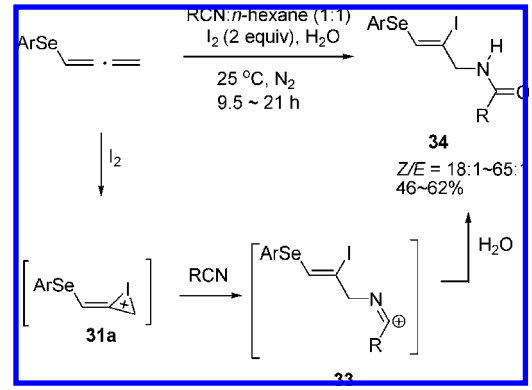
the stereodefined allylic ethers **32**, which may further be elaborated to form cyclic products (Scheme 22).[24]

SCHEME 22. Iodohydroxylation of 1,2-Propadienyl Sulfides and Selenides



In addition, the **31a**-type intermediates formed in the reaction of propadienyl selenides with I_2 in a 1:1 mixed solvent of a nitrile and *n*-hexane at 25 °C are relatively stable toward the presence of a limited amount of water.[25] They underwent the Ritter-type reaction with the nitrile[26] first, followed by the reaction with water to afford the corresponding amides **34** (Scheme 23).[25]

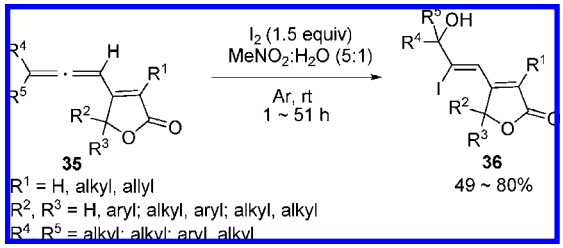
SCHEME 23. Ritter-type Reaction of Intermediate **31a**—Regio- And Stereoselective *Z*-Iodoamidation of Propadienyl Sulfides and Selenides



2(5*H*)-Furanonyl-Substituted Allenes. Recently, we developed an efficient synthesis of 4-(1,2-allenyl)butenolides **35** from the Pd-catalyzed cyclization of 2,3-allenoic acids in the presence of propargylic carbonates.[27] We decided to pursue the possible halohydroxylation of **35** by applying the steric and electronic properties of the furanone ring to control the regio- and stereoselectivity. The *Z*-iodohydroxylation was successfully observed in the related reaction of **35**

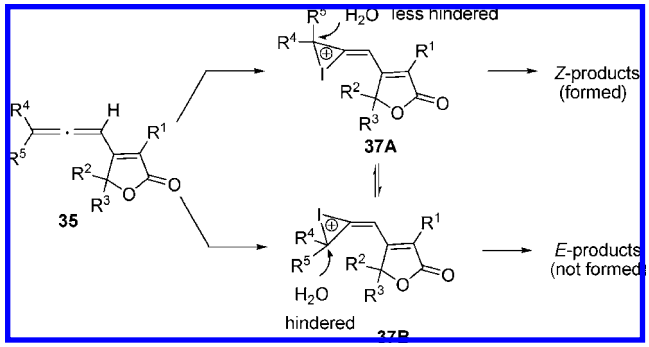
(Scheme 24). The stereoselectivity of the corresponding reaction in aqueous MeCN is much lower.[28]

SCHEME 24. *Z*-Iodohydroxylation of β-(1,2-Allenyl)butenolides



The addition of iodine to allenes **35** may be reversible, and the stereoselectivity may be explained by the steric effect[23] in the step of nucleophilic attack at the three-membered iodinonium intermediates by water (**37A** vs **37B**) (Scheme 25).[28]

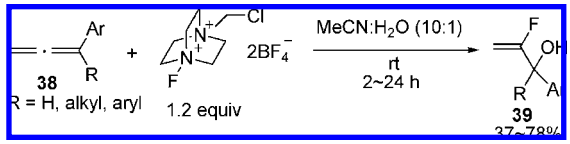
SCHEME 25. Rationale for the Stereoselectivity-Steric Effect



Part 3. Fluorohydroxylation of 3-Aryl-1,2-allenes with Reversed Regioselectivity

In all the reactions discussed above, we applied a relatively complicated functionality to control the regio- and stereoselectivity. Thus, it would be of high interest to control the selectivity in the reaction of the readily available simple alkyl- or aryl-substituted allenes. This idea led to the development of the fluorohydroxylation of 3-aryl-substituted-1,2-allenes with Selectfluor in aqueous MeCN at rt. This electrophilic reaction occurred highly regioselectively with the more substituted and electron-rich C=C bond (Scheme 26).[29] However, the success with simple allenes is so far still very limited since the presence of the aryl group is important for the success of this transformation.

SCHEME 26. Regioselective Fluorohydroxylation of 3-Aryl-1,2-Allenes

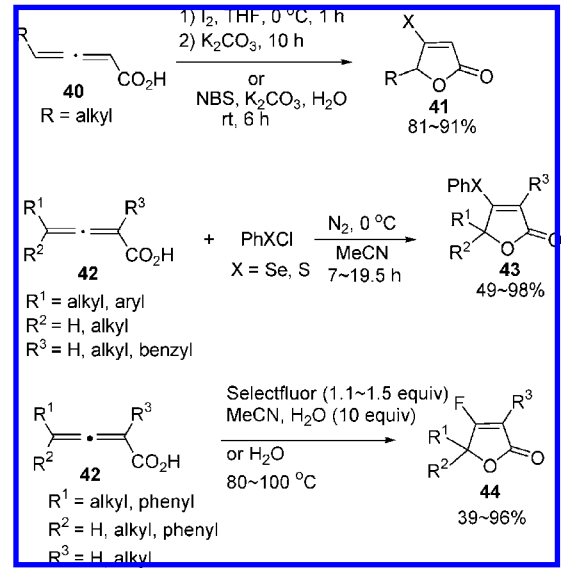


Part 4. Electrophilic Cyclizations of Allenes with a Nucleophilic Functionality[1b]

In all the reactions discussed above, intermolecular electrophilic attack occurs; however, if the starting allenes contain a nucleophile, electrophilic cyclization may be realized to afford cyclic products.

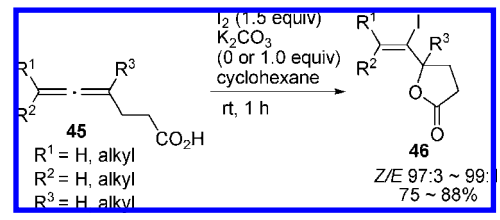
Allenoic Acids. For the selective formation of lactones or lactams,[30] we have found that CuX_2 (X = Br, Cl) may trigger the halocyclization of 2,3-allenoic acids,[31] or of salts formed by the reaction of 2,3-allenoic acids with optically active amines,[32] 2,3-allenoates,[33] and 2,3-allenoamides.[34,35] With I_2 or *N*-bromosuccinimide (NBS), 2,3-allenoic acids may also be cyclized to afford β-halobutenolides (Scheme 27).[36,37] This type of transformation may also be realized by using PhSeCl,[38] PhSCl,[38] or Selectfluor[39] as the electrophiles (Scheme 27).

SCHEME 27. Halo- or Selenolactonization of 2,3-Allenoic acids



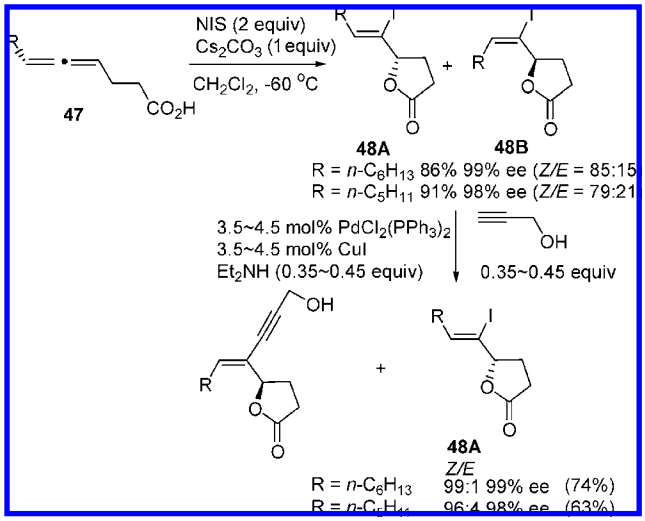
In all these electrophilic lactonization reactions, the more electron-rich C=C bond reacts with *trans*-attack of the carboxylic acid or ester functionality. With 4,5-allenoic acids, the iodolactonization reaction in cyclohexane with I_2 afforded the five-membered lactones exclusively in fairly good yields and a very high *Z*/*E* selectivity (Scheme 28).[40]

SCHEME 28. Regioselective Iodolactonization of 4,5-Allenoic Acids



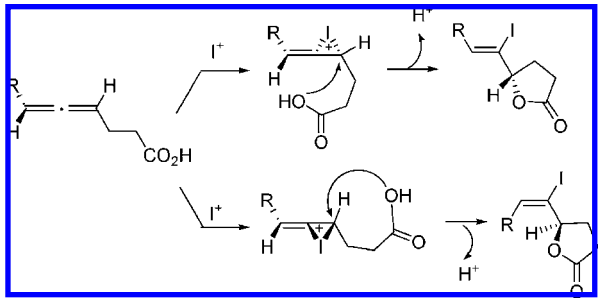
However, the reaction of optically active 4,5-allenoic acids with axial chirality under the same conditions afforded the racemic lactones. In order to solve this problem, new electrophiles and solvent effects were screened. This led to the observation that the reaction should be conducted with NIS in the presence of Cs_2CO_3 in CH_2Cl_2 to ensure the high efficiency of chirality transfer. However, the *Z*/*E* selectivity is poor. Finally, this problem was solved by applying the kinetic resolution with the Sonogashira coupling reaction to afford the pure *Z*-isomer (Scheme 29).[40]

SCHEME 29. Iodolactonization of Optically Active 4,5-Allenoic Acids and the Kinetic Resolution via the Sonogashira Coupling



The regioselectivity involves formation of the five-membered products. The *Z*/*E*-selectivity and chirality transfer is rationalized by the *anti*-nature of this iodolactonization reaction (Scheme 30).

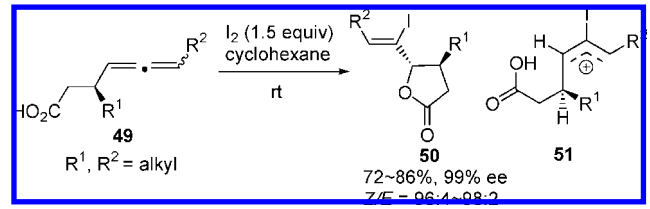
SCHEME 30. Rationale for the *Z*/*E*-Selectivity and Chirality Transfer



The reaction of 3-substituted 4,5-allenoic acids with I_2 in cyclohexane at rt afforded the *trans*-isomers **50** with high yields, excellent *Z*/*E* ratios, diastereoselectivity, and enantiopurity via the 1,2-chiral induction in the π-allyl cationic intermediate **51** (Scheme 31).[40]

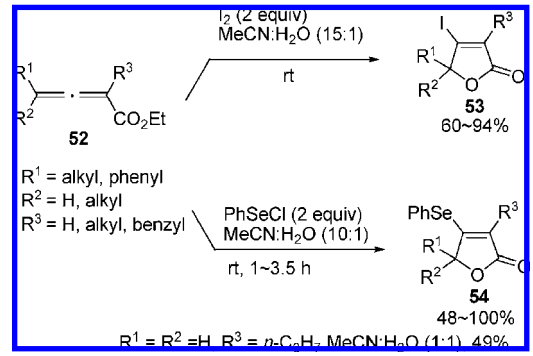
2,3-Allenoates. The 2,3-allenoic acids are usually prepared from the hydrolysis of 2,3-allenonates. Direct lactonization of esters would be highly desired in terms of synthetic

SCHEME 31. 1,2-Chiral Induction in Iodolactonization of 3-Substituted 4,5-Allenoic Acids



efficiency. With this notion in mind, we successfully developed direct iodolactonization of 2,3-allenoates with I_2, affording β-iodobutenolides **53** in good-to-excellent yields (Scheme 32).[41] With PhSeCl, the reaction of 2,3-allenoates in aqueous MeCN also afforded the β-phenylselenobutenolides **54** in high yields (Scheme 32). It is obvious that the water in the mixed solvent is mediating the lactonization process.[42] As noticed in Scheme 17, the carbonyl oxygen attacks the carbon atom at the 4-position to afford the lactone ring.

SCHEME 32. Iodolactonization of 2,3-Allenoates



Conclusion

Through these studies, it is obvious that the regio- and stereoselectivity of the electrophilic reactions of allenes with electrophiles may be finely tuned by the nature of the substitutents. *E*- or *Z*-Halo- or seleno-hydroxylations have become one of the most common electrophilic addition reactions for allenes: sulfoxide, sulfone, phosphile oxide, and carboxylate functionalities lead to the *E*-selectivity due to the formation of the cyclic intermediates; the related reaction of 2,3-allenoates affords the *E*-selenohydroxylation products, which are further oxidized to ketones;[21] *Z*-selectivity may be realized in the reactions of 1,2-allenyl sulfides/selenides and β-allenylbutenolides. Water can influence these transformations. Generally speaking, aqueous MeCN is the most commonly used media for these types of reactions, although in some cases aqueous $MeNO_2$ has also been applied. The readily available optically active allenes for the synthesis of optically active products with center chiralities, and the vari-

ety of products that can be formed should give these reactions synthetic potential.

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BIOGRAPHICAL INFORMATION

Shengming Ma was born in 1965 in Zhejiang, China. He graduated from Hangzhou University (1986) and received his Ph.D. degree (1990) from Shanghai Institute of Organic Chemistry (SIOC). He became an assistant professor of SIOC in 1991. After his postdoctoral research experience at ETH of Switzerland and Purdue University of U.S.A. from 1992−1997, he joined the faculty of Shanghai Institute of Organic Chemistry again (1997). From February 2003 to September 2007, he was jointly appointed by SIOC and Zhejiang University. In October 2007, he moved to East China Normal University in Shanghai to help build the research program in organic chemistry there. Currently he is also the Director of State Key Laboratory of Organometallic Chemistry, SIOC, CAS and Qiu Shi Adjunct Professor at Zhejiang University. He received Mr. and Mrs. Sun Chan Memorial Award in Organic Chemistry (2004), OMCOS Springer Award (2005), and National Award for Research in Natural Science in China (Second Class, 2006). The work discussed in this Account was conducted at ZJU and SIOC.

FOOTNOTES

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REFERENCES

1 (a) Hoffman-Röder, A.; Krause, N. Synthesis and Properties of Allenic Natural Products and Pharmaceticals. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216. For the most recent reviews, see: (b) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **2005**, *105*, 2829–2871. (c) Ma, S. Recent Advances in the Chemistry of Allenes. *Aldrichim. Acta* **2007**, *40*, 91–102. (d) Brasholz, M.; Reissig, H.-U.; Zimmer, R. Sugars, Alkaloids, and Heteroaromatics: Exploring Heterocyclic Chemistry with Alkoxyallenes. *Acc. Chem. Res.* **2009**, *42*, 45–56. (e) For a complete list of the monographs and reviews or accounts in this area, see refs 4 of 1c in this manuscript.

2 For the most recent monograph, see:Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, Germany, 2004.

3 For some of the recent reviews, see: (a) Smit, W. A.; Caple, R.; Smoliakova, I. P. Stepwise Electrophilic Addition. Some Novel Synthetic Ramifications of an Old Concept. *Chem. Rev.* **1994**, *94*, 2359–2382. (b) French, A. N.; Bissmire, S.; Wirth, T. Iodine Electrophiles in Stereoselective Reactions: Recent Developments and Synthetic Applications. *Chem. Soc. Rev.* **2004**, *33*, 354–362. (c) Armstrong, A.; Convine, N. J. One or More CC Bonds Formed by Addition: Addition of Carbon Electrophiles and Nucleophiles to CC Multiple Bonds. *Compr. Org. Funct. Group Transformations II,* Katritzky, A. R.; Taylor, R. J. K., Eds., Elsevier, 2004, 1.07, 287–311.

4 (a) McDonald, F. E. Alkynol *endo*-Cycloisomerizations and Conceptually Related Transformations. *Chem.—Eur. J.* **1999**, *5*, 3103–3106. (b) Larock, R. C. Synthesis of Heterocycles and Carbocycles by Electrophilic Cyclization of Alkynes. *Acetylene Chemistry: Chemistry, Biology and Material Science*, Diederich, F., Stang, P. J.; Tykwinski, R. R., Eds., Wiley-VCH: Weiheim, Germany, 2005; Chapter 2, pp 51–99.

5 Ma, S. Ionic Addition Reactions of Allenes Chapter 10 in ref 2. Ma, S. Control of Regio- and Stereoselectivity in Electrophilic Addition Reactions of Allenes. *Pure Appl. Chem.* **2007**, *79*, 261–267.

6 For an account in this area, see: Ma, S.; Li, L. An Efficient New Methodology for the Synthesis of 1-Functionalized 2-Halo-2-alkenes via Hydrohalogenation Reaction of Electron-Deficient Allenes. *Synlett* **2001**, 1206–1213.

7 Ma, S.; Wei, Q. Hydrohalogenation Reaction of 1,2-Allenic Sulfoxides with AlX_3 and H_2O: Efficient Synthesis of 2-Haloallyl Sulfoxides. *Eur. J. Org. Chem.* **2000**, 1939–1943.

8 Morgan, J. L. R.; Lammert, O. M; Crist, R. H. Photochemical Reactions in Solutions of the Alkali Halides in Acetophenone. *J. Am. Chem. Soc.* **1924**, *46*, 1170–1178.

9 Ma, S.; Wei, Q.; Wang, H. Unique Selectivity of Iodohydroxylation Reaction of Allenyl Phenyl Sulfoxides in Aqueous MeCN. A Stereodefined Synthesis of (*E*)-2-Iodo-3-hydroxy-1-alkenyl Sulfoxides. *Org. Lett.* **2000**, *2*, 3893–3895.

10 For a very brief study on the electrophilic addition reaction of 1,2-allenyl sulfoxides with Br_2, see: Horner, L.; Binder, V. Zur Chemie der Allensulfoxide. *Liebigs Ann. Chem.* **1972**, *757*, 33–68.

11 (a) Ma, S.; Ren, H.; Wei, Q. Highly Regio- and Stereoselective Halohydroxylation Reaction of 1,2-Allenyl Phenyl Sulfoxides. Reaction Scope, Mechanism, and the Corresponding Pd- or Ni-Catalyzed Selective Coupling Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 4817–4830. (b) Fu, C.; Chen, G.; Deng, Y.; Huang, X.; Ma, S. Effect of EtOH on the *E*-Iodohydroxylation of 1,2-Allenylic Sulfoxides with I_2. *Chin. J. Chem.* **2004**, *22*, 990–993.

12 He, Q.; Ma, S. Synthesis of Optically Active Propargylic Alcohols. *Chin. J. Org. Chem.* **2002**, *22*, 375–387.

13 Fu, C.; Huang, X.; Ma, S. Convenient Stereoselective Synthesis of 3-Hydroxy-2-iodo-2(*E*)-alkenyl Sulfides via Iodohydroxylation of 1,2-Allenyl Sulfoxides in the Presence of BnSH. *Tetrahedron Lett.* **2004**, *45*, 6063–6065.

14 He, G.; Zhou, C.; Fu, C.; Ma, S. Studies on the Highly Regio- and Stereoselective Selenohydroxylation of 1,2-Allenylic Sulfoxides with PhSeCl. *Tetrahedron* **2007**, *63*, 3800–3805.

15 Zhou, C.; Fu, C.; Ma, S. Studies on Electrophilic Reaction of Br_2 with 1,2-Allenylic Sulfones. A highly Regio- and Stereoselective Synthesis of 1-Phenylsulfonyl-2-bromo-1(*E*)-alken-3-ols and 1-Phenylsulfonyl-2-bromo-1(*E*),3(*E*)-butadienes. *Tetrahedron* **2007**, *63*, 7612–7616.

16 Zhou, C.; Fu, C.; Ma, S. Highly Selective Thiiranation of 1,2-Allenylic Sulfones with Br_2 and $Na_2S_2O_3$: Mechanism and Asymmetric Synthesis of Alkylidenethiiranes. *Angew. Chem., Int. Ed.* **2007**, *46*, 4379–4381.

17 Optically pure 1,2-allenyl sulfones were synthesized easily by the oxidation of chiral allenyl sulfoxides with *m*-chloroperbenzoic acid in an ice bath.

18 Guo, H.; Qian, R.; Guo, Y.; Ma, S. Neighboring Group Participation of Phosphine Oxide Functionality in the Highly Regio- and Stereoselective Iodohydroxylation of 1,2-Allenylic Diphenyl Phosphine Oxides. *J. Org. Chem.* **2008**, *73*, 7934–7938.

19 Boisselle, A. P.; Meinhardt, N. A. Acetylene−Allene Rearrangements. Reactions of Trivalent Phosphorus Chlorides with α-Acetylenic Alcohols and Glycols. *J. Org. Chem.* **1962**, *27*, 1828–1833.

20 (a) Muthukrishnan, R.; Kannan, R.; Swaminathan, S. Participation of *o*-Carboxylate Groups in Aromatic Nucleophilic Substitution. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2949–2956. (b) Tomioka, H.; Hirai, K.; Tabayashi, K.; Murata, S.; Izawa, Y.; Inagaki, S.; Okajima, T. Neighboring Group Participation in Carbene Chemistry. Effect of Neighboring Carboxylate Group on Carbene Reactivities. *J. Am. Chem. Soc.* **1990**, *112*, 7692–7702. (c) Krow, G. R.; Lin, G.; Rapolu, D.; Fang, Y.; Lester, W. S. The Rearrangement Route to 2-Azabicyclo[2.1.1]hexanes. Solvent and Electrophile Control of Neighboring Group Participation. *J. Org. Chem.* **2003**, *68*, 5292–5299. (d) Krow, G. R.; Gandla, D.; Guo, W.; Centafont, R. A.; Lin, G.; DeBrosse, C.; Sonnet, P. E.; Ross, C. W., III; Ramjit, H. G.; Carroll, P. J.; Cannon, K. C. Neighboring Group Participation in the Addition of Iodonium and Bromonium Ions to *N*-Alkoxycarbonyl-2-azabicyclo[2.2.*n*]alk-5-enes ($n = 1, 2$). *J. Org. Chem.* **2008**, *73*, 2114–2121.

21 Chen, G.; Fu, C.; Ma, S. Electrophilic Interaction of 2,3-Allenoates with PhSeCl. An Unexpected Highly Stereoselective Synthesis of 3-Phenylseleno-4-oxo-2(*E*)-Alkenoates. *J. Org. Chem.* **2006**, *71*, 9877–9879.

22 (a) Ma, S.; Hao, X.; Huang, X. Reversed Stereoselectivity in Iodohydroxylation of Allenyl Sulfides. An Efficient Synthesis of (*Z*)-3-Organosulfur-2-iodo-2-propenols. *Org. Lett.* **2003**, *5*, 1217–1219. (b) Ma, S.; Hao, X.; Meng, X.; Huang, X. Studies on the Regio- and Stereoselectivity of Halohydroxylation of 1,2- Alleny Sulfides or Selenides. *J. Org. Chem.* **2004**, *69*, 5720–5724.

23 Waters, W. L.; Linn, W. S.; Caserio, M. C. Stereochemistry of Additions of Allenes. I. Methoxymercuration and Halogenation of 1,3-Dimethylallene. *J. Am. Chem. Soc.* **1968**, *90*, 6741–6749.

24 Fu, C.; Chen, G.; Liu, X.; Ma, S. Stereoselective *Z*-Iodoalkoxylation of 1,2-Allenyl Sulfides or Selenides. *Tetrahedron* **2005**, *61*, 7768–7773.

25 Ma, S.; Hao, X.; Huang, X. Highly Regio- and Stereoselective Four-Component Iodoamination of Se-Substituted Allenes. An Efficient Synthesis of *N*-(3-Organoseleno-2-iodo-2(Z)-propenyl) Acetamides. *Chem. Commun*. **2003**, 1082–1083.

26 (a) Ritter, J. J.; Minieri, P. P. A New Reaction of Nitriles. I. Amides from Alkenes and Mononitriles. *J. Am. Chem. Soc*. **1948**, *70*, 4045–4048. (b) Ritter, J. J.; Kalish, J. A New Reaction of Nitriles. II. Synthesis of *t*-Carbinamines. *J. Am. Chem. Soc*. **1948**, *70*, 4048–4050.

27 (a) Ma, S.; Gu, Z.; Deng, Y. From Allene to Allene: A Palladium-catalyzed Approach to β-Allenyl Butenolides and Their Application to the Synthesis of Polysubstituted Benzene Derivatives. *Chem. Commun*. **2006**, 94–96. (b) Ma, S.; Gu, Z. Sequential Rearrangement of 1,2,4*Z*,7-Tetraenes Involving [1,5]-Hydrogen Migration and Electrocyclization: An Efficient Synthesis of Eight-Membered Cyclic Compounds. *J. Am. Chem. Soc*. **2006**, *128*, 4942–4943. (c) Gu, Z.; Ma, S. Studies on Thermal Reactivity of β-(1,2-Allenyl)butenolides and 2-Allyl-3-allenylcyclohex-2-enones. *Chem.—Eur. J*. **2008**, *14*, 2453–2464.

28 Gu, Z.; Deng, Y.; Shu, W.; Ma, S. Highly Regio- and Stereoselective Iodohydroxylation of Non-Heteroatom-Substituted Allenes: An Efficient Synthesis of 4-[3′-Hydroxy-2′-iodoalk-1′(*Z*)-enyl]-2(5*H*)-furanone Derivatives. *Adv. Synth. Catal*. **2007**, *349*, 1653–1656.

29 Zhou, C.; Li, J.; Lü, B.; Fu, C.; Ma, S. An Efficient Approach for Monofluorination via Highly Regioselective Fluorohydroxylation Reaction of 3-Aryl-1,2-allenes with Selectfluor. *Org. Lett*. **2008**, *10*, 581–583.

30 Ma, S. Transition Metal-Catalyzed/Mediated Reaction of Allenes with a Nucleophilic Functionality Connected to the α-Carbon Atom. *Acc. Chem. Res*. **2003**, *36*, 701–712.

31 Ma, S.; Wu, S. CuX_2-Mediated Cyclization Reaction of 2,3-Allenoic Acids. An Efficient Route to β-Halobutenolides. *J. Org. Chem*. **1999**, *64*, 9314–9317.

32 Ma, S.; Wu, S. Novel CuX_2-Mediated Cyclization of Acid-Base Salts of (L)-Cinchonidine or (D)-/(L)-α-Methylbenzylamine and 2,3-Allenoic Acids in Aqueous Medium. An Efficient Entry to Optically Active β-Halobutenolides. *Chem. Commun*. **2001**, 441–442.

33 Ma, S.; Wu, S. $CuBr_2$-Mediated Direct Aqueous Bromolactonization Reaction of 2,3-Allenoates. An Efficient Access to β-Bromobutenolides. *Tetrahedron Lett*. **2001**, *42*, 4075–4077.

34 Ma, S.; Xie, H. Unexpected Facile Sequential Halolactamization-Hydroxylation of 2,3-Allenamides with CuX_2 for the Efficient Synthesis of 4-Halo-5-hydroxypyrrol-2(5H)-ones. *Org. Lett*. **2000**, *2*, 3801–3803.

35 Ma, S.; Xie, H. Study on Halolactamization-γ-hydroxylation or Haloiminolactonization of 2,3-Alkadienamides. *Tetrahedron* **2005**, *61*, 251–258.

36 Ma, S.; Shi, Z.; Yu, Z. Synthesis of β-Halobutenolides and Their Pd(0)/CuI-Catalyzed Cross-Coupling Reactions with Terminal Alkynes. A General Route to β-(1′-Alkynyl)butenolides. *Tetrahedron Lett*. **1999**, *40*, 2393–2396.

37 Ma, S.; Shi, Z.; Yu, Z. Synthesis of β-Halobutenolides and Their Pd(0)-Catalyzed Cross-Coupling Reactions with Terminal Alkynes and Organozinc Reagents. A General Route to β-Substituted Butenolides and Formal Synthesis of *cis*-Whisky Lactone. *Tetrahedron* **1999**, *55*, 12137–12148.

38 Ma, S.; Pan, F.; Hao, X.; Huang, X. Reaction of PhSeCl or PhSCl with 2,3-Allenoic Acids: An Efficient Synthesis of β-Organoselenium or β-Organosulfur Substituted Butenolides. *Synlett* **2004**, 85–88.

39 Zhou, C.; Ma, Z.; Gu, Z.; Fu, C.; Ma, S. An Efficient Approach for Monofluorination via Aqueous Fluorolactonization Reaction of 2,3-Allenoic Acids with Selectfluor. *J. Org. Chem*. **2008**, *73*, 772–774.

40 Jiang, X.; Fu, C.; Ma, S. Highly Stereoselective Iodolactonization of 4,5-Allenoic Acids—An Efficient Synthesis of 5-(1′-Iodo-1′(*Z*)-alkenyl)-4,5-dihydro-2(3*H*)-furanone. *Chem.—Eur. J*. **2008**, *14*, 9656–9664. For a correction, see: *Chem.—Eur. J*. **2009**, *15*, 1295.

41 Fu, C.; Ma, S. Efficient Preparation of 4-Iodofuran-2(5*H*)-ones by Iodolactonisation of 2,3-Allenoates with I_2. *Eur. J. Org. Chem*. **2005**, 3942–3945.

42 Chen, G.; Fu, C.; Ma, S. Studies on Electrophilic Addition Reaction of 2,3-Allenoates with PhSeCl. *Tetrahedron* **2006**, *62*, 4444–4452.