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PERSPECTIVE

A novel class of tunable cyclopropanation reagents ($RXZnCH_2Y$) and their synthetic applications

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The Simmons–Smith cyclopropanation is a widely used method to synthesize cyclopropanes from alkenes using methylene iodide and a zinc reagent. A novel class of organozinc species, $RXZnCH_2Y$, has been found to efficiently cyclopropanate alkenes, including traditionally unreactive unfunctionalized alkenes. The reactivity and selectivity of this class of organozinc reagents can be regulated by tuning the electronic and/or steric nature of the RX group attached to Zn. During recent years, this class of organozinc reagent has been widely used in organic synthesis as a reagent for cyclopropanation and other useful synthetic transformations. Catalytic, asymmetric versions of this reaction have been developed providing high enantiomeric excess for unfunctionalized olefins.

Introduction

Cyclopropanes are versatile building blocks in organic chemistry. These three-membered rings are present in a variety of biologically active compounds and natural products,[1] including those possessing enzyme inhibitions, plant growth and fruit ripening controls, insecticidal, antifungal, and herbicidal activities, as well as carcinogenic and antitumoral properties. Due to their unique bonding and ring-strain, cyclopropanes can also undergo synthetically useful ring-opening reactions to build molecular complexity rapidly.[2] The Simmons–Smith cyclopropanation has proven to be a powerful method to synthesize cyclopropanes from alkenes.[3] In 1958, Simmons and Smith reported the cyclopropanation of alkenes using methylene iodide and zinc–copper couple.[4] The active zinc species is likely to be iodomethylzinc iodide (ICH_2ZnI).[4b,5–7] This reaction proceeds in a concerted manner with retention of the stereochemistry of the starting alkene. Since the original report of this reaction, different modifications have been developed, including the use of sonication to activate the Zn metal;[8] preparation of Zn metal by reduction with lithium;[9] the replacement of Zn/Cu couple with Zn/Ag couple;[10] addition of $TiCl_4$,[11] acetyl chloride,[12] or TMSCl[13] to promote the reaction; and various other methods.[14]

Variations of the active Zn species have also been reported. In 1959, Wittig and coworkers reported the preparation of

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Richard G. Cornwall

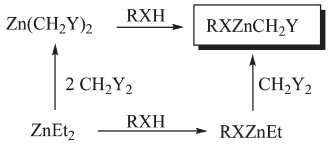
Richard G. Cornwall was born in Bloomington, Indiana in 1982. He received his B.S. degree in Chemistry, as well as his B.A. degree in German from Arizona State University in 2008. He is currently a graduate student in the research group of Professor Yian Shi at Colorado State University working on the development of metal-catalyzed vicinal diamination reactions.

O. Andrea Wong

On Lo Andrea Wong was born in Hong Kong in 1981. She moved to Honolulu, Hawai'i in 1994 and received her B.Sc. degree in chemistry from the University of Hawai'i at Mānoa in 2003. She completed her doctoral dissertation in 2009 with Professor Yian Shi at Colorado State University. She is currently a postdoctoral fellow in Professor Christopher Ackerson's laboratory working on the synthesis of monodispersed thiolate-protected gold nanoparticles at Colorado State University.

XCH_2ZnX reagents by reacting ZnX_2 with CH_2N_2.[15] In 1966, Furukawa and coworkers reported that active Zn species $EtZnCH_2I$ or $Zn(CH_2I)_2$, could be prepared by alkyl exchange between Et_2Zn and CH_2I_2.[16–18] A later study indicated that traces of oxygen are beneficial for cyclopropanation.[19] Charette and coworkers reported the isolation of a bipyridine·$Zn(CH_2I)_2$ complex, which can be stored for several months in the freezer and can cyclopropanate alkenes with addition of ZnI_2.[20] In 1991, Denmark and coworkers conducted a comparison study between (chloromethyl)zinc reagents and the traditional (iodomethyl)zinc reagents, and showed that (chloromethyl)zinc reagents, derived from Et_2Zn and ICH_2Cl, are generally more reactive and work well toward a variety of alkenes using 1,2-dichloroethane as the solvent.[21] In 1999, Charette and coworkers reported the generation of a mixed iodomethylzinc reagent using Et_2Zn, CH_2I_2 and trimethylsilylmethyl iodide, and its subsequent use as a cyclopropanantion reagent.[22] Acyloxymethyl zinc species have also been reported as cyclopropanation reagents. In 1967, Wittig reported that a bis(benzoyloxymethyl)zinc species, $(PhCO_2CH_2)_2Zn$, generated from CH_2N_2 and $(PhCO_2)_2Zn$, is effective for the cyclopropanation of olefins upon activation by ZnI_2.[15d] In 2001, Charette and coworkers reported that *n*-$C_4F_9CO_2CH_2ZnEt$, which was generated from Et_2Zn and *n*-$C_4F_9CO_2CH_2I$, is an active cyclopropanation reagent.[23] Progress has also been made on the structural elucidation of the active zinc species. NMR studies have been carried out to characterize the structures of several (halomethyl)zinc reagents,[24] and the X-ray structures of several (halomethyl)zinc compounds have been reported by Denmark[24a,b] and Charette.[20,23,25,26]

The presence of a heteroatom-directing moiety of a substrate greatly enhances the reactivity of the Simmons–Smith cyclopropanation and has also played an integral role in achieving selectivity.[3,27] Lack of such a moiety results in substrates that often suffer from sluggish reactivity and poor selectivity. Therefore, the development of new strategies, or new reagents, to meet these challenges is of interest.



Scheme 1 Strategies for developing novel cyclopropanation reagents.

Development of a new class of cyclopropanation reagent ($RXZnCH_2Y$)

The active species in the Simmons–Smith cyclopropanation ($XZnCH_2Y$) is electrophilic in nature and variation in X is often restricted to halogens, Et, YCH_2 or other alkyl groups. In 1998, Shi and coworkers reported a new class of cyclopropanation reagent generated by reacting RXH with an appropriate organozinc reagent (Scheme 1).[28a] Reaction of $ZnEt_2$ with RXH, followed by CH_2Y_2, allows formation of the active cyclopropanating reagent using 1 equiv. less CH_2Y_2, compared to the alternate pathway.

The reactivity of $RXZnCH_2Y$ can be tuned simply by changing the electronic and/or steric nature of the modifier RXH. Various modifiers, ranging from alcohols to acids, were examined and it was found that reactivity increased as the acidity of RXH increased from alcohols to phenols to acids (Fig. 1).[28] Among the modifiers that were studied, CF_3CO_2H was found to greatly accelerate the cyclopropanation. For example, the cyclopropanation of *trans*-β-methylstyrene was essentially complete within 30 min. (Fig. 1, curve I).

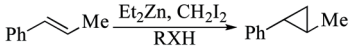
With this reagent (likely to be $CF_3CO_2ZnCH_2I$), various olefins, including previously unreactive substrates, are efficiently cyclopropanated in high yields and short reaction times (Scheme 2).[28] The reaction conditions are slightly acidic, but alternative forms of RXH can be adapted for acid sensitive olefins.

Haifeng Du

Haifeng Du was born in Jilin province, China in 1974. He received his B.Sc. degree in 1998 and M.Sc. degree in 2001 from Nankai University. He then moved to the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, and obtained his Ph.D. degree in 2004 under the supervision of Professor Kuiling Ding. In the fall of 2004, he joined the Department of Chemistry at Colorado State University as a postdoctoral fellow with Professor Yian Shi. In 2008, he joined the Institute of Chemistry, Chinese Academy of Sciences, as a professor supported by the "100 talent project of CAS". His research interests include the development of novel synthetic methodology and asymmetric synthesis.

Thomas A. Ramirez

Thomas A. Ramirez was born in Corpus Christi, Texas in 1980. He received his B.S. and M.S. degrees from Texas A&M University-Kingsville in 2004 and 2006, respectively, working under the guidance of Professor Apurba Bhattacharya. He is currently a graduate student in the research group of Professor Yian Shi at Colorado State University. Thomas is a Ronald E. McNair Fellow and a BMS Minority Chemist Fellow (2009–2011).



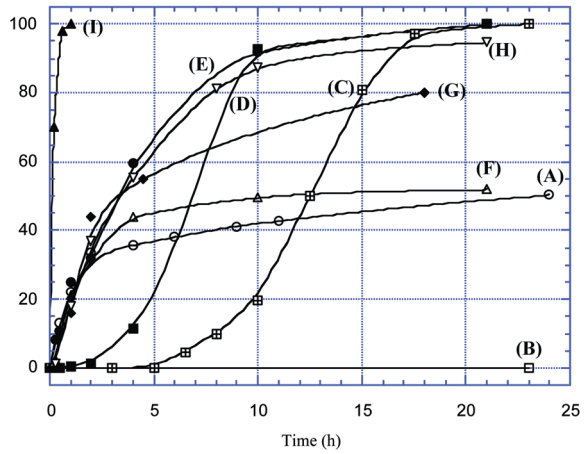


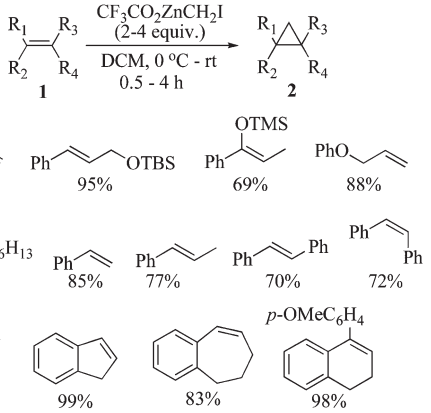
Fig. 1 Plot of conversion of *trans*-β-methylstyrene against time. The curves presented are: (A) no RXH, (B) EtOH, (C) Cl_2CHCH_2OH, (D) CCl_3CH_2OH, (E) CF_3CH_2OH, (F) 2-chlorophenol, (G) 2,6-dichlorophenol, (H) $PhCO_2H$, and (I) CF_3CO_2H.

Mechanistic experimentation shows that a [2 + 1] reaction pathway is likely to be occurring based upon the exclusive formation of product **5** when *trans*-1,6-diiodo-3-hexene is subjected to the reaction conditions (Scheme 3).[28b,29,30]

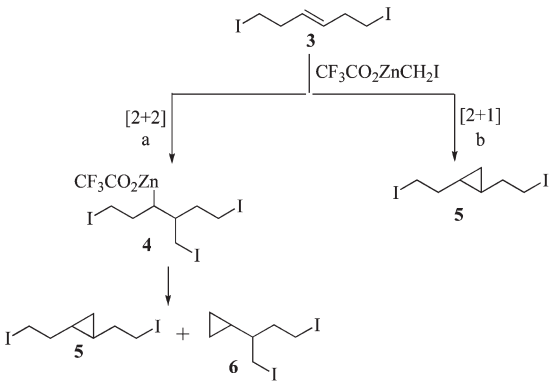
Studies have shown that the reactivity of relatively unreactive ROZnX species can be accelerated by addition of Lewis acids.[28,31–34] For example, the reactivity of zinc reagent $Cl(CH_2)_2OZnCH_2I$ was enhanced when $AlCl_3$, $SnCl_4$, $TiCl_4$, $AlEt_3$, or Et_2AlCl were added (Table 1).[28b] It is possible that the Lewis acid complexes with the oxygen atom in $ROZnCH_2I$, which breaks up the zinc aggregate[35] and/or increases the electrophilicity of the reagent.

Yian Shi

Yian Shi was born in Jiangsu, China in 1963. He obtained his B.Sc. degree from Nanjing University in 1983, M.Sc. degree from University of Toronto with Professor Ian W. J. Still in 1987, and Ph.D. degree from Stanford University with Professor Barry M. Trost in 1992. After a postdoctoral study at Harvard Medical School with Professor Christopher Walsh, he joined Colorado State University as assistant professor in 1995 and was promoted to associate professor in 2000 and professor in 2003. His current research interests include the development of new synthetic methods, asymmetric catalysis, and synthesis of natural products.

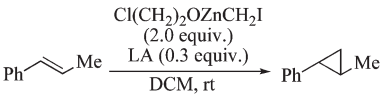


Scheme 2 Cyclopropanation of olefins accelerated by CF_3CO_2H.



Scheme 3 Cyclopropanation of *trans*-1,6-diiodo-3-hexene with $CF_3CO_2ZnCH_2I$.

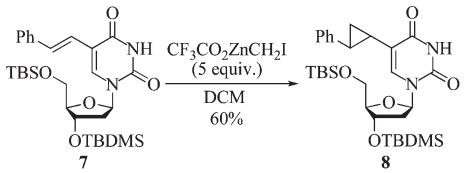
Table 1 Effect of Lewis acid on cyclopropanation using $Cl(CH_2)_2OZnCH_2I$



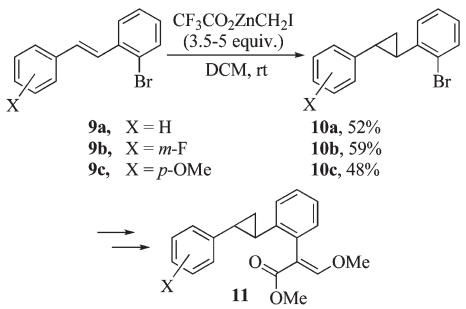
Entry	LA	Time (h)	Conversion (%)
1	$Ti(Oi\text{-}Pr)_4$	45	<1
2	$Cu(OTf)_2$	36	5
3	$FeCl_3$	36	41
4	$AlCl_3$	40	70
5	$SnCl_4$	40	73
6	$TiCl_4$	36	76
7	$AlEt_3$	36	97
8	Et_2AlCl	48	100

Applications of the $ROZnCH_2Y$ cyclopropanation reagent

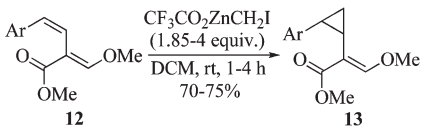
The high reactivity and tunability of this new class of reagent has led to numerous applications in the synthesis of complex and biologically active molecules containing cyclopropanes. These carbenoids have also found use in ring expansion and chain extension reactions, as well as other useful synthetic



Scheme 4 Synthesis of cyclopropane **8**.



Scheme 5 Synthesis of strobilurin analogues **11**.



Scheme 6 Synthesis of cyclopropanes **13**.

transformations. The following section highlights some of these applications.

In 2000, in their studies to elucidate the mechanism of thiyl radical damage in DNA, Schiesser, Greenberg, and coworkers synthesized cyclopropane **8** in 60% yield as a single diastereomer from pyrimidine nucleoside **7** using the $CF_3CO_2ZnCH_2I$ reagent (Scheme 4).[36]

In their study of strobilurin analogues, Rossi, Carpita, and coworkers synthesized cyclopropanes **10** in moderate yield from (*E*)-2-bromostilbenes using the $CF_3CO_2ZnCH_2I$ reagent at room temperature (Scheme 5).[37] Cyclopropanes **13** were also synthesized as strobilurin analogues using the same method in 70–75% yield (Scheme 6).[38] In both of these examples it was found that the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system was more efficient than the cyclopropanation method using diazomethane/$Pd(OAc)_2$.

In 2003, Lam and coworkers at Bristol-Myers Squibb demonstrated that vinyl amides are reactive substrates towards cyclopropanation using the $CF_3CO_2ZnCH_2I$ reagent, giving cyclopropanation products **14** and **15** in good yield (Fig. 2).[39] Fardis and coworkers at Gilead Sciences synthesized cyclopropanes **16** and **17** from their corresponding vinyl amides *via* the same method as a part of their search for potential inhibitors of HIV-1 integrase enzymes (Fig. 2).[40]

The ability of the $RXZnCH_2Y$ reagents to be fine-tuned as needed is exemplified in the cyclopropanation of intermediate **18** en route to the synthesis of ketone **21**. Frey and coworkers at Merck installed the cyclopropane unit of **19** through the reaction of vinylic ether **18** (Scheme 7).[41] While the reaction using

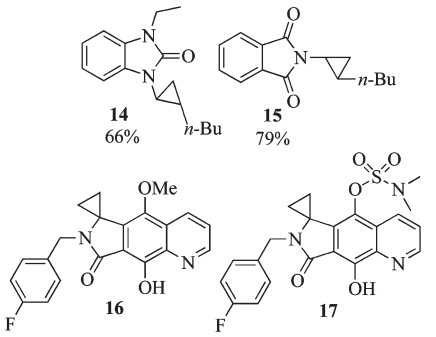
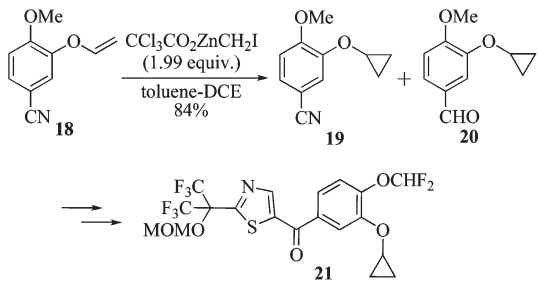
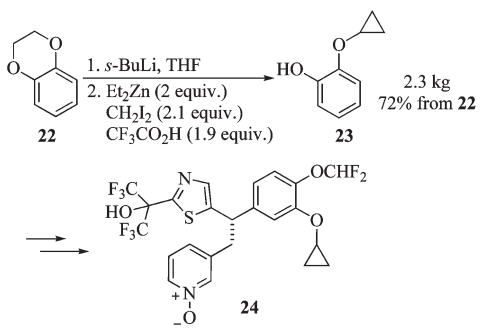


Fig. 2 Cyclopropanation of *N*-vinyl substrates.



Scheme 7 Synthesis of **21** *via* cyclopropane **19**.



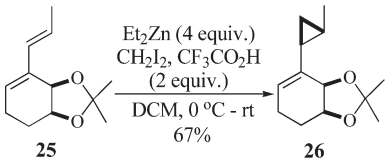
Scheme 8 Synthesis of PDE4 Inhibitor **24**.

CF_3CO_2H worked well on a small scale, failure to control the temperature upon scale-up resulted in the increased yield of undesired aldehyde **20**. Replacement of CF_3CO_2H with CCl_3CO_2H reduced the amount of side product formed and yielded cyclopropane **19** in 55 grams.

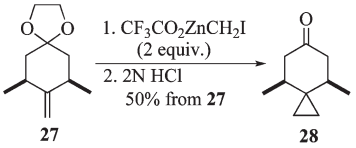
In a large scale synthesis of potent PDE4 inhibitor **24**, O'Shea, Chen, and coworkers at Merck demonstrated that a vinyl ether, generated *in situ* from benzodioxane **22** and *s*-BuLi, can be cyclopropanated using the $CF_3CO_2ZnCH_2I$ reagent, affording 2.3 kg of desired product **23** in 72% overall yield (Scheme 8).[42]

To determine the absolute configuration of products obtained by whole-cell fermentation using toluene dioxygenase, Hudlicky and coworkers prepared cyclopropane **26** as a single diastereomer in 67% yield using the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system (Scheme 9).[43]

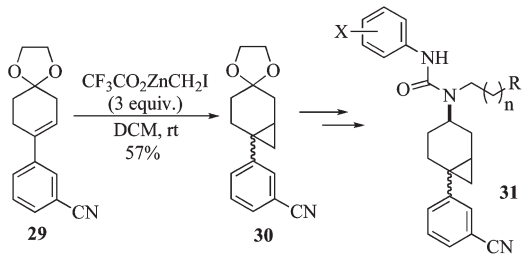
Mihovilovic and coworkers synthesized cyclopropane **28** as a substrate for a microbial Baeyer–Villiger oxidation study. After



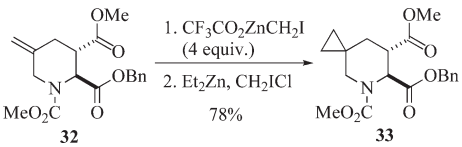
Scheme 9 Synthesis of cyclopropane **26** as a single diastereomer.



Scheme 10 Synthesis of **28** for an enzymatic oxidation study.



Scheme 11 Synthesis of MCH receptor antagonists (**31**) *via* cyclopropane **30**.



Scheme 12 Synthesis of cyclopropanated pipecolic acid derivative **33**.

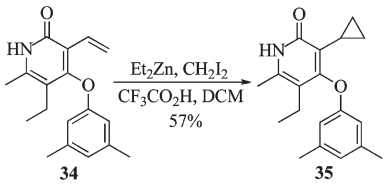
screening Simmons–Smith conditions using Cu/Zn couple and activated Zn, the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system gave the best results for the cyclopropanation (Scheme 10).[44]

McBriar, Xu, and coworkers at Schering–Plough synthesized and studied a series of melanin concentrating hormone (MCH) receptor antagonists **31** as potential treatments for obesity. Intermediate cyclopropane **30** was obtained in 57% yield using $CF_3CO_2ZnCH_2I$ (Scheme 11).[45] It was indicated that cyclopropanation of **29** could only be realized by using this method.

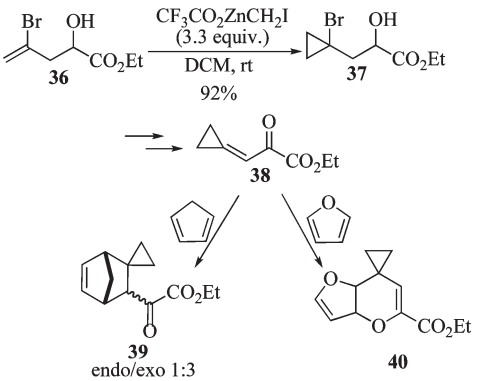
Zhuo, Yao, and coworkers at Incyte synthesized pipecolic acid derivative **33**, an intermediate in the synthesis of *trans*-2,3-piperidine-dicarboxylic acid derivatives, in 78% yield from allylic amine **32** using the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system (Scheme 12).[46]

Cyclopropane **35** was synthesized by Benjahad, Nguyen, and coworkers using the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system in 57% yield as part of a structure–activity relationship study of non-nucleoside reverse transcriptase inhibitors (NNRTI) for probing anti-HIV activity (Scheme 13).[47]

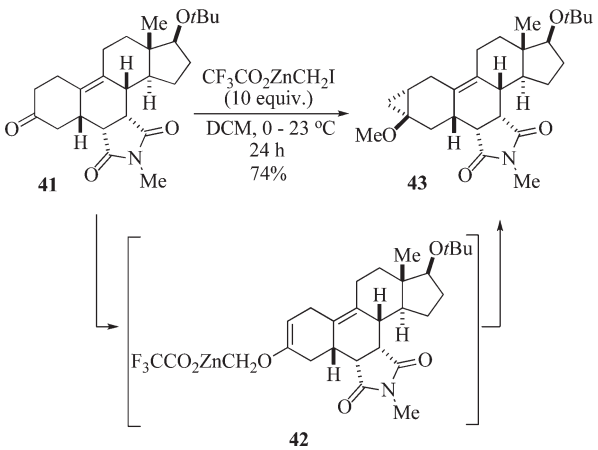
De Meijere and coworker cyclopropanated vinyl bromide **36** in 92% yield, which was subsequently transformed into



Scheme 13 Synthesis of cyclopropanated NNRTI analogue **35**.



Scheme 14 Synthesis of methylene cyclopropane **38** and subsequent transformations.

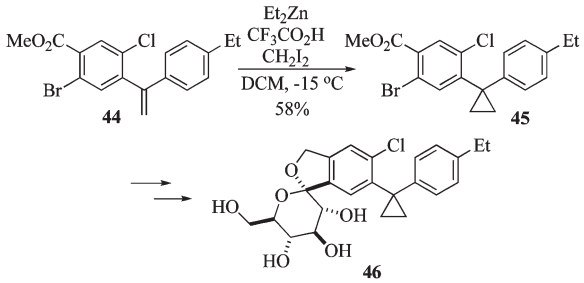


Scheme 15 Cyclopropanation of steroid **41**.

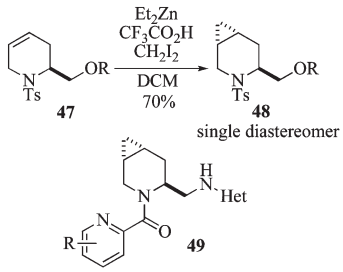
methylene cyclopropane **38**, using the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system. Compound **38** is a useful building block which can undergo various organic transformations such as Diels–Alder reactions and hetero-Diels–Alder reactions to yield useful synthetic targets (Scheme 14).[48]

In their studies of steroidal tetracycles, de Meijere and coworkers reported steroid **41** was cyclopropanated in 74% yield using the $CF_3CO_2ZnCH_2I$ reagent, possibly *via* zinc-substituted methyl ether intermediate **42** (Scheme 15).[49] Cyclopropane steroid analogues of **43** have shown to exhibit irreversible inhibition of cholesterol oxidase.

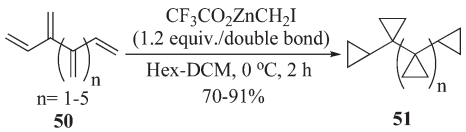
As part of their investigation into possible sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors, Lv, Chen, and coworkers reported the cyclopropanation of 1,1-disubstituted olefin **44** in 58% yield using the $CF_3CO_2ZnCH_2I$ reagent (Scheme 16).[50] Compound **46** displayed 5 times the potency and



Scheme 16 Synthesis of SGLT2 inhibitor **46** *via* cyclopropane **45**.



Scheme 17 Synthesis of cyclopropane **48**.



Scheme 18 Synthesis of ivyanes through poly-cyclopropanation.

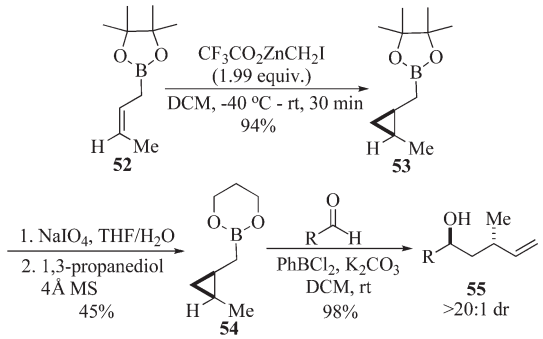
50 times the selectivity for SGLT2 inhibition than the methylene derivative.

In order to study how small molecules affect the orexin ligand and receptor system for the treatment of sleeping disorders, orexin receptor antagonists **49** were synthesized by Maton and coworkers at GlaxoSmithKline. Key intermediate **48** was synthesized using the $CF_3CO_2ZnCH_2I$ reagent and obtained as a single diastereomer in 70% yield (Scheme 17).[51]

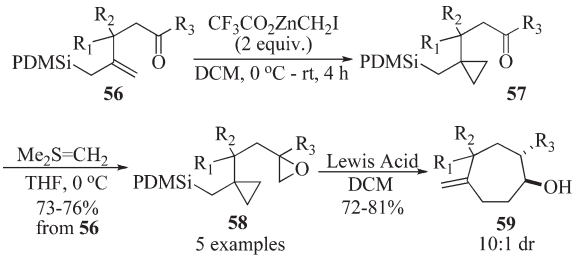
In 2011, Sherburn and coworkers synthesized a new class of hydrocarbon chains **51**, termed "ivyanes", accessed by the cyclopropanation of the corresponding dendralenes **50**. After screening various conditions for cyclopropanation, only the $CF_3CO_2ZnCH_2I$ reagent was able to provide complete conversion of the starting material in good to high yield, and the reaction was also amenable to gram scale (Scheme 18).[52] These new compounds adopt helical conformations in the gas and solid phases and therefore have potential biological applications.

Krauss and coworker recently disclosed the use of the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system for the synthesis of cyclopropane allylborane reagent **53** in 94% yield. Borane **53** is converted to **54** which can then undergo diasteroselective homocrotylboration of aldehydes to yield homocrotylated alcohols **55** in high yields and high diastereoselective ratios (Scheme 19).[53]

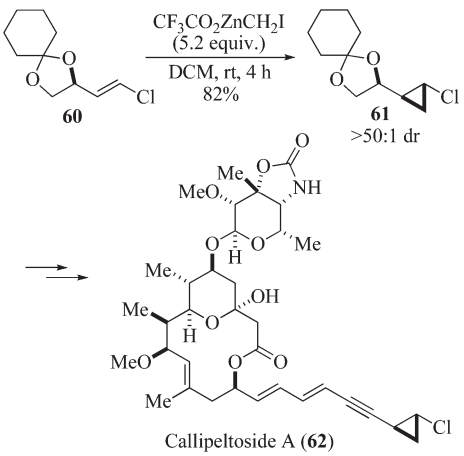
Pulido and coworkers recently reported that allyl silanes **56** can be cyclopropanated in good yields using the $CF_3CO_2ZnCH_2I$ carbenoid to give compounds **57**. Cyclopropanes **57** can be



Scheme 19 Synthesis of homocrotylated alcohols **55**.



Scheme 20 Synthesis of cycloheptanols **59** from oxoallylsilanes **56**.

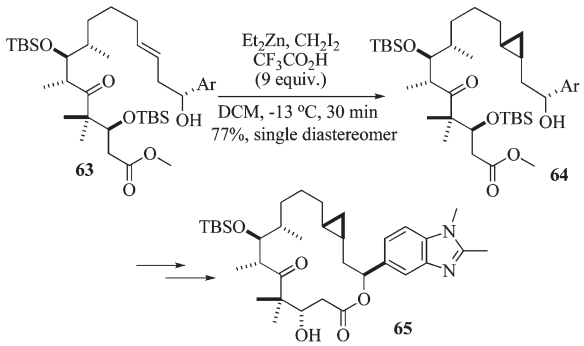


Scheme 21 Total synthesis of callipeltoside A (**62**).

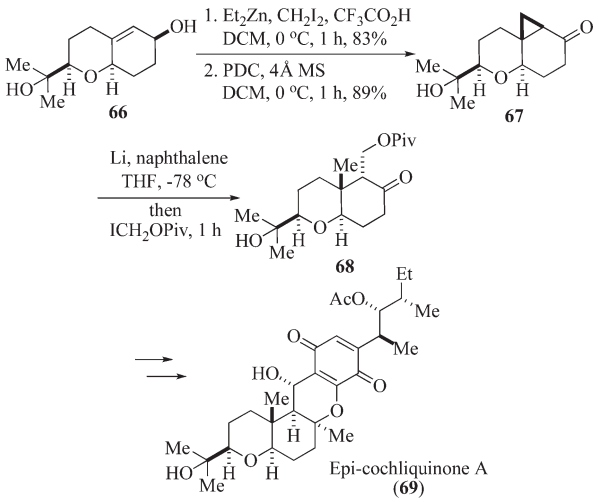
converted to functionalized cycloheptanols **59** upon epoxidation of the ketone and cyclization in good yields and diastereoselective ratios up to 10 : 1 *trans*/*cis* (Scheme 20).[54]

The $CF_3CO_2ZnCH_2I$ reagent has also found applications in large molecule synthesis. In 2001, Evans and coworkers synthesized cyclopropane **61** as an intermediate in the synthesis of Callipeltoside A (**62**) (Scheme 21). Cyclopropanation of vinyl chloride **60** proved to be challenging under a variety of Simmons–Smith conditions, however using the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system, desired cyclopropane **61** was obtained in 82% yield and >50 : 1 dr.[55]

During the synthesis of cyclopropane-based epothilone analogues, Altmann and coworkers used the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system for the efficient and stereoselective cyclopropanation of *trans*-homoallylic alcohol **63** to obtain **64** in 77% yield as



Scheme 22 Synthesis of epothilone analogue **65**.



Scheme 23 Synthesis of epi-cochliquinone A (**69**).

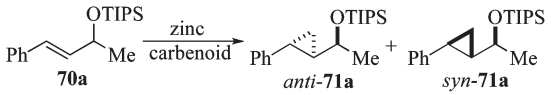
essentially one diastereomer (Scheme 22).[56] The corresponding *cis* isomer was also synthesized by the same method from the corresponding *cis* alkene, resulting in 89% yield as a 5 : 1 mixture of diastereomers.

Hosokawa, Tatsuta, and coworkers reported the first total synthesis of epi-cochliquinone A (**69**), an inhibitor of cholesterol acyl transferase. Using the $CF_3CO_2ZnCH_2I$ carbenoid, the trisubstituted double bond of **66** was stereospecifically cyclopropanated in 83% yield.[57] This transformation set the desired stereochemistry of the resulting methyl group after the ring opening of **67** (Scheme 23).

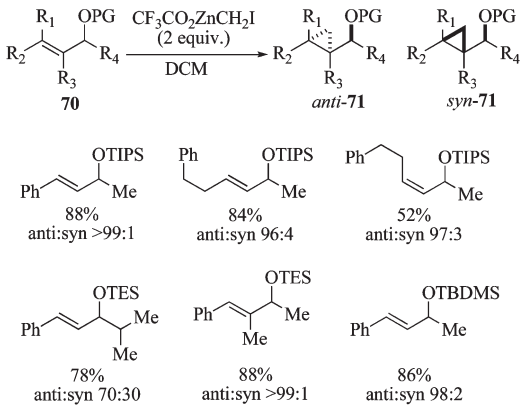
The $RXZnCH_2I$ carbenoid has also demonstrated high diastereoselectivity in various acyclic systems. In a study comparing various Zn carbenoids in the cyclopropanation of silyl-protected allylic alcohol **70a**, Charette and coworkers found that $CF_3CO_2ZnCH_2I$ afforded *anti*-cyclopropylcarbinol silyl ether **71a** with the highest reactivity and diastereoselectivity (Table 2).[58] The $CF_3CO_2ZnCH_2I$ carbenoid efficiently cyclopropanated a wide range of protected allylic alcohols in high yield and high diastereoselectivity (Scheme 24).

In 2005, Walsh and coworkers used the $RXZnCH_2Y$ carbenoids to synthesize *syn* cyclopropyl and iodocyclopropyl alcohols with up to four stereocenters in good yields and high selectivity *via* an elegant, tandem asymmetric addition/cyclopropanation reaction sequence (Scheme 25).[59a] Allylic zinc

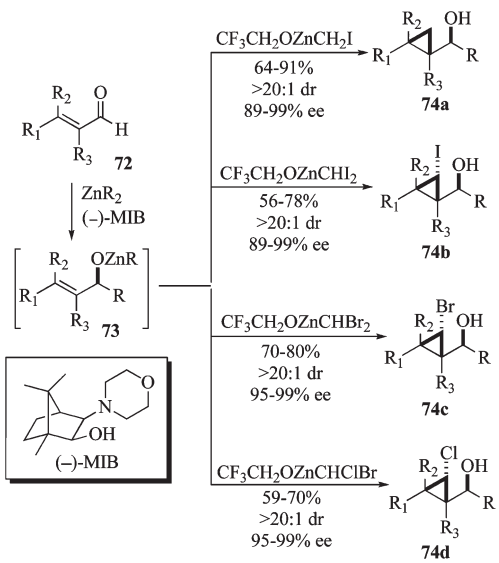
Table 2 Cyclopropanation of protected allylic alcohol **70a**



Entry	Carbenoid	Conv (%)	*anti*-**71a** : *syn*-**71a**
1	$IZnCH_2I$	8	84 : 16
2	$EtZnCH_2I$	48	92 : 8
3	$EtZnCH_2Cl$	92	94 : 6
4	$Zn(CH_2I)_2$	44	90 : 10
5	$Zn(CH_2Cl)_2$	88	97 : 3
6	$2,4,6\text{-}Cl_3C_6H_2OZnCH_2I$	60	89 : 11
7	$2,4,6\text{-}F_3C_6H_2OZnCH_2I$	52	93 : 7
8	**$CF_3CO_2ZnCH_2I$**	**>99**	**>99 : 1**

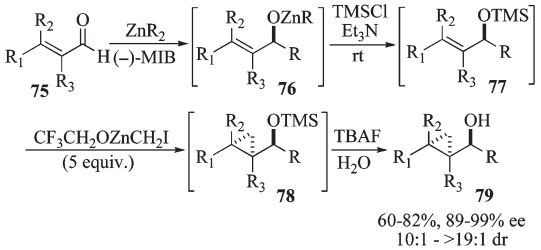


Scheme 24 Cyclopropanation of protected allylic alcohols.

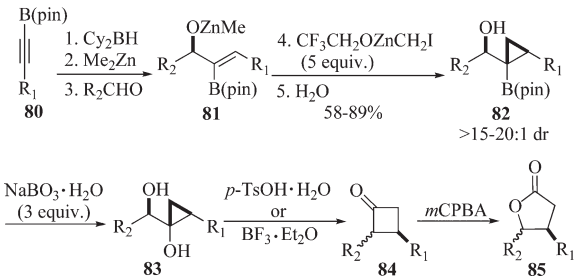


Scheme 25 Diastereoselective cyclopropanation and halocyclopropanation.

alkoxide **73** is generated *in situ* in the presence of (−)-(morpholino)isoborneol [(−)-MIB)] and undergoes cyclopropanation to form **74a** (or iodocyclopropanation to form **74b**) using $ZnEt_2$,



Scheme 26 Synthesis of *anti*-cyclopropyl alcohols.

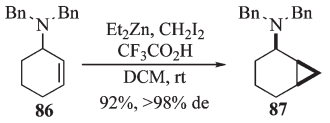


Scheme 27 Cyclopropanation of heterobimetallic alkoxide **81** and subsequent transformations.

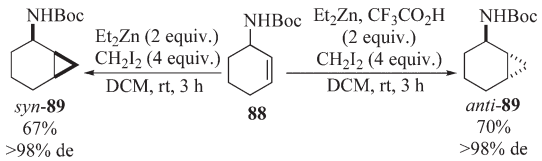
CF_3CH_2OH and CH_2I_2 (or CHI_3). In their subsequent studies, bromo- (**74c**) and chlorocyclopropanation (**74d**) were developed using $CHBr_3$ and $CHBr_2Cl$, respectively, as surrogates for CHI_3 or CH_2I_2.[59b] Interestingly, it was found that the halogen can be *cis* or *trans* to the carbinol, depending on the substituents of the olefin. The resulting halocyclopropyl alcohols (**74b–d**) are potentially useful for the synthesis of 1,2,3-trisubstituted cyclopropanes by various functionalization methods. Recently, they also reported that *anti*-substituted cyclopropyl alcohols **79** can be obtained in high yields and high stereoselectivity from achiral α,β-unsaturated aldehydes upon conversion of the Zn alkoxide **76** to the TMS silyl enol ether **77** before cyclopropanation (Scheme 26).[59c]

Walsh and coworkers also employed the $CF_3CH_2OZnCH_2I$ carbenoid in their studies of the applications of 1-alkenyl-1,1-heterobimetallics, such as **81** (Scheme 27).[60a] The alkoxide-directed cyclopropanation of **81** was carried out with Et_2Zn, CF_3CH_2OH, and CH_2I_2 to afford cyclopropyl boronate ester **82** in >15–20 : 1 dr and 58–89% yield, which can be further elaborated into compounds such as trisubstituted α- hydroxycyclopropyl carbinols **83**, cyclobutanones **84**, and lactones **85** (Scheme 27). Recently, as an extension of this chemistry, the enantio- and diastereoselective synthesis of aminocyclopropyl carbinols from *N*-tosyl substituted ynamides was reported *via* a pathway analogous to Scheme 27.[60b]

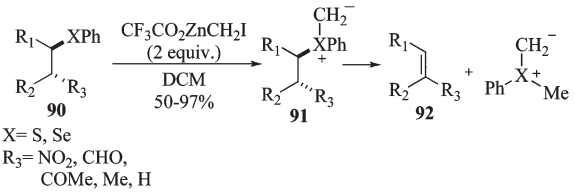
In 2007, Davies and coworkers utilized the CF_3CO_2H-accelerated cyclopropanation system in the reaction of allylic amines **86** and **88**.[61a] 3-(*N*,*N*-Dibenzylamino)cyclohexene (**86**) was cyclopropanated to form *syn*-**87** in 92% yield and >98% de (Scheme 28). It was found that the diastereoselectivity was heavily influenced by the *N*-protecting group. For instance, when the *N*-protecting group is Boc (**88**), the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system gave *anti*-**89** in 70% yield and >98% de, whereas Furukawa's conditions (Et_2Zn/CH_2I_2) gave *syn*-**89** in 67% yield and



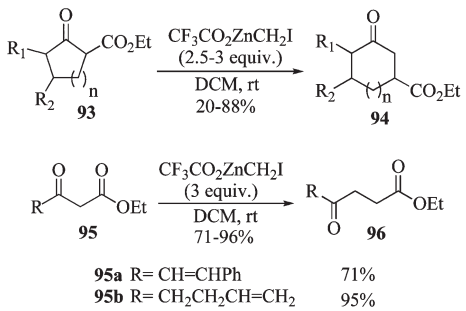
Scheme 28 Diastereoselective cyclopropanation of allylic amine **86**.



Scheme 29 Diastereoselective cyclopropanation using different Zn carbeniods.



Scheme 30 Carbenoid-mediated elimination of sulfides and selenides.

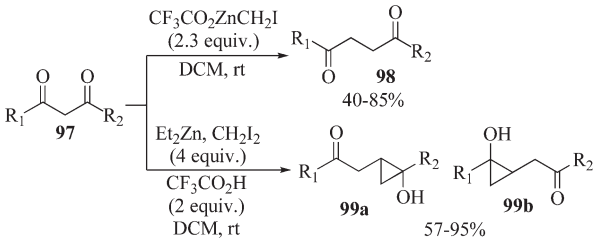


Scheme 31 Ring expansion and chain extension of β-keto esters.

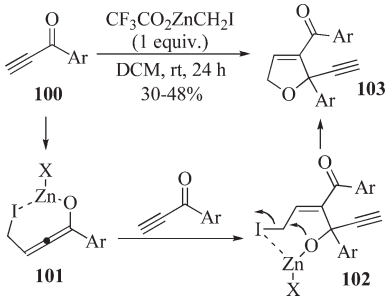
>98% de (Scheme 29). It was proposed that $CF_3CO_2ZnCH_2I$ forms a complex with the substrate *via* deprotonation of the carbamate **88**, which makes the *syn* face of the olefin inaccessible for cyclopropanation. In the case of $Zn(CH_2I)_2$, it is proposed that the carbamate directs the cyclopropanation to the same face of the substrate. This stereodivergent cyclopropanation protocol has recently been extended to 5, 7 and 8-membered rings.[61b,c]

$RXZnCH_2Y$ reagents have also found utility in a variety of other synthetic transformations. In 2002, Gautier, Piettre, and coworkers reported the synthesis of alkenes (**92**) *via* the $CF_3CO_2ZnCH_2I$ carbenoid-mediated elimination of sulfides and selenides in moderate to high yields (Scheme 30).[62] The elimination likely proceeds *via* ylide **91**, generated by methylation of the sulfur or selenium atom.

Xue and coworkers demonstrated the ring expansion of cyclic β-keto esters using the $Et_2Zn/CH_2I_2/CF_3CO_2H$ system (Scheme 31).[63] Highest yields were obtained with large ring ketones (**93**, n = 2, 3, 4 or 8). The chain extension of acyclic β-keto esters was also achieved in good to high yields using



Scheme 32 Chain extension of 1,3-diketones and synthesis of 1,2-disubstituted cyclopropanols.



Scheme 33 Synthesis of 2,5-dihydrofurans **103** using $CF_3CO_2ZnCH_2I$.

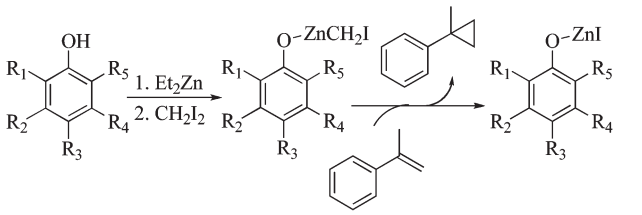
$CF_3CO_2ZnCH_2I$, and bulky R groups do not decrease the efficiency (Scheme 31).[64] When R = CH=CHPh (**95a**), the substrate selectively underwent a chain extension reaction leaving the double bond unreacted, and the corresponding product was obtained in 71% yield. When R = $CH_2CH_2CH{=}CH_2$ (**95b**), the corresponding product, which was both cyclopropanated as well as chain extended, was obtained in 95% yield. Subsequently, the chain extension of 1,3-diketones **97** was also achieved using $CF_3CO_2ZnCH_2I$ to synthesize 1,4-diketones **98** in good yields (Scheme 32).[65] Under slightly modified conditions, 1,2-disubstituted cyclopropanols (**99**) can be obtained, with the ratio of **99a** to **99b** depending on the nature of R_1 and R_2.

In 2008, Xue and coworkers reported that 2,5-dihydrofurans (**103**) can be formed in modest yields upon reaction of the $CF_3CO_2ZnCH_2I$ carbenoid with acetylenic ketones **100** (Scheme 33).[66] It is proposed that the active Zn carbenoid reacts in a Michael-type addition with the substrate **100**, followed by addition of a second equivalent of ketone to form **102**, and upon cyclization the 2,5-dihydrofurans **103** were obtained.

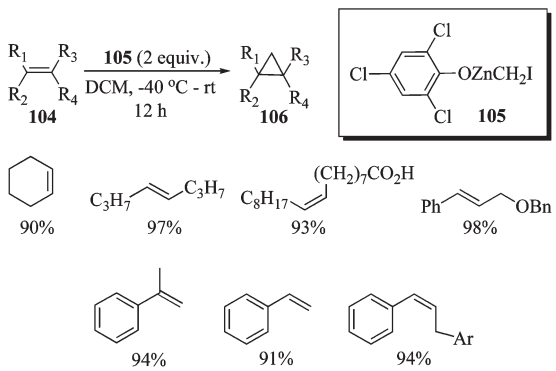
Investigation of $ArOZnCH_2I$ and $(RO)_2P(O)OZnCH_2I$ reagents

In 2000, Charette and coworkers reported their detailed investigations of zinc carbenoids derived from various phenols for the cyclopropanation of olefins.[67] Reactivity of the reagents can be tuned based upon the acidity of the phenol additives, which vary in their substitution patterns (Table 3).[68] The 2,4,6-trichlorophenol-derived zinc reagent (Table 3, entry 5) exhibited the highest reactivity and various alkyl- and arylsubstituted alkenes could be cyclopropanated in high yields after reacting over 12 h (Scheme 34).

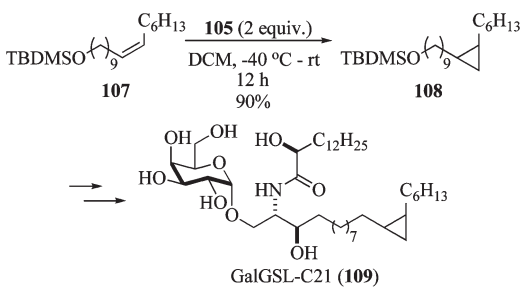
Table 3 Reactivity of various $ArOZnCH_2I$ reagents



Entry	Phenol	Conv. (%)
1	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	22
2	$R_1 = R_2 = H$, $R_3 = F$, $R_4 = R_5 = H$	45
3	$R_1 = R_2 = H$, $R_3 = Br$, $R_4 = R_5 = H$	60
4	$R_1 = R_2 = H$, $R_3 = NO_2$, $R_4 = R_5 = H$	NR
5	$R_1 = R_3 = R_5 = Cl$, $R_2 = R_4 = H$	>95
6	$R_1 = R_3 = R_5 = Br$, $R_2 = R_4 = H$	>95
7	$R_1 = R_3 = R_5 = Me$, $R_2 = R_4 = H$	66
8	$R_1 = R_5 = Me$, $R_2 = R_4 = H$, $R_3 = Br$	>95
9	$R_1 = R_2 = R_3 = R_4 = R_5 = F$	>95



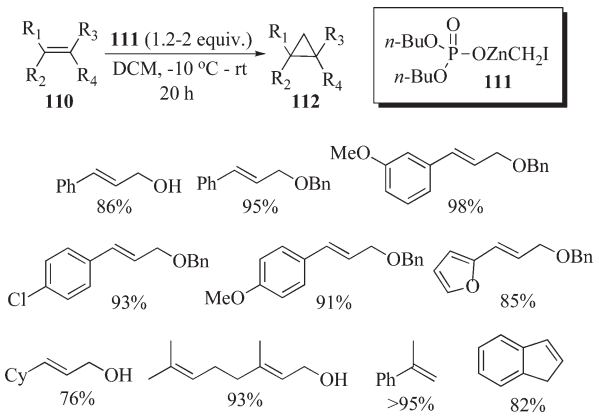
Scheme 34 Cyclopropanation of alkyl- and arylsubstituted olefins using reagent **105**.



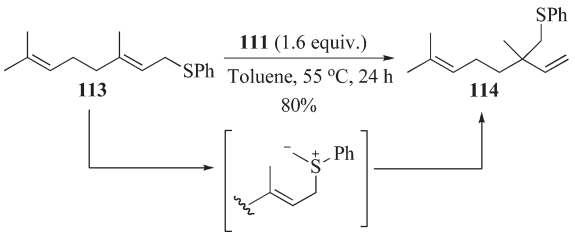
Scheme 35 Synthesis of GalGSL-C21 (**109**).

In their studies of natural Sphingomonas Glycolipids' abilities to activate natural killer T cells, Kronenberg and coworkers employed reagent **105** for the cyclopropanation of *cis* alkene (**107**) to synthesize **108** in 90% yield.[69] Intermediate **108** was carried on to synthesize GalGSL-C21 (**109**) (Scheme 35).

Charette and coworkers have also reported the use of iodomethylzinc phosphates as cyclopropanating reagents.[70,71] Recently, the iodomethylzinc phosphate **111** was synthesized through the reaction of di-*n*-butylphosphoric acid with Et_2Zn



Scheme 36 Cyclopropanation using $(n\text{-BuO})_2P(O)OZnCH_2I$ (**111**).



Scheme 37 [2,3]-Sigmatropic rearrangement of allylic sulfide **113**.

and CH_2I_2.[71] Reagent **111** was shown to be effective in cyclopropanating a variety of allylic alcohols and ethers as well as two unfunctionalized alkenes in high yields (Scheme 36).

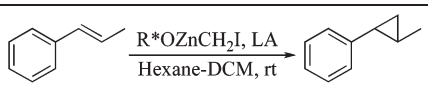
Charette and coworkers used the $(n\text{-BuO})_2P(O)OZnCH_2I$ carbenoid (**111**) to achieve the [2,3]-sigmatropic rearrangement of allylic sulfide **113** in 80% yield (Scheme 37).[71]

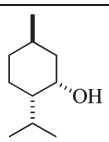
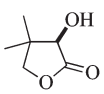
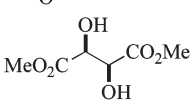
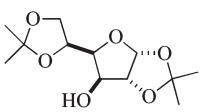
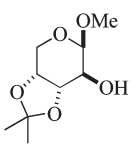
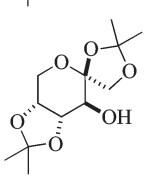
Asymmetric cyclopropanation using R*XZnCH$_2$Y

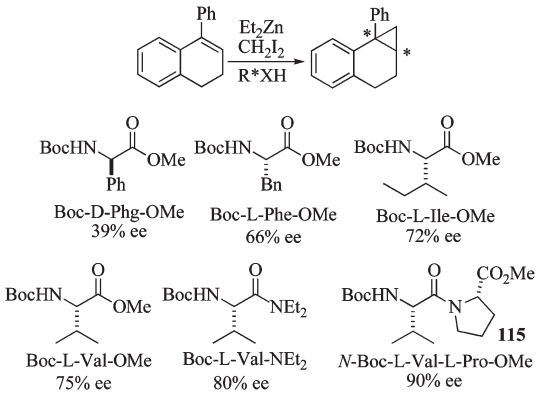
Tremendous growth has been achieved in the development of the asymmetric Simmons–Smith reaction, employing chiral auxiliaries,[72–76] reagents,[77] and catalysts,[78] and the topic has been extensively reviewed.[3] In general, these methods require substrates that contain heteroatom-directing functionalities which is beneficial for reactivity and critical for the stereocontrol of the reaction. Asymmetric Simmons–Smith cyclopropanation of substrates lacking a directing group remains however challenging.[79] With the discovery that the $RXZnCH_2I$ type zinc reagents are a class of very effective cyclopropanation reagents, the opportunity to induce chirality by substituting a chiral RX additive provides a very attractive strategy for the asymmetric cyclopropanation of olefins, particularly those without directing groups.

In their 1998 studies, Shi and coworkers also reported a 51% ee could be obtained for *trans*-β-methyl styrene when using a fructose-derived chiral modifier in the presence of a Lewis acid (Table 4, entry 6).[28a] This represents the first example of the

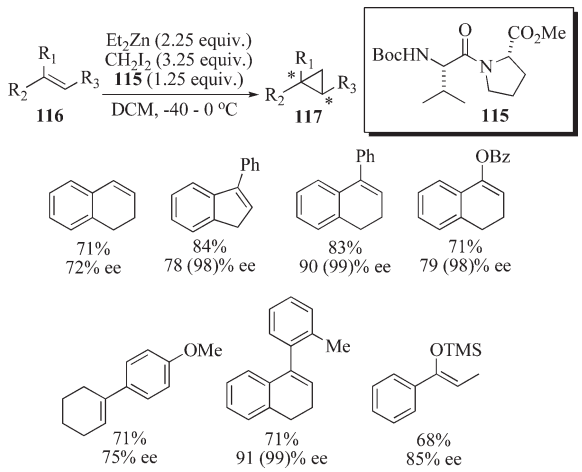
Table 4 Cyclopropanation of *trans*-β-Methylstyrene Using R*OZnCH$_2$I



Entry	R*OH	LA	Time (h)	Conversion (%)	ee (%)
1		Et_2AlCl	44	85	8
2		Et_2AlCl	45	91	17
3		Et_2AlCl	36	4	nd
4		$TiCl_4$	64	6	8
5		Et_2AlCl	45	19	20
6		Et_2AlCl	44	74	51



Scheme 38 Asymmetric cyclopropanation with amino acid derivatives as modifiers.



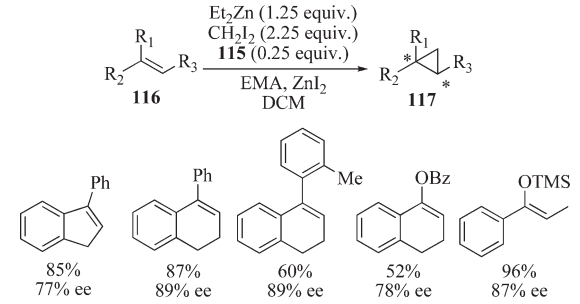
Scheme 39 Asymmetric cyclopropanation of olefins with *N*-Boc-L-Val-L-Pro-OMe (**115**).

asymmetric Simmons–Smith-type cyclopropanation of unfunctionalized olefins affording reasonable enantioselectivities. Other chiral alcohols were also examined, but they resulted in lower facial selectivity (Table 4).[28b]

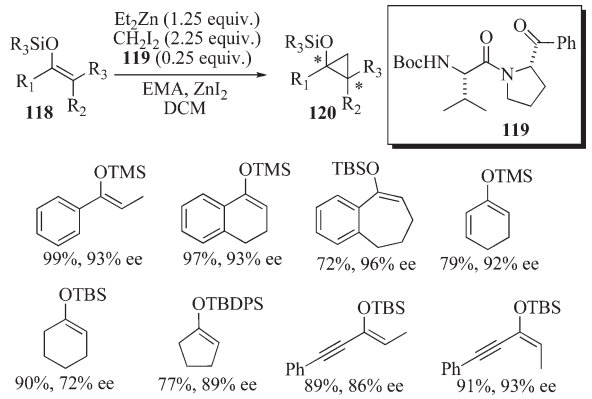
In 2003, Shi and coworkers reported various amino acid derivatives as chiral modifiers, and 90% ee was obtained in the reaction of 1-phenyl-3,4-dihydronaphthylene when *N*-Boc-L-Val-L-Pro-OMe **115** was used (Scheme 38).[80]

N-Boc-L-Val-L-Pro-OMe (**115**) is readily available from the peptide coupling of commercially available L-Pro-OMe·HCl and Boc-L-Val using triethylamine and diethylphosphoryl cyanide.[81] Approximately 80% of dipeptide **115** can be recovered from the cyclopropanation reaction mixture and use of the recycled ligand is equally effective in promoting high reactivity and enantioselectivity. Up to 91% ee was obtained for the unfunctionalized olefins studied (Scheme 39). Simple *cis*, *trans*, and trisubstituted olefins are effective substrates for this system and enols were also found to be reactive. The isolated ee's can be improved in some cases by recrystallization.

In 2005, Shi and coworkers reported the catalytic asymmetric process of this reaction using sub-stoichiometric amounts of ligand. Initial studies showed that as the amount of dipeptide



Scheme 40 Asymmetric cyclopropanation of olefins with catalytic amount of **115**.



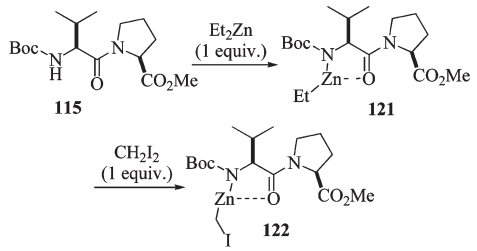
Scheme 41 Asymmetric cyclopropanation with catalytic amount of dipeptide **119**.

was decreased to catalytic amounts, the enantioselectivity was likewise lowered, probably due to competing achiral background reactions. It was found that adding achiral additives, such as ethylmethoxyacetate (EMA), suppressed the background reaction and maintained enantioselectivities.[82] The yields and selectivity obtained with the catalytic system are comparable to the system using stoichiometric loading (Scheme 39 *vs.* Scheme 40). To the best of our knowledge, this constitutes the first catalytic enantioselective Simmons–Smith type cyclopropanation of unfunctionalized olefins with good enantioselectivities.

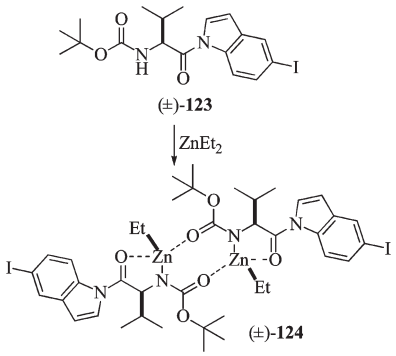
This catalytic system was expanded to a variety of cyclic and acylic silyl enol ethers. Improved ee's were obtained by using slightly modified dipeptide **119** (Scheme 41).[83] Approximately 90% of the dipeptide could be recovered after the reaction and the recycled ligand provided similar levels of reactivity and enantioselectivity for subsequent cyclopropanations.

No cyclopropanation took place when *N*-methylated dipeptide *N*-Boc-*N*-Me-L-Val-L-Pro-OMe was used in the reaction of 1-phenyl-3,4-dihydronaphthalene, indicating that the N–H bond of the dipeptide is important for the reaction.[84] It was shown that upon treatment of **115** with Et_2Zn, the nitrogen was deprotonated to form compound **121** (Scheme 42). Subsequent treatment with CH_2I_2 forms **122**, whose structure is consistent with ^1H and ^{13}C NMR data. While the X-ray structures of **121** and **122** were found to be very difficult to obtain, a suitable crystal of related analogue **124** was attained by treating ligand **123** with Et_2Zn, thus providing evidence for the existence of a Zn–N bond (Scheme 43 and Fig. 3).[84]

Zinc species **122**, prepared *via* the aforementioned method (Scheme 42), exhibited very low reactivity in the cyclopropanation reaction. The reactivity of **122** for cyclopropanation was greatly enhanced upon addition of ZnI_2. While the precise role of ZnI_2 in the cyclopropanation awaits further study, ZnI_2 could activate **122** for cyclopropanation *via* coordination to $ZnCH_2I$, or it could break up possible inactive dimers, such as analogues of **124**, to facilitate the opening of a vacant orbital for iodine to coordinate and activate the methylene group for delivery.[85]



Scheme 42 Generation of compound **122**.



Scheme 43 Synthesis of compound **124**.

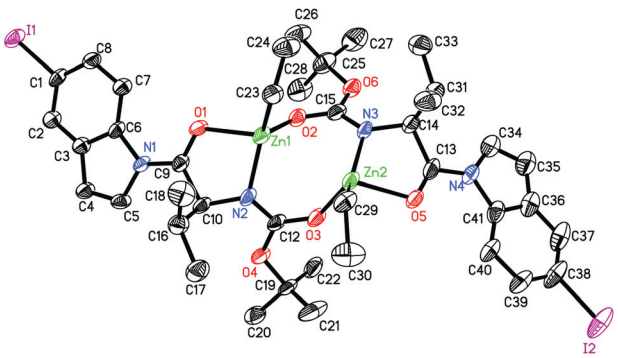


Fig. 3 X-ray structure of **124**.

Based upon these and other mechanistic studies, plausible catalytic cycles are proposed in Scheme 44. Compound **122**, which is formed by reaction of ligand **115**, $ZnEt_2$, and CH_2I_2, is activated by XZnI to form complex **126** which cyclopropanates the alkene and generates **125**. Active species **126** is then regenerated by the rapid transmetalation between **125** and $Zn(CH_2I)_2$ (Scheme 44, pathway **A**). Alternatively, compound **115** could be converted to compound **125** upon deprotonation of **115** and subsequent transmetalation with XZnI. Compound **125** could then act as a chiral Lewis acid to activate $XZnCH_2I$ and form complex **127** which cyclopropanates the alkene (Scheme 44, pathway **B**). As indicated by the X-ray structure of **124** as well as theoretical studies,[86] the oxygen of the Boc group could also coordinate to the Zn atom in **126** and **127** as shown in Fig. 4 (**126′**, **127′**).

In 2005, Charette and coworkers reported the use of chiral phosphoric acid **129** for the asymmetric cyclopropanation of allylic ethers.[70] Upon reaction of **129** with Et_2Zn and CH_2I_2, the resulting iodomethylzinc phosphate efficiently cyclopropanates various ethers derived from cinnamyl alcohol and a homoallylic ether, in high yields and high enantioselectivities (Scheme 45).

The system could also be made catalytic for allylic ethers **131**, with the addition of 1,2-dimethoxyethane to suppress the achiral background reaction (Scheme 46). Reactivity, as well as selectivity, was found to be comparable to the process using stoichiometric amounts of **129**. The authors report that 73% of phosphoric acid **129** could be recovered after isolation from the reaction mixture and purification. Based upon these observations, the authors propose the catalytic cycle shown in Scheme 47. The active iodomethylzinc phosphate catalyst **133** is

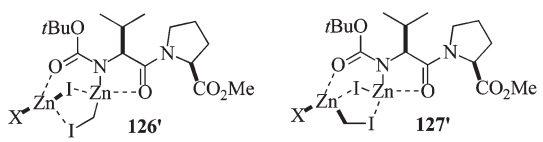
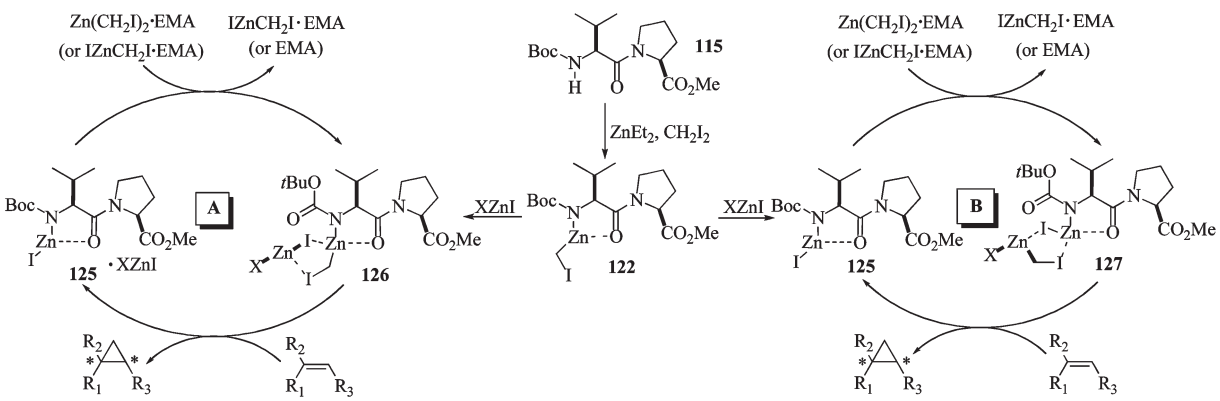
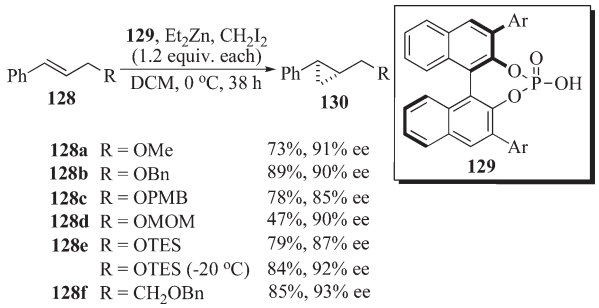


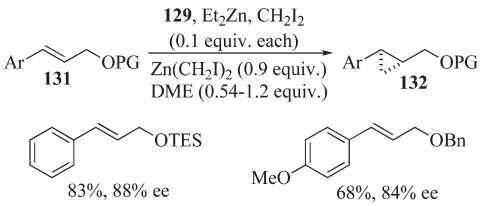
Fig. 4 Coordination of Boc oxygen to Zn.



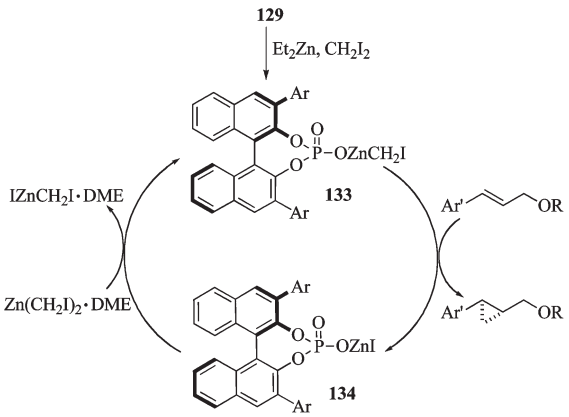
Scheme 44 Plausible catalytic cycles for asymmetric cyclopropanation using dipeptide **115**.



Scheme 45 Asymmetric cyclopropanation of allylic ethers using chiral phosphoric acid **129**.



Scheme 46 Catalytic asymmetric cyclopropanation of allylic ethers using chiral phosphate **129**.



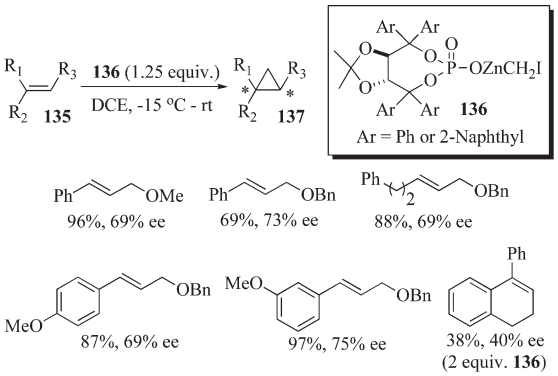
Scheme 47 Plausible catalytic cycle for asymmetric cyclopropanation using phosphoric acid **129**.

formed by reaction of the phosphoric acid **129** and Et_2Zn and CH_2I_2. Upon cyclopropanation of the olefin, $Zn(CH_2I)_2$ serves to regenerate the active catalyst by rapid transmetalation or alkyl exchange with **134**.

In 2006, Charette and coworkers reported the application of chiral TADDOL-derived phosphates (**136**) for the cyclopropanation of allylic ethers and 1-phenyl-3,4-dihydronaphthylene.[87] The TADDOL-derived phosphate ligands are obtained in three steps from their corresponding (*R*,*R*)-TADDOL precursors in 95–99% yield. Using this method, allylic ethers proved to be more reactive than unfunctionalized olefins, resulting in high yields and up to 75% ee (Scheme 48).

Conclusion

The Simmons–Smith reaction has proven to be a highly useful approach in the direct methylene transfer to alkenes to form



Scheme 48 Asymmetric cyclopropanation using chiral TADDOL-derived phosphate **136**.

cyclopropanes. Since the first report in 1958, numerous studies and modifications have greatly advanced the ease and synthetic utility of this reaction. Among the notable recent advances in this area is the class of adjustable organozinc reagents ($RXZnCH_2Y$) compiled in this review. The reactivity and selectivity of the reagent can be rationally and conveniently regulated by finely tuning the steric and/or electronic factors of the complexing additive RX. Derived reagents, such as $CF_3CO_2ZnCH_2I$, have exhibited dramatically increased reactivity for historically-sluggish unfunctionalized olefins and found a variety of applications in synthesis. Encouragingly high ee's are obtained for functionalized and unfunctionalized olefins when chiral modifiers are used. Catalytic asymmetric variations have also been demonstrated. This new class of tunable organozinc reagents provides a vast range of possible combinations for further reaction development.

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