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Regio- and Diastereoselective Carbometalation Reaction of Cyclopropenes

Yair Cohen and Ilan Marek*

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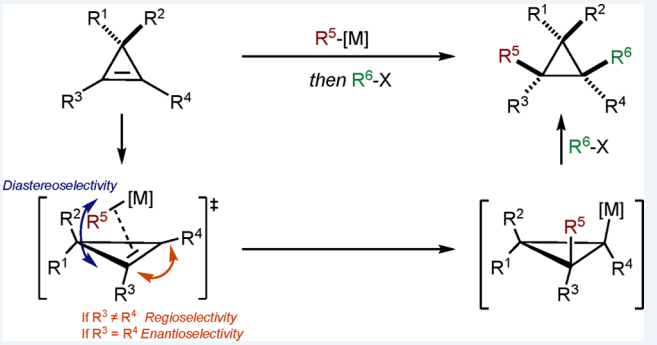
CONSPECTUS: The various facets of the chemistry of cyclopropane derivatives, the smallest carbocycle, are amazingly diverse and continue to fascinate theoreticians, synthetic or structural chemists having interest in fundamental physical, medicinal chemistry, and natural product synthesis. The challenges generated by this intriguing cyclic arrangement of only three tetravalent carbons represent a wide area of the chemical spectrum. From fundamental aspects of bonding through the synthesis of highly strained molecules, the understanding of the mode of action in biological systems to the selective cleavage into acyclic substrates makes the chemistry of these small rings fascinating. Therefore, efficient routes to prepare differently polysubstituted cyclopropanes have always been of a primordial importance. In the past decade, we and others have expanded the scope of the carbometalation reaction of cyclopropenes as a broad and general method to the formation of stereodefined cyclopropane derivatives. Although cyclopropenes, with their even higher strain energy, easily undergo addition reactions of organometallic reagents, their carbometalation reactions generate new regio-, diastereo-, and enantioselectivity issues that needed to be addressed. These various stereochemical aspects accompanied our research from its origins to today, and we are proposing in this Account, a didactic overview of the different ways by which cyclopropenes can lead to the formation of polysubstituted cyclopropanes or open-products possessing several stereogenic centers as a single regio- and diastereomer.



We initially launched our research campaign on the chemistry of these strained three-membered rings by the regio- and diastereoselective copper-catalyzed carbomagnesiation of enantiomerically enriched cyclopropenyl carbinols. The directing alcohol governed both the regio- and diastereoselectivity of the addition and also served as a good leaving group as it undergoes a selective 1,2-elimination reaction to provide enantioenriched alkylidenecyclopropanes in excellent yields and enantiomeric excesses. Then, we turned our attention to the regio- and stereoselective synthesis of stereodefined tri- and tetrasubstituted cyclopropanes through the diastereoselective addition to sp^2-monosubstituted cyclopropenyl ester derivatives. With the aim to further expand this concept to the formation of penta- and hexa-substituted cyclopropanes as single isomer, we had first to design the preparation of the required 1,2-disubstituted cyclopropenes that would control the regioselective addition of the organometallic derivatives. The synthesis of penta- and hexa-substituted cyclopropanes was then reported for the first time as a single regio- and diastereomer. It should be noted that the *in situ* formed cyclopropyl-metal intermediate is configurationally stable and can be subsequently functionalized with pure retention of the configuration by addition of electrophiles. Then, the enantioselective-catalyzed carbometalation reaction of achiral cyclopropenes allowed the synthesis of several new classes of cyclopropane derivatives in high enantiomeric ratios. Finally, by combining the regio- and diastereoselective carbometalation reaction of a cyclopropene with a subsequent reaction of the resulting cyclopropylmetal species, a selective carbon−carbon bond cleavage was observed to lead to the preparation of acyclic substrates possessing several stereocenters including a quaternary carbon stereogenic center. Our original vision of using strain within an embedded double bond in a three-membered ring has provided new routes to the stereoselective synthesis of polysubstituted cyclopropanes and has been extremely successful, as it represents a current new tool for the synthesis of persubstituted cyclopropanes as a single diastereomer.

KEY REFERENCES

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report was the starting point of our study for the regio- and diastereoselective addition to cyclopropenes. Following a selective *syn*-β-elimination reaction, enantioenriched alkylidenecyclopropanes were obtained with excellent selectivities.

- Didier, D.; Delaye, P.-O.; Simaan, M.; Island, B.; Eppe, G.; Eijsberg, H.; Kleiner, A.; Knochel, P.; Marek, I. Modulable and Highly Diastereoselective Carbometalations of Cyclopropenes. *Chem. Eur. J.* **2014**, *20*, 1038−1048.[2] A comprehensive study was performed to understand all aspects related to carbometalation of sp^2-monosubstituted cyclopropenyl ester derivatives.
- Dian, L.; Müller, D. S.; Marek, I. Asymmetric Copper-Catalyzed Carbomagnesiation of Cyclopropenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 6783−6787.[3] This publication described the enantioselective copper-catalyzed addition of Grignard reagents to achiral cyclopropenes. Reacting the resulting cyclopropyl magnesium species with a broad range of electrophiles affords highly substituted cyclopropanes in excellent enantiomeric ratios.
- Cohen, Y.; Augustin, A. U.; Levy, L.; Jones, P. G.; Werz, D. B.; Marek, I. Regio- and Diastereoselective Copper-Catalyzed Carbomagnesiation for the Synthesis of Penta- and Hexa-Substituted Cyclopropanes. *Angew. Chem. Int. Ed.* **2021**, *60*, 11804−11808.[4] Despite the highly strained nature of persubstituted cyclopropanes, the regio- and diastereoselective carbometalation of sp^2-disubstituted cyclopropenes proceeds smoothly, providing a unique access to persubstituted cyclopropanes as a single diastereomer.

1. INTRODUCTION

The triangular geometry of cyclopropanes induces unique properties to the carbon skeletons. Through the angle of 60° between carbon atoms, eclipsed interactions of all substituents are produced. These properties grant an exceptional reactivity making cyclopropanes excellent building blocks for a multitude of chemical transformations such as ring opening, ring expansion, cycloaddition, and rearrangement.[5] Moreover, cyclopropanes take part in a wide range of biological processes ranging from enzyme inhibitors, antibacterial, antifungal, to insecticidal agents.[6] Among all reported approaches to synthesize stereodefined cyclopropanes,[7] the most classical is based either on transition-metal-catalyzed decomposition of diazo esters,[8] on the Simmons−Smith−Furukawa cyclopropanation reaction,[9] or on the Corey−Chaykovsky addition−elimination sequence[10] on isolated olefins (Scheme 1a). These three approaches led collectively to utmost all reported efficient preparations of cyclopropanes to date, despite that any variation of substituents on the cyclopropyl core required each time a different starting material. Due to these intrinsic limitations, we envisioned the development of a single and unified approach that would allow the synthesis of many different types of cyclopropanes from a common starting material. By analogy to alkynes,[11] we marked the carbometalation reaction of cyclopropenes as a potential strategy. We first experienced this transformation as part of our efforts to prepare enantioenriched alkylidenecyclopropane derivatives **2** through the copper-catalyzed Grignard addition to cyclopropenyl carbinols **1** (Scheme 1b).[1] We were pleased to observe that the carbinol function governed both the regio- and diastereoselectivity of the addition. Furthermore, the alcohol also served as a good leaving group as the cyclopropyl magnesium bromide intermediate undergoes a 1,2-*syn* elimination to yield enantioenriched alkylidenecyclopropane **2** (Scheme 1c). The success of this transformation together with previous reports from other research groups[12] convinced us to investigate in detail the carbometalation of cyclopropenes as a general approach to synthesize stereodefined polysubstituted cyclopropanes.

2. STEREOSELECTIVE SYNTHESIS OF POLYSUBSTITUTED CYCLOPROPANE DERIVATIVES

2.1. Carbometalation Reactions on sp^2-Monosubstituted Cyclopropene Derivatives

Based on the knowledge acquired in numerous studies for the carbometalation reactions of alkynes,[11] pioneering reports of carbon nucleophilic additions to cyclopropenes started to appear already in the 1970s.[13] Many of the basic principles that led to all subsequent studies were already established by these pioneering reports. For instance, the regioselectivity for the addition on sp^2-monosubstituted cyclopropene **3** should favor the formation of the least substituted organometallic species **4** (Scheme 2a). Furthermore, the presence of a polar functional group incorporated in the cyclopropenyl scaffold could cleverly be used to direct the facial selectivity of the addition, representing the diastereoselective step of the reaction (Scheme 2a).

This concept was widely described by Fox for the addition of alkyl, alkenyl, alkynyl, and aryl Grignard reagents to hydroxymethyl cyclopropenyl derivatives.[12b] The addition was regio- and diastereoselective, delivering the corresponding cyclopropanes **5** in excellent yields (Scheme 2b). From those foundations, we then began our own exploration on the reactivity of cyclopropenes.

2.1.1. Diastereodivergent Carbometalation Reaction.

As it was reported that Grignard reagents were compatible with many functional groups,[14] we envisioned to perform the copper-catalyzed addition of Grignard reagents to cyclopropenyl esters. These potential substrates are easily obtained from the Rh-catalyzed decomposition of diazoesters in the presence of terminal alkynes.[15] When this transformation was performed in the presence of a chiral ligand, the corresponding cyclopropenes were obtained with high enantiomeric ratios.[15] We then started our investigation by reacting our model cyclopropenyl esters **6**, with various Grignard reagents in the presence of 10 mol % of copper iodide in Et_2O. We were delighted to observe a rapid addition reaction at −30 °C to give the expected cyclopropyl magnesium intermediate **7** (Scheme 3a). The latter was trapped with various electrophiles to give the corresponding functionalized cyclopropanes **8** possessing a quaternary stereocenter (Scheme 3b). These results confirmed our assumption that Grignard reagents are compatible, at low temperature, with the ester functionality. At this temperature, the addition to the double bond embedded in the three-membered ring is faster than the direct attack on the carbonyl group. Moreover, the syn-addition to the double bond was directed by the presence of the ester group (syn-facial selectivity). The obtained cyclopropyl magnesium bromide intermediate **7** is configurationally stable under our reaction conditions, and therefore the stereochemical outcome of the product provided insight on the stereochemistry of the intermediate. However, unlike the case of hydroxymethyl cyclopropenes,[12b] the intermediate **7** should be kept at a low temperature to avoid a ring fragmentation that easily occurs by warming the reaction mixture to room temperature (Scheme

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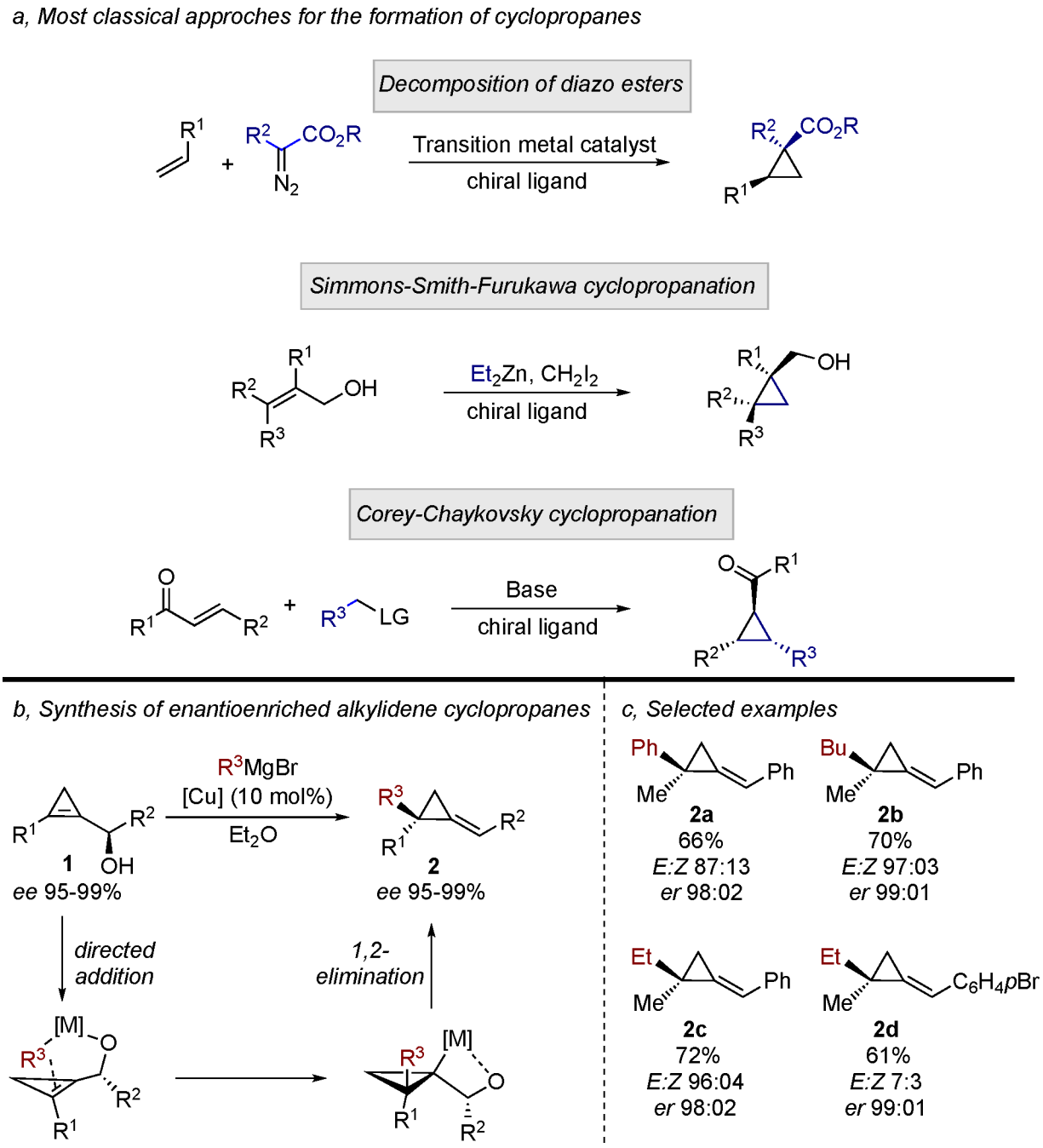
Scheme 1. General Approaches to the Preparation of Stereodefined Cyclopropanes



3c). This molecular rearrangement leads to the formation of stereodefined trisubstituted alkenes **9** with excellent isomeric ratios.[2]

To avoid the above-mentioned ring fragmentation, the preparation of a more covalent cyclopropyl metal should be considered. Therefore, instead of performing the copper-catalyzed carbomagnesiation reaction leading to a potentially labile cyclopropyl Grignard intermediate **7** (Scheme 3a), we surmised that the addition of an organocopper reagent (carbocupration) would lead to a more stable cyclopropyl copper intermediate **10**. Organocopper reagents are easily achieved by the stoichiometric addition of a Grignard or organolithium reagent to a copper salt (in a 1:1 ratio) (Scheme 4a). We were indeed delighted to observe the formation of **10**, through an ester-chelated syn-facial addition in nonpolar solvent with excellent regio- and diastereoselectivities (Scheme 4a). As expected, since the carbon−copper bond is more covalent than its respective carbon−magnesium bond, **10** showed a higher stability toward fragmentation allowing us to expand the scope of potential electrophiles (Scheme 4b).[2] Interestingly, when the Lewis acid character of the organocopper decreases, the syn-facial selectivity induced by the chelation of the ester also decreases to eventually reach a complete anti-addition. For instance, when MeLi was added to CuCN, the formed lower-order cyanocuprate[16] showed a different reactivity toward the same cyclopropenyl ester as an anti-facial addition was observed (Scheme 4c). This phenomenon could be explained by the electronegative nature of the cyanocuprate with regards to a classical organocopper reagent. The cyano ligand is tightly bound to the copper atom, leading to the formation of an "ate"

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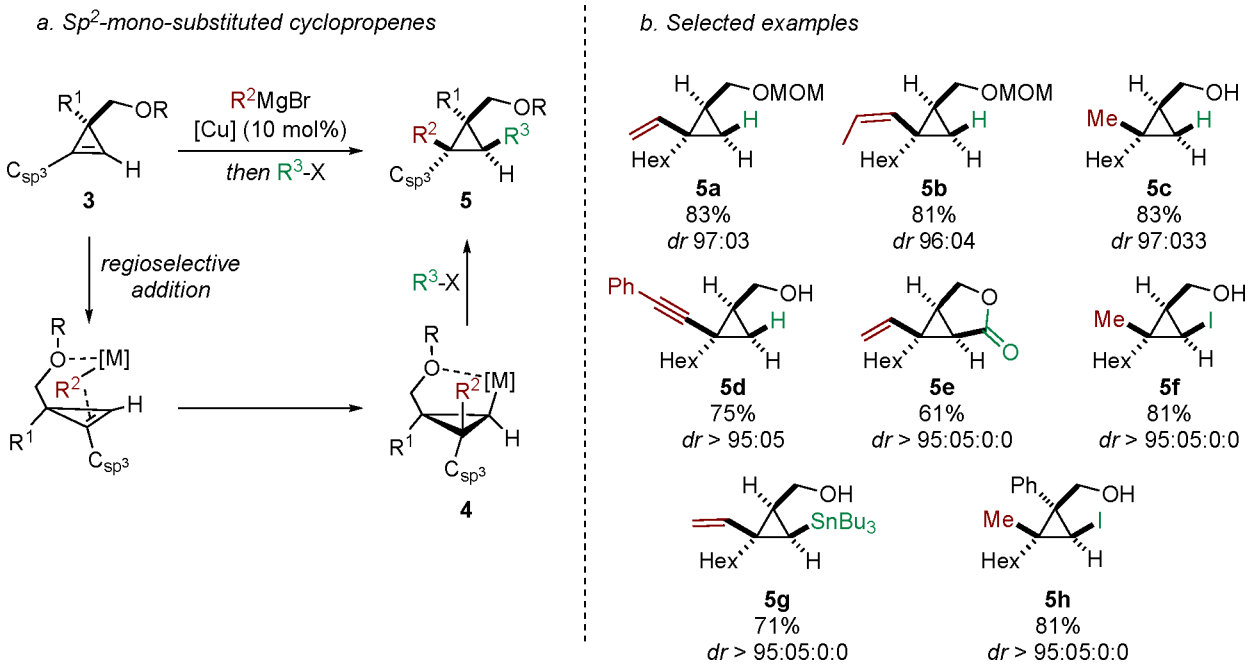
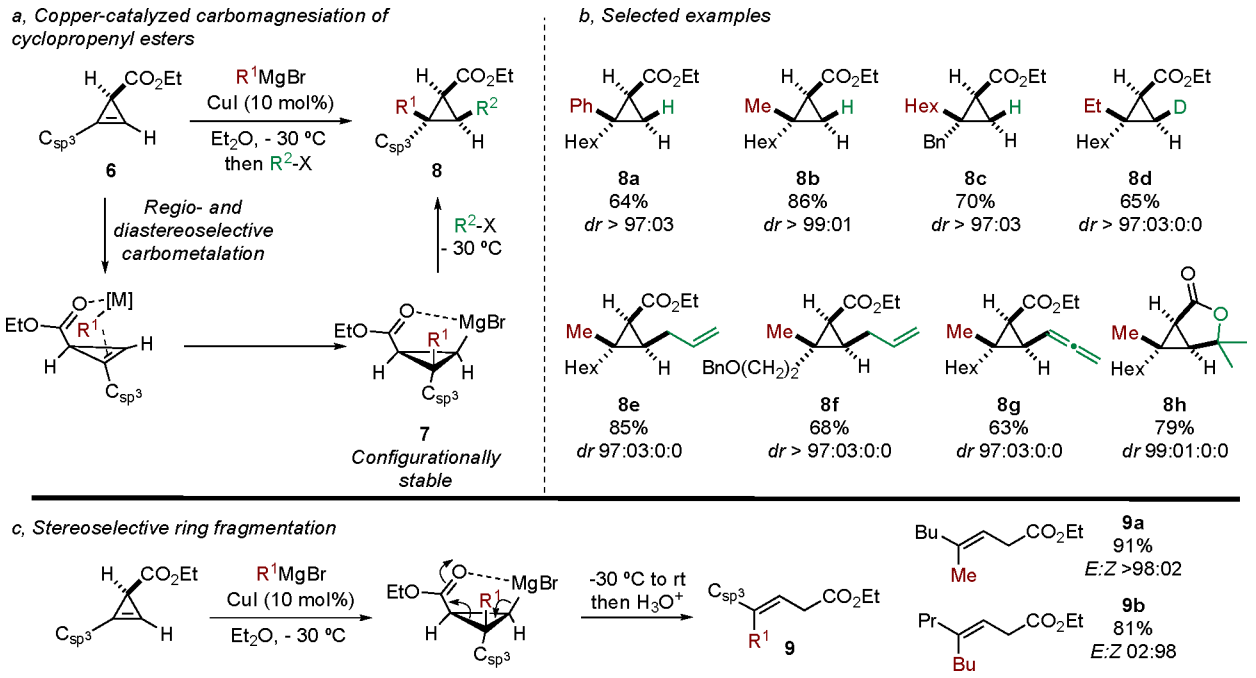
Scheme 2. Carbometalation of Methoxymethyl Cyclopropenyl Derivatives



Scheme 3. Copper-Catalyzed Carbomagnesiation of Cyclopropenyl Esters



complex. The Lewis acidity of this negatively charged species is drastically decreased and therefore is less prone to intramolecular chelation by the basic oxygen of the cyclopropenyl ester (Scheme 4d). Following the same logic, a polar solvent should also be able to disrupt the intramolecular chelation of the ester. Indeed, when the reaction was performed with an organocopper in a more polar solvent such as THF, the anti-addition was quantitatively observed (Scheme 4e).[17] In this case, the better solvation of the organocopper by the polar solvent, yet again, prevent the intramolecular chelation from the ester. It should be noted that the anti-addition intermediate **12** is also configurationally stable, recognizing again the beneficial effect of the covalent nature of the carbon−copper bond toward potential fragmentation reactions.

To illustrate the power of this diastereodivergent carbometalation reaction, an interesting application was the synthesis of bicyclopropyl methanol **13**. Indeed, in nonpolar solvent, the syn-facial copper-catalyzed carbomagnesiation of **6** provided **7** that was unable to undergo a second carbometalation reaction with a more reactive cyclopropene such as **14**. Our hypothesis for this unsuccessful second addition was that the high torsional strain that would have been generated impeded the second carbometalation to occur. However, the anti-facial addition providing **12** could easily and smoothly proceed with **14** to give

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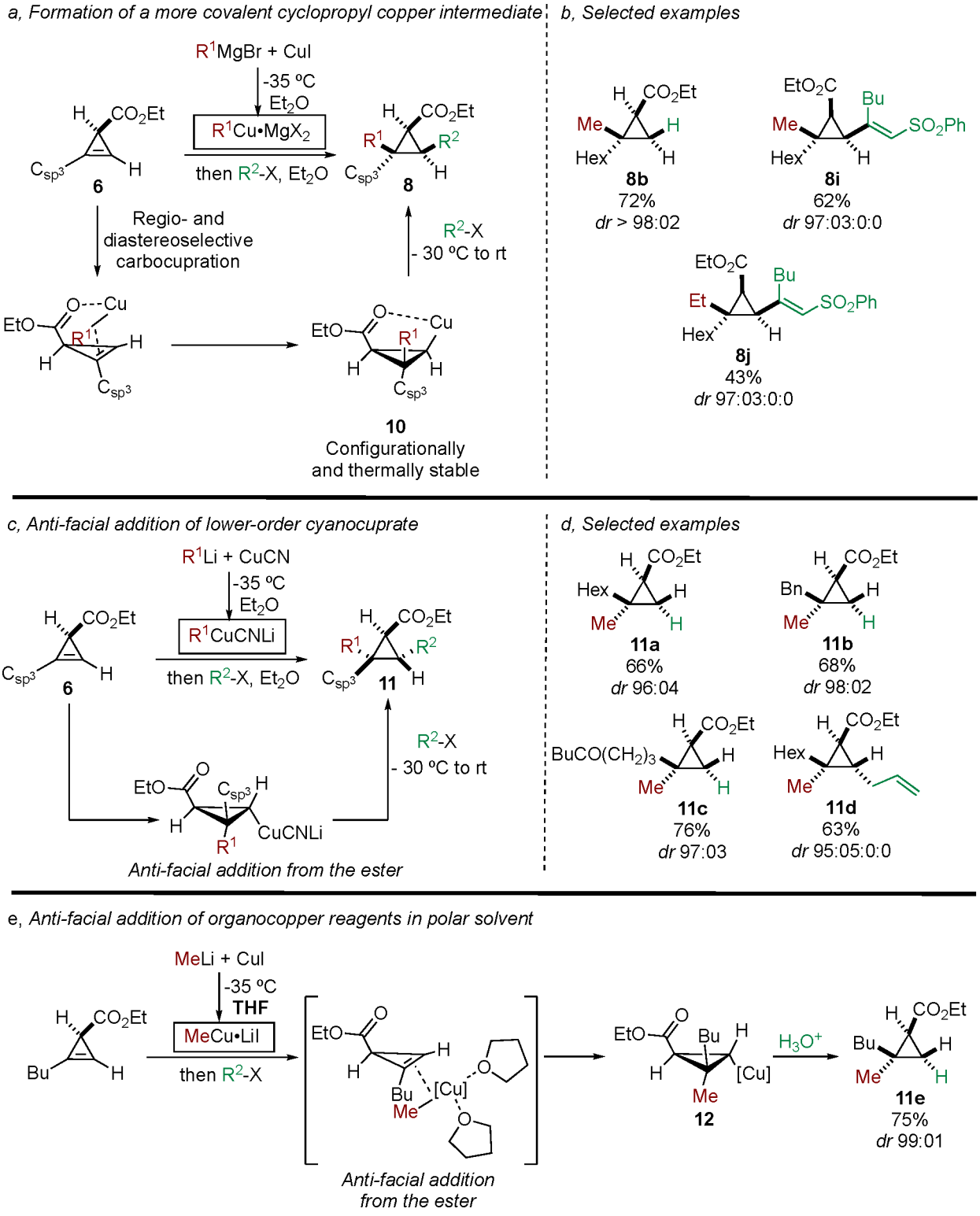
Scheme 4. Carbocupration of Cyclopropene Derivatives



the two diastereomers of the addition product, resulting from the addition either on the C_1-C_2 or the C_2-C_1 double bond, respectively. In both cases, the addition proceeds diastereoselectively on the face of the Me group and will be discussed in one of the following subsections. By reaction with allyl bromide, the two corresponding bicyclopropyl esters **13a** and **13b** were obtained, each one as a single diastereomer, and were easily separated by column chromatography (Scheme 5).[18]

2.1.2. Stereoselective Synthesis of Alkenyl Cyclopropanes Derivatives. Confident in the complete control of the facial stereoselective addition, we wanted to extend our approach to the synthesis of polysubstituted alkenyl cyclopropanes as a single diastereomers. Alkenyl cyclopropanes represent an important category of reactive cyclopropane derivatives that undergo a multitude of cycloaddition reactions.[19] For the preparation of these alkenyl cyclopropanes,

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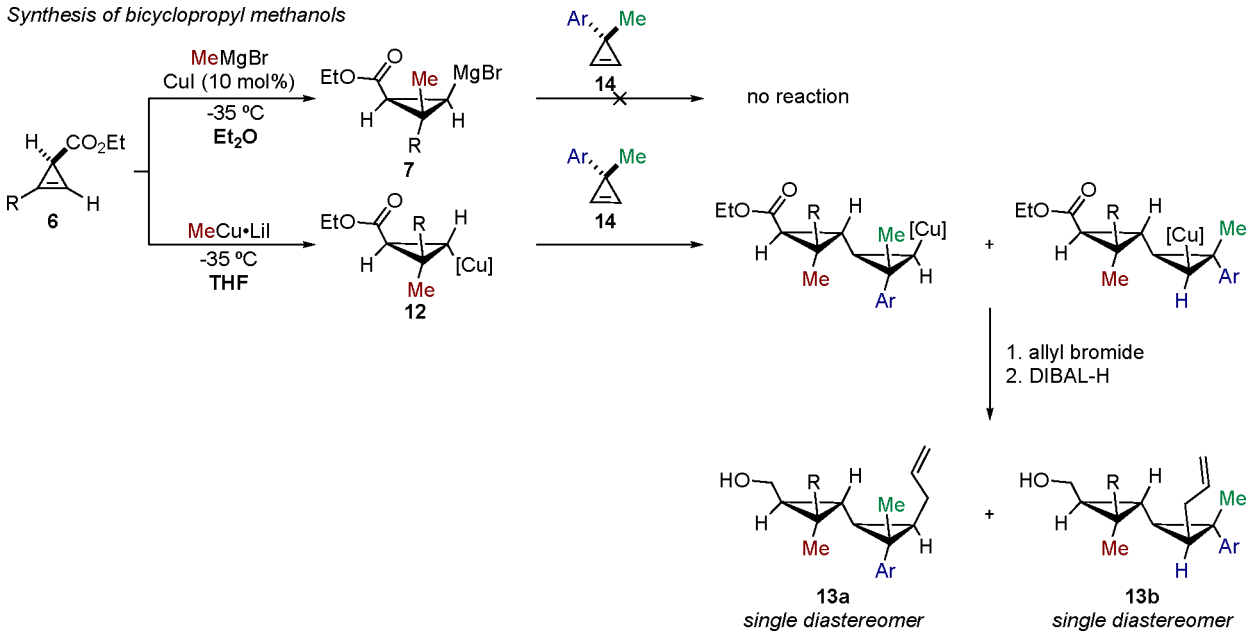
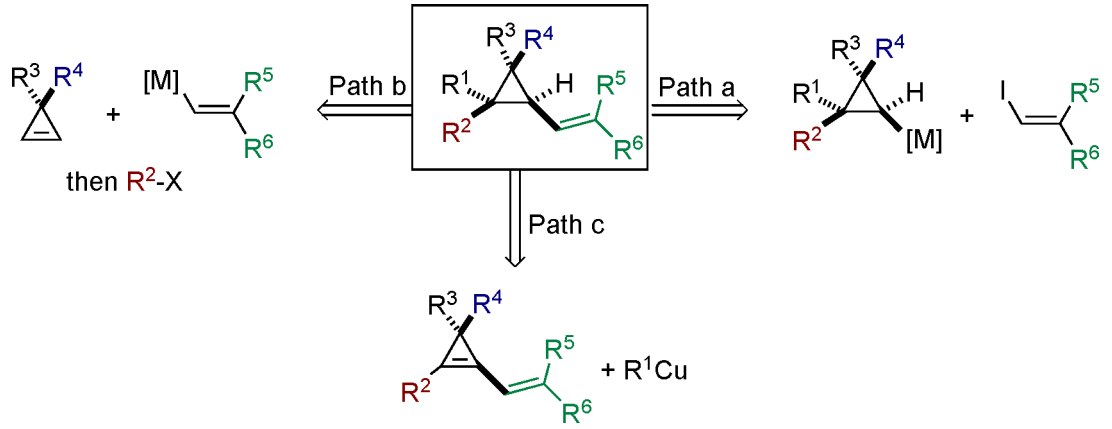
Scheme 5. Synthesis of Bicyclopropyl Methanols



Scheme 6. Retrosynthetic Analysis for the Preparation of Stereodefined Alkenyl Cyclopropanes



three possibilities were considered (Scheme 6): (1) a metal-catalyzed cross-coupling reaction of the resulting cyclopropyl metal intermediate with alkenyl halide (path a, Scheme 6); (2) a diastereoselective alkenyl carbometalation of cyclopropenes (path b, Scheme 6); and (3) a regio- and stereoselective carbometalation of alkenyl cyclopropenes (path c, Scheme 6). All possibilities were tested (path c of Scheme 6, discussed in section 3, that concerns the carbometalation of sp^2-disubstituted cyclopropenes).

Based on our previous expertise for the diastereoselective carbometalation of cyclopropenes, it was only natural to trap the resulting cyclopropyl metal intermediate with various vinyl halides (X = I or Br, Scheme 6, path a). After a comprehensive optimization, transmetalation to zinc and increase of the polarity of the reaction medium enabled the Pd-catalyzed cross coupling reaction to proceed in high yield (Scheme 7a). Noteworthy, the stereochemistry was preserved along the process, underlining that no epimerization of the carbon−metal bond was detected during the transmetalation neither during the coupling reaction (Scheme 7b).[20] Yields are based on the reduced products of **15**.

Alternatively, we also envisioned the diastereoselective copper-catalyzed addition of alkenyl organometallic species (Scheme 6, path b). Alkenyl lithium reagent, smoothly prepared through lithium-halide exchange, could be added to a copper salt and to a cyclopropene (Scheme 7c). In all cases, the facial selectivity of the addition of the organometallic species was controlled by the in situ generated alkoxide (Scheme 7d).[21]

2.1.3. Regio- and Stereoselective Carbocupration of Cyclopropenes and Reaction with Oxenoid: New Access to Cyclopropanol Derivatives. Various oxidation reactions of organometallic species have been described in the literature,[22] but a sharp contrast exists in the stereochemistry of the resulting products between an aerobic oxidation and oxidation with oxenoids. For instance, when cyclopropyl lithium was treated with O_2, a mixture of cyclopropanols was obtained through the formation of interconverting radical pairs, whereas when the same stereochemically defined cyclopropyl lithium was treated with lithium oxenoid *t*BuOOLi, the exclusive formation of a single isomer was observed.[23] Therefore, the electrophilic oxygen transfer by an S_N2-type mechanism has been suggested for the transformation mediated by *t*BuOOLi. The same stereochemical study of cyclopropyl metal species was investigated for the oxidation of Gilman-type cuprates.[24] This reaction is particularly important since organocuprates are

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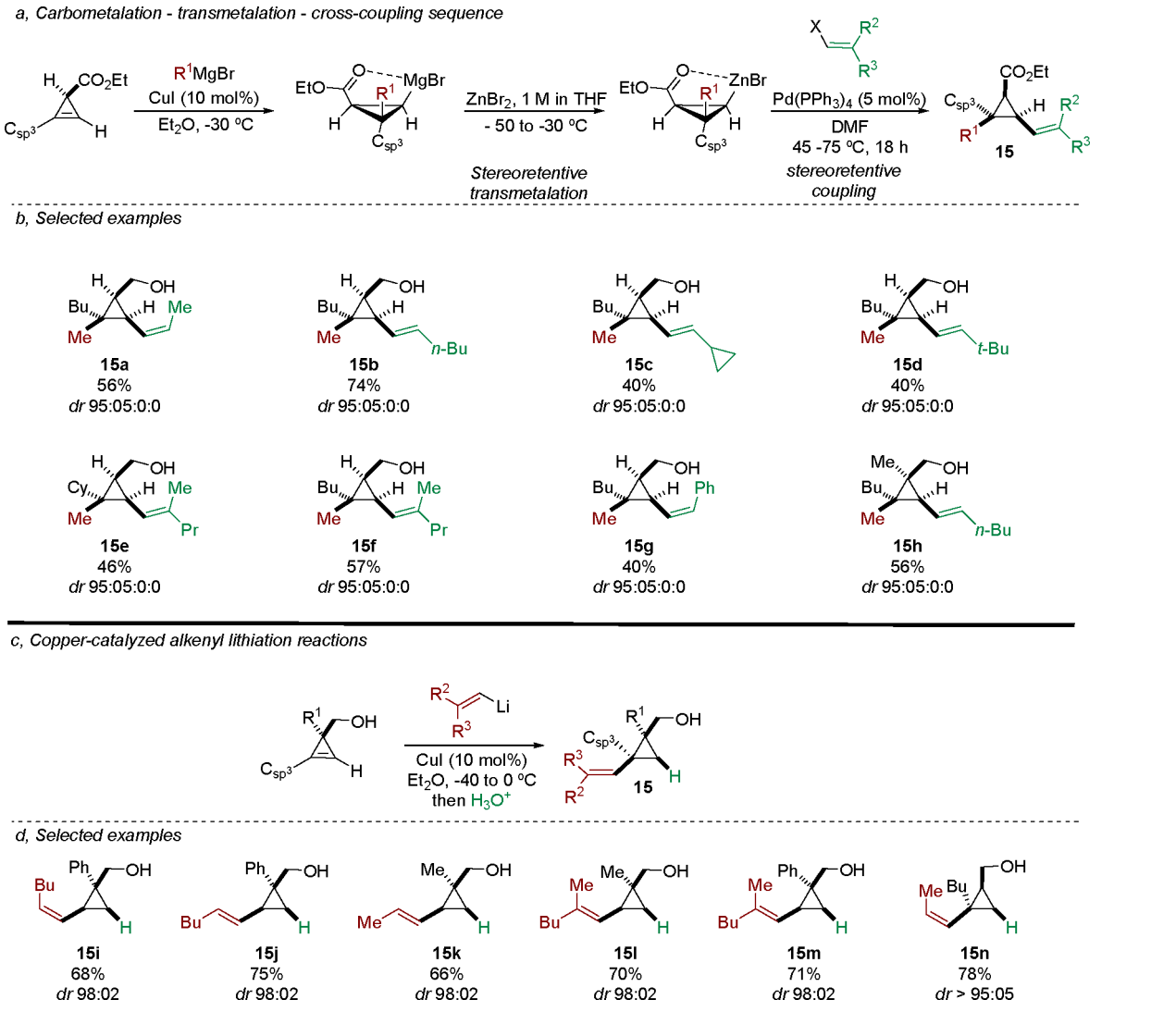
Scheme 7. Synthesis of Stereodefined Alkenyl Cyclopropanes



known to undergo extremely rapid degradation (i.e., oxidative R−R dimerization) upon reaction with molecular oxygen. Our study considered the unique abilities of oxenoid to oxidize organocopper derivatives with retention of configuration,[25] and we therefore explored the carbometalation−oxidation sequence of cyclopropenyl esters as a new route to stereodefined cyclopropanol derivatives.[26] When methoxymethyl cyclopropene derivatives **3** (Scheme 8a) were treated with an organocuprate, the *syn*-diastereomer **4** was obtained as a unique isomer. By subsequent addition of an oxenoid, easily prepared by simple metalation of *t*BuOOH with *n*BuLi, a stereoretentive oxidation reaction provided the expected cyclopropanol **17**, after hydrolysis. Remarkably, cyclopropanol **17** was isolated with up to three stereocenters as a unique diastereomer through the proposed 1,2-metalate rearrangement **16** (Scheme 8b). When the starting cyclopropenyl methyl ether **3** is prepared enantiomerically enriched (*er* 93:07), the diastereoselective carbometalation followed by the stereoretentive oxidation provided the corresponding cyclopropanol with the same enantiomeric ratio than the starting material (**17e**, *dr* 99:01:0:0, *er* 93:07).

In the same vein, we envisioned to complete the picture of this sequence by investigating the reactivity of another subclass of sp^2-monosubstituted cyclopropenes, particularly nonfunctionalized cyclopropenes **18** (Scheme 8c). Here again, a smooth addition of cyanocuprates to the latter followed by an oxidation reaction with oxenoid yielded cyclopropanols **19** with two quaternary centers as a unique diastereomer (Scheme 8d).[27]

2.1.4. Regio- and Stereoselective Carbocupration of Cyclopropenes and Reaction with Prochiral Electrophiles: New Access to Polysubstituted Cyclopropyl Carbinols. While we were investigating the diastereoselective copper-catalyzed addition of alkenyl organomagnesium species to cyclopropenes, we were also interested to understand if the addition of a prochiral electrophile could allow the formation of an additional stereocenter with a complete control of the diastereoselectivity (Scheme 9a). We were pleased to observe that addition of various aldehydes provided a single diastereomer at the carbinol center (Scheme 9b).[28] However, for unclear reasons, when the addition of *alkyl* magnesium halides followed by aldehydes were added to similar cyclopropenyl rings, the diastereoselectivity was drastically lower.[29] This drawback could be circumvented by addition of acylsilane to cyclopropenyl ester using slightly different experimental conditions (Scheme 9c).[30] The formation of a unique diastereomer at the three cyclopropyl carbon atoms as well as

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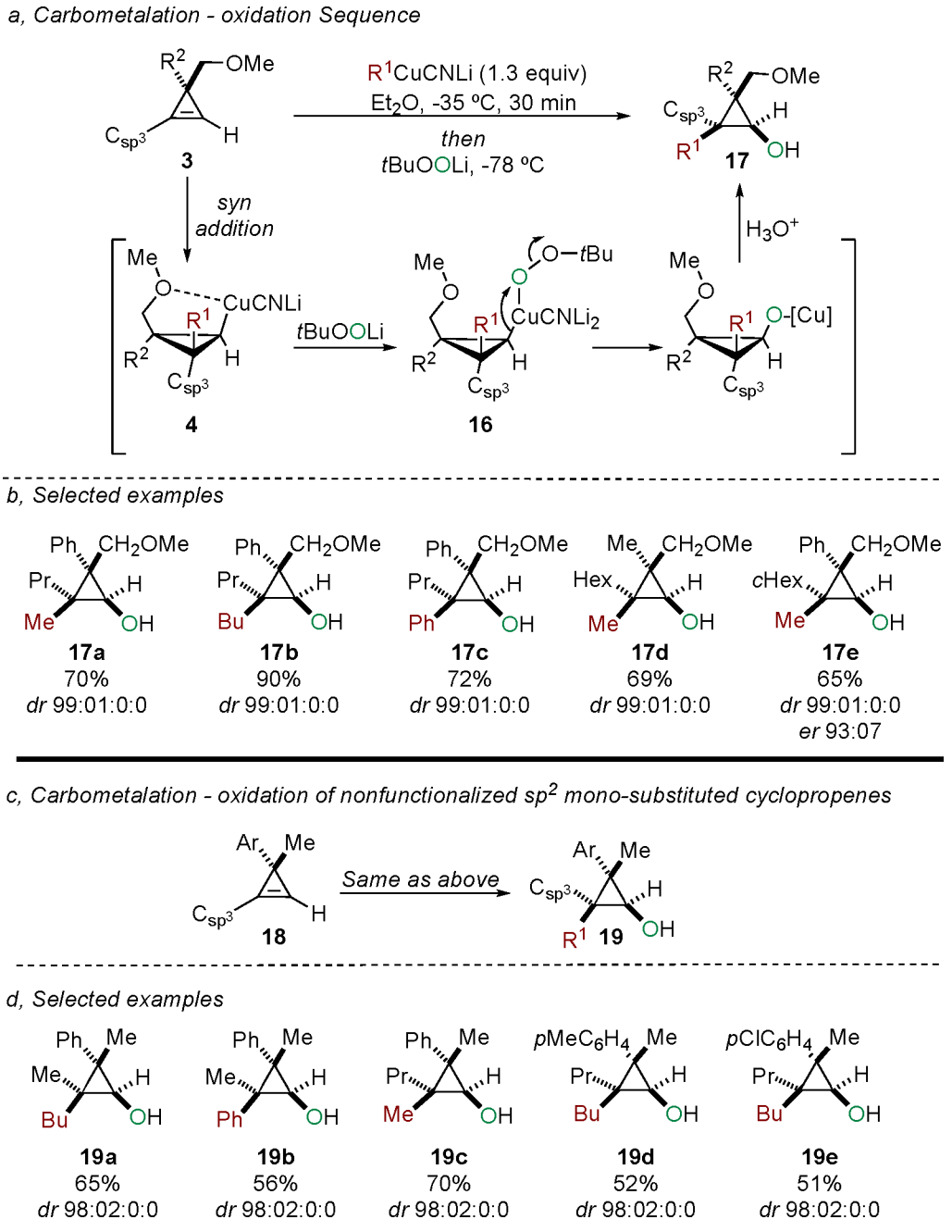
Scheme 8. Carbometalation−Oxidation Sequence



at the carbinol centers is worth mentioning, even if the products were isolated as lactones **18** (Scheme 9d). To avoid the subsequent cyclization into lactones, cyclopropyl amides were considered, and when treated under the same experimental conditions (Scheme 9e), the expected tertiary alcohols could be obtained as single diastereomers over the 4 stereogenic centers (Scheme 9f).[31]

Even more interesting was the necessity to have a Lewis basic moiety to control the diastereoselectivity of the carbinol center (compare **25a−d** with **25e,f** in Scheme 8h).[32] This requirement underlines a potential chelation of the carbonyl group of the acylsilane with a metal associated with the heteroatom, forcing the bulky Me_3Si group to point away from the cyclopropyl core. As the reaction with acylsilane showed excellent diastereoselectivity, one could use the reactivity of the resulting α-silyl carbinol to undergo a stereoinvertive protiodesilylation reaction by addition of *t*BuOK in protic DMSO to provide the respective secondary alcohols **26** with excellent diastereomeric ratios, alleviating the limitation previously mentioned (Scheme 10).[31]

2.2. Carbometalation Reactions on sp^2-Disubstituted Cyclopropene Derivatives

With the broad experience that was acquired in the carbometalation reaction of sp^2-monosubstituted cyclopropenes, it was only natural to further push the boundaries of potentially accessible cyclopropanes by extending our chemistry to the carbometalation of sp^2-disubstituted cyclopropenes. Despite the obvious expected difficulties due to the lack of reliable access to the required starting materials coupled with the potential high torsional strain that would be generated, we envisioned the synthesis of fully substituted stereodefined

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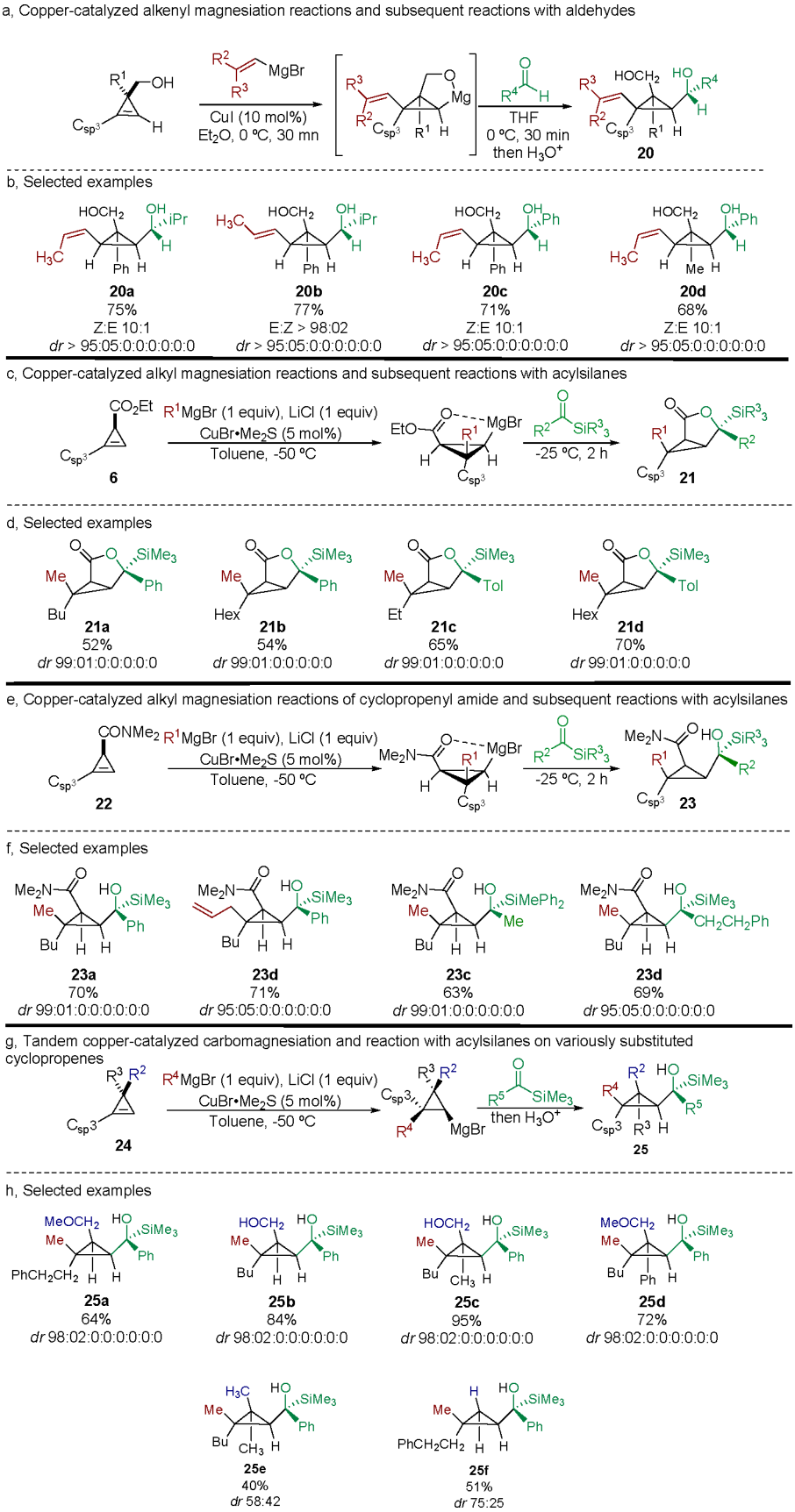
Scheme 9. Reaction of Cyclopropyl Magnesium Species with Prochiral Electrophiles



cyclopropanes through the same type of regio- and diastereoselective carbometalation reaction. Two complementary conceptual designs were considered for a successful regioselective carbometalation reaction, and two different starting

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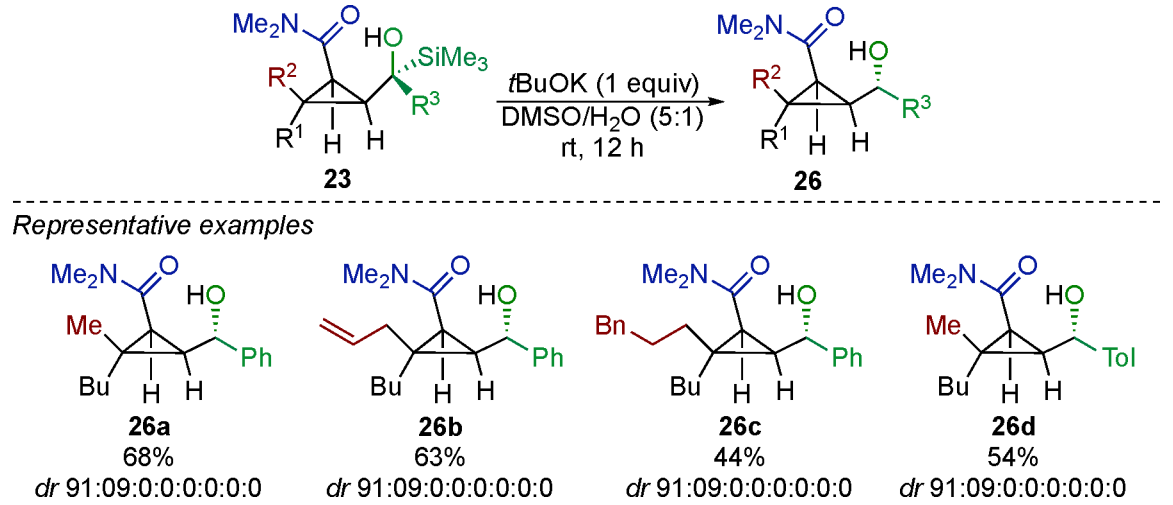
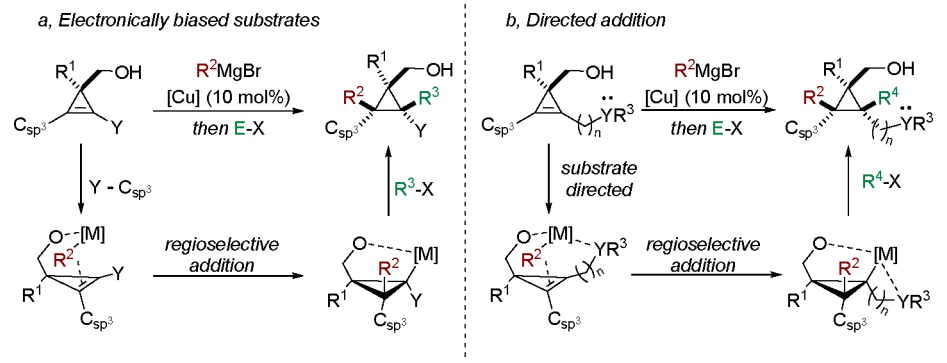
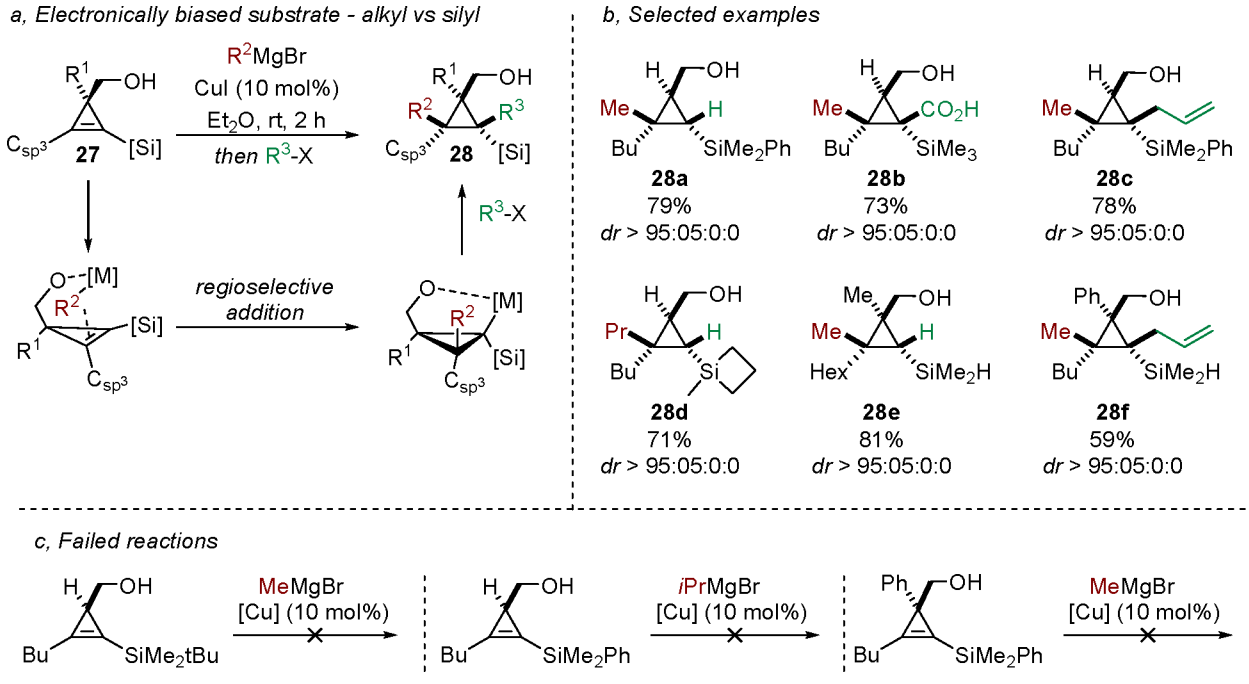
Scheme 10. Protiodesilylation of Cyclopropyl Silyl Methanols



Scheme 11. Regioselective Carbometalation Reaction of sp^2-Disubstituted Cyclopropenes



Scheme 12. Regioselective Carbometalation Reaction of Cyclopropenyl Silanes



materials were prepared. The first (Scheme 11a), inspired by our experience in the carbometalation of sp^2-monosubstituted cyclopropenes, leaned on inherently two different substituents on the two sp^2 carbon centers of the double bond that would lead, after carbometalation, to the formation of an electronically stabilized cyclopropyl metal species. The second approach

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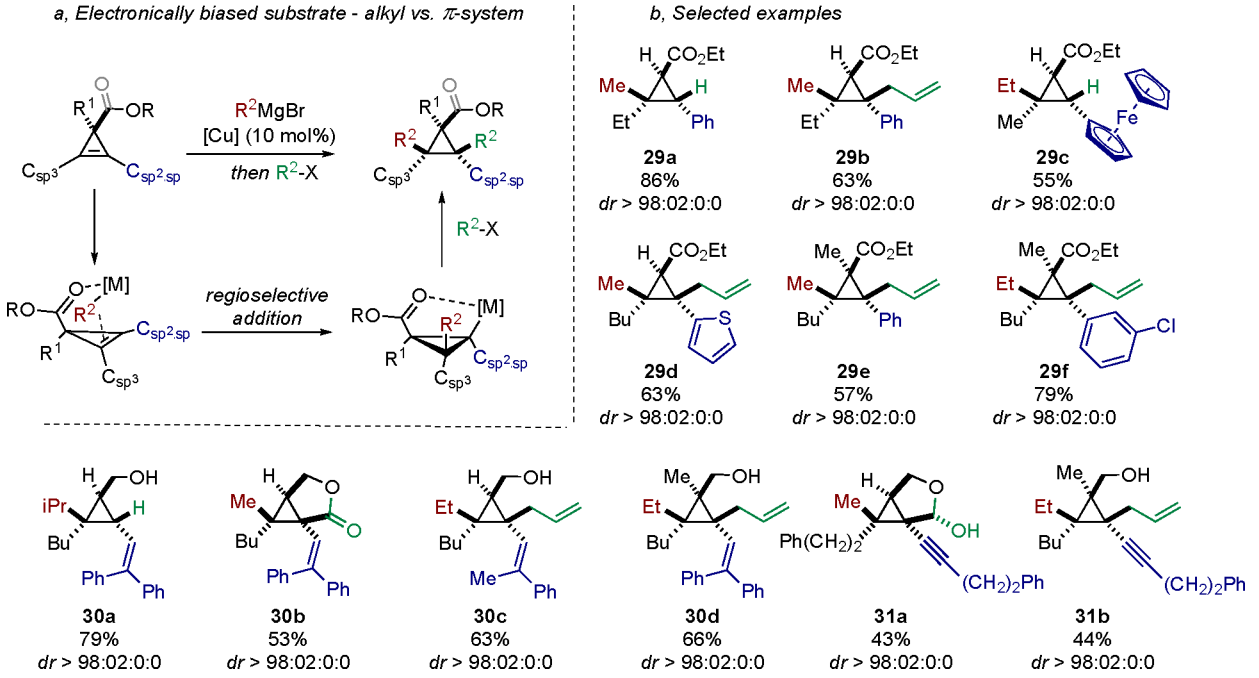
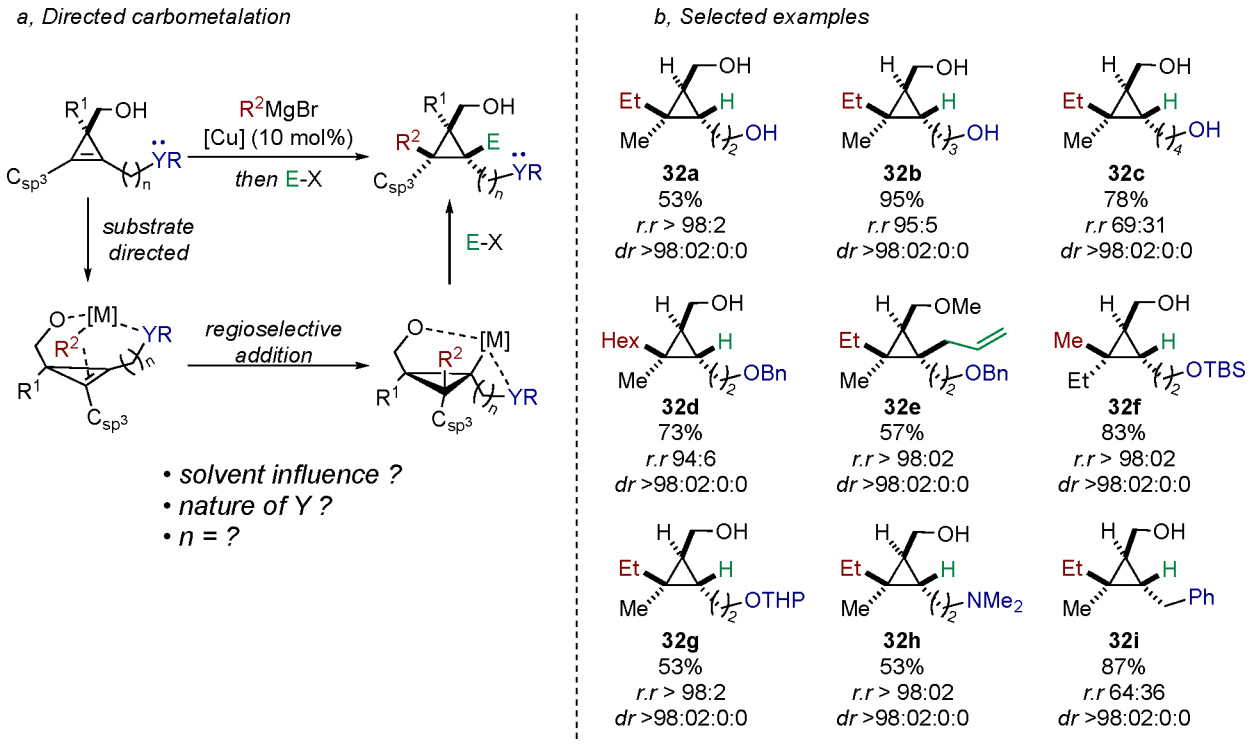
Scheme 13. Carbometalation of sp^2-π-Substituted Cyclopropenes



Scheme 14. Directed Carbometalation



would consider a template effect, based on a Lewis basic group tethered on one sp^2-carbon center that would control the regioselectivity of the organometallic addition (Scheme 11b).

2.2.1. Electronically Biased Substates. Silyl groups have been known from previous studies to stabilize geminated carbanions.[33] Based on this fundamental principle, coupled with the facile access to disubstituted cyclopropenyl silanes by lithiation−silylation sequence of sp^2-monosubstituted cyclopropenes, we have investigated the copper-catalyzed carbomagnesiation of cyclopropenylsilanes **27** in a nonpolar solvent. We were pleased to observe that primary alkyl Grignard reagents could successfully be added to the strained double bond of **27** with a perfect regioselectivity (Scheme 12a). Motivated by the goal to synthesize stereodefined polysubstituted cyclopropanes as a single diastereomer, we stereospecifically trapped the reactive cyclopropyl magnesium bromide intermediate with various electrophiles to provide the first example of defined hexa-substituted cyclopropane **28f** as a single isomer (Scheme 12b).[34] It is however important to note that the transformation is very sensitive to steric hindrance and although several silyl

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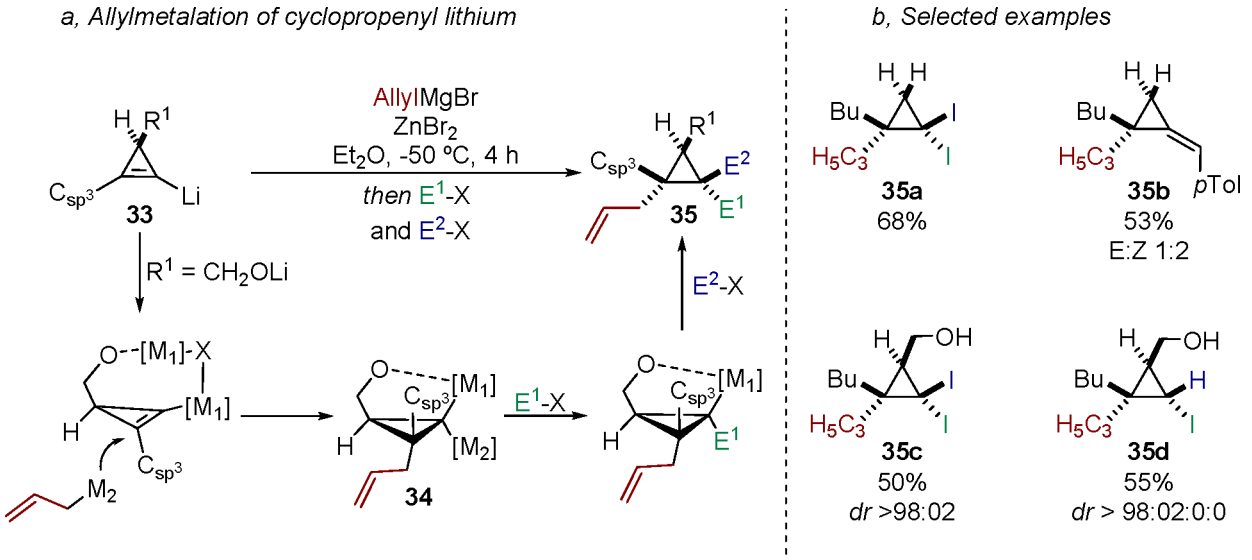
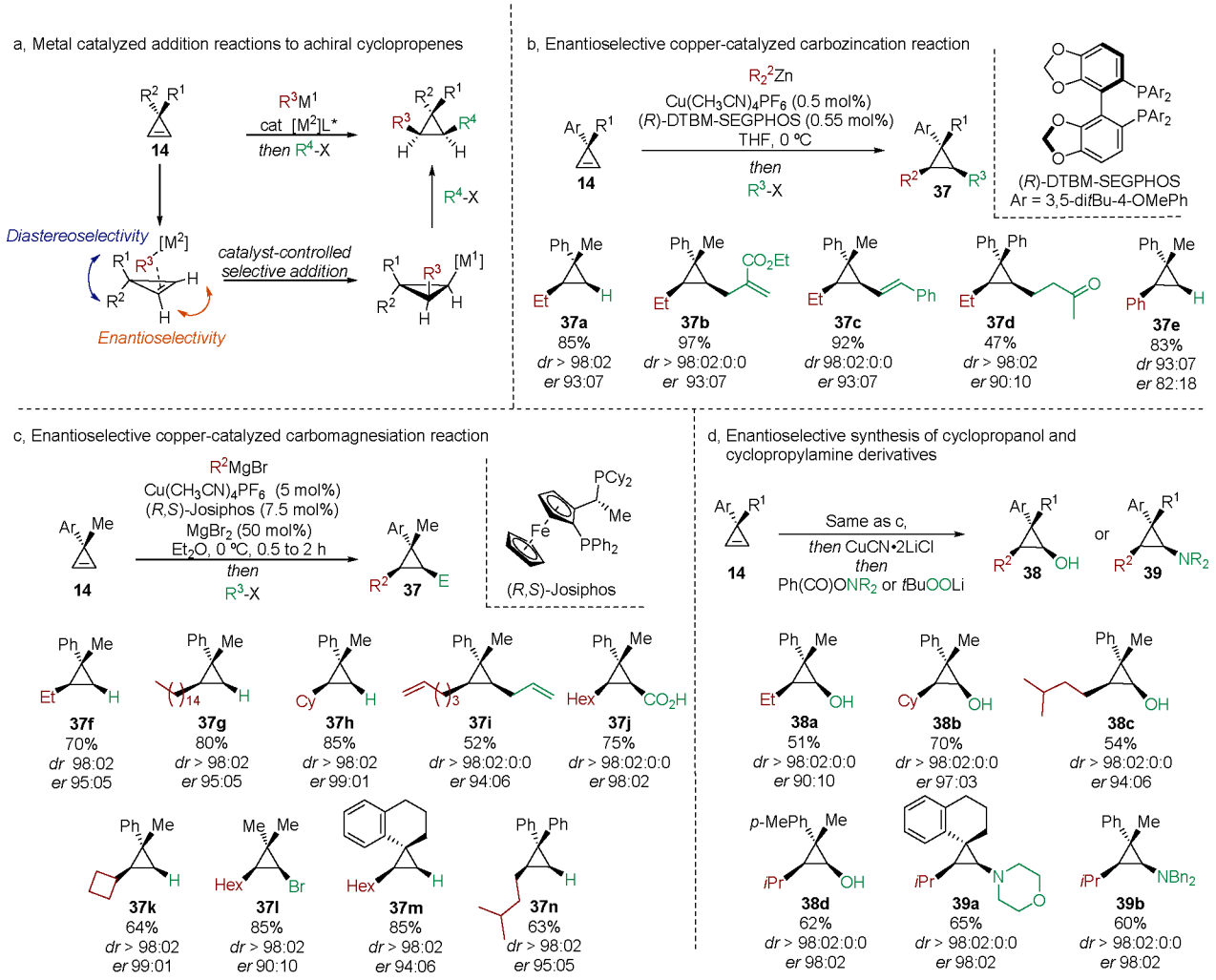
Scheme 15. Regio- and Diastereoselective Carbometalation Reaction of Cyclopropenyllithium Species



Scheme 16. Carbometalation Reactions of Achiral Cyclopropenes with sp^3-Hybridized Nucleophiles



substituents could be used, larger substituents on the silyl group impede the reaction to proceed [compare the successful formation of **28a** when the cyclopropenyl silane possesses the $SiMe_2Ph$ group with the failed addition of the same Grignard reagent with cyclopropenyl silane having a $SiMe_2tBu$ group (Scheme 12c). In consequence, only in the case of the less sterically demanding silyl group ($SiMe_2H$), we could prepare the fully (hexa)-substituted cyclopropane **28**.

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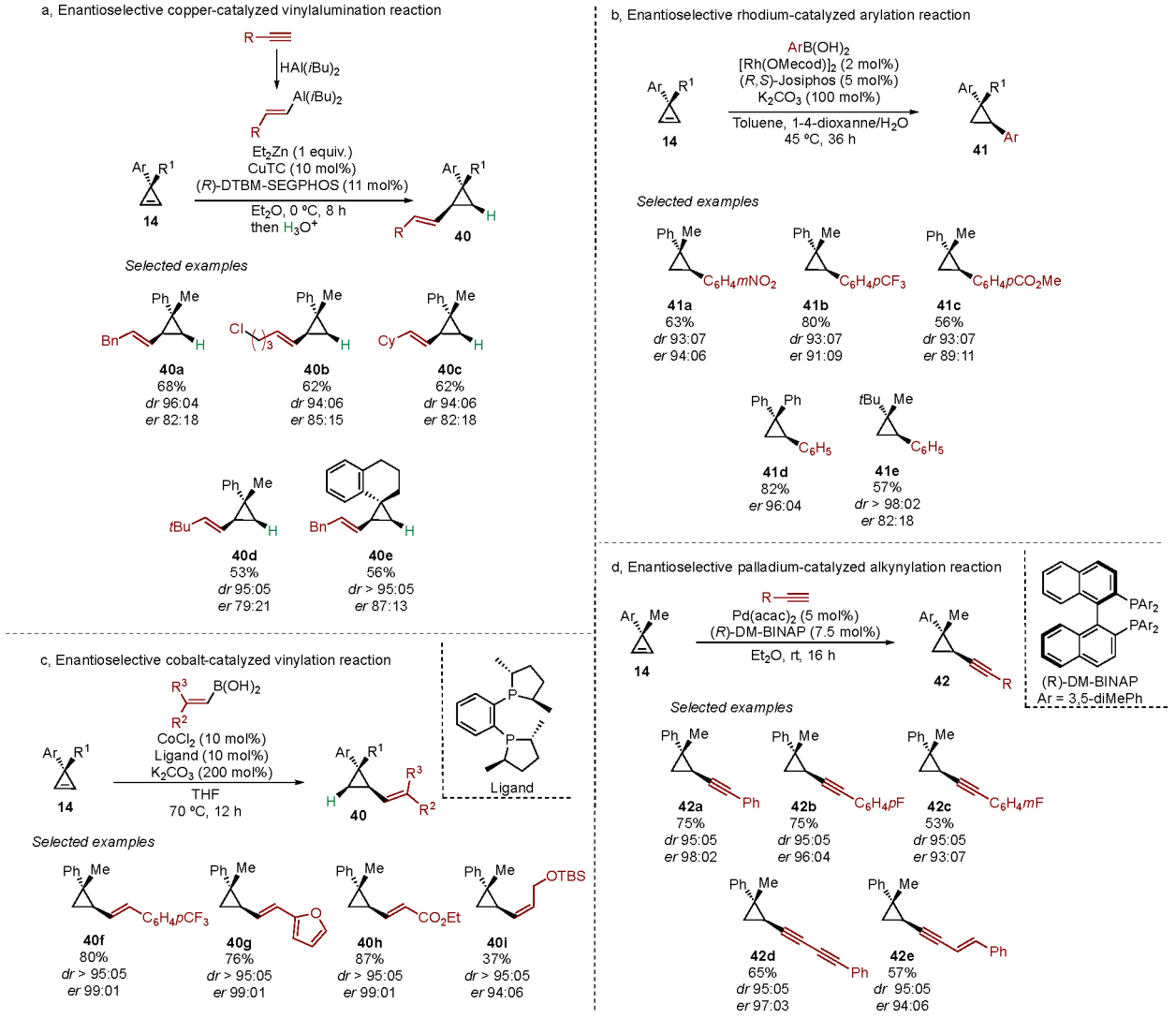
Scheme 17. Carbometalation Reactions of Achiral Cyclopropenes with sp- and sp^2-Hybridized Nucleophiles



Considering this transformation as only a partial success, we were motivated to further pursue our quest toward the formation of hexa-substituted three-membered rings as a single diastereomer. Therefore, we turned our attention to the synthesis of sp^2-π-substituted cyclopropenes, namely aryl-, vinyl-, and alkynyl-cyclopropene derivatives. We hypothesized that conjugation of the newly formed carbon−metal bond to the π-system should induce a regioselective addition (Scheme 13a). Indeed, all these three subclasses demonstrated excellent regio- and diastereoselectivities to provide the corresponding poly-substituted cyclopropanes **29**−**31** as single diastereomers (Scheme 13b).[4]

Primary alkyl Grignard reagents as well as allyl, benzyl, and even secondary nucleophiles (in the case of vinyl- and alkynyl-cyclopropenes) showed a good reactivity. The organometallic intermediate proved to be configurationally stable and could be trapped by addition of allyl and propargyl bromide, carbon dioxide, DMF, or Se metal. By the synthesis of several persubstituted cyclopropyl rings bearing three vicinal quaternary centers (**29e** and **29f**; **30d** and **31b**), we demonstrated the strength and versatility of this approach.[4]

2.2.2. Directed Addition. Our second approach for a regioselective carbometalation reaction of sp^2-disubstituted cyclopropenes is rooted in the concept of template inducing proximity effect (Scheme 14). Although successfully used for the regiodivergent carbometalation of alkynes[11] and for the synthesis of various alkylidenecyclopropanes,[35] a comprehensive and systematic investigation on the effect of heteroatom-directing the regioselectivity of addition on cyclopropene was still missing, along with the ability to synthesize poly alkylated saturated cyclopropanes. Hence, we started analyzing the various parameters influencing the directing ability of a tethered Lewis basic group (Scheme 14a). The best combination was found to be two methylene units between the cyclopropene and the directing group along with the use of low polarity solvent, as the longer alkyl tether shows a decreased regioselectivity. Under these conditions, the differentiation between the two electronically similar carbon atoms on the double bond allowed the synthesis of polysubstituted cyclopropane as single regio- and diastereomers. We were pleased to find that linear and branched primary alkyl, allyl, and aryl Grignard reagents were able to undergo a smooth addition (Scheme 14b). Several oxygen-based Lewis bases, including the bulky *t*butyldimethyl silyl protected alcohol **32f**, were able to direct the addition with a complete regioselectivity. Nitrogen group **32g** equally delivered the expected product with an excellent regioselectivity. Even a

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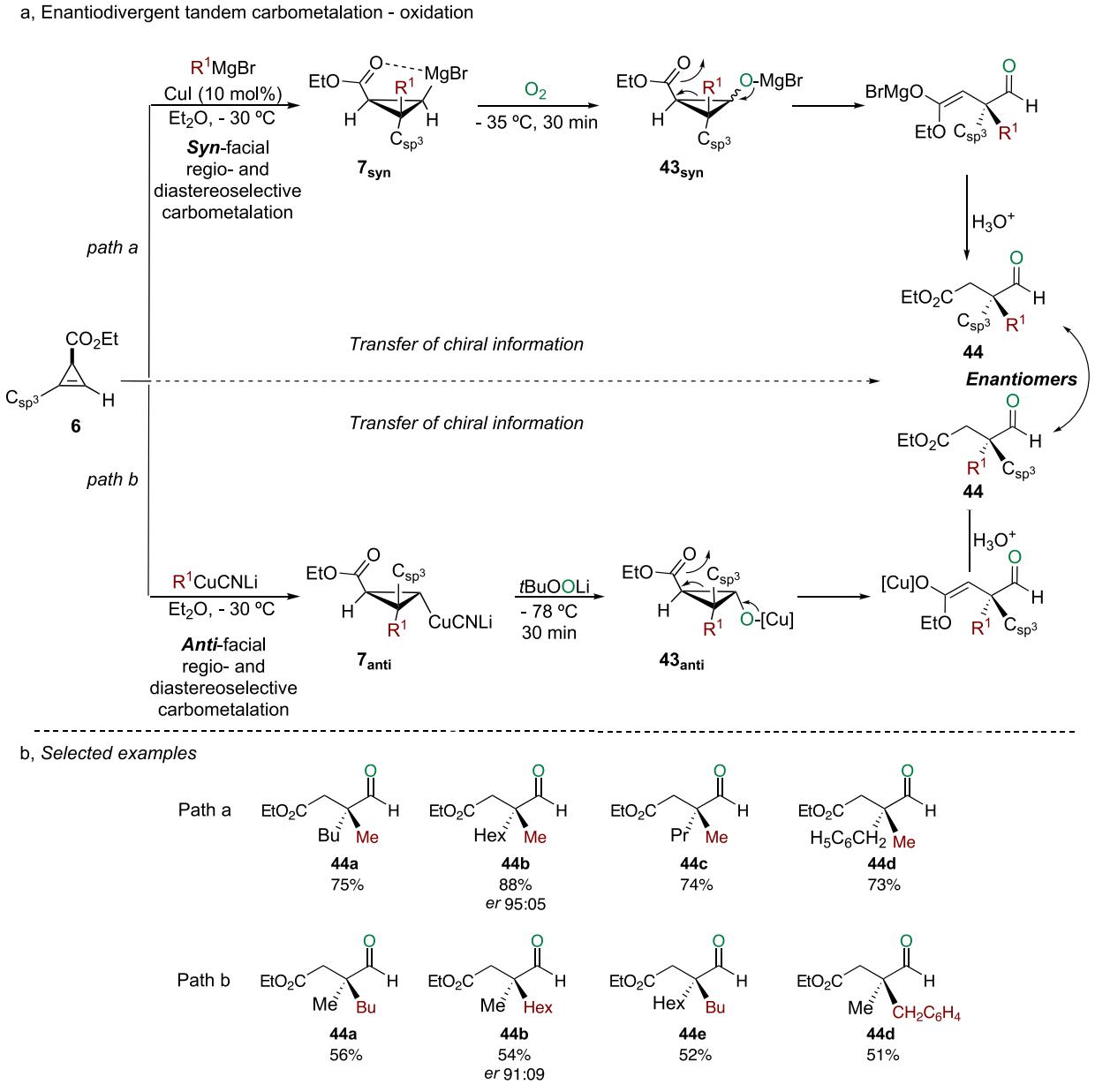
Scheme 18. Sequence of Carbometalation−Oxidation−Ring Fragmentation on Cyclopropenyl Esters



weak electron donor such as a π-system allowed, to some extent, a preference between the two competing regioisomers (**32i**). Trapping the organometallic intermediate with a carbon electrophile led to a penta-sp^3-substituted cyclopropane **32e**.[36]

2.2.3. Miscellaneous. Cyclopropenyllithium **33** represents a particular case of sp^2-disubstituted alkene that smoothly reacts with allylmagnesium bromide in the presence of zinc salt to give the corresponding cyclopropyl 1,1-bismetalated species **34**,[37] as a stable intermediate (Scheme 15a).[38] The presence of intermediate **34** was evidenced by the transformation of the latter into the corresponding 1,1-bisiodo cyclopropyl species **35a** (by addition of I_2) or by the formation of alkylidenecyclopropane **35b** (by addition of an aldehyde, Scheme 15b). The diastereoselectivity of the reaction was subsequently probed by the allylzincation of functionalized cyclopropenyllithium derivatives and trapped with I_2 to afford the gem-diiodo cyclopropane product **35c**. From previous studies on the formation of geminated bismetallic species, internal chelation was able to differentiate the reactivity of the two metals toward two different electrophiles. The chelation of the oxygen atom to the metal M_1 decreases the reactivity of the latter, and thus, the nonchelated metal M_2 reacts preferentially with the first electrophile. Then, the chelated metal M_1 subsequently reacts with the second electrophile to lead to the functionalized product (i.e., **35d**, Scheme 15b) as a single diastereoisomer for the creation of the three stereogenic centers.

2.3. Carbometalation Reactions on Achiral Cyclopropene Derivatives

As the outset of our research with achiral cyclopropenes, it was clear that a chiral catalyst would be required to perform an enantiotopic (left or right) and diastereotopic (top or bottom when $R^1 \neq R^2$) facial selection (Scheme 16a). As several enantioselective additions have already been reported and recently reviewed,[13,39] we will just summarize a few recent examples underlining the power of metal-catalyzed enantioselective carbometalation reaction of achiral cyclopropenes. Our

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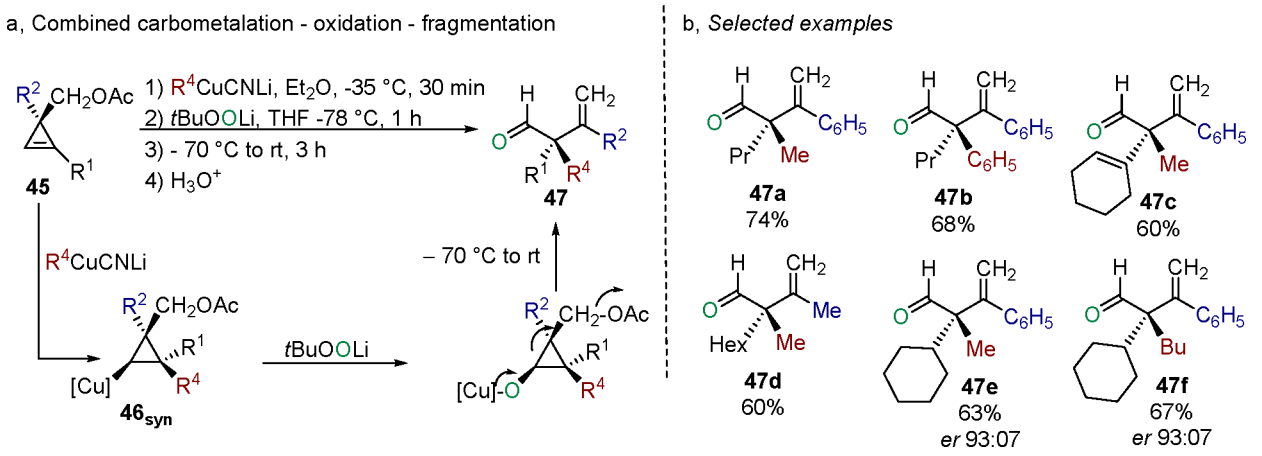
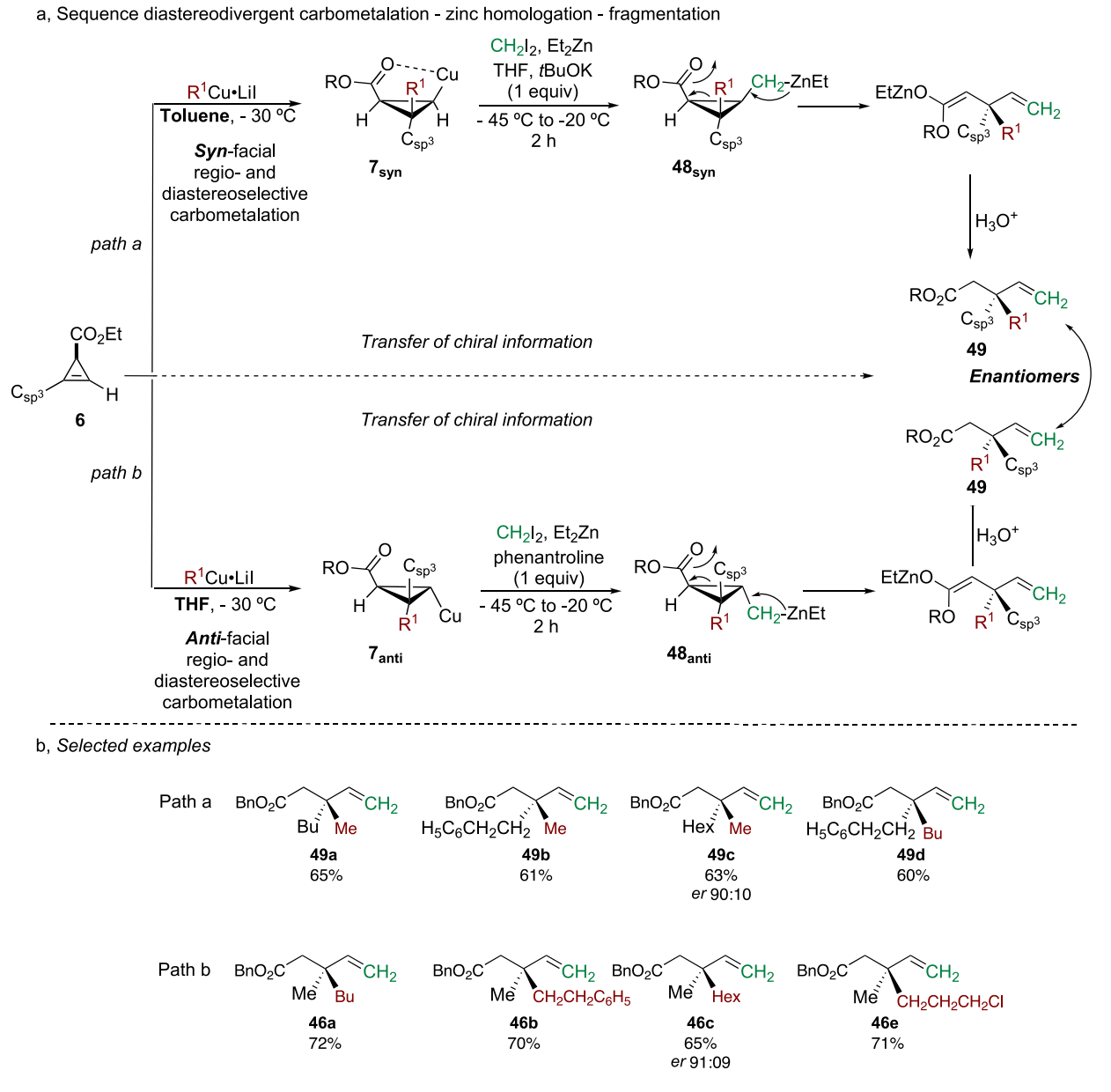
Scheme 19. Sequence of Carbometalation−Oxidation−Selective Ring Fragmentation on Cyclopropenyl Acetates



Scheme 20. Sequence of Carbometalation−Homologation−Selective Ring Fragmentation on Cyclopropenyl Esters



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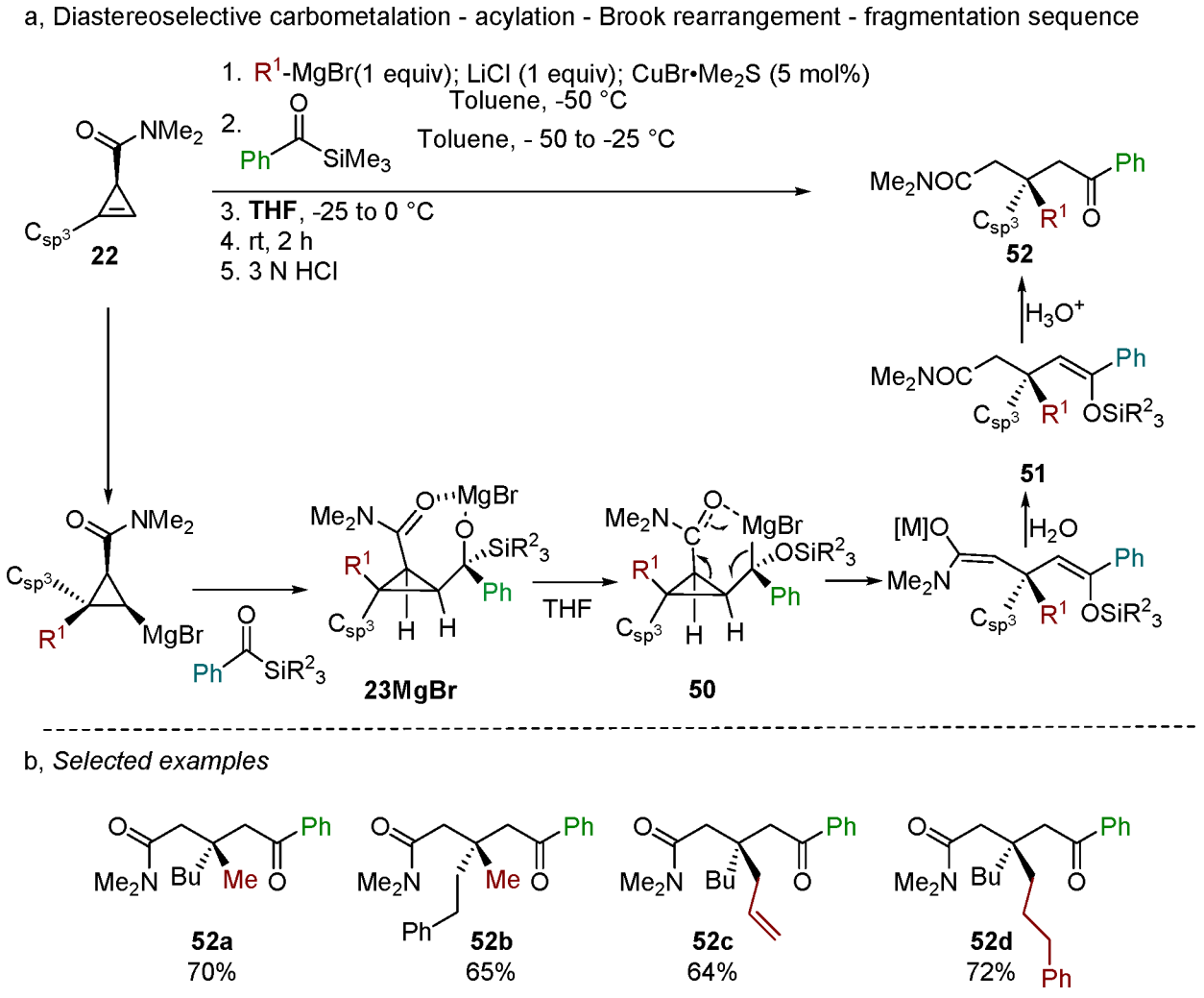
Scheme 21. Sequence of Carbometalation−Acylation−Brook Rearrangement−Selective Ring Fragmentation on Cyclopropenyl Esters



initial study started by the enantioselective copper-catalyzed carbozincation reaction in the presence of (*R*)-DTBM-SEGPHOS to provide the desired products in excellent yields and enantioselectivities with perfect diastereoselectivities (Scheme 16b). The configurational stability of the cyclopropyl-zinc intermediate allowed directly, or after transmetalation, subsequent functionalization for the creation of an additional controlled stereocenter (Scheme 16b).[40] However, the scope of the reaction was rather limited (i.e., Ph_2Zn already gave lower enantiomeric ratio, i.e., **37e**), and it was then necessary to extend this concept to a larger variety of carbon nucleophiles. Therefore, an extension of this chemistry to Grignard reagents was considered. Although Grignard reagents are easy to synthesize, with potentially a very large variation of the alkyl groups, enantioselective catalysis with alkyl magnesium halide is usually more difficult to control due to their high reactivity[41] and structural complexity.[42]

We were pleased to observe a constant highly enantioselective copper-catalyzed addition of Grignard reagents, in the presence of 0.5 equiv of $MgBr_2$ and Josiphos as ligand, to provide the corresponding cyclopropanes possessing a rather large scope of nucleophiles. The particularly high enantioselectivity observed for the addition of secondary alkyl magnesium bromide species (**37h** and **37k**) should be noted. By subsequent addition of an electrophile, polysubstituted cyclopropanes were obtained as single diastereomers with high enantiomeric ratios. In all cases, the nucleophile reacts with an anti diastereofacial preference to the aryl group (Scheme 16c).[3] As an interesting group of electrophiles, the addition of oxenoid or electrophilic aminating reagents allowed the formation of enantiomerically enriched cyclopropanol and cyclopropyl amine derivatives (Scheme 16d).[43] This approach allows the introduction of a large variety of sp^3-hybridized nucleophiles with excellent selectivities. However, the addition of sp^2-hybridized Grignard reagents led to a racemic product. Further continuing our quest to provide a general and complete tool for a rapid access to differently substituted cyclopropanes, we started first to investigate the copper-catalyzed vinylalumination reaction in the presence (*R*)-DTBM-SEGPHOS as chiral ligand (Scheme 17a). Importantly, we found that the addition of Et_2Zn was crucial to promote a clean and reproducible vinylmetalation of cyclopropenes, most probably by an initial transmetalation of the corresponding vinyl aluminum to its Zn counterpart helping the second and final transmetalation into the copper species. However, the selectivity was only moderate reaching a maximum of 90:10 enantiomeric ratios in the best cases.[44] To overcome this limitation, an alternative Co-catalyzed alkenyl boronic acid strategy was successfully developed (Scheme 17c), and very high enantio-

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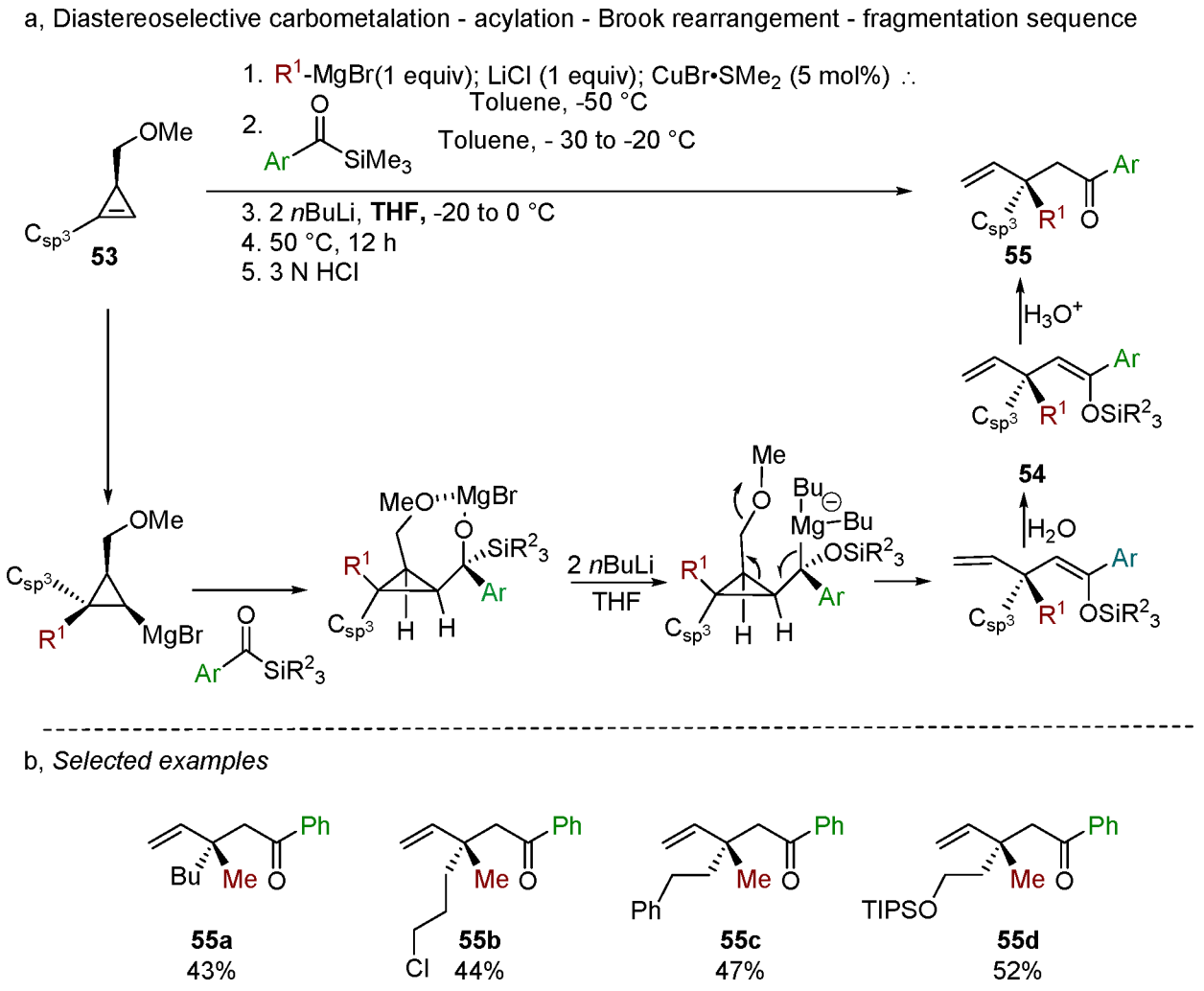
Scheme 22. Sequence of Carbometalation−Acylation−Brook Rearrangement−Selective Ring Fragmentation on Cyclopropenyl Methoxy Methanols



meric and diastereomeric ratios were observed for a very large number of sp^2-hybridized boronic acids.[45] In a similar vein, the Rh-catalyzed enantioselective arylation was previously developed by using aryl boronic acids, and the scope was again broad, thanks to the numerous commercially available aryl boronic acids, even for symmetrical cyclopropenes (**41d**, Scheme 17b).[46] Finally, pleased by the successful addition of sp^3 and sp^2-hybridized nucleophiles to cyclopropenes, we turned our attention to the last missing nucleophiles, namely sp-nucleophiles (alkynyl derivatives).

To answer this last remaining limitation, the Pd-catalyzed addition of alkynes, diynes, and even enynes was developed using (*R*)-DM-BINAP as chiral ligand, and in all cases, excellent selectivities were obtained (Scheme 16d).[47]

3. COMBINED DIASTEREOSELECTIVE CARBOMETALATION: SELECTIVE CARBON−CARBON BOND CLEAVAGE

In contrast to classical cyclopropanation of alkenes, an additional advantage of the diastereoselective (and/or enantioselective) carbometalation reaction of cyclopropenes is that the resulting cyclopropyl metal species can eventually undergo, through specific in situ reactions, a selective carbon−carbon bond cleavage to produce interesting acyclic molecular backbones. By a judicious design of the molecular architecture of the substrate, the diastereoselectivity generated during the carbometalation step could be translated in the enantioselective formation of a carbon stereocenter located at a different position in the product (Scheme 18). For instance, the syn-facial directed diastereoselective copper-carbomagnesiation of cyclopropenyl ester **6** leads to the formation of cyclopropyl magnesium species $\mathbf{7}_{syn}$ that undergoes an oxidation reaction with simple oxygen to produce the corresponding cyclopropanolate $\mathbf{43}_{syn}$ as two diastereomers at the carbinol center. In $\mathbf{43}_{syn}$, a 'push−pull' effect induced on one hand by the magnesium cyclopropanolate and on the other hand, by the presence on the electron withdrawing group promotes a rapid fragmentation to give the acyclic aldehyde **44** after hydrolysis. The chiral information on the starting cyclopropene is therefore transferred through the carbometalation process to the quaternary carbon stereocenter of the aldehyde. When the same cyclopropenyl ester **6** was treated with an organocuprate, an anti-facial carbometalation reaction was observed, and the resulting cyclopropyl copper $\mathbf{7}_{anti}$ could then stereoretentively be oxidized by the addition of lithium oxenoid to provide copper cyclopropanolate $\mathbf{43}_{anti}$.

The same selective carbon−carbon bond fragmentation produces the enantiomer of **44** with excellent selectivity. From the same starting material, by simply changing the nature of the

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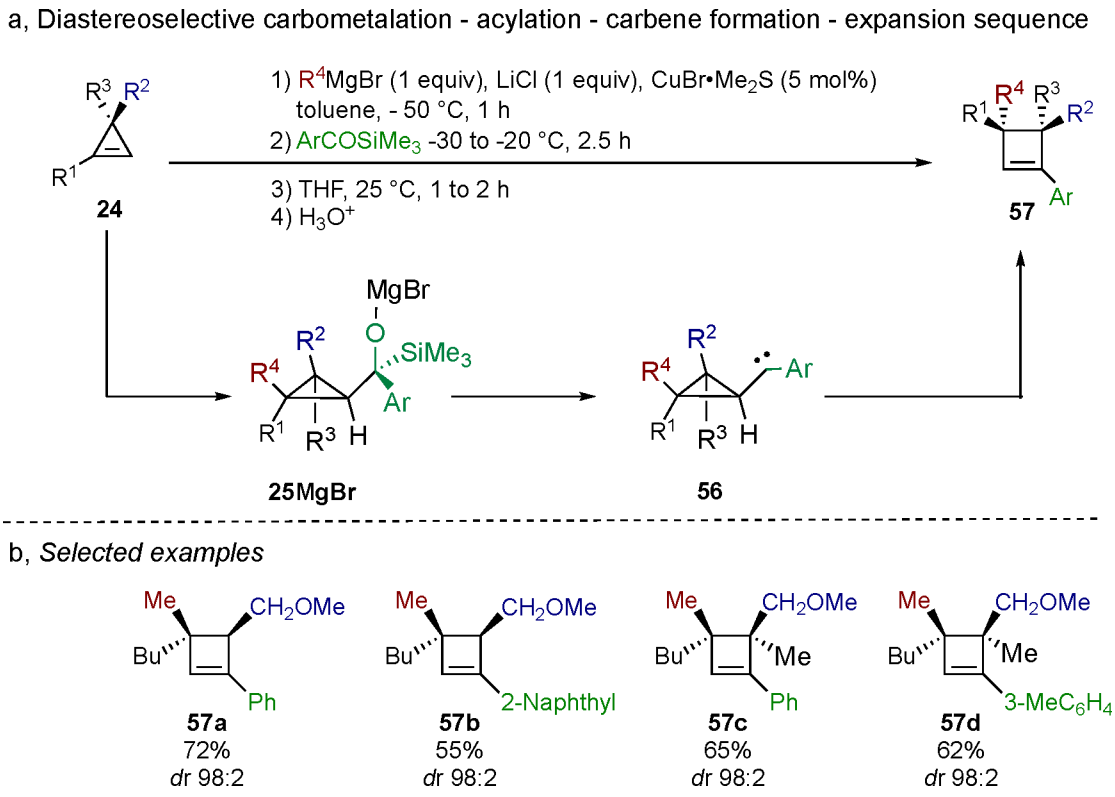
Scheme 23. Carbometalation−Acylation−Ring Expansion Sequence



organometallic species for the carbometalation step, both enantiomers of the products were, at will, obtained (Scheme 18b).[17] A slight change in the design of the starting cyclopropenyl substrate might lead to a completely different molecular architecture of the final product. For instance, if the cyclopropenyl methanol acetates **45** are now used, the syn-facial carbocupration lead to the unique formation of the cyclopropyl copper $\mathbf{46}_{syn}$. In this case, although a cuprate was used, the steric hindrance induced by the substituent R^2 impedes all anti-addition to occur (Scheme 19a). Oxidation with lithium oxenoid leads to the formation of a cyclopropanolate species that undergoes a spontaneous fragmentation to give butenal **47** possessing a quaternary carbon stereocenter in excellent yield and selectivity (Scheme 19b).[26]

Keeping now the structure of the starting material constant (i.e., **6**) but changing the nature of the homologation step, a third type of molecular backbone could be envisaged. The sequence would still consist in a syn-facial (path a, Scheme 20a) or anti-facial (path b, Scheme 20a) carbometalation reaction, controlled by the nature of the solvent, followed by a homologation with a zinc carbenoid that would in situ generate a cyclopropyl methyl zinc intermediate **48**. This intermediate would undergo a spontaneous selective ring fragmentation to produce the corresponding two enantiomers of the allylic substrates **49** possessing a quaternary carbon stereocenter (Scheme 20b).

The zinc homologation is easily performed in situ by mixing Et_2Zn and CH_2I_2 in the reaction flask. However, the presence of additional ligands was necessary to increase the reactivity of the zinc homologation. This sequence of syn- or anti-diastereoselective carbometalation−zinc homologation and finally carbon−carbon bond cleavage allow the easy transformation of enantiomerically enriched cyclopropenyl esters into acyclic allylic moieties bearing quaternary carbon stereocenters in a single-pot operation through the formation of two new carbon−carbon bonds.[18] Using now the cyclopropenyl amide derivative **22**, a sequence of copper-catalyzed carbometalation, addition of acylsilane, Brook rearrangement−fragmentation could lead to the formation of *δ*-ketoamide **52** possessing the quaternary carbon stereocenter (Scheme 21). Indeed, we have previously described that the copper-catalyzed carbomagnesiation of **22** followed by reaction with acylsilane led to the formation of a single diastereomer of polysubstituted *α*-cyclopropyl magnesium silanolate **23MgBr** when toluene was used as solvent (Scheme 9e). Then, the simple addition of THF as an additional cosolvent and stirring the reaction mixture at room temperature for 2 h promotes a 1,2-Brook rearrangement. The rearrangement product **50** subsequently induces a selective ring fragmentation to give *δ*-ketoamide **52**.[32] Interestingly, the formation of **52** results from a Brook rearrangement proceeding with a complete inversion of configuration at the benzylic carbon center before ring fragmentation (Scheme 21b). Additionally, a mild hydrolysis allows the isolation of *E*-enol ethers **51**.

If no electron-withdrawing group is present (ester or amide), the Brook rearrangement does not promote the ring fragmentation. However, by generating a more nucleophilic species from the Brook rearrangement, one could hope that a selective carbon−carbon bond cleavage would still be possible in the presence of an appropriate leaving group. Various substituted cyclopropyl methyl ethers **53** were therefore carbometalated, and the resulting cyclopropyl magnesium intermediates were treated with acylsilane to provide the corresponding *α*-alkoxysilane intermediates. Then, addition of 2 equiv of RLi in THF *in situ* generated a magnesiate that indeed underwent the expected Brook rearrangement and fragmenta-

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tion to first give the corresponding enol ethers **54** and ketones **55** after acidic hydrolysis (Scheme 22).[33a]

Interestingly, and although less common, α-alkoxysilane could also serve as a source of carbene,[48] and we were wondering if the intermediate cyclopropyl-containing α-hydroxysilane **25MgBr** (Scheme 9f) could be used to trigger the formation of a carbene **56** that would undergo a selective ring expansion into polysubstituted cyclobutenes **57** (Scheme 23). Obviously, to allow this transformation, the electron-withdrawing group should be removed to avoid the fragmentation previously described. Several cyclopropenes **21** possessing different R^2 and R^3 groups were submitted to the sequence of copper-catalyzed carbomagnesiation reaction followed by reaction with acylsilane. THF was then added to the intermediate **25MgBr** to promote the Brook rearrangement. As no ring fragmentation could be observed due to the lack of push−pull effect, the α-hydroxysilane undergoes an α-elimination to provide the carbene intermediate **56**.

Then, a very selective carbon−carbon bond migration occurs to provide cyclobutene **57** as a single diastereomer.[33c] It should be noted that no ring expansion was observed when only a secondary alcohol was present (no C−Si bond), underlining that the Brook rearrangement is essential to promote the formation of the carbene intermediate **56**. Rules were proposed for the selectivity of the ring expansion.

4. SUMMARY

After a decade of research focusing on the carbometalation reactions of cyclopropenes as a tool to synthesize stereodefined cyclopropanes, we learned and keep learning about the unique properties, reactivity, and behavior of these carbocycles. Many subclasses of cyclopropanes are now synthetically available through this method. By judicious retrosynthetic analysis and clever design of the starting cyclopropenyl substrate as well as by the proper choice of the nucleophilic partner, different cyclopropane derivatives are easily accessible in stereodefined manner. Substitution patterns include alkyl, allyl, aryl, vinyl, alkynyl, silyl substituents that decorate the cyclopropyl core as well as heteroatom functionalities as alcohols and amines; all of these in anti or syn relationships, from minimal trisubstituted cyclopropanes up to persubstituted cyclopropanes. Nevertheless, some challenges are yet unmet such as the formation of polysubstituted spiropentanes as single diastereomers. In addition, steric factors might prevent functionalization of the resulting cyclopropyl metal due to an increase of steric interactions with the increase of degree of substitution. Furthermore, efficient synthetic routes to starting cyclopropenes remain a significant limitation, particularly for the cyclopropenation of internal alkynes. Despite all of those, we are now closer than ever to be able to synthesize any desirable cyclopropane at will from a common precursor.

AUTHOR INFORMATION

Corresponding Author

Ilan Marek − *Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa 32000, Israel;* orcid.org/0000-0001-9154-2320; Email: chilanm@technion.ac.il

Author

Yair Cohen − *Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa 32000, Israel*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.accounts.2c00424

Author Contributions

CRediT: **Ilan Marek** conceptualization (lead), funding acquisition (lead), supervision (lead), writing-original draft (equal), writing-review & editing (equal); **Yair Cohen** investigation (equal), methodology (equal), writing-original draft (equal).

Notes

The authors declare no competing financial interest.

Biographies

Yair Cohen was born in Ra'anana, Israel, in 1987. After his mandatory military service in the Israel Defense Forces, he obtained his BSc in chemistry from the Technion − Israel Institute of Technology in 2015. He then joined the group of Prof. Ilan Marek as a Ph.D. student to investigate the stereoselective copper-catalyzed carbometalation reactions of polysubstituted cyclopropenes.

Ilan Marek is a Professor at the Schulich Faculty of Chemistry at the Technion − Israel Institute of Technology. Since 2005, he has held the Sir Michael and Lady Sobell Academic Chair, and he is a member of the French Academy of Sciences, the Israel Academy of Sciences and Humanities and of the Academia Europaea. He was educated in France and received his Ph.D. in 1988 from the University Pierre et Marie Curie (Paris, France) with Prof. Jean F. Normant. After 1 year as a postdoctoral fellow in Louvain-la-Neuve (Belgium) with Prof. Leon Ghosez, he obtained a research position at the Centre National de la Recherche Scientifique (CNRS) at the University Pierre et Marie Curie in France in 1990. After obtaining his Habilitation in Organic Chemistry, he moved to the Technion − Israel Institute of Technology in 1997.

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