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Cyclopropanes and cyclopropenes: synthesis and applications

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Gold-catalyzed ethylene cyclopropanation

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Full Research Paper

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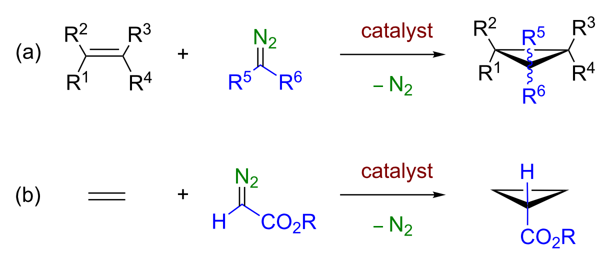
Abstract

Ethylene can be directly converted into ethyl 1-cyclopropylcarboxylate upon reaction with ethyl diazoacetate (N_2CHCO_2Et, EDA) in the presence of catalytic amounts of IPrAuCl/NaBAr$^F_4$ (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene; BAr$^F_4$ = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate).

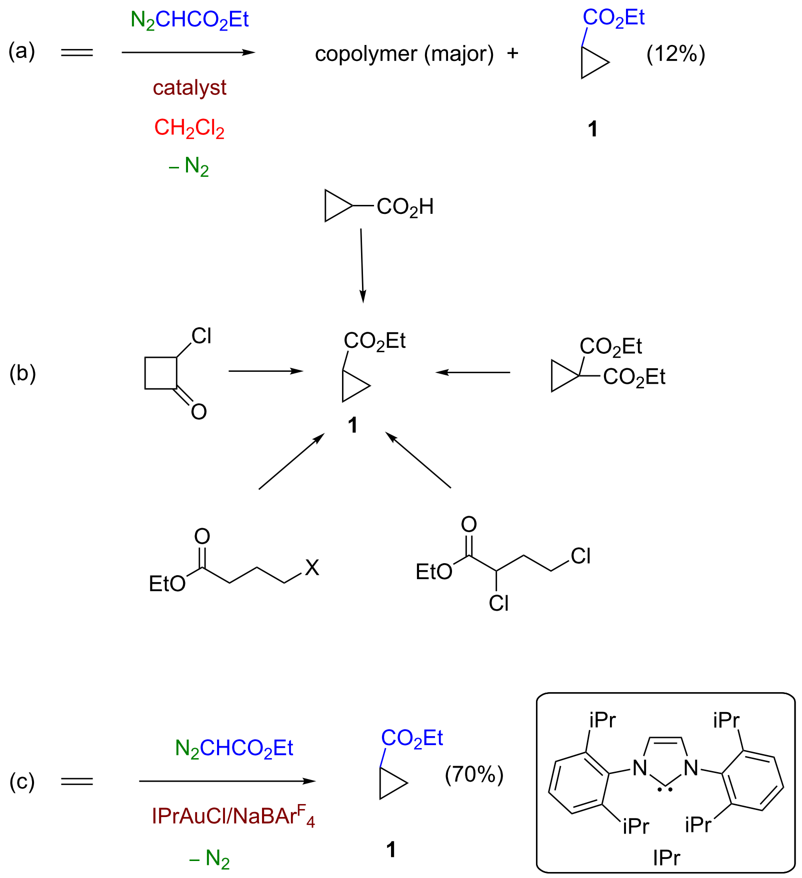
Introduction

Nowadays the olefin cyclopropanation through metal-catalyzed carbene transfer starting from diazo compounds to give olefins constitutes a well-developed tool (Scheme 1a), with an exquisite control of chemo-, enantio- and/or diastereoselectivity being achieved [1,2]. Previous developments have involved a large number of C=C-containing substrates but, to date, the methodology has not been yet employed with the simplest olefin, ethylene, for synthetic purposes [3]. Since diazo compounds bearing a carboxylate substituent are the most commonly employed carbene precursors toward olefin cyclopropanation, their use with ethylene leads to cyclopropane (Scheme 1b). De Bruin and co-workers have described [4] such product in a minor, secondary reaction (yields <12%) while studying the copolymerization of ethylene and ethyl diazoacetate with rhodium-based catalysts (Scheme 2a).



Scheme 1: (a) General metal-catalyzed olefin cyclopropanation reaction with diazo compounds. (b) The ethylene cyclopropanation with diazoacetates leads to cyclopropanecarboxylates.

Ethyl cyclopropanecarboxylate has been prepared in several ways, alternative to the direct carbene addition to ethylene (Scheme 2b): ring contraction of 2-halocyclobutanone [5],



Scheme 2: Routes toward ethyl cyclopropanecarboxylate (**1**). (a) Ethylene cyclopropanation described by De Bruin and co-workers as secondary reaction. (b) Stoichiometric transformations. (c) Gold-catalyzed ethylene cyclopropanation described in this work.

cyclization of alkyl 4-halobutanoates [6], electroreductive dehalogenation [7] and decarboxylation of diethyl 1,1-cyclopropyldicarboxylate [8]. Other methods include the transesterification of other alkyl cyclopropanecarboxylates [9] and the esterification with ethanol of the cyclopropanecarboxylic acid [10]. This product finds applications as lubricant additives [11], alkylating reagent in the Friedel–Crafts synthesis of indanones [12] or as synthon toward the introduction of cyclopropyl moieties in compounds with medicinal or biological interest [13,14].

In view of the lack of examples of direct conversions of ethylene into cyclopropanecarboxylates, and given our experience with group 11 metal-based catalysts for carbene-transfer reactions from diazoacetates [15,16], we have investigated this transformation and found that the gold complex IPrAuCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) along with one equivalent of $NaBAr^F_4$ (BAr^F_4 = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) catalyzes the ethylene cyclopropanation with ethyl diazoacetate as the carbene precursor, under mild conditions, with moderate yields (ca. 70%, EDA-based).

Results and Discussion

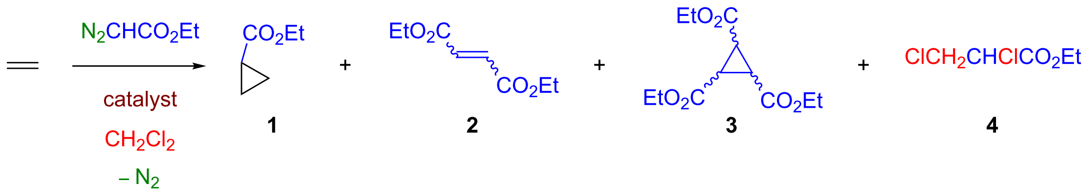
Diazo compounds N_2=CRR' usually react with metal complexes of groups 8–11 with formation of electrophilic metal–carbene intermediates L_nM=CRR' [1,2] that further react with nucleophiles such as olefins en route to cyclopropanes. However, these intermediates can also react with another molecule of the diazo reagent promoting the formation of olefins RR'C=CRR' [17]. This side reaction frequently is avoided upon maintaining a low diazo compound/catalyst ratio, employing slow addition devices to incorporate a solution of the diazo reagent into the reaction mixture containing the olefin and the catalyst. Unfortunately, the use of ethylene as the olefin requires a pressure vessel and thus the diazo reagent must be added in one portion before pressurizing the system. This fact constitutes the main drawback when working with this alkene, and a highly chemoselective catalyst toward cyclopropanation over carbene dimerization is needed to enhance the former transformation.

In a first array of experiments, we tested several group 11 metal-based catalysts that have been described in our group for the catalytic transfer of the $CHCO_2Et$ group from ethyl diazoacetate ($N_2{=}CHCO_2Et$, EDA), as well as a rhodium-based catalyst. The experimental procedure started upon placing the catalyst (0.02 mmol) into a Fischer–Porter vessel and addition of an EDA solution in 10 mL of dichloromethane via cannula under ethylene atmosphere, and then it was pressurized to 8 bar with the same gas. The mixture was stirred for 14 h and then investigated by GC (see the experimental section). The results are collected in Table 1. The complex $Tp^{Ms}Cu(thf)$, previously described as an excellent catalyst for olefin cyclopropanation [18], led to negative results, since only the olefins **2** (mixtures of diethyl fumarate and maleate) were detected at the end of the reaction. The second copper-based catalyst tested $Tp^{(CF3)2,Br}Cu(thf)$ [19] gave some of the desired product **1** (Table 1, entry 2), albeit in low yield (15%). Olefins **2** were also formed, although mass balance was not verified by GC studies. When the crude was analyzed by NMR, broad signals characteristic of polymeric materials were observed. Given that our goal was the development of a catalytic route for cyclopropane **1**, we have not invested efforts in the characterization of such materials.

The silver complex $Tp^{(CF3)2,Br}Ag(thf)$ [19] (Table 1, entry 3) was not effective toward the aforementioned target, since only 5% of **1** was formed. In this case, the product derived from the insertion of the carbene $CHCO_2Et$ group into the C–Cl of the solvent was the major one, accordingly with previous work from this and other laboratories using silver-based catalysts [20,21]. Therefore, we moved onto gold-based catalysts that had already been validated for EDA decomposition and carbene-transfer reactions [22,23]. Neutral IPrAuCl was not effective (Table 1, entry 4), assessing the need of a cationic, halide-free gold species toward that end. The choice of the halide scavenger is not innocent: on the other hand, it is key for the success of this search. Thus, addition of one equiv of AgOTf with respect to the gold complex resulted in low consumption of EDA, and minor amounts of **1**, olefins **2** and cyclopropane **3** derived from carbene addition to **2** were detected. The use of $AgSbF_6$ led to different results: the yield into desired **1** increased up to 25% but the functionalization of the solvent (**4**) constituted the main transformation. This is probably the effect of the silver in the reaction medium, since simple silver salts promote such reaction. The use of $NaBAr^F{}_4$ delivered ethyl cyclopropanecarboxylate (**1**) in 62% yield, with only 2% of olefins **2** as byproducts, the remaining 36% of initial EDA appearing unreacted at the end of the 14 h period. When the dirhodium complex $Rh_2(CF_3COO)_4$ was submitted to the same experimental conditions, compound **1** was detected in 41% yield, along with 14% of olefins **2**. Again, the analysis of the crude mixture through NMR revealed the presence of polymeric material.

Once the IPrAuCl/$NaBAr^F{}_4$ was identified as the best choice toward the catalytic formation of **1**, several reaction conditions were explored. As shown in Table 2, and plotted in Figure 1, four experiments carried out at 1, 2, 4 and 8 bar of ethylene

Table 1: Catalyst screening for the reaction of ethylene and ethyl diazoacetate.[a]



Entry	Catalyst	% **1**	% **2**	% **3**	% **4**	% EDA
1	$Tp^{Ms}Cu(thf)$	0	>95	nd	nd	nd
2	$Tp^{(CF3)2,Br}Cu(thf)$	15	15	nd	nd	nd[b]
3	$Tp^{(CF3)2,Br}Ag(thf)$	5	nd	nd	>75	13
4	IPrAuCl	0	4	0	0	40[b]
5	IPrAuCl + AgOTf	2	2	9	nd	80
6	IPrAuCl + $AgSbF_6$	25	0	nd	>70	nd
7	IPrAuCl + $NaBAr^F{}_4$	62	2	nd	nd	36
8	$Rh_2(CF_3COO)_4$	41	14	nd	nd	nd[b]

[a] Reaction carried out with 0.02 mmol of catalyst, 0.2 mmol of EDA except with the rhodium catalyst, which was run with 0.4 mmol of EDA. Ethylene pressure = 8 bar. Solvent: 10 mL of dichloromethane. Room temperature. Product determination and quantification by GC with calibration curves, yields based on initial EDA. nd = not detected. [b] NMR studies show broad signals characteristic of polymeric materials accounting for 100% of initial EDA.

Table 2: Catalytic activity of IPrAuCl/NaBAr$^F{}_4$ in the reaction of ethylene and ethyl diazoacetate.[a]

Entry	P(C_2H_4) (bar)	V(CH_2Cl_2) (mL)	% **1**	% **2**	% **3**	% EDA
1	1	5	5	>90	nd	nd
2	2	5	39	2	35	12
3	4	5	66	0	33	nd
4	8	5	73	0	15	nd[b]
5[c]	8	5	70	0	0	nd[b]
6	8	10	62	2	0	36

[a]Conditions and product numbering as described in Table 1. nd = not detected. [b]NMR studies show broad signals characteristic of polymeric materials accounting for 100% of initial EDA. [c]Reaction performed at 40 °C.

(Table 2, entries 1–4) revealed that the latter was the optimal value. This is clearly the effect of the need of a high concentration of the olefin in the reaction mixture, which is proportional to the partial pressure above the solution. Also, the use of a 5 mL volume of the solvent instead of 10 mL not only allowed to increase the yield up to 73% but also to induce complete consumption of ethyl diazoacetate. The effect of the temperature when moving from ambient (Table 2, entry 4) to 40 °C (Table 2, entry 5) was negligible, albeit in the former the cyclopropane **3** was observed. Again, some polymeric material was detected by NMR spectroscopy. It is worth mentioning that when diethyl diazomalonate or ethyl 2-phenyldiazoacetate were employed as the carbene precursor, no cyclopropanes were detected, only olefins formed from carbene dimerization as well as unreacted diazo compounds were identified at the end of the reaction.

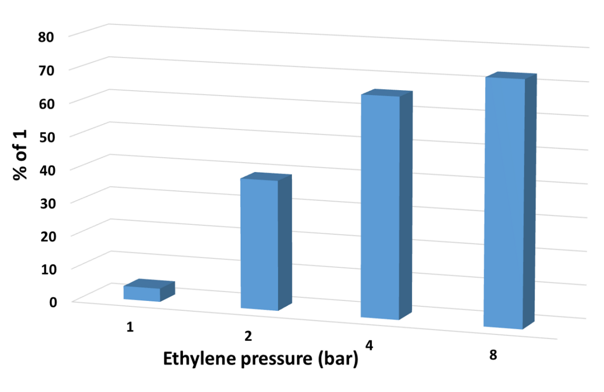


Figure 1: Effect of the pressure of ethylene on the yields of ethyl cyclopropanecarboxylate in the reaction of ethylene and EDA catalyzed by IPrAuCl/NaBAr$^F{}_4$.

Conclusion

We have found that the complex IPrAuCl in the presence of one equivalent of NaBAr$^F{}_4$ catalyzes the reaction of ethyl diazoacetate and ethylene, at room temperature, leading to ethyl cyclopropanecarboxylate with yields of ca. 70% (EDA-based). This is the first example of a direct cyclopropanation of ethylene by this methodology with significant conversions.

Experimental

General methods

All preparations and manipulations were carried out under an oxygen-free nitrogen atmosphere using conventional Schlenk techniques. Solvents were rigorously dried prior to use. The substrates as well as compound **1** (for calibration curves) were purchased from Aldrich. The catalysts were prepared according to literature procedures, as well as NaBAr$^F{}_4$ [24]. NMR spectra were performed on Agilent 400 MR and 500 DD2. GC data were collected with an Agilent 7820A equipped with an FID detector and an Agilent HP-5 column of 30 m × 320 μm × 0.25 μm. Method: 50 °C × 1.5 min, 10 °C/min, 250 °C × 25 min.

Catalytic experiments

Ethylene cyclopropanation with EDA. A 175 mL high pressure Fischer–Porter vessel equipped with a manometer and a valve was charged with 0.02 mmol of IPrAuCl (24 mg) and 0.02 mmol of NaBAr$^F{}_4$ (17 mg). The vessel was deoxygenated and filled with ethylene. A solution of 0.2 mmol of EDA (24 μL) in 5 mL anhydrous dichloromethane was added via cannula and the ethylene pressure was increased up to 8 bar. The reaction mixture was stirred for 14 hours and the pressure was released.

Reaction mixture analysis. The crude reaction mixture was diluted to 10 mL and directly analyzed by GC. The amounts of ethyl cyclopropanecarboxylate (**1**), EDA, diethyl maleate and diethyl fumarate (**2**) were determined using calibration curves ranging from 2 mM to 20 mM, previously prepared using commercially available products. Retention times of products: **1**, 5.78 min; EDA, 5.90 min; diethyl maleate, 10.73 min; diethyl fumarate, 10.93 min. To determine the quantity of triethyl 1,2,3-cyclopropanetriscarboxylate (**3**) formed, the solution was evaporated and analyzed by NMR using $CDCl_3$ as solvent and ethyl chloroacetate as internal standard.

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Oxidative radical ring-opening/cyclization of cyclopropane derivatives

Yu Liu*, Qiao-Lin Wang, Zan Chen, Cong-Shan Zhou, Bi-Quan Xiong, Pan-Liang Zhang, Chang-An Yang and Quan Zhou*

Review

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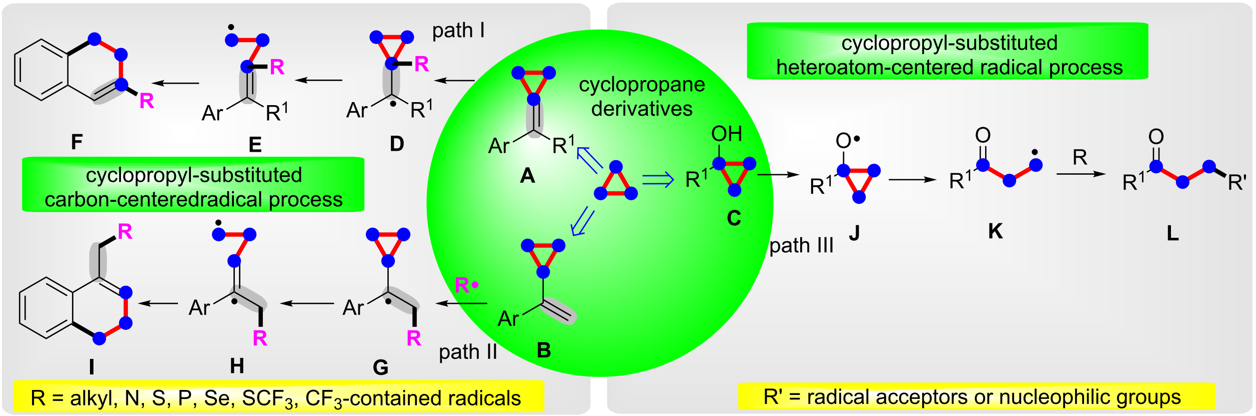
Abstract

The ring-opening/cyclization of cyclopropane derivatives has drawn great attention in the past several decades. In this review, recent efforts in the development of oxidative radical ring-opening/cyclization of cyclopropane derivatives, including methylenecyclopropanes, cyclopropyl olefins and cyclopropanols, are described. We hope this review will be of sufficient interest for the scientific community to further advance the application of oxidative radical strategies in the ring-opening/cyclization of cyclopropane derivatives.

Introduction

Cyclopropane is a cycloalkane molecule with the molecular formula C_3H_6, consisting of three carbon atoms linked to each other to form a ring, with each carbon atom bearing two hydrogen atoms resulting in D_{3h} molecular symmetry. The small size of the ring creates substantial ring strain in the structure. The cyclopropane skeleton easily can take part in ring-opening reactions under certain conditions. Cyclopropane derivatives, with their three-membered carbocyclic frameworks, have spurred considerable attention especially in the domain of organic and pharmaceutical synthesis because of their highly strained three-membered carbocyclic skeletons and their easy availability [1-16]. The cyclopropane derivatives, especially methylenecyclopropanes [17-21], cyclopropyl olefins [22] and cyclopropanols [23,24] undergo ring-opening/cyclization reactions to provide a huge number of fascinating compounds with different functional groups [25-31]. However, most recently reported methods usually proceed via a radical pathway. As shown in Scheme 1 path I, the cyclopropyl-substituted carbon radical **D** is formed by the addition of radical **R** to the C–C double bond in methylenecyclopropanes (compounds **A**). The cyclopropyl-substituted carbon radical **D** easily goes through a ring-opening to generate the alkyl radical **E**, and then cyclizes with the phe-



Scheme 1: The oxidative radical ring-opening/cyclization of cyclopropane derivatives.

nyl ring to afford the terminal product **F** (path I). The cyclopropyl olefins (compounds **B**) also react in the same cyclopropyl-substituted carbon radical pathway to finish the ring-opening and cyclization transformation (path II). The cyclopropanols **D** firstly go through homolytic cleavage of the O–H bond to give the oxygen-centered radical **J**. The alkyl radical **K**, produced by ring-opening of intermediate **J**, reacts with a radical acceptor or a nucleophilic group to obtain the product **L** (path III).

Free radical reactions have flourished and became a powerful tool in organic synthesis [32-38]. With the significant potential, this strategy has captured the human's attention and solved considerable problems in the past several decades [39-42]. The free radical reaction was applied in a range of organic transformations because of its unique advantages such as excellent reactivity, mild conditions, functional group tolerance, and atom economy. A series of radicals, such as carbon, Se, CF_3, halogen, S and N-containing radicals, were introduced into the products through oxidative radical ring-opening/cyclization of cyclopropane derivatives. In this review, we conclude recent advance in the oxidative radical ring-opening/cyclization of cyclopropane derivatives (including methylenecyclopropanes, cyclopropyl olefins and cyclopropanols) over the last 20 years.

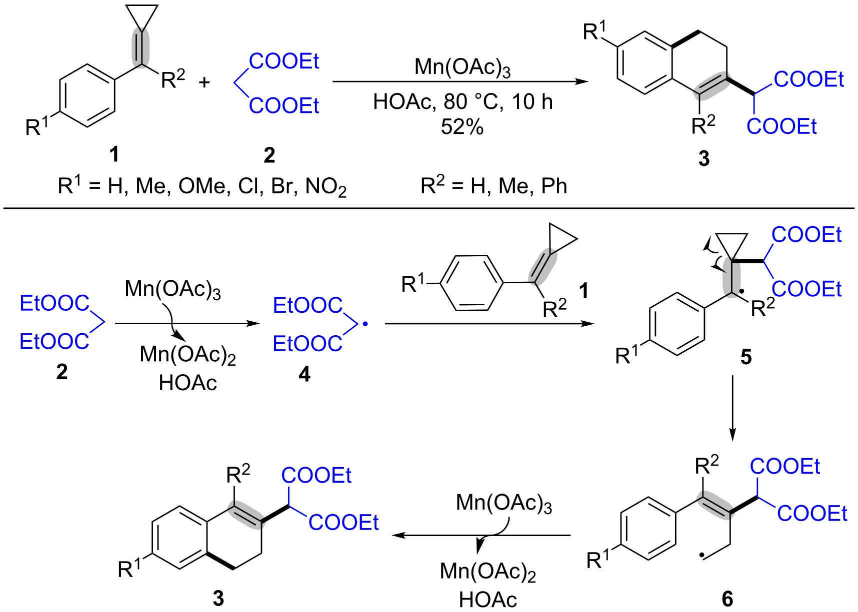
Review

Oxidative radical ring-opening and cyclization of methylenecyclopropanes (MCPs)

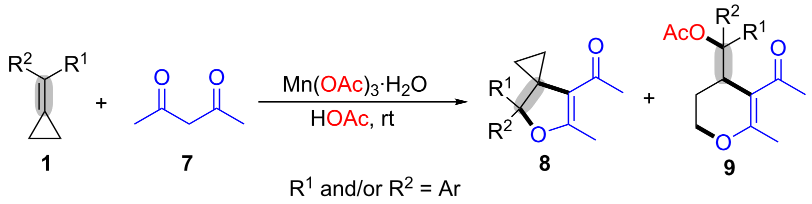
In 2004, Huang and co-workers reported the first manganese(III) acetate-mediated radical ring-opening and cyclization of methylenecyclopropanes (MCPs, **1**) with malonic acid diethyl esters (**2**, Scheme 2) [43]. This strategy provided a novel, convenient and efficient approach to construct 2-(3,4-dihydronaphthalen-2-yl)malonic acid diethyl esters **3**. The MCPs **1** with the electron-deficient or electron-rich groups were all suitable for this reaction system. The mechanism for the $Mn(OAc)_3$-mediated oxidative radical ring-opening and cyclization of MCPs with malonates is outlined in Scheme 2. Initially, the malonic acid diethyl ester (**2**) was transformed into radical **4** [44] under the action of $Mn(OAc)_3$. Then, the selective addition of the radical **4** to the C–C double bond of MCPs **1** formed the more stable benzyl radical intermediate **5** [45,46], which underwent a ring-opening to generate the alkyl radical **6** [47]. Finally, the desired product **3** was generated through intramolecular cyclization of radical intermediate **6** with an aryl ring and oxidation deprotonation by another molecule $Mn(OAc)_3$ [48].

Later, Shi et al. demonstrated an oxidative annulation of MCPs **1** with 1,3-dicarbonyl compounds **7** using manganese(III) catalysis under room temperature conditions, which afforded 4,5-dihydrofuran derivatives **8** as [3 + 2] annulation products (cyclopropyl retained adducts) in moderate to good yields [49]. This transformation also gave another six-membered cyclic compounds **9** (cyclopropyl opened adducts) via ring-opening and cyclization process (Scheme 3). However, the [3 + 2] annulation reaction did not occur under the standard conditions when the MCPs **1** was without an aromatic group.

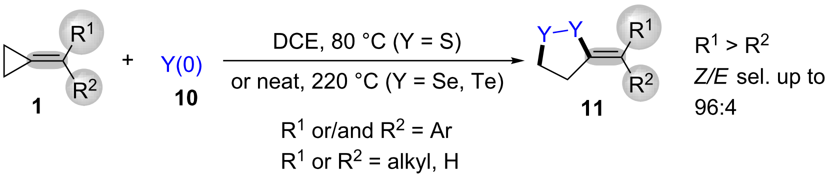
The first method for direct [3 + 2] radical cycloaddition of MCPs **1** with elemental chalcogens **10** (S, Se, Te) was developed by Yu and co-workers. This strategy presented a simple and efficient method for the synthesis of methylene-1,2-dichalcogenolanes **11** (Scheme 4) [50]. This reaction proceeded via a radical pathway, which could take place smoothly under cartalyst- and additive-free conditions. However, the addition of the radical initiator AIBN in this reaction did not accelerate the reaction.



Scheme 2: $Mn(OAc)_3$-mediated oxidative radical ring-opening and cyclization of MCPs with malonates.



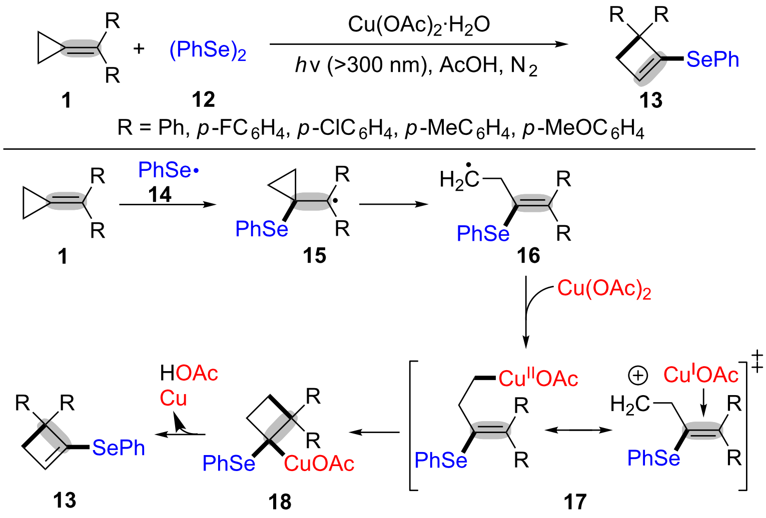
Scheme 3: Mn(III)-mediated oxidative radical ring-opening and cyclization of MCPs with 1,3-dicarbonyl compounds.



Scheme 4: Heat-promoted ring-opening/cyclization of MCPs with elemental chalgogens.

Next, Huang's group proposed the copper-catalyzed ring-opening and cyclization of MCPs **1** with diphenyl diselenides **12** for the synthesis of 2-phenylseleny-3,3-diarylcyclobutenes **13** under visible light irradiation (Scheme 5) [51]. The desired products **13** contained a cyclobutene group and a selenium atom, which makes the products possess unique biological and pharmaceutical activities. The mechanism of the copper(II) acetate-mediated oxidative radical ring-opening/cyclization of MCPs with diphenyl diselenides is outlined in Scheme 5. Firstly, the phenylselenyl radical **14**, generated from the homolytic cleavage of diphenyl diselenide, is added to the C–C double bond of MCPs to afford the intermediate **15**, which undergoes a ring-opening process to form the radical intermediate **16** [52,53]. Then, the radical **16** reacts with copper(II) acetate to produce organocopper intermediate **17**. Finally, the intramolecular insertion of C–Cu in compounds **17** to the carbon–carbon double bond takes place to produce the intermediate **18** followed by β-elimination to generate the desired product **13** [54-56].

In 2005, Yu et al. described a novel and efficient oxidative radical ring-opening and cyclization of MCPs **1** with benzene-

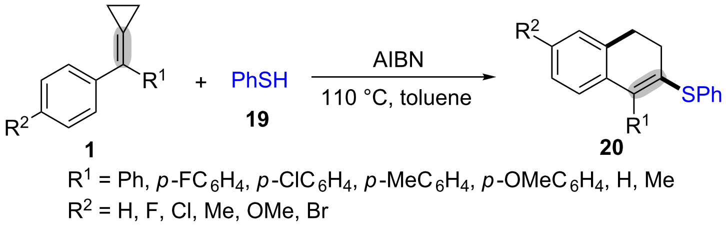


Scheme 5: Copper(II) acetate-mediated oxidative radical ring-opening and cyclization of MCPs with diphenyl diselenides.

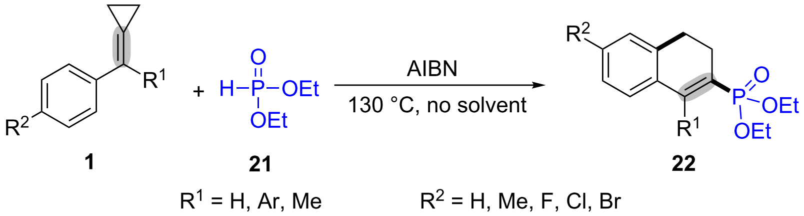
thiol (**19**) for the synthesis of 3-phenylsulfanyl-1,2-dihydronaphthalenes **20** in moderate to good yields (Scheme 6) [57]. Additionally, using benzeneselenol instead of benzenethiol under the standard conditions generated the corresponding products in 31% yields.

In the same year, Huang's group also reported a similar ring-opening and cyclization of MCPs **1** with diethyl phosphites **21** for building diethyl 3,4-dihydro-2-naphthylphosphonates **22** (Scheme 7) [58]. This was the first example to synthesize the diethyl 3,4-dihydro-2-naphthylphosphonates **22** that have great potential applications in organic chemistry and biochemistry.

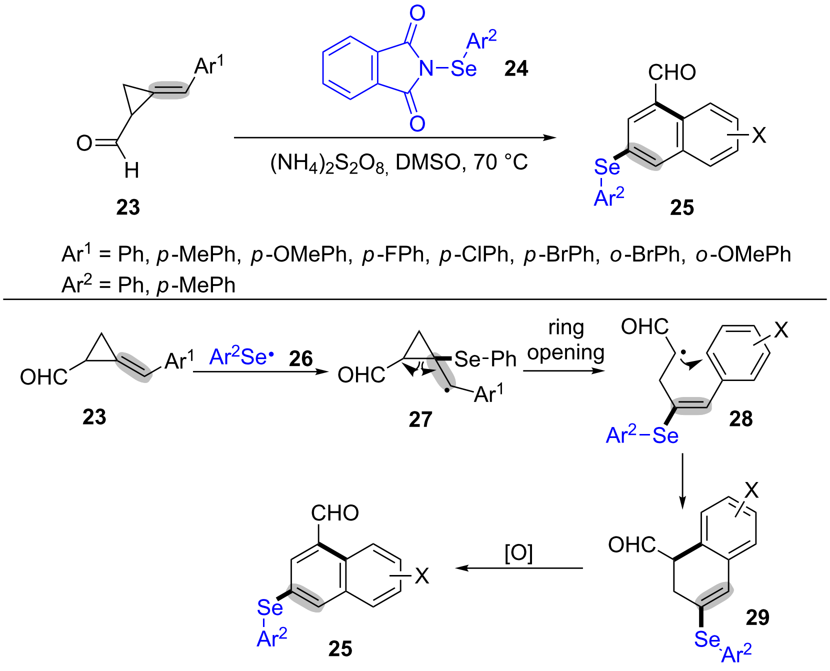
In 2009, Miao's group also discovered another method for the synthesis of 1-naphthaldehydes **25** under mild conditions via a radical-mediated ring-opening and intramolecular cyclization of MCPs **23** with organic selenium reagents **24** (Scheme 8) [59]. In this reaction, the MCPs with electron-withdrawing groups gave lower yields than that with electron-donating groups. Additionally, the use of other organoselenium reagents, such as phenylselenyl bromide or phenylselenyl chloride provided only



Scheme 6: AIBN-promoted oxidative radical ring-opening and cyclization of MCPs with benzenethiol.



Scheme 7: AIBN-mediated oxidative radical ring-opening and cyclization of MCPs with diethyl phosphites.



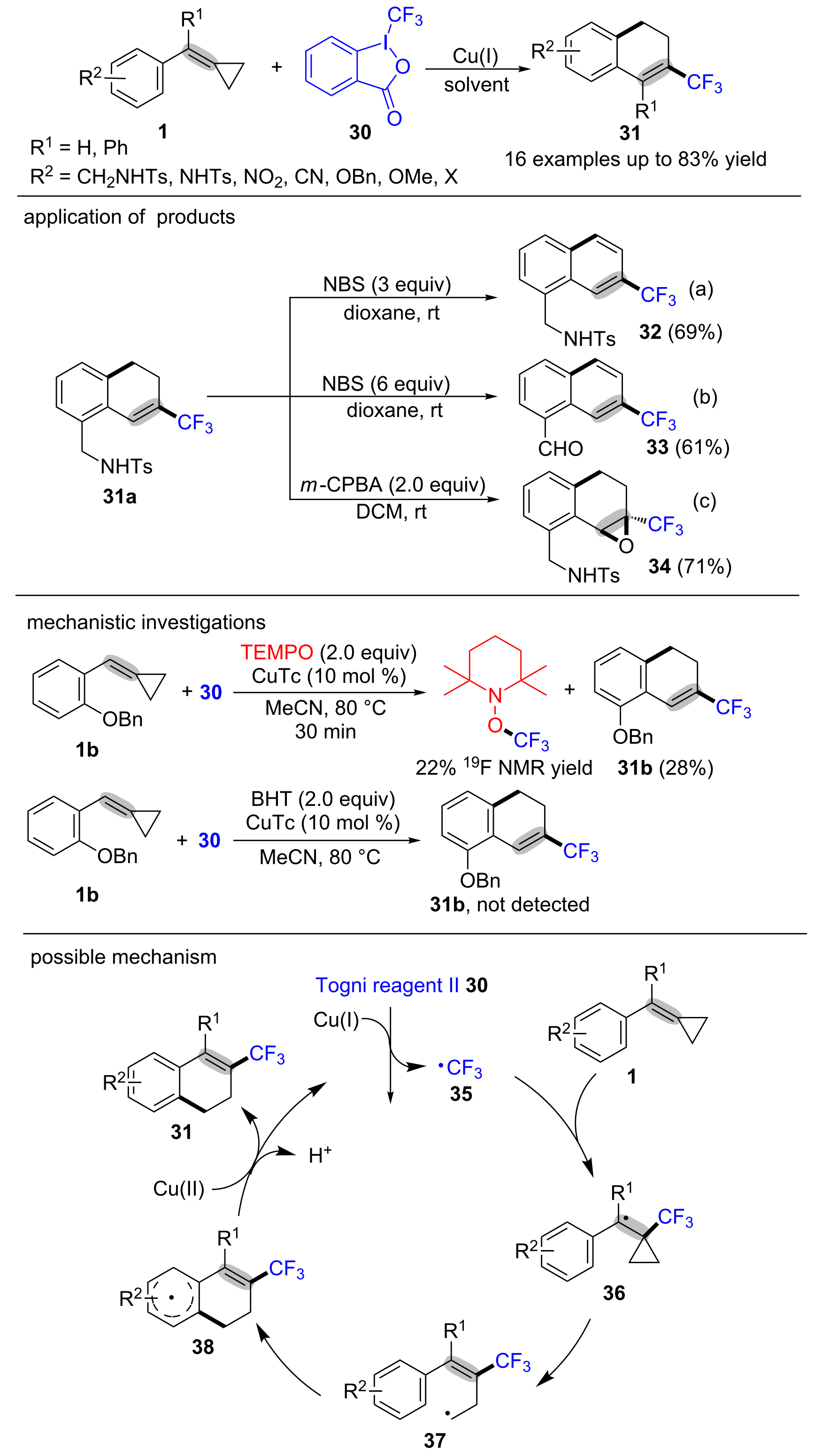
Scheme 8: Organic-selenium induced radical ring-opening and cyclization of MCPs derivatives (cyclopropylaldehydes).

trace amounts of the desired products. The mechanism for the organoselenium induced radical ring-opening and cyclization of MCPs derivatives is showed in Scheme 8. Firstly, phenylselenyl radical **26** was produced in the presence of free radical initiator $(NH_4)_2S_2O_8$ [60,61]. Next, the intermediate **26** was added to the C–C double bond of MCPs **23**, and then went through a series of ring-opening, intramolecular cyclization, oxidation and dehydrogenation to generate 3-arylselanylnaphthaldehyde **25**.

In 2015, Shi and co-workers reported a novel and efficient method to construct CF_3-substituted dihydronaphthalene derivatives **31** in moderate to excellent yields under mild conditions through the Cu(I)-catalyzed trifluoromethylation/ring-opening/cyclization of MCPs **1** with Togni reagent II (**30**, Scheme 9) [62]. In this transformation, many substituted MCPs **1** with alkyl groups, Ts-protected amino groups, or halogens were tolerated well and gave the desired products **31** in good yields. Moreover, the product **31a** could go through a further oxidation to afford two different products in the presence of different amount of NBS (*N*-bromosuccinimide). The corresponding CF_3-substituted naphthalene **32** could be obtained in 69% yield when the product **31a** was oxidized by 3 equiv of NBS (Scheme 9, reaction a). When the amount of NBS was increased to 6 equiv under identical conditions, the CF_3-substituted naphthaldehyde **33** was obtained in 61% yield (Scheme 9, reaction b). Furthermore, the product **31a** could also be transformed to the CF_3-substituted epoxide **34** in the presence of 2 equiv *m*-CPBA (*m*-chloroperbenzoic acid) (Scheme 9, reaction c). A radical-trapping experiment was conducted with the addition of TEMPO or BHT under the standard conditions, and the reactions were suppressed by radical scavengers, which suggested that the reaction underwent a radical process. The proposed mechanism is depicted in Scheme 9. Initially, the CF_3 radical **35** is generated from the Togni reagent II (**30**) under the action of Cu(I) [63,64]. Then the CF_3 radical **35** adds to the C–C double bond in MCPs **1** to give the more stable benzyl radical intermediate **36** which went through a ring-opening process to provide the alkyl radical intermediate **37**. The intermediate **37** undergoes intramolecular cyclization with the aromatic ring to generate intermediate **38** which is oxidized by Cu(II) to provide the CF_3-substituted dihydronaphthalenes derivatives **31** along with releasing a proton [65,66].

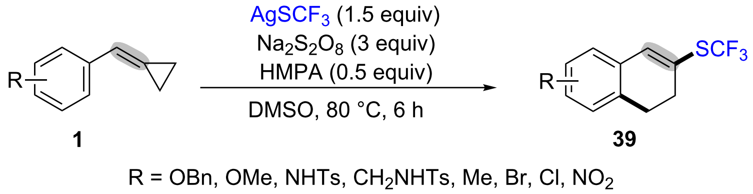
The trifluoromethylthiolation of MCPs **1** with $AgSCF_3$ was achieved by Shi et al. which proceeds through a sequence of radical addition, ring-opening, cyclization, oxidation and dehydrogenation and successfully furnished trifluoromethylthiolated 1,2-dihydronaphthalene derivatives **39** (Scheme 10) [67]. This reaction was achieved in the presence of 3.0 equiv of $Na_2S_2O_8$ as the oxidants, 0.5 equiv of HMPA (*N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphorotriamide) as the additive in DMSO.

With a similar oxidative radical ring-opening and cyclization strategy, our group developed a novel method for ring-opening and cyclization of MCPs **1** with ethers **40** afforded 2-substituted 3,4-dihydronaphthalenes **41** in moderate to excellent

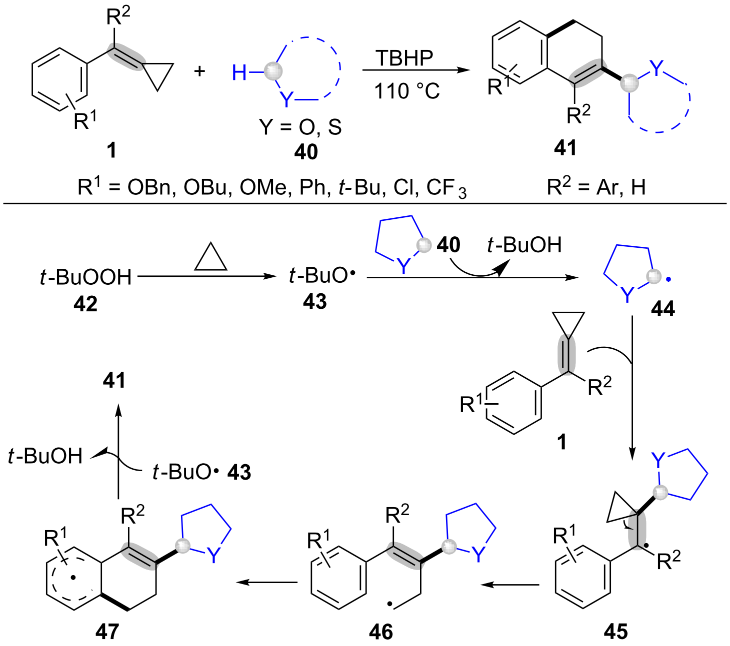


Scheme 9: Copper(I)-catalyzed oxidative radical trifluoromethylation/ring-opening/cyclization of MCPs with Togni reagent II.

yields (Scheme 11) [68]. This transformation just needed 2 equiv of TBHP (**42**), avoiding using transition metal catalysts, ligands, and bases. In the proposed mechanism (Scheme 11), the *tert*-butoxyl radical **43**, which was formed from THBP (**42**) under heating conditions, attackes the ether **40** to afford the radical **44** [69-72]. Next, the addition of radical **44** to the C–C



Scheme 10: Ag(I)-mediated trifluoromethylthiolation/ring-opening/cyclization of MCPs with $AgSCF_3$.

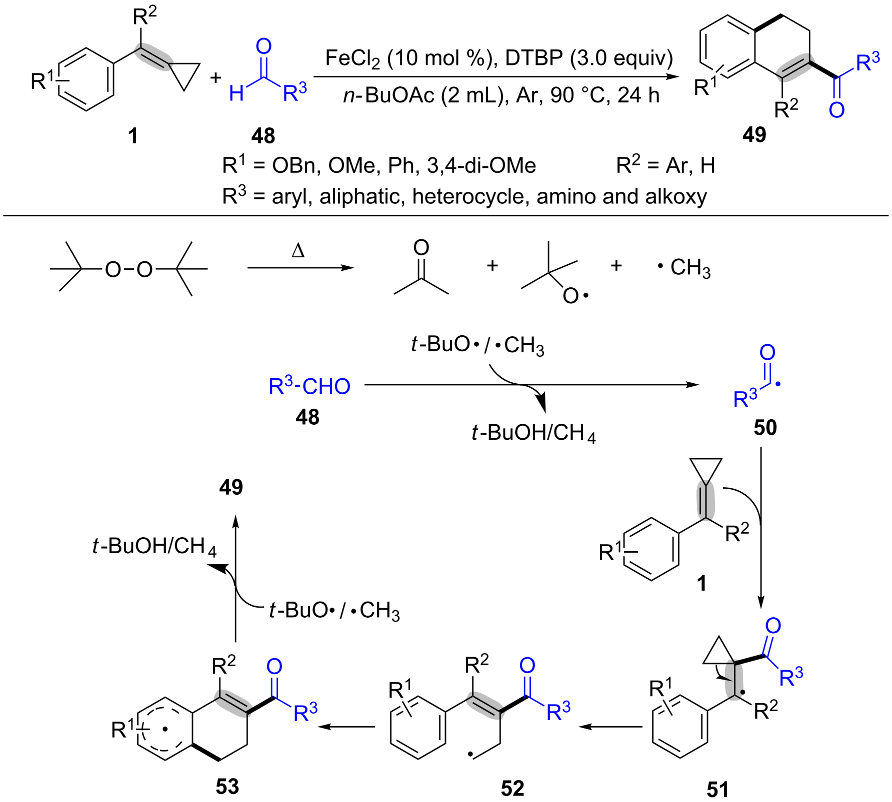


Scheme 11: oxidative radical ring-opening and cyclization of MCPs with α-C(sp^3)—H of ethers.

double bond of MCPs **1** generats a more stable benzyl radical **45**. Final ring-opening, intramolecular cyclization, oxidation, and dehydrogenation finally delivers the desired product **41**.

Next, our group reported the first oxidative ring-opening and cyclization between MCPs **1** and aldehydes **48** to provide 2-acyl-3,4-dihydronaphthalenes **49** in moderate to excellent yields via a series of radical addition, ring-opening and cyclization in the presence of DTBP (di-*tert*-butyl peroxide) and Lewis acids (Scheme 12) [73]. Moreover, the experimental results showed MCPs **1** with electron-rich aryl groups could deliver higher yields than that with electron-deficient ones. As outlined in Scheme 12, a *tert*-butoxy radical and a methyl radical were generated from cleavage of DTBP at the reaction temperature. Aldehyde **48** is easily transformed into acyl radical **50** in the presence of an alkoxy radical or a methyl radical [74-77]. The acyl radical **50** adds to the C–C double bond of MCPs giving the benzyl radical intermediate **51**. The ring-opening of radical intermediate **51** occurres to form the alkyl radical intermediate **52** which intermolecularly cyclizes with the aryl ring. The following oxidation and dehydrogenation gives the target product **49**.

A new and first achievement for the synthesis of CF_3-contained seven-membered ring compounds **55** and **56** through trifluoromethylation of acrylamide-tethered alkylidenecyclopropanes **54** was presented by Shi and co-workers (Scheme 13) [78]. The possible reaction pathway is outlined in Scheme 13. Initially, the Togni reagent II (**30**) goes through a single-electron transfer (SET) under the action of Fe^{2+} to generate the CF_3 radical **35**. The CF_3 radical **35** is trapped by the C–C double bond of substrate **54** to produce the alkyl radical intermediate **57**. Then, the intramolecular addition of an alkyl radical to the less hindered central carbon of MCPs **54** gives the benzyl radical intermediate **58**, which undergoes a ring-opening process to provide the alkyl radical intermediate **59** [79,80]. Because of the different substituent groups on the MCPs **54** (whether R^1 was a *para*-methoxy substituent or not), this reaction proceeds through two



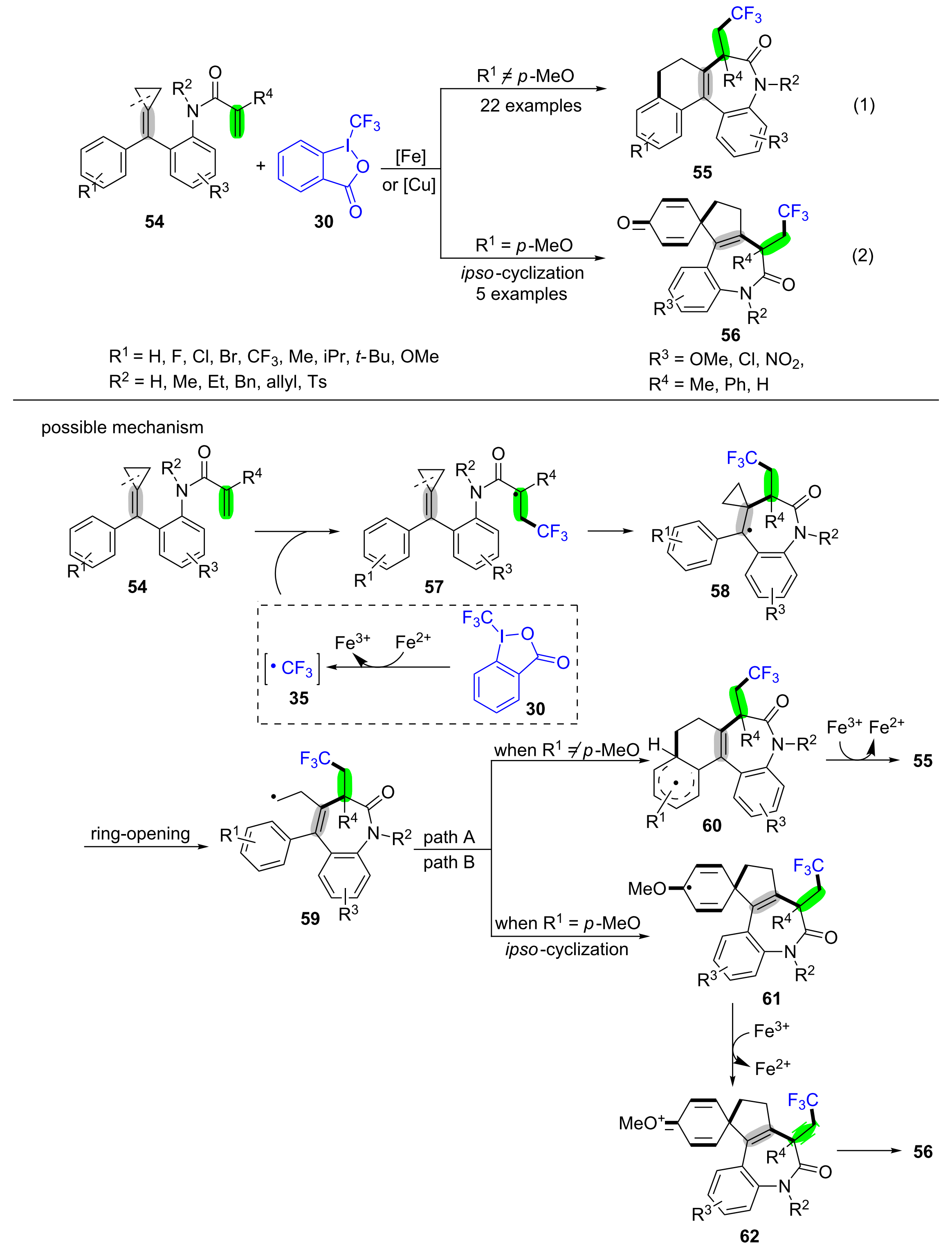
Scheme 12: Oxidative radical ring-opening and cyclization of MCPs with aldehydes.

different pathways. When R^1 is not a *para*-methoxy group, the intermediate **59** undergoes a conventional cyclization with aromatic ring to afford the radical intermediate **60**. After oxidation and aromatization, the corresponding product **55** is formed. An *ipso*-cyclization with aromatic ring occurres and gives the intermediate **61** when R^1 is a *para*-methoxy group. The oxonium ion **62** is produced by the oxidation of the intermediate **61** under the action of Fe^{3+} [81]. Lastly, the oxonium ion **62** is transformed into the desired product **56** in the presence of 2-indobenzoic acid anion.

Recently, Shi's group developed the first ring expansion of MCPs **63** with a nitrogen atom to furnish azetidines **64** (Scheme 14) [82]. The author proposed that Rh(II) had an effective impact on the reactions and could improve the reaction yields. Unfortunately, the MCPs **63** with the groups R^1 and R^2 = H were not suitable for this transformation. The reason was because the formed intermediate was unstable under this conditions. A possible mechanism is outlined in Scheme 14. Initially, the Rh-nitrene intermediate **65** [83-86] is generated from the coordination of azide to $Rh_2(esp)_2$ complex (bis[rhodium-(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]) and extrusion of N_2. Then, the Rh-nitrene intermediate **65** goes through an intramolecular single electron transfer (SET) to give the nitrogen-centered radical intermediate **66** [87-90]. Next, the radical addition of intermediate **66** to the C–C double bond in MCPs moiety furnishes the more stable benzyl radical intermediate **67**, which is ring-opened to give alkyl radical **68**. Finally, intermediate **68** goes through SET with the Rh(III) species and intramolecular cyclization with the 2-position of the indole moiety to afford the target product **64** along with the regenerated Rh(III) catalyst.

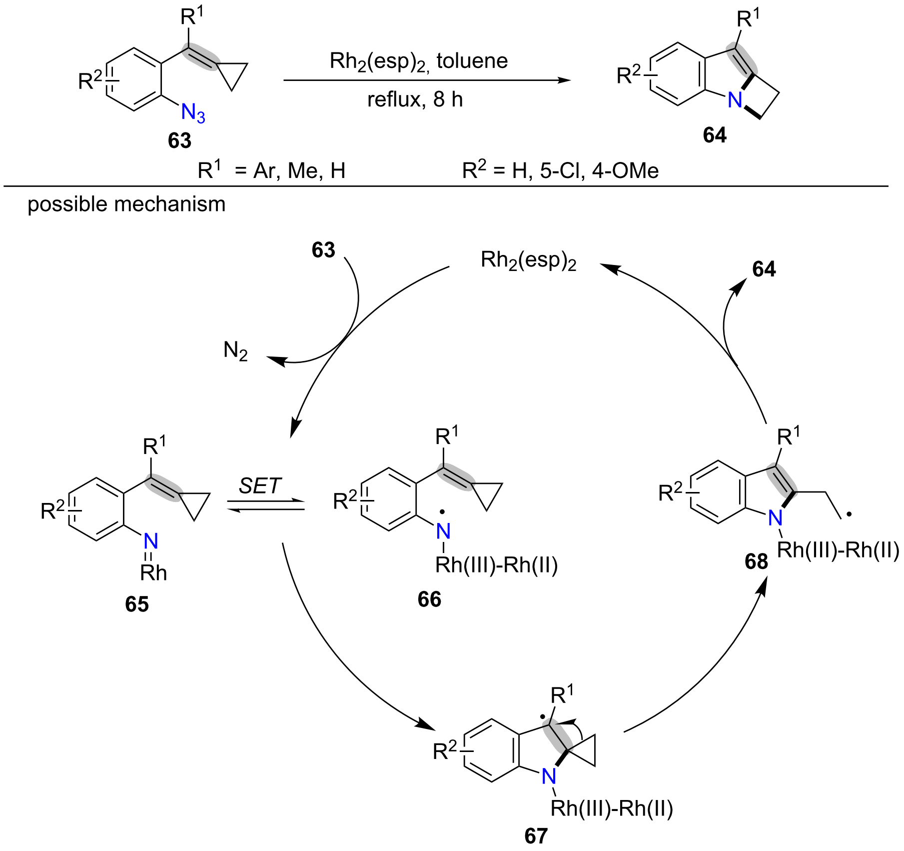
A silver-catalyzed intramolecular cascade amination/ring-opening/cyclization of a variety of substituted MCPs **69** was proposed by Fan and co-workers, which provided a simple and efficient way for the building of [2,3-*c*]dihydrocarbazoles **70** and [2,3-*c*]carbazoles **71** (Scheme 15) [91]. This process permitted the use of readily available and cheap AgOAc as the catalyst and oxidant, and DMF as the solvent. Notably, the product **70** was easily transformed into **71** in the presence of chloranil (1.4 equiv) at 120 °C under Ar atmosphere for 5 h. In this transformation, substrates with electron-donating groups showed higher yields than the ones with electron-withdrawing groups.

In the same year, Shi et al. reported an effective ring-opening and cyclization of arylvinylidenecyclopropanes **72** with diaryl

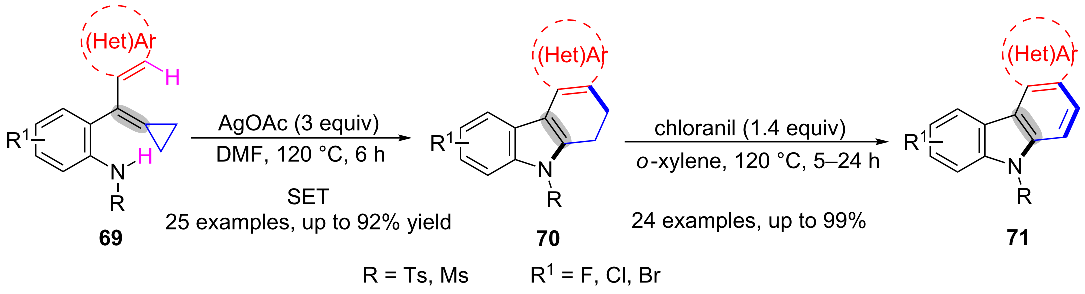


Scheme 13: Cu(I) or Fe(II)-catalyzed oxidative radical trifluoromethylation/ring-opening/cyclization of MCPs derivatives (acrylamide-tethered alkylidenecyclopropanes).

diselenides **73** for the synthesis of 1,2-diarylselenocyclopentene **74** in moderate to good yields at 150 °C for 1.5 h (Scheme 16) [92]. The electron-rich, electron-neutral and electron-poor arylvinylidenecyclopropanes were tolerated well in this transformation. The detailed mechanism is outlined in Scheme 16. Initially, the homolysis of diphenyldiselenide **73**



Scheme 14: Rh(II)-catalyzed oxidative radical ring-opening and cyclization of MCPs.

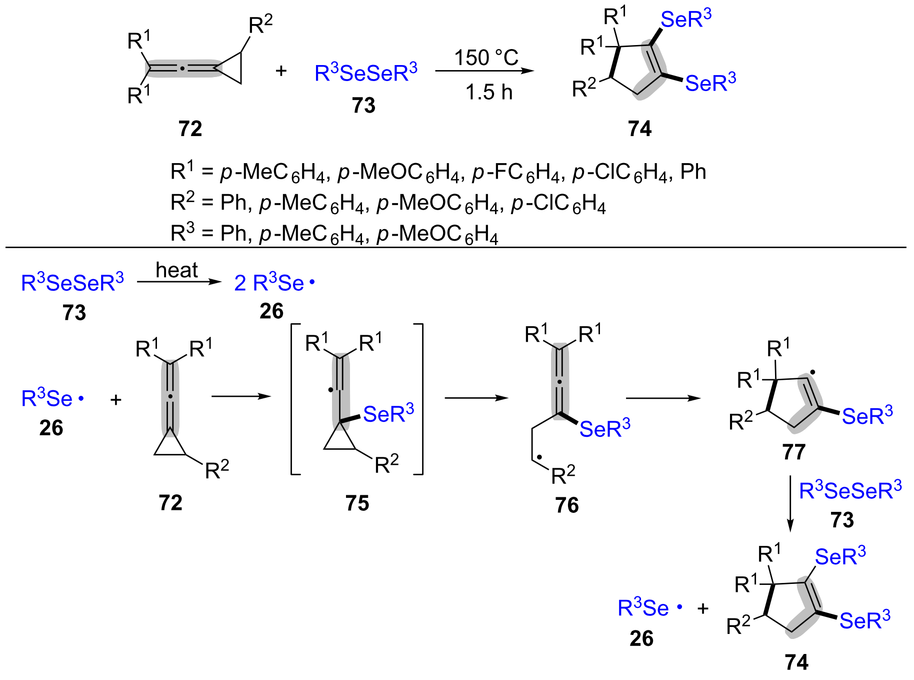


Scheme 15: Ag(I)-catalyzed oxidative radical amination/ring-opening/cyclization of MCPs derivatives.

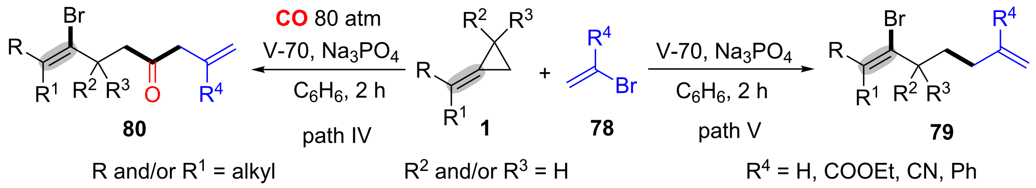
under heating conditions produces the phenylseleno radical **26** [93]. Then, the additon of radical **26** to the C–C double bond of MCPs derivatives **72** affords the radical intermediate **75** [94]. Next, the radical **75** goes through a ring-opening process to give the radical intermediate **76**. The intermediate **77**, produced by the intramolecular cyclization of intermediate **76**, reactes with diphenyl diselenide **73** to form the target product **74** via homolytic substitution (S_H).

In 2013, Ryu and co-workers developed the bromine radical-mediated ring-opening and alkylation of alkylidenecyclopropanes **1** with allylic bromides **78** for the synthesis of 2-bromo-1,6-dienes **79** via radical ring-opening and S_H2' reactions (path V in Scheme 17) [95]. The experimental results suggested that radical carbonylation could also be incorporated in the reaction sequence, leading to 2-bromo-1,7-dien-5-ones **80** (path IV in Scheme 17).

In 2016, Xu's group exploited the fluoroalkyl (R_F) radical-mediated ring-opening of MCPs **1** for the synthesis of fluorinated homoallylic compounds (**80** and **81**, Scheme 18) [96]. In this reaction system, the radical reaction of MCPs **1** with R_F-X



Scheme 16: Heating-promoted radical ring-opening and cyclization of MCP derivatives (arylvinylidenecyclopropanes) with diaryl diselenides.

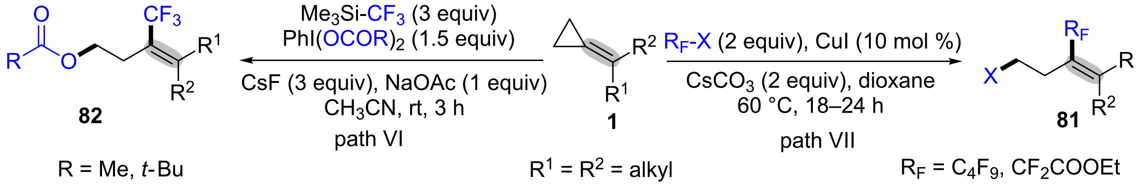


Scheme 17: Bromine radical-mediated ring-opening of alkylidenecyclopropanes.

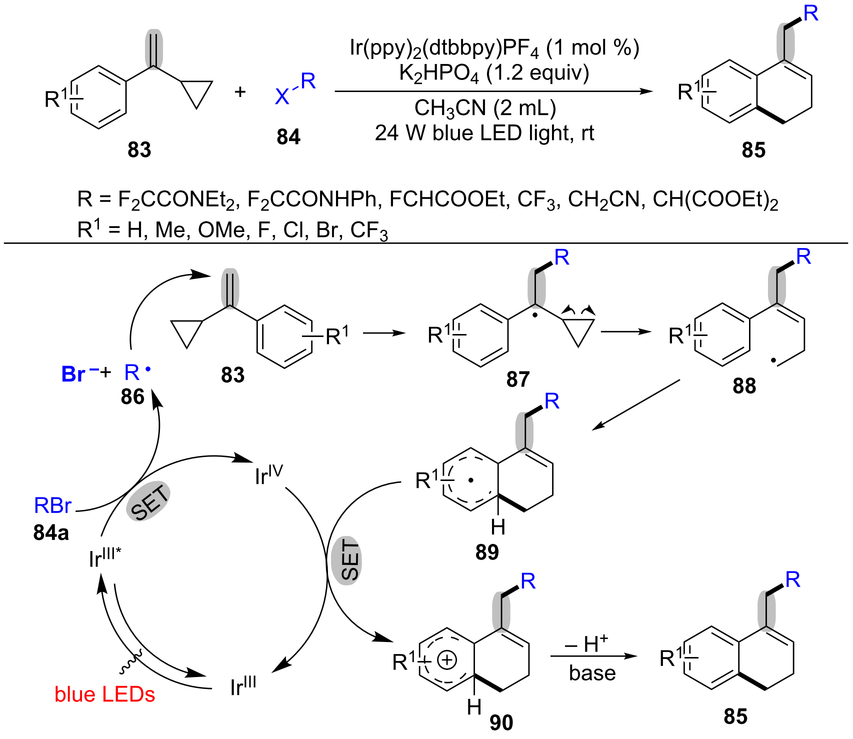
(X = Br, I) furnished homoallylic halides in excellent yields (path VII in Scheme 18). Similarly, the radical reaction of MCPs **1** with the R_FTMS/CsF/PhI(OAc)$_2$ gave homoallylic acohol esters in moderate to good yields (path VI in Scheme 18).

Oxidative radical ring-opening and cyclization of cyclopropyl olefins

In 2016, Li's group reported a photoredox catalysis oxidative radical ring-opening and cyclization of cyclopropyl olefins **83** with bromides **84** for the synthesis of partially saturated naphthalenes **85** in moderate to excellent yields (Scheme 19) [97]. It was the first example for alkylation, ring-opening and cyclization cascade reaction of the cyclopropyl olefins under photoredox catalysis. The alkylation reagents could be extended to other bromides, such as monofluoro-substituted bromides, trifluoro-substituted bromides, bromoacetonitrile and bromomalonate. This alkylation/ring-opening/cyclization was carried out by using Ir(ppy)$_2$(dtbbpy)PF$_4$ as photocatalyst, and K$_2$HPO$_4$ as base in MeCN under the irradiation of 24 W blue LED light at



Scheme 18: Fluoroalkyl (Rf) radical-mediated ring-opening of MCPs.



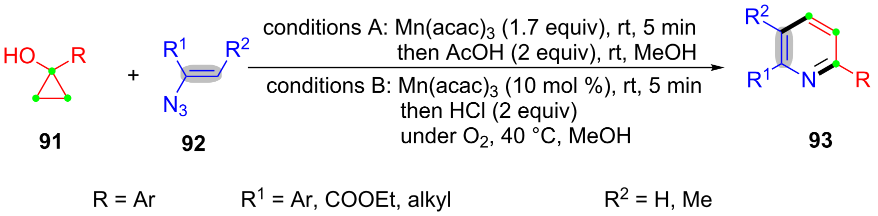
Scheme 19: Visible-light-induced alkylation/ring-opening/cyclization of cyclopropyl olefins with bromides.

room temperature for 12–36 h. A plausible mechanism is shown in Scheme 19. Firstly, the substrate **84a** underwent oxidative quenching under the action of an iridium photoredox catalyst to afford the alkyl radical **86**, which adds to the C–C double bond of MCPs **83** to deliver the benzyl radical **87**. Then, it undergoes a ring-opening process to afford the terminal alkyl radical **88**. Next, the alkyl radical **88** intramolecular cyclizes with the phenyl ring to give intermediate **89**. Finally, the resulting aryl radical intermediate **89** is oxidized and deprotonated to provide the target product **85**. In the process, two new C–C bonds and a new ring are formed.

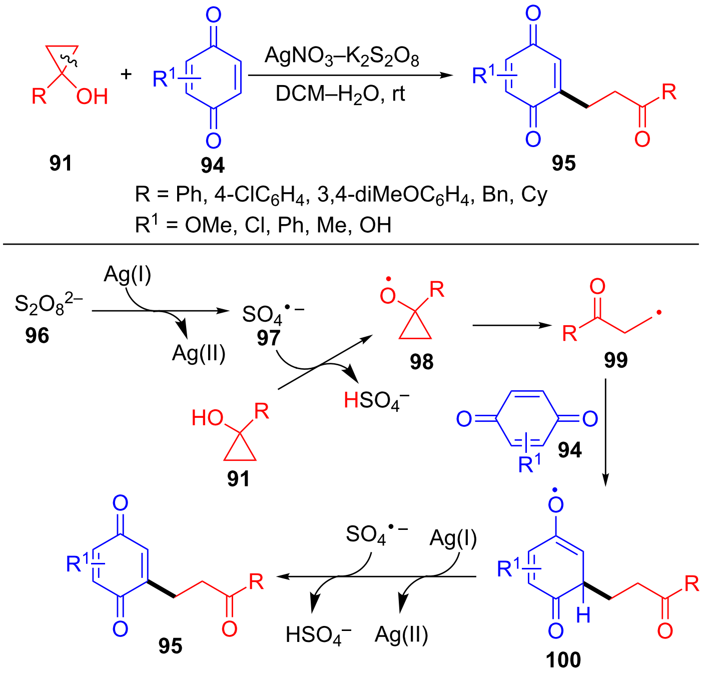
Oxidative radical ring-opening of cyclopropanols

In 2011, Chiba's group presented Mn(III)-mediated ring-opening and [3 + 3]-annulation of cyclopropanols **91** and vinyl azides **92** for the synthesis of azaheterocyles **93** (Scheme 20) [98]. This strategy could also be applied to the synthesis of the quaternary indole alkaloid and melinonine-E.

Quinones play an important role in organic chemistry because of their unique structure. In 2013, Malayappasamy and co-workers reported an efficient and convenient method for the synthesis of γ-carbonyl quinones **95** via ring-opening and functionalization of cyclopropanols **91** with quinones **94** (Scheme 21) [99]. In this transformation, both $AgNO_3$ and $FeSO_4$ were all efficient catalysts for the ring-opening and functionalization reaction. However, $AgNO_3$ was superior than $FeSO_4$ according to the reaction yields and time. Interestingly, aromatic cyclopropanols delivered higher yields than aliphatic ones. The mechanism for the Ag(I)-catalyzed oxidative ring-opening and functionalization of cyclopropanols with quinones



Scheme 20: Mn(III)-mediated ring-opening and [3 + 3]-annulation of cyclopropanols and vinyl azides.

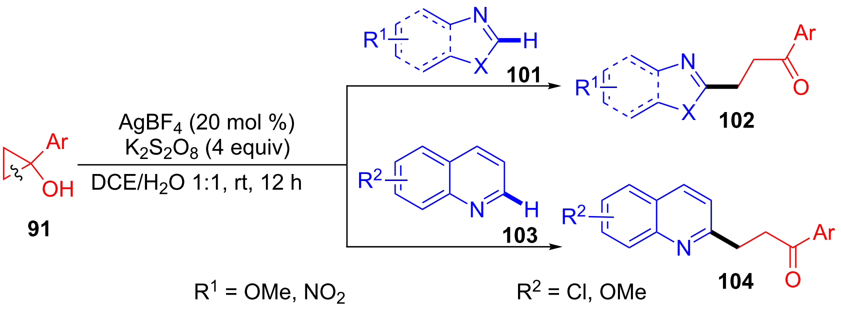


Scheme 21: Ag(I)-catalyzed oxidative ring-opening of cyclopropanols with quinones.

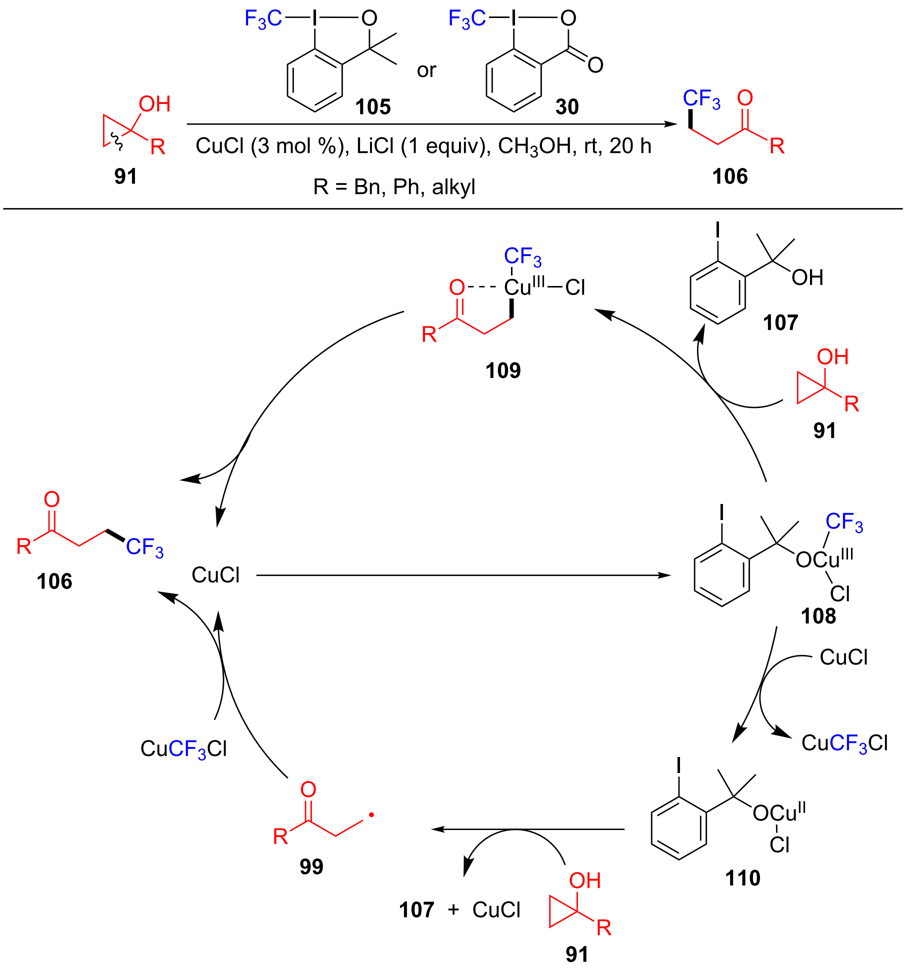
is outlined in Scheme 21. Firstly, the sulfate radical anion **97** is generated from persulfate **96** under the action of Ag(I). Next, the radical **97** reacts with cyclopropanol **91** to give the cyclopropoxy radical **98**, which undergoes a ring-opening process to produce β-keto radical **99**. The radical **100** is formed through the addition of radical **99** to the quinones **94**. Finally, the intermediate **100** occurres reoxidation with Ag(II) to provide the final product **95** along with regenerated Ag(I).

In 2015, Duan et al. developed a Ag(I)-catalyzed oxidative ring-opening of cyclopropanols **91** with heteroarenes **101** or **103** for the synthesis of carbonyl-containing alkyl-substituted heteroarenes **102** or **104** under mild conditions in moderate to good yields with good functional group tolerance (Scheme 22) [100]. This reaction went through a selective C(sp^3)–C(sp^3) bond cleavage, C–H activation and C(sp^3)–C(sp^2) bond formation. Notably, this finding was the first example for silver-catalyzed regioselective C2-alkylation of heterorarenes with primary alkyl radicals, generated from cyclopropanols through a radical ring-opening process.

Lopp's group also reported an efficient approach for copper-catalyzed ring-opening and trifluoromethylation of cyclopropanols **91** to construct β-trifluoromethyl-substituted ketones **106** (Scheme 23) [101]. Additionally, a series of cyclopropanols with different functional R groups were successfully scaled up to 1 mmol. In this transformation, there exist two possible pathways to produce the target product **106**. The Togni reagent (**105**) reacts with CuCl to generate Cu(III) complex **108**. Then, the intermediated **109** is generated from the electrophilic attack



Scheme 22: Ag(I)-catalyzed oxidative ring-opening of cyclopropanols with heteroarenes.



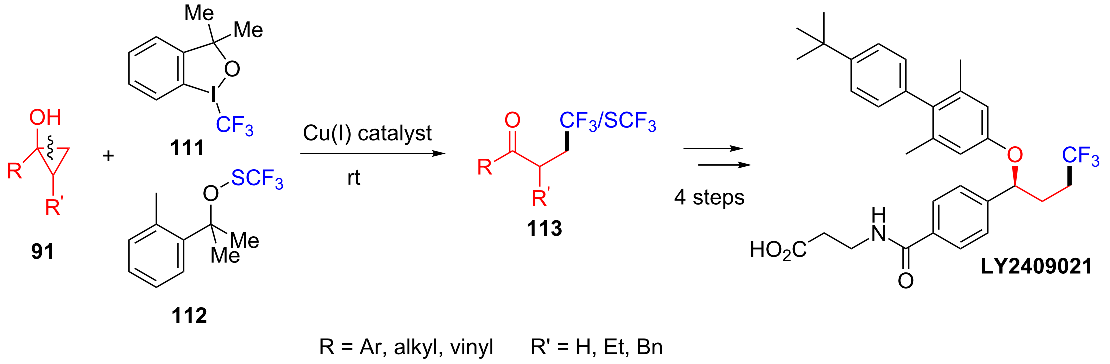
Scheme 23: Cu(I)-catalyzed oxidative ring-opening/trifluoromethylation of cyclopropanols.

of copper(III) **108** with cyclopropanol **91**. Finally, the desired product **106** is formed through reductive elimination of CuCl in intermediated **109**. On the other hand, the intermediated **108** can lose the CF_3 radical to generate the Cu(II) complex **110**. Next, the complex **110** reacts with **91** to give the radical **99**. The desired product **106** was produced by the interception of the CF_3 radical, which came from $CuCF_3Cl$.

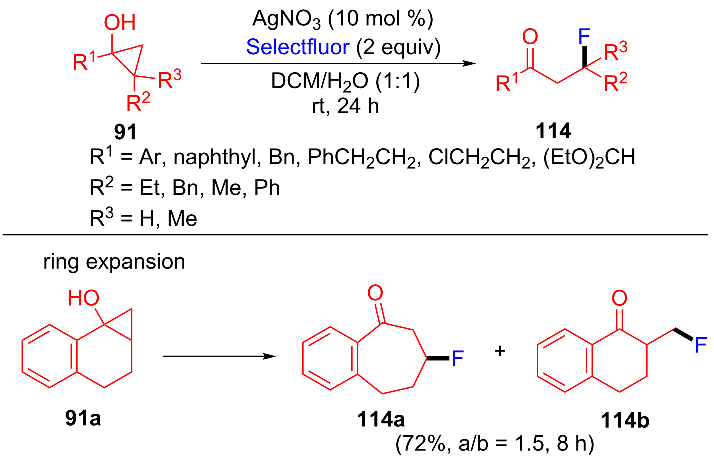
In the same year, Dai's group also reported a copper-catalyzed ring-opening and trifluoromethylation or trifluoromethylthiolation of cyclopropanols **91** for the synthesis of β-CF_3/SCF_3-substituted ketones **113** (Scheme 24) [102]. This strategy was also applied to the synthesis of LY2409021. The LY2409021 was a glucagon receptor antagonist and used in clinical trials for type 2 diabetes mellitus. Xu et al. also presented the similar ring-opening/trifluoromethylation of cyclopropanols for the synthesis of various β-trifluoromethyl ketones [103].

In this year, Loh et al. [104] and Zhu et al. [105] proposed a oxidative ring-opening and fluorination of cyclopropanols **91** with Selectfluor to construct β-fluorinated ketones **114** (Scheme 25). In Loh's work, the Fe(III)- or Ag(I)-catalyzed oxidative ring-opening and fluorination of cyclopropanols **91** via radical rearrangement is disclosed. Notably, this reaction proceeds at room temperature and tolerates a diverse array of cyclopropanols. In Zhu's work, the fluorination of **91a** was notable because the seven-membered cyclic product **114a** and five-membered cyclic product **114b** were formed.

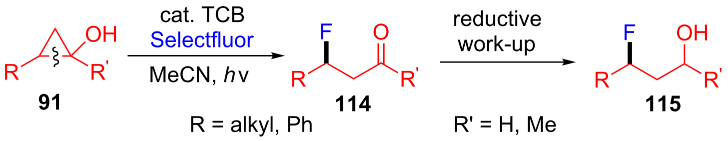
Lectka's group also presented a new approach to β-fluorinated ketones **114** via photocatalyzed ring-opening and fluorination of cyclopropanols **91** with Selectfluor under mild and simple conditions (Scheme 26) [106]. It is worth mentioning that a number of electronically and sterically diverse β-fluorinated carbonyl-containing compounds **114** and γ-fluoro alcohols **115** could be prepared through this method.



Scheme 24: Cu(I)-catalyzed oxidative ring-opening and trifluoromethylation/trifluoromethylthiolation of cyclopropanols.



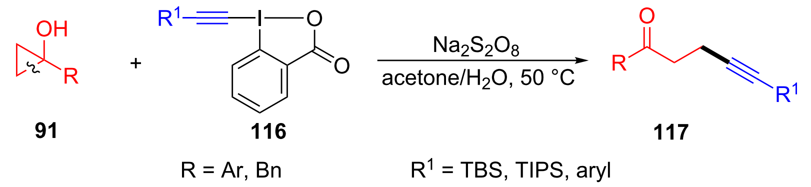
Scheme 25: Ag(I)-mediated oxidative ring-opening/fluorination of cyclopropanols with Selectfluor.



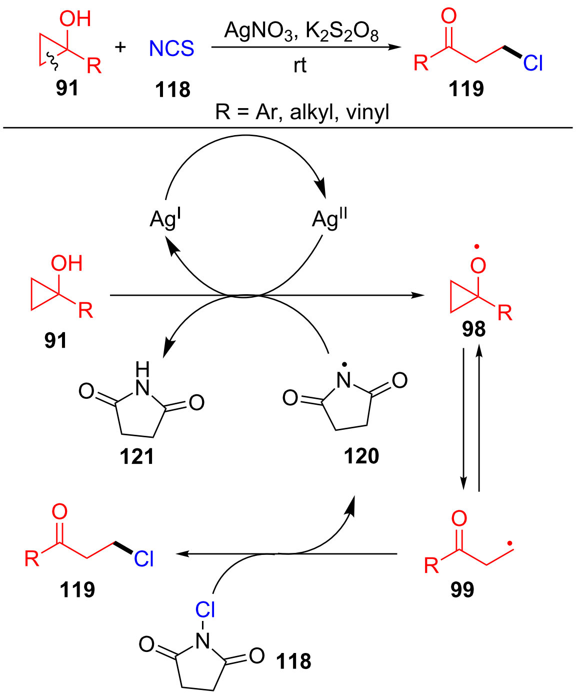
Scheme 26: Photocatalyzed ring-opening/fluorination of cyclopropanols with Selectfluor.

In 2015, Duan and co-workers introduced the $Na_2S_2O_8$-promoted ring-opening/alkynylation of cyclopropanols **91** with ethynylbenziodoxolones (EBX) **116** for the synthesis of the alkynylated ketones **117** (Scheme 27) [107]. This reaction involved a C–C bond cleavage, radical rearrangement, and C–C bond formation, and showed a wide substrates scope under mild conditions. Surprisingly, four- and five-membered cycloalkanols were suitable in this system.

In 2015, Zhu's group developed the silver-catalyzed ring-opening of cycloalkanols **91** with NCS **118** for the synthesis of distally chlorinated ketones **119** (Scheme 28) [108]. The reaction was carried out with inexpensive reagents and can also be applied to the distal bromination of cycloalkanols. The possible mechanism is outlined in Scheme 28. The cycloalkoxy radical **98** is generated from cyclopropanol **91** under the action of the metastable Ag(II) species, which is formed by the interaction of $AgNO_3$ and $K_2S_2O_8$. The radical **98** undergoes a ring-opening to give the alkyl radical **99**. Finally, the radical **99** is intercepted by NCS **118** to furnish the chlorinated ketone **119**. The generated imidyl radical **120** can also participate in hydrogen abstraction of cyclopropanol **91** to form the radical **98**.



Scheme 27: $Na_2S_2O_8$-promoted ring-opening/alkynylation of cyclopropanols with EBX.



Scheme 28: Ag(I)-catalyzed ring-opening and chlorination of cyclopropanols with aldehydes.

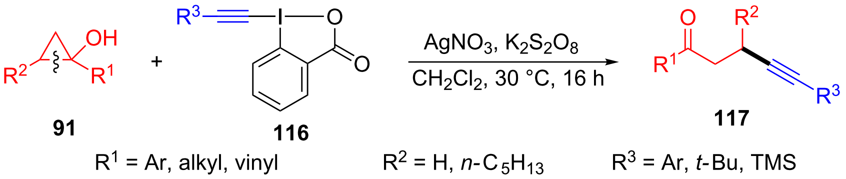
In 2016, the silver-promoted oxidative ring-opening/alkynylation of cyclopropanols **91** with ethynylbenziodoxolones (EBX) **116** had been presented by Li and co-workers (Scheme 29) [109]. Both silver(I) nitrate and potassium persulfate played an important role in this transformation.

In 2016, Hu and co-workers developed a novel ring-opening of cyclopropanols **91** with acrylamides **122** for the synthesis of oxindoles **123** (Scheme 30) [110]. A series of desired γ-carbonylalkyl-substituted oxindoles **123** were synthesized between *N*-phenyl acrylamides **122** and tertiary cyclopropanols **91** through $Na_2S_2O_8$-promoted radical cyclization under transition-metal free conditions. With the addition of a radical scavenger such as TEMPO or BHT, the reaction was suppressed remarkably.

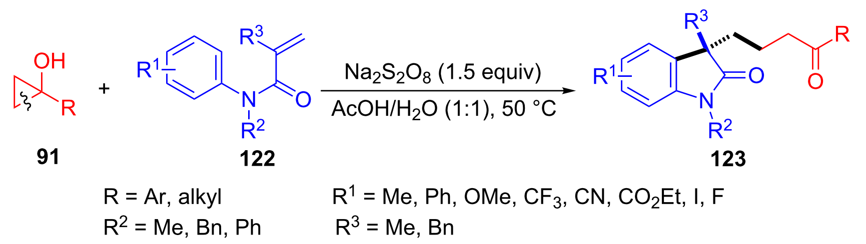
In the same year, Dai's group also reported the ring-opening-initiated tandem cyclization of cyclopropanols **91** with acrylamides **122** or 2-isocyanobiphenyls **124** (Scheme 31) [111]. This transformation involved a C–C bond cleavage and two C–C bond formations, and showed excellent functional group tolerance, satisfactory yields and operational simplicity.

In 2017, Mohr's group proposed a straightforward approach to synthesize β-fluorinated ketones **114** by using AgF_2 as both oxidant and fluorine atom source via the silver(II)-mediated ring-opening and fluorination of cyclopropanols **91** (Scheme 32) [112]. Through this method, a fluorine atom could easily be introduced in the β-position of a ketone. The mechanism is outlined in Scheme 32, the Ag-alkoxide complex **126** is initially formed from the process of ligand exchange between the substrate and AgF_2. The alkoxy radical **98** is produced via a single-electron oxidation by Ag–O bond homolysis. As a feature of the cyclopropane system, the radical **98** goes through a ring fission to form the alkyl radical **99**. Finally, the radical **99** abstracted an F-atom from another molecule of AgF_2 to produce the target product **114**.

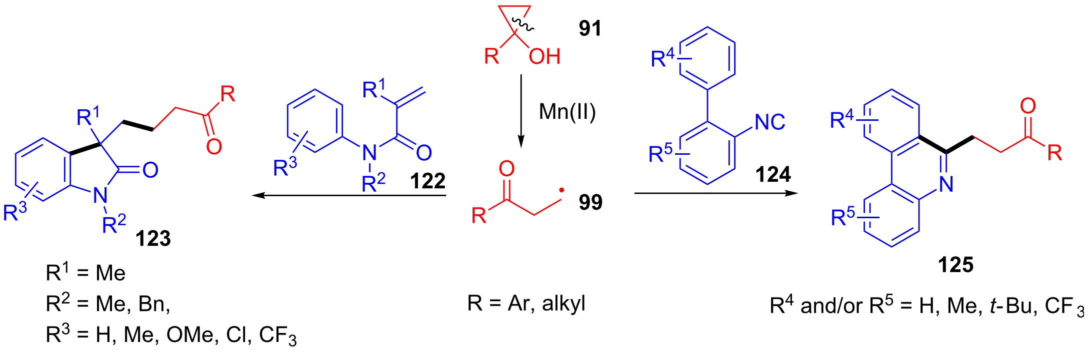
Kananovich and co-workers demonstrated the copper-catalyzed ring-opening and trifluoromethylation of teriary cyclopropanols **91** with fluorinated sulfinate salts **127** for the synthesis of β-tri-



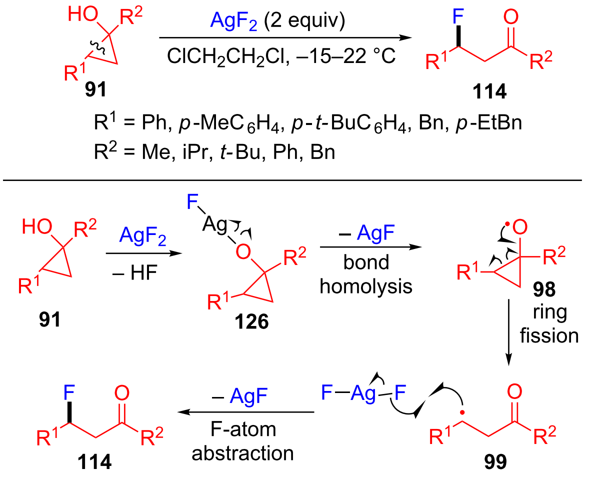
Scheme 29: Ag(I)-catalyzed ring-opening/alkynylation of cyclopropanols with EBX.



Scheme 30: $Na_2S_2O_8$-promoted ring-opening/alkylation of cyclopropanols with acrylamides.



Scheme 31: Cyclopropanol ring-opening initiated tandem cyclization with acrylamides or 2-isocyanobiphenyls.



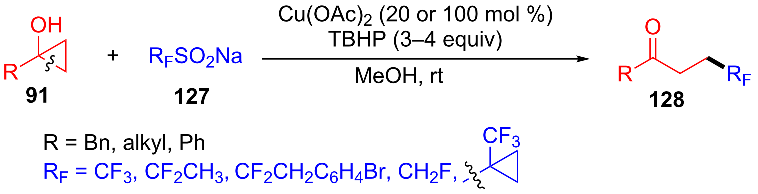
Scheme 32: Ag(II)-mediated oxidative ring-opening/fluorination of cyclopropanols with AgF_2.

fluoromethyl ketones **128** at room temperature and in an open flask (Scheme 33) [113]. The presented results provided an efficient and convenient method for the synthesis of diverse fulorinated ketones from cyclopropanols.

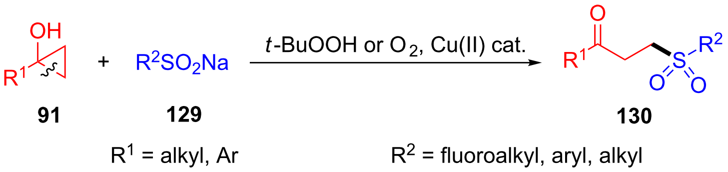
In the same year, this group developed a similar copper-catalyzed ring-opening and sulfonylation of teriary cyclopropanols **91** with sodium sulfinates **129** for the synthesis of γ-keto sulfones **130** in excellent yields (Scheme 34) [114]. The reaction was compatible with a series of fluoroalkyl, aryl and alkyl sulfinate salts. Notably, oxygen instead of THBP as oxidation was viable in this transformation.

In 2017, Reddy and co-workers reported the first radical cyclization of propiolamides (**131** and **133**) with cyclopropanols **91** for the synthesis of azaspiro[4.5]deca-3,6,9-triene-2,8-diones **132** and 6,7-dihydro-3*H*-pyrrolo[2,1-*j*]quinoline-3,9(5*H*)-diones **134** (Scheme 35) [115]. Interestingly, this transformation proceeded under transition-metal-free conditions with high selectivity and yields. A series of substituents such as methoxy, dimethoxy, trimethoxy, methyl, chloro, bromo, and fluoro on the aromatic ring of cyclopropanols were tolerated well. The mechanism is outlined in Scheme 35. A β-carbonylalkyl radical **99** is produced from cyclopropanol **91** through a SET process. Then, addition of the radical **99** at the α-position of carbonyl in the substrate **131** furnishes the vinyl radical **135**. Next, the vinyl radical **135** occurred 5-*exo* cyclization with the phenyl ring to generate the intermediate **136**. Finally, the intermediate **136** underwent oxidation and deprotonation to give the desired product **132**.

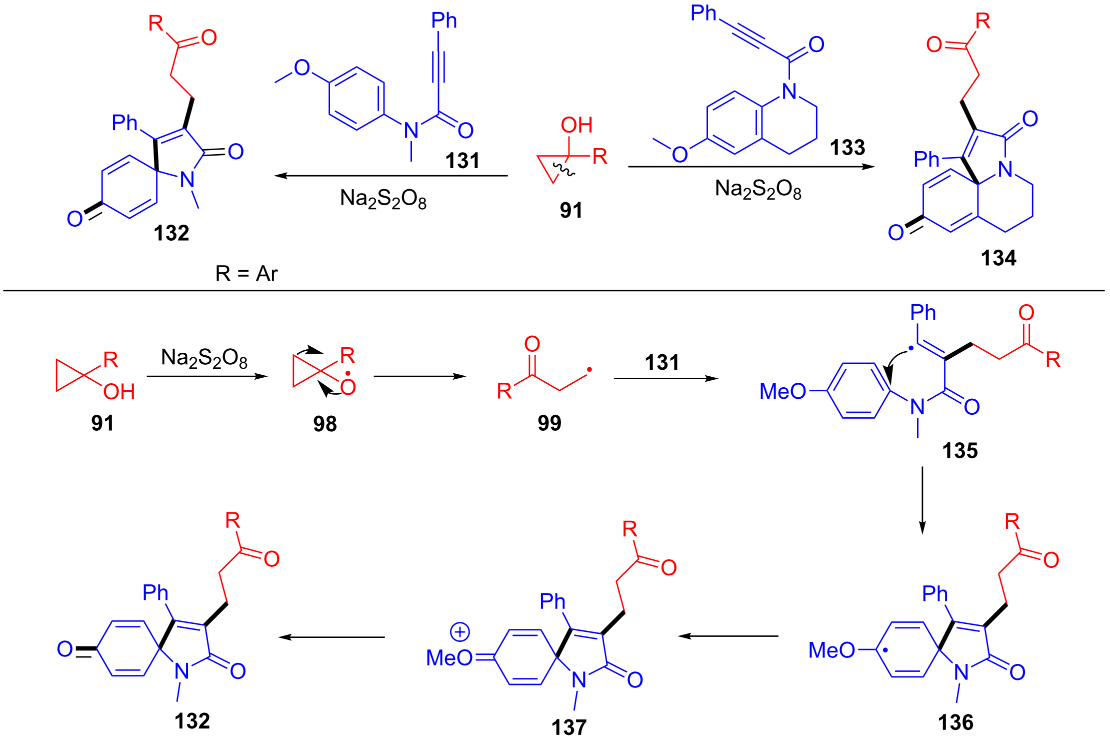
In this year, Melchiorre's group reported the ring-opening and [3 + 2]-annulation of cyclopropanols **91** with α,β-unsaturated



Scheme 33: Cu(II)-catalyzed ring-opening/fluoromethylation of cyclopropanols with sulfinate salts.



Scheme 34: Cu(II)-catalyzed ring-opening/sulfonylation of cyclopropanols with sulfinate salts.

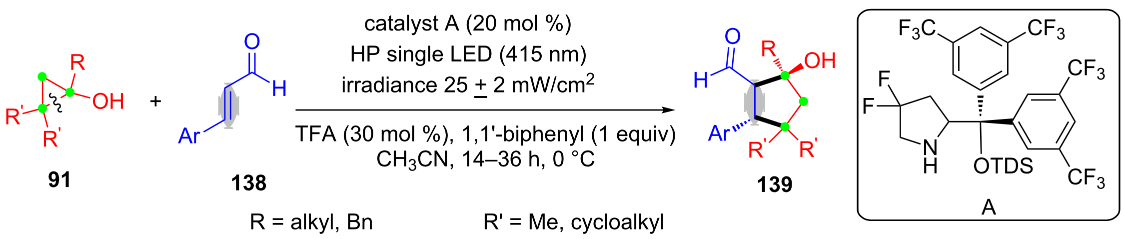


Scheme 35: Na$_2$S$_2$O$_8$-promoted ring-opening/arylation of cyclopropanols with propiolamides.

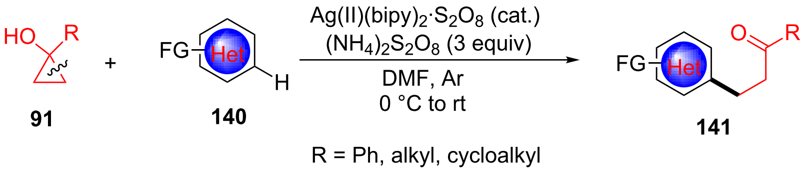
aldehydes **138** for the synthesis of stereochemically dense cyclopentanols **139** with excellent enantioselectivity (Scheme 36) [116]. This transformation merged a stereocontrolled radical pattern with a classical ionic process in a cascade sequence.

In 2018, Orellana et al. developed the Ag(II)-catalyzed ring-opening and functionalization of cyclopropanols **91** with electron-poor aromatic nitrogen heterocyles **140** under acid-free conditions and used a well-defined catalyst [Ag(II)(bipy)$_2$S$_2$O$_8$] at low loadings (Scheme 37) [117]. This finding indicated that the silver pyridine complex plays an important role in single electron oxidants of cyclopropanols.

In the same year, a silver-catalyzed ring-opening and difluoromethylthiolation of cyclopropanols **91** with PhSO$_2$SCF$_2$H



Scheme 36: The ring-opening and [3 + 2]-annulation of cyclopropanols with α,β-unsaturated aldehydes.



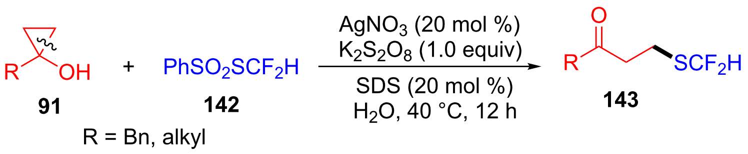
Scheme 37: Cu(II)-catalyzed ring-opening/arylation of cyclopropanols with aromatic nitrogen heterocyles.

142 for the synthesis of difluoromethylthioethers **143** was reported by Shen and co-workers (Scheme 38) [118]. $AgNO_3$ was utilized as catalyst, $K_2S_2O_8$ as oxidant, and SDS (sodium dodecyl sulfate) as addictive in water. The SDS plays a key role in this transformation, and it enhances the solubility of both reactants in water. The cycloalkanol derivatives with electron-rich substituents on the phenyl rings deliver the corresponding products in higher yields than that with electron-deficient substituents.

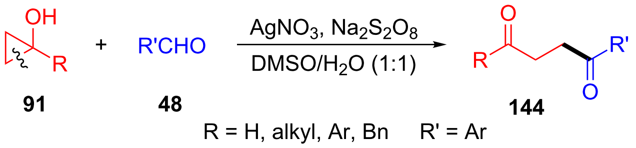
In 2018, Zhu and co-workers also reported the first silver-catalyzed ring-opening and acylation of cyclopropanols **91** with aldehydes **48** for the synthesis of 1,4-diketones **144** (Scheme 39) [119]. They proposed that the involvement of an uncommon water-assisted 1,2-HAT process was strongly exothermic and it promoted the addition of alkyl radicals to C=O bonds in aldehydes. The electronic effect of the phenyl rings in the aldehydes showed important influence on the reaction yields.

In 2017, Kananovich developed a simple and efficient one-pot method for the preparation of enantiomerically enriched 2-oxyranyl ketones **146** by aerobic oxidation of easily available cyclopropanols **91** via intermediate formation of peroxyketone intermediates **145**, followed by enantioselective epoxide formation in the presence of a poly-L-leucine catalyst and DBU (Scheme 40) [120].

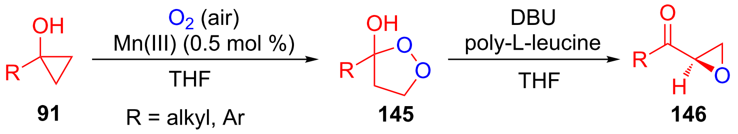
In 2014, a practical method for the conversion of 1,2-disubstituted cyclopropanols **91** derived from Kulinkovich cyclo-



Scheme 38: Ag(I)-catalyzed ring-opening and difluoromethylthiolation of cyclopropanols with $PhSO_2SCF_2H$.

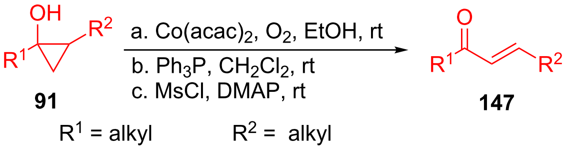


Scheme 39: Ag(I)-catalyzed ring-opening and acylation of cyclopropanols with aldehydes.



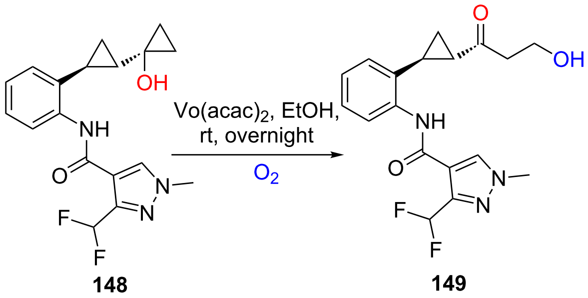
Scheme 40: Aerobic oxidation ring-opening of cyclopropanols for the synthesis of 2-oxyranyl ketones.

propanation into linear enones **147** was developed by Wu and co-workers [121]. The approach features the regioselective cleavage of the cyclopropane rings in EtOH at room temperature with cheap and readily available Co(acac)$_2$ as the catalyst and air as the reagent (Scheme 41).



Scheme 41: Aerobic oxidation ring-opening of cyclopropanols for the synthesis of linear enones.

In 2015, Tyagi's group presented a biomimetic synthesis of metabolite **149** from intermediate **148** by using catalytic vanadyl acetylacetonate and molecular O$_2$ (Scheme 42) [122]. The transformation went through aerobic oxidation ring-opening of cyclopropanols. The results showed that the oxygen atom of newly-formed hydroxy group came from molecular O$_2$.



Scheme 42: Aerobic oxidation ring-opening of cyclopropanols for the synthesis of metabolite.

Conclusion

In the past 20 years, the field of oxidative radical ring-opening/cyclization of cyclopropane derivatives (including methylenecyclopropanes, cyclopropyl olefins and cyclopropanols) has experienced significant advances. This utility has been highlighted in a number of complex natural product syntheses. In this review, we have systematically summarized various oxidative radical strategies developed for the ring-opening and cyclization of cyclopropane derivatives. Despite these advances, there still exist opportunities for exploration and many questions to be addressed. Although oxidative radical ring-opening/cyclization of functionalized cyclopropane derivatives has been well developed, the ring-opening/cyclization of common cyclopropane derivatives is conspicuously absent. On the other hand, green and environmentally friendly strategies, such as photocatalysis or electrocatalysis, can be another orientation for further developments. This review opens the scope for future developments in new methodologies which promise the synthesis of novel fused cyclic systems with a wide range of medicinal and synthetic applications.

Acknowledgements

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of 1,2-divinylcyclopropanes by metal-catalyzed cyclopropanation of 1,3-dienes with cyclopropenes as vinyl carbene precursors

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Letter

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Abstract

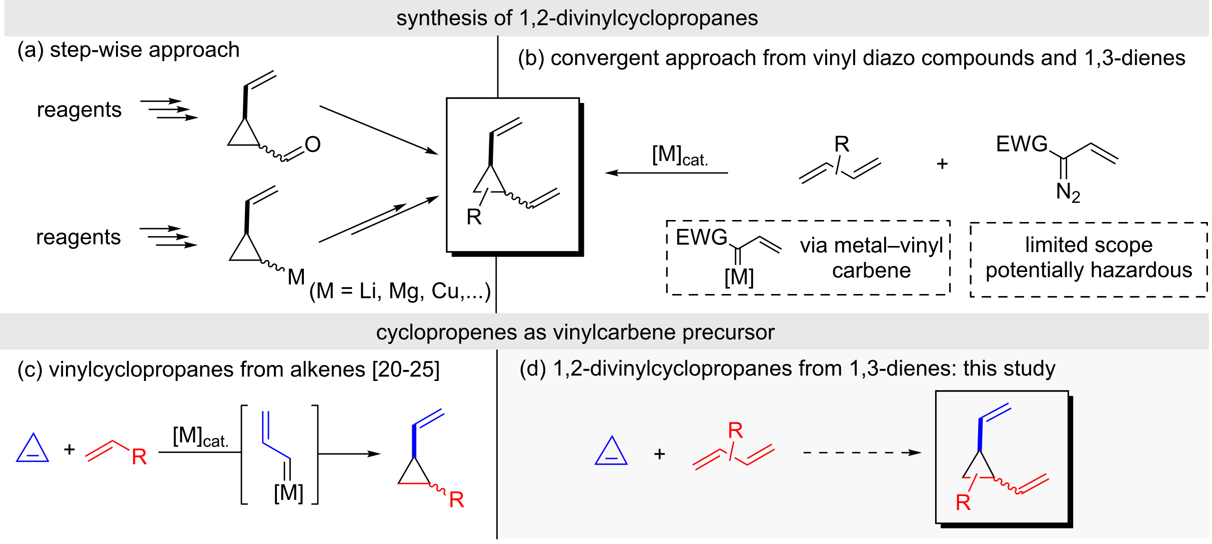
The synthesis of 1,2-divinylcyclopropanes by the reaction of cyclopropenes with 1,3-dienes is reported. The process relies on the ability of $ZnCl_2$ or $[Rh_2(OAc)_4]$ to generate metal–vinyl carbene intermediates from cyclopropenes, which effect cyclopropanation of 1,3-dienes. Most of the reactions proceeded in reasonable yields while the diastereoselectivity strongly depends on the structure of the diene. An example of an intramolecular process as well as the use of furan and 1,4-cyclohexadiene as dienes are also reported.

Introduction

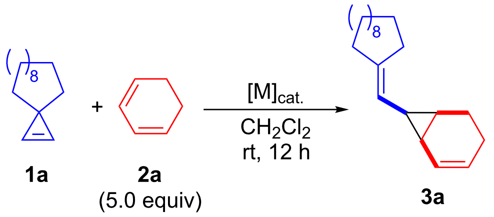
Far from being considered exotic molecules, cyclopropane derivatives constitute an interesting class of compounds. Indeed, far over 4000 natural products bearing a cyclopropane ring have been discovered [1-3], and cyclopropane-containing molecules are recurrent in medicinal chemistry [4-6]. Likewise, due to its unique structure and bond properties, cyclopropanes have exclusive yet useful synthetic utilities [7], which are closely connected with the substitution pattern. For instance, the presence of vinyl groups directly attached to a cyclopropane ring allows sigmatropic rearrangements leading to odd-numbered carbocyclic derivatives [8]. In this sense, seven-membered carbocycles, namely 1,4-cycloheptadienes, can be forthrightly prepared from *cis*- or *trans*-1,2-divinylcyclopropanes through a Cope rearrangement [8,9]. The potential of this type of cyclopropanes contrasts with the existence of few straightforward routes for their syntheses. Typical methods rely on the use of reagents containing the required cyclopropane ring, which involve multistep sequences for the installation of adequate functionalization. Thus, Wittig-type olefination with cyclopropanecarboxaldehydes [10] or reactions of metallated vinylcyclopropanes with suitable electrophiles are commonly employed (Scheme 1a) [11-13]. In a more convergent approach where the cyclopropane ring is created at the last stage, divinylcyclopropanes can be prepared by cyclopropanation of 1,3-dienes with metal–vinyl carbenes generated from vinyldiazoacetates (Scheme 1b) [14-16]. This reaction has been fruitfully exploited, although it is inherently limited by the restricted availability of potentially explosive diazo compounds. Consequently, the use of alternative vinyl carbene precursors is highly desirable to expand the accessibility to 1,2-divinylcyclopropanes [17-19]. In this regard, cyclopropenes have demonstrated to be suitable precursors of metal–vinyl carbenes [20,21], which can be easily trapped with alkenes [22-25]. Our recent studies showed that simple $ZnCl_2$ could be used to generate the corresponding zinc–vinyl carbene to efficiently prepare vinylcyclopropane derivatives with a remarkable broad scope (Scheme 1c) [26]. In view of these precedents, we decided to study the feasibility of this reaction in the synthesis of 1,2-divinylcyclopropanes by using 1,3-dienes as trapping reagents (Scheme 1d). Herein, we present the results of this study.

Results and Discussion

At the outset, the reaction of cyclopropene **1a** and freshly distilled 1,3-cyclohexadiene (**2a**, 5.0 equiv) in the presence of $ZnCl_2$ as catalyst was performed under the reaction conditions previously employed for simple alkenes, namely $ZnCl_2$ 10 mol %, CH_2Cl_2, at ambient temperature (Scheme 2) [26]. Pleasantly, 1,2-divinylcyclopropane **3a** was obtained in good yield (81%) with moderate *endo* (*syn*) selectivity (*endo*/*exo* = 6:1). It should be indicated that the preference for the *endo* isomer has already been observed in related reactions [17]. Other metals capable of promoting both carbene generation from cyclopropenes and cyclopropanation reactions were also evaluated. Interestingly, when $[Rh_2(OAc)_4]$ (1.0 mol %) was employed, compound **3a** was isolated in 71% yield, a slightly lower value when compared to $ZnCl_2$, but more importantly, with complete *endo* (*syn*) selectivity. The use of gold,



Scheme 1: Typical syntheses of 1,2-divinylcyclopropanes and rationale hypothesis for their syntheses from cyclopropenes and 1,3-dienes.



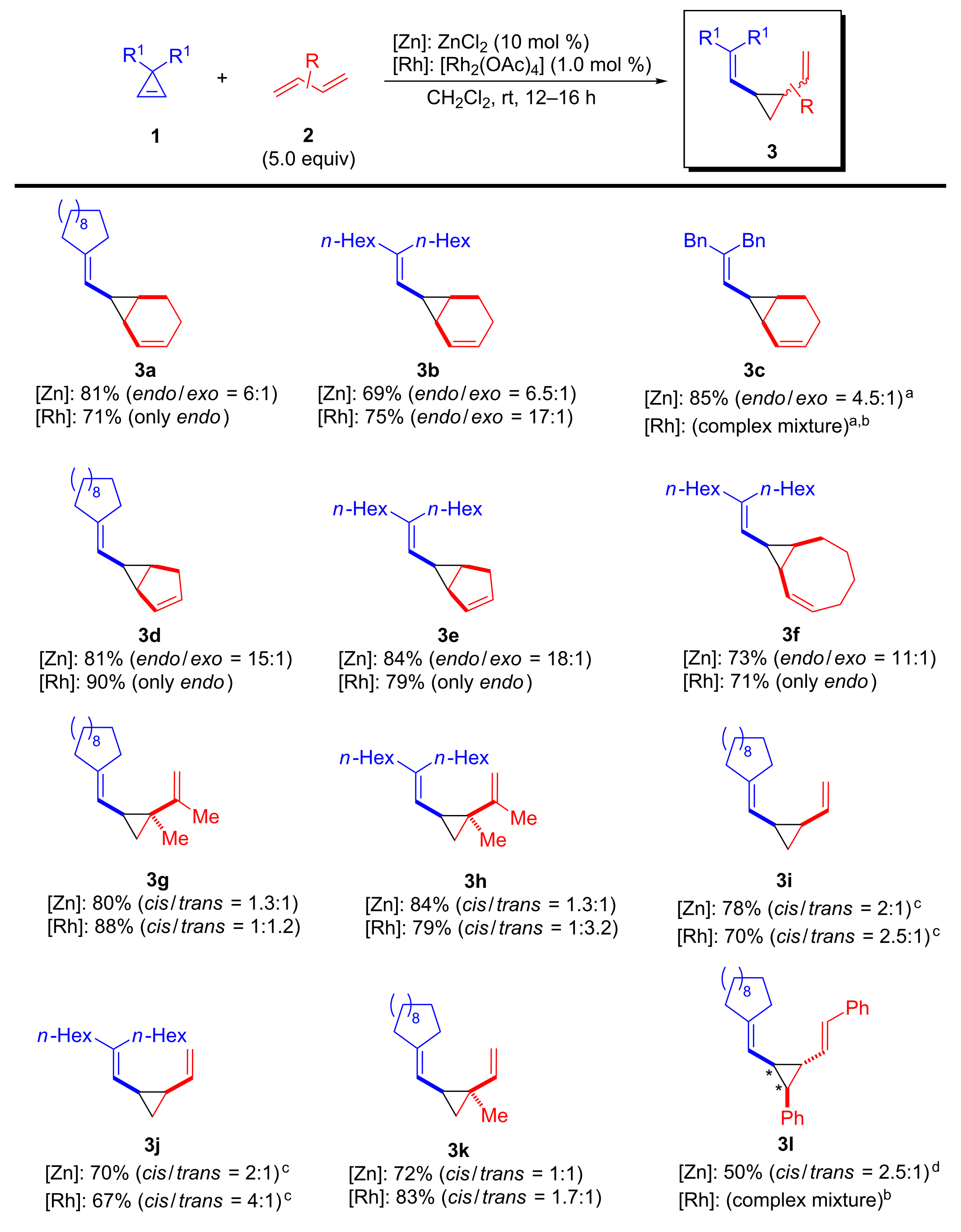
$[M]_{cat.}$	**3a** (%)[a]	*endo*/*exo*[b]
$ZnCl_2$ (10 mol %)	81%	6:1
$[Rh_2(OAc)_4]$ (1.0 mol %)	71%	only *endo*
$[(IPr)Au(NTf_2)]$ (5.0 mol %)	68%	2:1
$PtCl_2$ (5.0 mol %)	20%[c]	2:1
$[Ru(CO)_3Cl_2]_2$ (5.0 mol %)	50%	25:1

Scheme 2: Synthesis of 1,2-divinylcyclopropane **3a**: Optimization studies. [a]Isolated yield. [b]Determined by ^1H NMR on the reaction crude mixture (unaltered after purification). [c]Estimated by ^1H NMR. (IPr = 1,3-bis(2,6-diisopropylphenylimidazol-2-ylidene).

platinum or ruthenium catalysts showed poorer results with respect to reaction yield and *endo*/*exo* (*syn*/*anti*) selectivity, as indicated in Scheme 2.

Considering these results, the scope of the reaction with unbiased 1,3-dienes was next investigated using both $ZnCl_2$, as it provided the best yield being the most inexpensive catalyst, and $[Rh_2(OAc)_4]$, since it delivered the best result in terms of selectivity. The results are summarized in Scheme 3.

Using 1,3-cyclohexadiene (**2a**), the analogous reaction was accomplished with 3,3-dihexyl- (**1b**) and 3,3-dibenzylcyclopropene (**1c**). Thus, divinylcyclopropane **3b** was obtained in reasonable yields with both catalysts (69% Zn and 75% Rh),



3a
[Zn]: 81% (*endo*/*exo* = 6:1)
[Rh]: 71% (only *endo*)

3b
[Zn]: 69% (*endo*/*exo* = 6.5:1)
[Rh]: 75% (*endo*/*exo* = 17:1)

3c
[Zn]: 85% (*endo*/*exo* = 4.5:1)[a]
[Rh]: (complex mixture)[a,b]

3d
[Zn]: 81% (*endo*/*exo* = 15:1)
[Rh]: 90% (only *endo*)

3e
[Zn]: 84% (*endo*/*exo* = 18:1)
[Rh]: 79% (only *endo*)

3f
[Zn]: 73% (*endo*/*exo* = 11:1)
[Rh]: 71% (only *endo*)

3g
[Zn]: 80% (*cis*/*trans* = 1.3:1)
[Rh]: 88% (*cis*/*trans* = 1:1.2)

3h
[Zn]: 84% (*cis*/*trans* = 1.3:1)
[Rh]: 79% (*cis*/*trans* = 1:3.2)

3i
[Zn]: 78% (*cis*/*trans* = 2:1)[c]
[Rh]: 70% (*cis*/*trans* = 2.5:1)[c]

3j
[Zn]: 70% (*cis*/*trans* = 2:1)[c]
[Rh]: 67% (*cis*/*trans* = 4:1)[c]

3k
[Zn]: 72% (*cis*/*trans* = 1:1)
[Rh]: 83% (*cis*/*trans* = 1.7:1)

3l
[Zn]: 50% (*cis*/*trans* = 2.5:1)[d]
[Rh]: (complex mixture)[b]

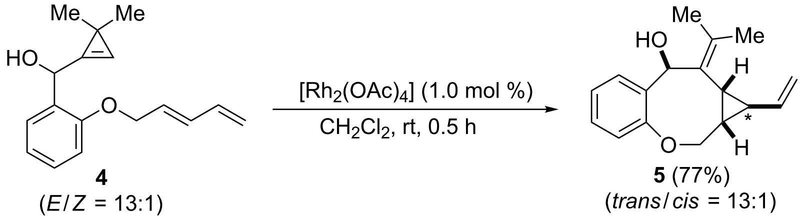
Scheme 3: Synthesis of 1,2-divinylcyclopropanes **3** from cyclopropenes **1** and unbiased 1,3-dienes **2**: Scope. (Yields of isolated products, diastereoisomeric ratios were determined by ^1H NMR). [a]At 50 °C. [b]**1** was completely consumed. [c]1,3-Butadiene was used in large excess (ca. 0.5 mL condensed prior the reaction). [d]*cis* relationship is referred to substituents labelled with an asterisk.

albeit better selectivity was obtained again with rhodium(II) catalyst (*endo*/*exo* = 17:1). In contrast, the reaction with **1c** led to the corresponding cyclopropane **3c** only when $ZnCl_2$ was used as catalyst (85%, *endo*/*exo* = 4.5:1) at slightly higher temperature (50 °C). In this case, $[Rh_2(OAc)_4]$ completely failed under different reaction conditions leading inevitably to degradation of starting cyclopropene. Other cyclic 1,3-dienes were then evaluated. For instance, the use of cyclopentadiene in the reaction with **1a** and **1b** enabled the preparation of divinylcyclopropanes **3d**,**e** in good yields. Both catalysts provided similar yields, while complete *endo* selectivity was only reached with $[Rh_2(OAc)_4]$. Interestingly, the use of 1,3-cyclooctadiene led to the formation of compound **3f** (Zn: 73%, *endo*/*exo* = 11:1; Rh: 71%, only *endo*), in which the 1,2-divinylcyclopropane moiety is embedded within a bicyclo[6.1.0]-nonane core. Then, we studied the reaction with various representative unbiased acyclic 1,3-dienes. Unsurprisingly, these substrates could be easily converted into the corresponding 1,2-divinylcyclopropanes but with very low selectivities. For instance, when 2,3-dimethyl-1,3-butadiene was employed with cyclopropenes **1a**,**b**, the corresponding 1,2-divinylcyclopropanes **3g**,**h** were prepared in good yields regardless of the catalyst employed. However, **3g**,**h** were obtained as an almost equimolar mixture of *cis/trans* diastereoisomers (*cis* refers to both vinyl substituents). Even though the lack of selectivity was already noticed by Uemura and co-workers in related reactions [17], we attempted the reaction with other zinc salts or rhodium(II) carboxylates as catalysts. Unfortunately, these experiments were futile and led to similar low selectivities. Besides, gaseous 1,3-butadiene could be also employed, as demonstrated by the preparation of compounds **3i**,**j**, which were obtained in moderate yields and low *cis* selectivities. The reaction with isoprene showed a remarkable selectivity for the most substituted alkene, allowing the synthesis of 1,2-divinylcyclopropane **3k** within the typical range of yields and *cis/trans* selectivities. Finally, 1,2,3-trisubstituted divinylcyclopropane **3l** was prepared in 50% (*cis*/*trans* = 2.5:1) from cyclopropene **1a** and (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene through a stereoselective reaction. Once more, simple $ZnCl_2$ was particularly effective for this reaction in sharp contrast to the incompetence of $[Rh_2(OAc)_4]$.

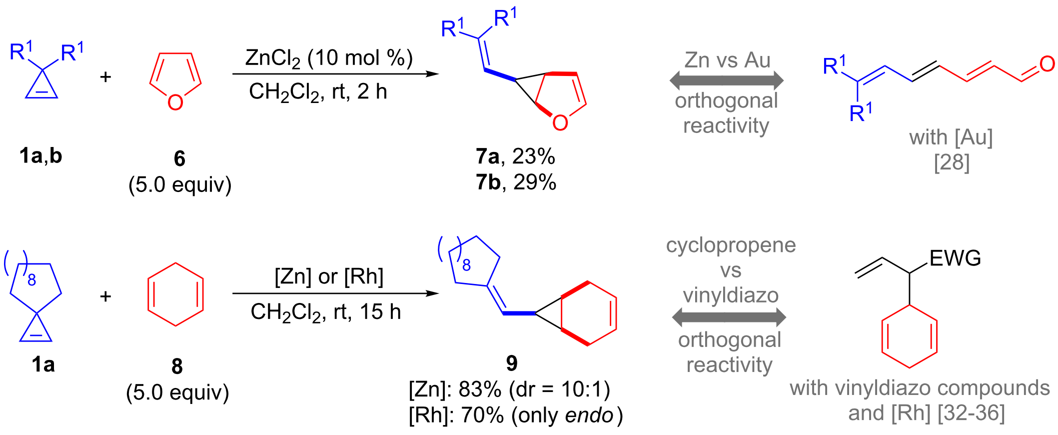
It should be noticed that 1,2-divinylcyclopropanes **3a**–**l** did not undergo [3,3]-Cope rearrangements under the reaction conditions. Moreover, when pure *endo*-**3e** was refluxed in toluene (24 h) partial isomerization was observed (*endo*/*exo* = 1:1.6). This behavior can be attributed to the high substitution at one of the alkenes, which might lead to sterically overcrowded transition states required for the rearrangement [27]. Besides, the diastereoisomeric mixture of **3j** suffered complete degradation under the same reaction conditions.

In recent years, Cossy and co-workers elegantly prepared various bicyclo[*n*.1.0] derivatives through intramolecular cyclopropanation reactions using adequately decorated 1,*n*-cyclopropenenes [24]. Hence, we preliminarily explored the feasibility of an analogous reaction with 1,3-dienes preparing dienylcyclopropene **4**. While treatment of **4** with $ZnCl_2$ led to complex mixtures, likely due to the Lewis acid sensitivity of the benzylic cyclopropenylcarbinol moiety, the use of $[Rh_2(OAc)_4]$ (1.0 mol %, CH_2Cl_2, rt) led to the tricyclic compound **5** in good yield (77%) in a stereoctive manner (Scheme 4).

Finally, we were curious to study the reactivity of metal–vinyl carbenes generated from 3,3-disubstituted cyclopropenes with some particular dienes (Scheme 5). Interestingly, we found that the reaction of cyclopropenes **1a**,**b** with furan (**6**) using $ZnCl_2$ as catalyst allowed the isolation of diastereomerically pure *endo*-**7a**,**b** oxabicycles showing the 1,2-divinylcyclopropane moiety. In contrast, $[Rh_2(OAc)_4]$ afforded complex reaction mixtures. In spite of the modest yields, this zinc-catalyzed reaction deserves some comments as it constitutes a rare example of isolation of these structures. Indeed, Lee and co-worker found that the corresponding gold-catalyzed reaction leads to ring-opened products through a facile oxy-Cope-rearrangement [28]. Moreover, these structures are also not accessible with metal–vinyl carbenes generated from vinyldiazo compounds, which led again to oxy-Cope rearranged or [4 + 3]-cycloaddition products using rhodium catalysts [14,28-30], or to a C2-allylation of furan with gold catalysts [31]. Finally, to compare the reactivity of cyclopropenes and vinyldiazo compounds, we probed the reaction of **1a** with 1,4-cyclohexadiene (**8**). Under otherwise identical reaction conditions, both $ZnCl_2$



Scheme 4: Rh-catalyzed intramolecular cyclopropanation with dienylcyclopropene **4** (the *trans*/*cis* ratio is related to the C-atom labelled with an asterisk).



Scheme 5: Zn- or Rh-catalyzed reactions of cyclopropenes **1** with furan (**6**) and 1,4-cyclohexadiene (**8**) and comparison with related processes (**1b**, R^1 = *n*-Hex).

and [$Rh_2(OAc)_4$] yielded exclusively cyclopropane **9** in practical yields and *endo* selectivity. This reaction outcome differs from the comparable reactions with vinyldiazo compounds and rhodium(II) catalysts, which preferentially undergo C–H allylic insertions [31-35].

Conclusion

In summary, we have described a straightforward method for the synthesis of 1,2-divinylcyclopropane derivatives by cyclopropanation reactions using unbiased 1,3-dienes and cyclopropenes, which served as metal–vinyl carbene precursors. The use of cyclic dienes allowed the synthesis of the corresponding 1,2-divinylcyclopropanes with good-to-complete *endo* selectivity. In contrast, acyclic dienes were also efficiently converted into the expected cyclopropanes but with low *cis*/*trans* selectivities. In general, simple $ZnCl_2$ and [$Rh_2(OAc)_4$] proved to be adequate catalysts. An intramolecular version of this reaction is also reported. Finally, the use of other dienes, such as furan and 1,4-cyclohexadiene was explored showing interesting reaction outcomes that are complementary to previous related reports. Subsequent studies to expand the scope of this cyclopropanation reaction to biased 1,3-dienes as well as to increase selectivities are currently ongoing.

Supporting Information

Supporting Information File 1

Experimental details as well as ^1H and ^{13}C NMR spectra of new compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-25-S1.pdf]

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Sigmatropic rearrangements of cyclopropenylcarbinol derivatives. Access to diversely substituted alkylidenecyclopropanes

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Review

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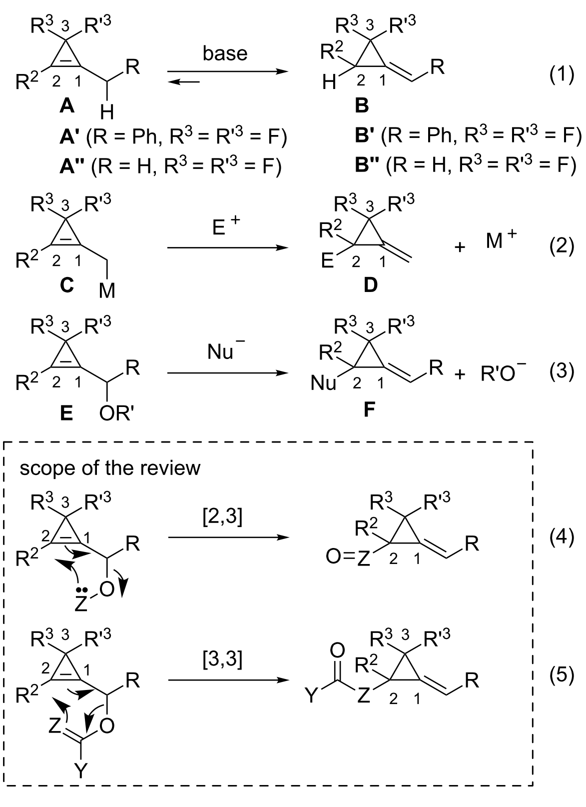
Abstract

Cyclopropenes constitute useful precursors of other classes of compounds incorporating a three-membered ring. Although the transformation of substituted cyclopropenes into alkylidenecyclopropanes can be accomplished through different strategies, this review is focusing specifically on the use of [2,3]- and [3,3]-sigmatropic rearrangements involving cyclopropenylcarbinol derivatives as substrates. These sigmatropic rearrangements, which have been developed in recent years, allow a remarkably efficient and stereoselective access to a wide variety of heterosubstituted and/or functionalized alkylidenecyclopropanes which would not be readily accessible by other strategies. The different [2,3]- and [3,3]-sigmatropic rearrangements of cyclopropenylcarbinol derivatives disclosed to date, as well as the analysis of their substrate scope and some applications of the products arising from those reactions, are presented in this review.

Introduction

Among the ever expanding diversity of chemical transformations involving cyclopropenes, which are largely dominated by ring-cleavage processes to access functionalized acyclic compounds or to construct new carbocycles or heterocycles, those reactions that preserve the three-membered ring and enable access to diversely substituted cyclopropanes or alkylidenecyclopropanes are also synthetically useful [1-6]. The importance of this latter class of transformations is obviously related to the widespread occurrence of cyclopropanes in natural and/or bioactive compounds [7,8] and the great interest of the cyclopropyl core in new drugs development [9]. Alkylidenecyclopropanes also constitute another important class of strained carbocycles displaying a versatile chemistry owing to their multiple reactive sites (the exocyclic olefin and the proximal and distal bonds on the ring) [10-15]. Although the synthesis of alkylidenecyclopropanes can be achieved by many different routes, controlling the configuration of the exocyclic olefin as well as that of stereocenters on and adjacent to the three-membered ring remains a challenging task [15]. In this context, cyclopropenes can serve as useful precursors of substituted and functionalized alkylidenecyclopropanes. The transformation of cyclopropenes into alkylidenecyclopropanes has been achieved through different strategies (Scheme 1). The first one relies on the isomerization of the olefin in alkylcyclopropenes **A** from the endocyclic to the exocyclic position (Scheme 1, reaction 1) [16-18]. Owing to the relief of ring-strain, the formation of the alkylidenecyclopropane **B** is generally thermodynamically favored [19,20]. However, in the particular case of *gem*-difluorocyclopropenes **A'** ($R^3 = R'^3 = F$) which possess a cyclopropenium (aromatic) character, the position of the equilibrium depends on the substituent at C1. Whereas conjugation with the phenyl group (R = Ph) provides the driving force for the base-promoted isomerization of 1-benzyl-3,3-difluorocyclopropene (**A'**, R = Ph) into the corresponding benzylidene(*gem*-difluorocyclopropane) (**B'**) [18], methylene(*gem*-difluorocyclopropane) (**B''**, R = H) is isomerized into 1-methyl-3,3-difluorocyclopropene (**A''**) [21] (Scheme 1, reaction 1). Another approach relies on the reaction of cyclopropenylmethyl organometallic species **C** with electrophiles through an S_E2' process leading to substituted alkylidenecyclopropanes **D** (Scheme 1, reaction 2). Examples of those transformations include the carboxylation of a (trimethylsilylmethyl)cyclopropene in the presence of a fluoride promoter [22], and also the addition of electrophiles to (lithiomethyl)cyclopropenes generated by lithiation of the corresponding methylcyclopropenylsulfone [23] or -sulfoxide [24]. More recently, the addition of cyclopropenylmethylboronates to aldehydes was also reported [25]. A complementary strategy involves the addition of nucleophiles, in particular organometallic reagents, to cyclopropenylcarbinols or their derivatives **E**, which leads to alkylidenecyclopropanes **F** through a formal S_N2' process (Scheme 1, reaction 3) [23,26-33]. Thus, methylenecyclopropanes have been prepared by diastereoselective addition of Grignard reagents to cyclopropenylmethyl ethers, possessing a hydroxymethyl directing substituent at C3, in the absence or in the presence of a catalyst (copper or iron salt) [28-30]. Another representative transformation is the copper-catalyzed addition of Grignard reagents to secondary unprotected cyclopropenylcarbinols which proceeds with high levels of chirality transfer to afford alkylidenecyclopropanes possessing a quaternary stereocenter at C2 [31,33]. In this review, we shall exclusively focus on alternative strategies that rely either on a [2,3]-sigmatropic rearrangement (Scheme 1, reaction 4) or a [3,3]-sigmatropic rearrangement of cyclopropenylcarbinol derivatives (Scheme 1, reaction 5). These transformations have emerged as useful tools over the past few years to access hetero-substituted and/or functionalized alkylidenecyclopropanes.



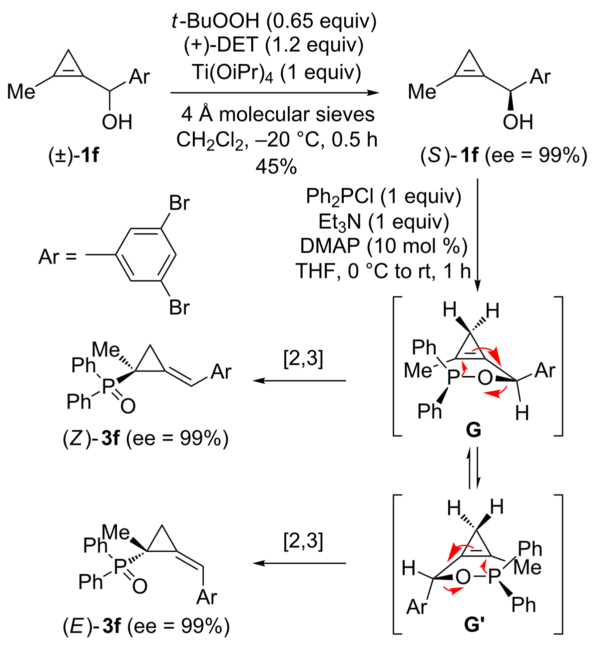
Scheme 1: Representative strategies for the formation of alkylidenecyclopropanes from cyclopropenes and scope of the review.

Review

[2,3]-Sigmatropic rearrangements involving cyclopropenylcarbinol derivatives

Following their report on the synthesis of chiral alkylidenecyclopropanes by copper-catalyzed addition of Grignard reagents to enantiomerically enriched cyclopropenylcarbinols [31], Marek et al. investigated other classes of transformations involving those latter strained analogs of allylic alcohols as substrates. In 2007, the [2,3]-sigmatropic rearrangement of cyclopropenylcarbinyl phosphinites was reported as a route to chiral phosphines possessing an alkylidenecyclopropane backbone [34]. The starting cyclopropenylcarbinols were readily prepared by addition of the corresponding cyclopropenyl organolithium reagents, generated in situ by treatment of 1,1,2-tribromocyclopropane with *n*-butyllithium (2 equiv) [35], to various aldehydes and ketones. Marek et al. observed that the treatment of cyclopropenylcarbinols **1a**–**h** with chlorodiphenylphosphine in the presence of triethylamine (THF, rt) resulted in a very rapid formation of (alkylidenecyclopropyl)diphenylphosphine oxides **3a**–**h** (85–94%), resulting from an efficient [2,3]-sigmatropic rearrangement of the in situ-generated phosphinites **2a**–**h**. Primary or tertiary cyclopropenylcarbinols reacted equally well, as shown with the formation of phosphine oxides **3a** (94%), **3b** (93%) and **3c** (87%). The [2,3]-sigmatropic rearrangement of phosphinites **2d**–**h** derived from secondary cyclopropenylcarbinols led to the corresponding phosphine oxides **3d**–**h** (85–93%) as a 80:20 mixture of *E*/*Z* geometric isomers, regardless of the substituent of the alcohol (at C4) and of the cyclopropene (at C2, Scheme 2) [33,34].

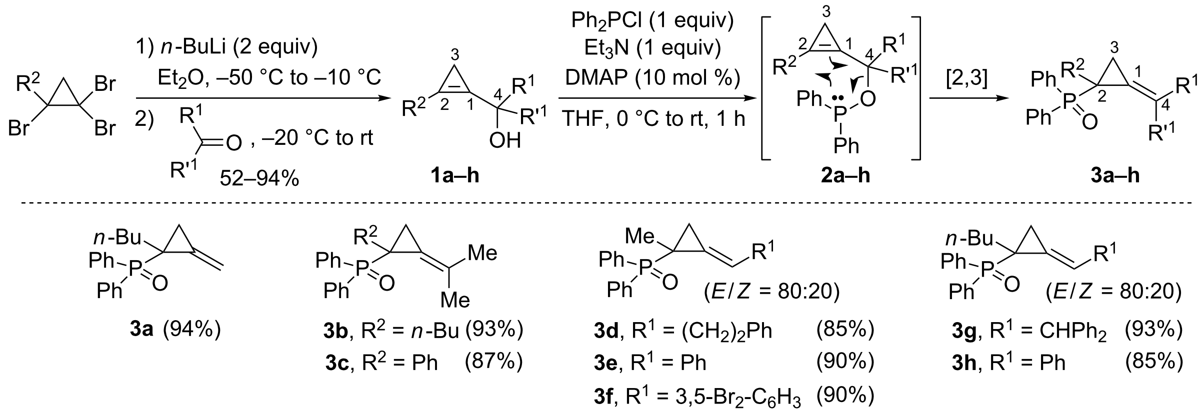
The [2,3]-sigmatropic rearrangement of an optically enriched phosphinite **2f**, prepared from the corresponding secondary cyclopropenylcarbinol (*S*)-**1f** (ee = 99%), which in turn is readily available by applying the Sharpless kinetic resolution procedure to (±)-**1f** [31], was also investigated. The resulting geometric isomers (*Z*)-**3f** and (*E*)-**3f**, which were separated by flash chromatography, were found to possess optical purities identical to that of the parent substrate (*S*)-**1f** (ee = 99%) thereby confirming that complete chirality transfer occurred (from C4 to C2) during the [2,3]-sigmatropic rearrangement [33,34]. It is also worth mentioning that the absolute configuration of (*Z*)-**3f** and (*E*)-**3f**, which is opposite at C2, was assigned by comparison of their computed and experimentally observed CD spectra [33,34]. To tentatively explain the observed stereochemical outcome in the absence of additional knowledge on the transition state of the rearrangement [36], two reactive conformers **G** and **G'** were considered which would lead to five-membered ring transition states in which the aryl group occupies a preferential pseudo-equatorial or a less favorable pseudo-axial orientation, respectively (Scheme 3) [33,34].



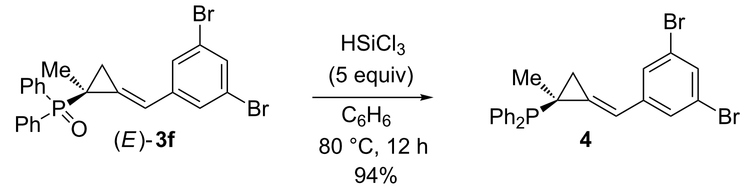
Scheme 3: [2,3]-Sigmatropic rearrangement of a phosphinite derived from enantioenriched cyclopropenylcarbinol (*S*)-**1f**.

The authors also showed that phosphine oxide (*E*)-**3f** could be reduced to the corresponding phosphine **4** (94%) by treatment with trichlorosilane, without affecting the (arylmethylene)cyclopropane moiety (Scheme 4).

The great efficiency of the [2,3]-sigmatropic rearrangement of phosphinites **2a**–**h** lacking substituents at C3 is in striking contrast with the reactivity of phosphinites possessing a geminal disubstitution at C3. In 2007, Rubin et al. reported their results on the [2,3]-sigmatropic rearrangement of cyclopropenylmethyl phosphinites derived from primary cyclopropenyl-

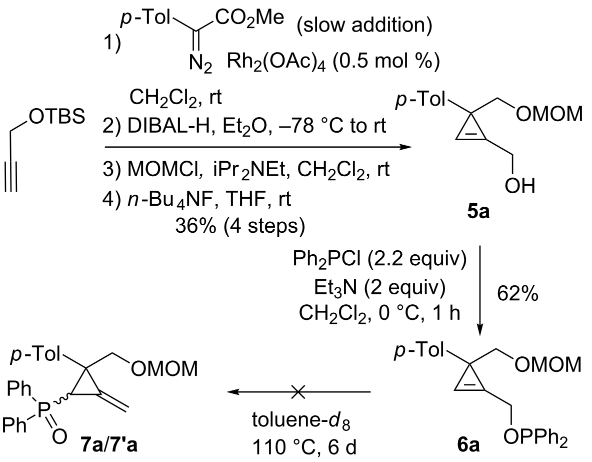


Scheme 2: [2,3]-Sigmatropic rearrangement of phosphinites **2a**–**h**.



Scheme 4: Selective reduction of phosphine oxide (*E*)-**3f**.

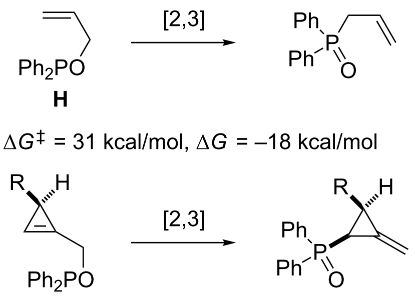
carbinols [37]. As illustrated in the case of **5a**, the substrates were prepared from the *tert*-butyldimethylsilyl (TBS) ether of propargyl alcohol by a rhodium-catalyzed cyclopropanation with an aryldiazoacetate followed by reduction of the ester moiety and protecting group manipulation. Phosphinite **6a**, generated from alcohol **5a** under standard conditions, did not undergo a [2,3]-sigmatropic rearrangement into the corresponding diastereomeric phosphine oxides **7a**/**7’a**, even upon prolonged heating (toluene, 110 °C), and underwent slow decomposition instead (Scheme 5).



Scheme 5: Attempted thermal [2,3]-sigmatropic rearrangement of phosphinite **6a**.

This observation was in agreement with DFT calculations which indicated that the rearrangement of cyclopropenylmethyl phosphinite **I**, although thermodynamically favored, displays a high activation barrier compared to that of the acyclic allyl analog **H**. An even higher activation barrier was calculated in the case of the 3-methyl and 3-phenyl-substituted cyclopropenes, **I’** and **I’’**, respectively, which indicates that the concerted [2,3]-sigmatropic rearrangement would require high temperatures incompatible with such thermally labile strained substrates (Scheme 6) [37].

Interestingly, the authors detected traces of methylenecyclopropanes **7a**/**7’a** when phosphinylation of alcohol **5a** was conducted at room temperature for several hours which led them to consider that the amine could play a role in promoting the [2,3]-sigmatropic rearrangement. After a screening of different tertiary amines, Rubin et al. found that DBU could be used as a base in the phosphinylation reaction but also as an efficient catalyst for the subsequent [2,3]-sigmatropic rearrangement of phosphinite **6a** which afforded a 73:27 mixture of the diastereomeric phosphine oxides **7a**/**7’a** (86%). The major diastereomer **7a** corresponds to a sigmatropic rearrangement occurring on the most hindered face (*cis* to the aromatic group) of the cyclopropene which was somewhat surprising. Substitution at the *para*-position of the aromatic group at C3 significantly affected the diasteomeric ratio with an increase observed with the mesomeric donor methoxy group in favor of diastereomer **7b** (**7b**/**7’b** = 78:22) compared to **7a**/**7’a**, and a drop of diastereoselectivity when a fluorine atom (**7c**/**7’c** = 60:40) or a hydrogen atom (**7d**/**7’d** = 52:48) were present. An inversion of the face selectivity was detected in favor of diastereomer **7’e** (**7e**/**7’e** = 43:57) arising from the rearrangement of phosphinite **6e** possessing a *p*-trifluoromethylphenyl substituent. Replacement of the acetal protecting group of the hydroxymethyl substituent at C3 (R^3 = CH_2OMOM = CH_2OCH_2OMe) by an acetate (R^3 = CH_2OAc) did not affect the results, as illustrated in the case of **7f**/**7’f**, but the presence of an ester moiety (R^3 = CO_2Me) led to the rearranged phosphine oxides **7g**/**7’g** in rather low yield (47%) although the diasteromeric ratio remains



$\Delta G^\ddagger$ = 31 kcal/mol, ΔG = –18 kcal/mol

I, R = H, $\Delta G^\ddagger$ = 25 kcal/mol, ΔG = –34 kcal/mol
I', R = Me, $\Delta G^\ddagger$ = 30 kcal/mol
I", R = Ph, $\Delta G^\ddagger$ = 37 kcal/mol

Scheme 6: Computed activation barriers and free enthalpies.

similar to that observed for **7a**/**7'a**. Other substituents were tolerated on the phosphorus atom including an isopropyl or a cyclohexyl group and the corresponding phosphine oxides **7h**/**7'h** and **7i**/**7'i** were isolated in good yields. Increasing the steric hindrance around the phosphorus atom resulted in a higher diastereoselectivity. However, the sigmatropic rearrangement of the highly hindered di(*tert*-butyl)phosphinite **6j** and tetra(isopropyl) phosphorodiamidite **6k** did not occur (Scheme 7) [37].

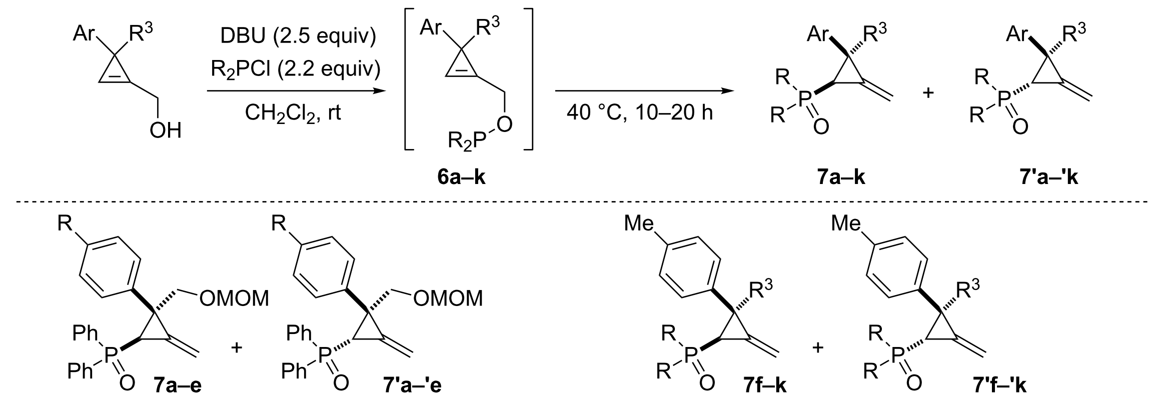
The mechanism proposed by Rubin et al. involves a reversible addition of the Lewis base (DBU) on the cyclopropene double bond at C2 leading to zwitterronic intermediates **8** and **8'**. This would result in an increase of conformational flexibility thereby facilitating the nucleophilic displacement of the ammonium by the phosphinite through transition states **TS1** and **TS2** (S_N2-type process), respectively. Oxaphospholanium zwitterions **9** and **9'** would then be obtained and would eventually produce the diastereomeric phosphine oxides **7** and **7'**. Computational studies indicated that the facial selectivity of the initial attack of the Lewis base (DBU) was not responsible for the observed diastereocontrol because of the low difference between the activation barriers of the reactions leading to **8** and **8'**, regardless of the aromatic substituent. Since **8** and **8'** were in rapid equilibrium with phosphinite **6**, the diastereoselectivity should depend on the relative stabilities of the transition states **TS1** and **TS'1**. An electron-donating group at the *para*-position of the aromatic ring could contribute to the stabilization of **TS1**, in which the Ar–C3–C2–P dihedral angle is close to 0°, by considering the mesomeric form **TS2**. The observed dependence of the diastereoselectivity on the σ^+ Hammett constant of the *para* substituents further supported the proposed mechanism (Scheme 8) [37].

To date and to the best of our knowledge, reports on [2,3]-sigmatropic rearrangements of cyclopropenylcarbinol derivatives appear to be limited to the synthesis of alkylidenecyclopropanes incorporating a phosphorus atom. Cyclopropenylcarbinol derivatives can also lead to other heterosubstituted alkylidenecyclopropanes by using [3,3]-sigmatropic rearrangements.

[3,3]-Sigmatropic rearrangements involving cyclopropenylcarbinol derivatives

Access to heterosubstituted alkylidenecyclopropanes

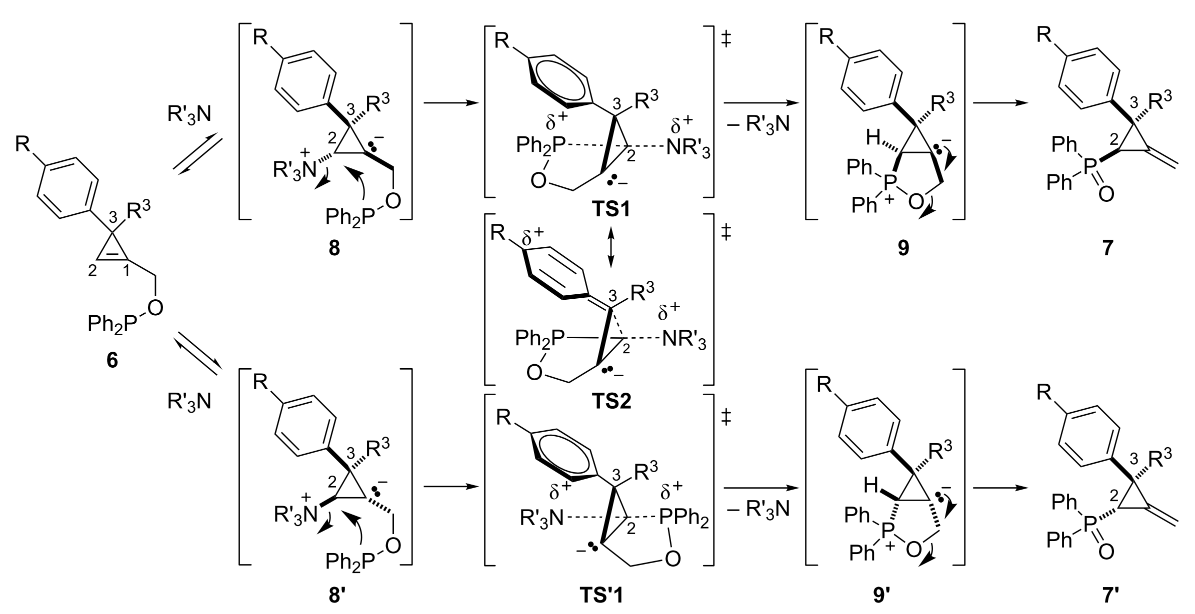
The interest of secondary cyclopropenylcarbinol derivatives in [3,3]-sigmatropic rearrangements was first highlighted by Marek et al. who investigated the transposition of cyclopropenylcarbinyl esters [33,34]. The [3,3]-sigmatropic rearrangement of acetate **10a** took place during filtration on silica gel and afforded alkylidene(acetoxycyclopropane) **11a** in 90% yield. The ease with which the rearrangement of **10a** occurred was attributed to the relief of ring strain but also to the favorable conjugation of the olefin with the two phenyl groups ($R^1 = R'^1 = Ph$). Alkylidenecyclopropane **11a** could also be obtained in similar yields (92% or 87%, respectively) by heating acetate **10a** in dichloromethane at reflux or by treatment with



R = Me	**7a**/**7'a** = 73:27	(86%)
R = OMe	**7b**/**7'b** = 78:22	(90%)
R = F	**7c**/**7'c** = 60:40	(96%)
R = H	**7d**/**7'd** = 52:48	(83%)
R = CF_3	**7e**/**7'e** = 43:57	(91%)

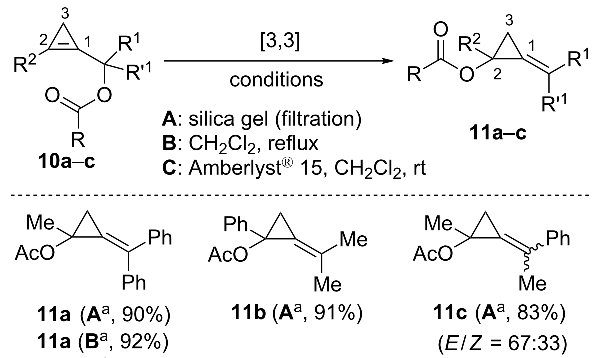
R = Ph, $R^3 = CH_2OAc$	**7f**/**7'f** = 74:26	(83%)
R = Ph, $R^3 = CO_2Me$	**7g**/**7'g** = 71:29	(47%)
R = iPr, $R^3 = CH_2MOM$	**7h**/**7'h** = 80:20	(74%)
R = Cy, $R^3 = CH_2OMOM$	**7i**/**7'i** = 84:16	(90%) (at 50 °C)
R = *t*-Bu, $R^3 = CH_2OMOM$	**7j**/**7'j**	(0%)
R = $NiPr_2$, $R^3 = CH_2OMOM$	**7k**/**7'k**	(0%)

Scheme 7: [2,3]-Sigmatropic rearrangement of phosphinites **6a**–**j**.



Scheme 8: Proposed mechanism for the Lewis base-catalyzed rearrangement of phosphinites **6**.

dry Amberlyst® 15 (a sulfonic acid resin) [33,34]. The rearrangement of the tertiary acetates **10b** ($R^1 = R'^1 = Me$) and **10c** ($R^1 = Ph$, $R'^1 = Me$) could also be achieved by filtration through silica gel and led to **11b** (91%) and **11c** (83%). The latter non-symmetrical tetrasubstituted alkene **11c** was obtained as a 67:33 mixture of geometric isomers (Scheme 9) [33,34].

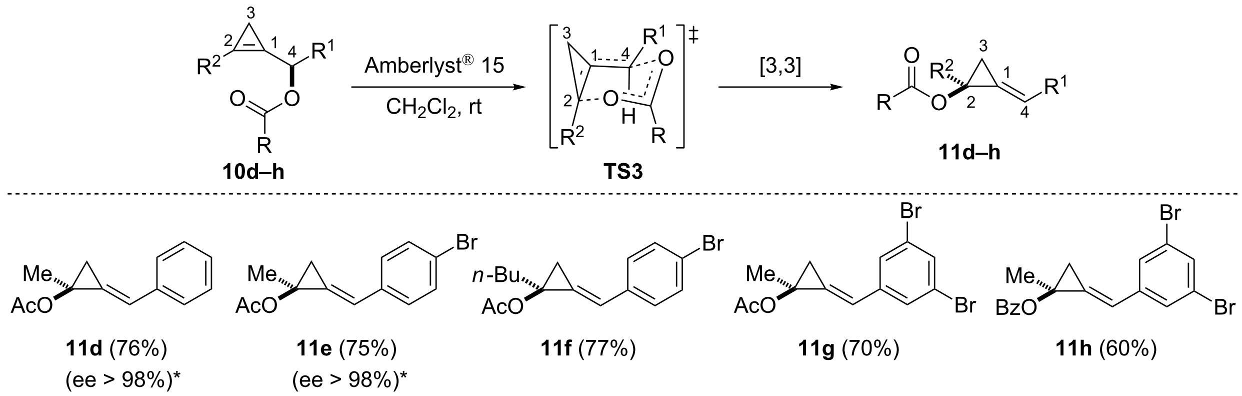


[a]conditions used.

Scheme 9: [3,3]-Sigmatropic rearrangement of tertiary cyclopropenylcarbinyl acetates **10a–c**.

The rearrangement of secondary cyclopropenylcarbinyl acetates **10d–g** could be achieved in the presence of Amberlyst® 15 and led exclusively to the (*E*)-alkylidene(acetoxycyclopropanes) **11d–g** (*E*/*Z* > 99:1) in good yields (70–77%). The acetate could also be replaced by a benzoate as illustrated with the formation of alkylidenecyclopropane **11h** (60%) from substrate **10h**. The authors mentioned that the sigmatropic rearrangement did not proceed under such mild conditions for substrates possessing an alkyl group instead of an aryl group at C4 but no additional details were provided. The high diastereoselectivity was explained by considering a six-membered chair-like cyclic transition state model **TS3** in which the substituent at the α position of the ester (C4) preferentially occupies a pseudo-equatorial position. Although a cationic mechanism could have also been envisioned under the acidic conditions used, the optically enriched acetates **10d** and **10e** (ee > 98%) led to the corresponding alkylidenecyclopropanes **11d** and **11e** with complete chirality transfer (ee > 98%) at C2, thereby probing the concerted suprafacial nature of the rearrangement (Scheme 10) [33,34]. The acidic promotor may be simply assisting the dissociation of the C4–O bond in the transition state **TS3** whilst an aromatic group ($R^1 = Ar$) would contribute to the stabilization of a developing positive charge at C4.

The [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl acetates provides a straightforward and stereoselective entry to alkylidene(acyloxycyclopropanes). Only a few compounds of this family had been previously generated by photochemical reactions (from 4-isopropylidene-3,3-dimethyl-1-thietan-2-thione [38] or from a 4-alkylidene-Δ^1-pyrazoline [39]) or by pyrolysis of the sodium salt of 3-propionyloxytetramethylcyclobutanone tosyl hydrazone [40]. It is also worth mentioning that completely divergent reactivities have also been reported for cyclopropenylcarbinyl esters in the presence of transition metal catalysts [41,42].



11d (76%) (ee > 98%)*

11e (75%) (ee > 98%)*

11f (77%)

11g (70%)

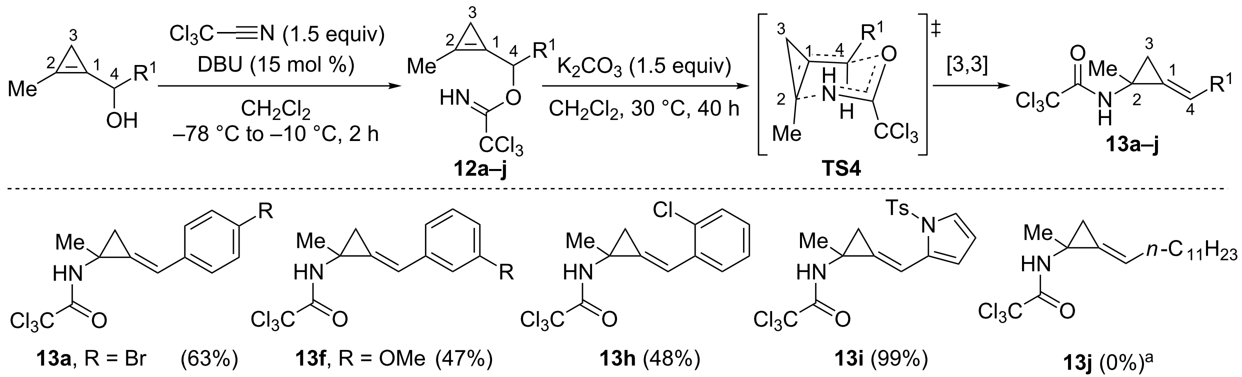
11h (60%)

*enantioenriched substrates **10d** and **10e** (ee > 98%) were used.

Scheme 10: [3,3]-Sigmatropic rearrangement of secondary cyclopropenylcarbinyl esters **10d**–**h**.

Alkylidene(aminocyclopropane) derivatives constitute another interesting class of heterosubstituted alkylidenecyclopropanes which have been previously synthesized by a Curtius rearrangement of acyl azides derived from alkylidenecyclopropane carboxylic acids [43] or by elimination reactions applied to suitably substituted aminocyclopropane derivatives [44-46].

In 2014, Hyland et al. disclosed the Overman rearrangement [47] of cyclopropenylcarbinyl trichloroacetimidates [48]. The optimal conditions for the generation of imidates **12a**–**i** involved treatment of secondary cyclopropenylcarbinols with trichloroacetonitrile in the presence of a catalytic amount of DBU (15 mol %) in CH_2Cl_2 (−78 °C to −10 °C, 2–3 h) [48,49]. The crude imidates **12a**–**i** were then directly engaged in the [3,3]-sigmatropic rearrangement step which was triggered by heating in the presence of K_2CO_3 in CH_2Cl_2 (30 °C, 40 h). These latter conditions, which were optimized for imidate **12a**, enabled the formation of *p*-bromobenzylidene[(*N*-trichloroacetylamino)cyclopropane] **13a** as a single (*E*)-isomer in 63% overall yield (two steps from the corresponding alcohol). Compound **13a** was obtained in lower yield in the absence of a base (21%) or when DMF was used as the solvent (53%) though a considerable rate acceleration (22 h instead of 40 h) was observed compared to CH_2Cl_2. In the presence of $PdCl_2(MeCN)_2$ (5 mol %), only traces of **13a** were detected and significant decomposition of **12a** took place. As in the case of the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl acetates, the observed stereoselectivity was explained by invoking a chair-like transition state model **TS4** in which the aryl group preferentially occupies a pseudo-equatorial orientation (Scheme 11) [48]. Although the presence of a halogen atom was tolerated, as illustrated with the formation of the benzyli-



13a, R = Br (63%)
13b, R = H (83%)
13c, R = Me (98%)
13d, R = OMe (77%)
13e, R = NO_2 (0%)

13f, R = OMe (47%)
13g, R = NO_2 (0%)

13h (48%)

13i (99%)

13j (0%)[a]

[a]imidate **12j** was not formed.

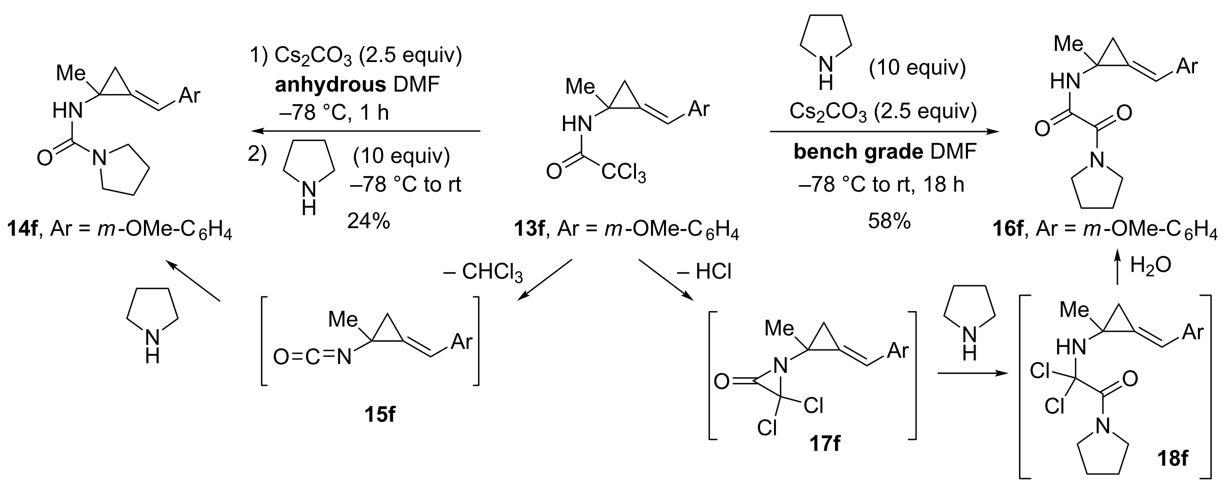
Scheme 11: [3,3]-Sigmatropic rearrangement of trichoroacetimidates **12a**–**i**.

denecyclopropanes **13a** (63%) and **13h** (48%), higher yields were obtained in the case of imidates **13b**–**d**, possessing an electro-neutral or an electron-rich aromatic group, which afforded compounds **13b** (83%), **13c** (98%) and **13d** (77%), substituted by a phenyl, a *p*-tolyl or a *p*-anisyl group, respectively. The rearrangement of imidate **12f** possessing a *m*-anisyl substituent afforded benzylidene cyclopropane **13f** in a lower yield (47%) compared to **13d** (77%). The rearrangement of imidate **12i** possessing an electron-rich *N*-tosylpyrrol-2-yl heteroaromatic group, afforded alkylidenecyclopropane **13i** in nearly quantitative yield. Conversely, no rearrangement took place in the case of imidates **12e** and **12g** in which the aromatic group was substituted by a strongly electron-withdrawing nitro group at the *para*- or the *meta*-position, respectively. All these observations point toward the development of a positive charge at the C4 carbon atom (adjacent to the R^1 substituent) in the transition state **TS4**, as was also suggested previously in the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl acetates. Alkylidenecyclopropane **13j** could not be synthesized because trichloroacetimidate **12j** was not obtained by treatment of the corresponding cyclopropenylcarbinol substituted by an *n*-undecyl group with trichloroacetonitrile, even under forcing conditions. The authors tentatively suggested this may be due to the sterically hindered *n*-undecyl chain although this issue was not fully investigated (Scheme 11) [48].

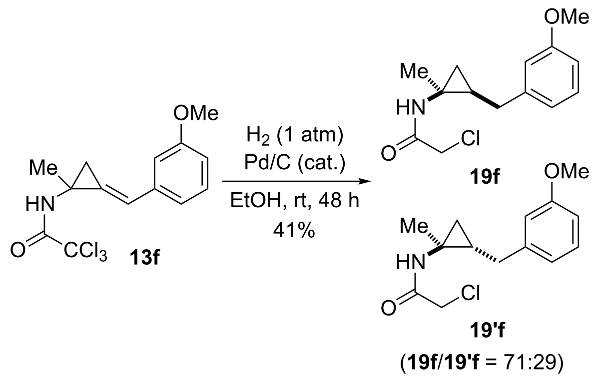
While attempts to access the free alkylidene(aminocyclopropanes) from the corresponding trichloroacetamides proved unsuccessful by hydrolysis (1 M aqueous HCl or KOH, EtOH) or reduction (DIBAL-H or $NaBH_4$), Hyland et al. showed that the treatment of (arylmethylene)cyclopropane **13f** with Cs_2CO_3 in anhydrous DMF, followed by the addition of an excess of pyrrolidine, produced urea **14f** (24%) [48,49]. The moderate yield of **14f** was attributed to the instability of the in situ-generated isocyanate **15f** under the reaction conditions [50]. When trichloroacetamide **13f** was treated with an excess of pyrrolidine and Cs_2CO_3 in bench grade (undried) DMF, the reaction followed a different pathway and delivered α-oxoacetamide **16f** (58%) instead of urea **14f** [48,49]. This type of transformation had already been reported [51] and interpreted by a Favorskii-type mechanism, presumably involving the formation of the *gem*-dichloro-α-lactam intermediate **17f** which would undergo ring opening by nucleophilic addition of pyrrolidine followed by hydrolysis of the resulting α,α-dichloro-α-aminoacetamide **18f** (Scheme 12).

To access aminocyclopropanes, the hydrogenation of (arylmethylene)cyclopropane **13f** was achieved in the presence of Pd/C as a catalyst. Concomitant hydrogenolysis of two carbon–chlorine bonds also took place under these conditions and a 71:29 diastereomeric mixture of the monochloracetamides **19f**/**19’f** was obtained (41%). The rather small difference of steric hindrance between the methyl and the *N*-acylamino group explained the modest face selectivity of hydrogen addition which preferentially occurred on the face of the olefin opposite to the *N*-chloroacetylamino substituent (Scheme 13) [48].

3,3-Disubstituted cyclopropenylcarbinols could not be used as substrates in the Overman rearrangement. This limitation of the substrate scope is due to the instability of the corresponding trichloroacetimidates. Thus cyclopropenylcarbinols **20a**–**c** possessing *gem*-dimethyl substitution at C3 were converted to imidates **21a**–**c** but upon treatment with silica gel (CH_2Cl_2, −10 °C), those latter compounds were converted into α-allenic tertiary alcohols **22a**–**c** (30–61%) The formation of alcohols **22a**–**c** was explained by a mechanism involving ionization of

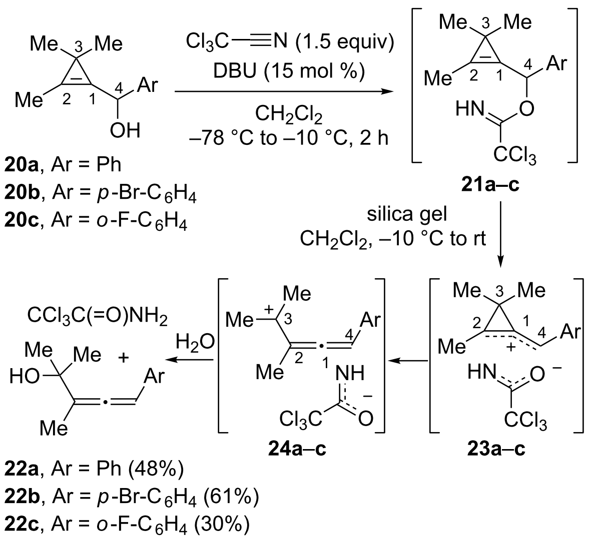


Scheme 12: Reaction of trichloroacetamide **13f** with pyrrolidine.



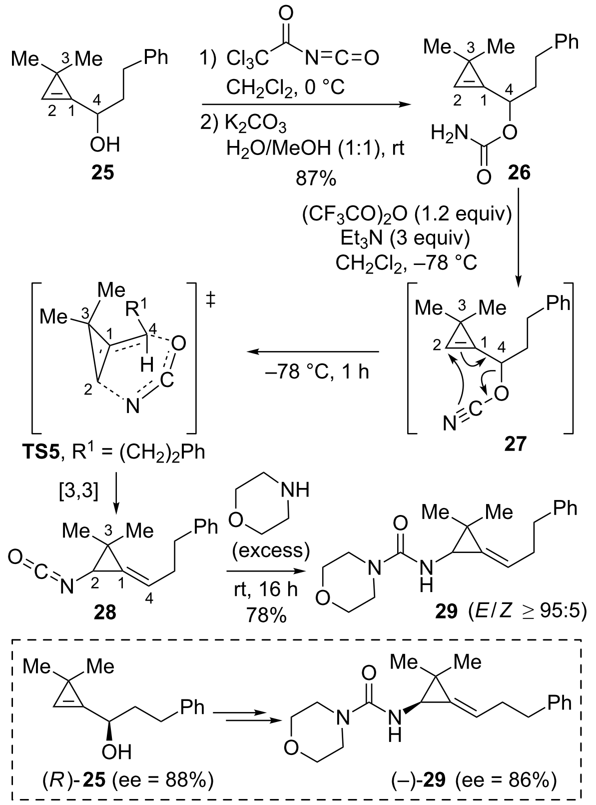
Scheme 13: Catalytic hydrogenation of (arylmethylene)cyclopropane **13f**.

the C4–O bond in imidates **21a**–**c**, followed by ring opening of the alkylidenecyclopropyl cationic intermediates **23a**–**c** [52] and addition of water to the resulting α-allenic carbocations **24a**–**c** (Scheme 14) [48].



Scheme 14: Instability of trichloroacetimidates **21a**–**c** derived from cyclopropenylcarbinols **20a**–**c**.

As a complementary strategy, our group examined the [3,3]-sigmatropic rearrangement of cyanates derived from cyclopropenylcarbinols [53]. The allyl cyanate to isocyanate rearrangement displays many interesting features such as the possibility to generate the reactive species by dehydration of carbamates under mild conditions and the ultimate formation of isocyanates which can be derivatized in situ [54]. The conditions were optimized with alcohol **25** substituted by a 2-phenylethyl group at the oxygen-bearing carbon atom (C4) and possessing *gem*-disubstitution at C3 on the three-membered ring. Alcohol **25** was readily converted to carbamate **26** by reaction with trichloroacetyl isocyanate followed by cleavage of the trichloroacetyl group by alkaline hydrolysis. Dehydration of carbamate **26** was achieved by treatment with trifluoroacetic anhydride in the presence of triethylamine under mild conditions (CH_2Cl_2, −78 °C) [55] and the in situ-generated cyanate **27** underwent a sigmatropic rearrangement into the corresponding isocyanate **28**. The formation of this reactive isocyanate intermediate was ascertained by the addition of morpholine which enabled the isolation of urea **29** in good yield (78%). It is worth noting that alkylidenecyclopropane **29** was formed with high diastereoselectivity ($E/Z \geq 95:5$) at low temperature (−78 °C) but a slight erosion of diastereoselectivity was observed ($E/Z = 88:12$) when the same sequence was performed at 0 °C. The stereochemical outcome was in agreement with a six-membered transition state model **TS5** in which the three atoms of the cyanate (O=C=N) moiety would be arranged in an almost linear fashion (an angle of 173° was calculated in the allyl cyanate to isocyanate transition state) [56] and the substituent at C4 would preferentially occupy a pseudo-equatorial orientation. Additionally, the same sequence applied to the enantioenriched alcohol (*R*)-**25** (ee = 88%) delivered urea (−)-**29** with essentially the same optical purity (ee = 86%), thereby indicating that chirality transfer (from C4 to C2) occurred during the sigmatropic rearrangement of cyanate **27** into isocyanate **28** (Scheme 15) [53].



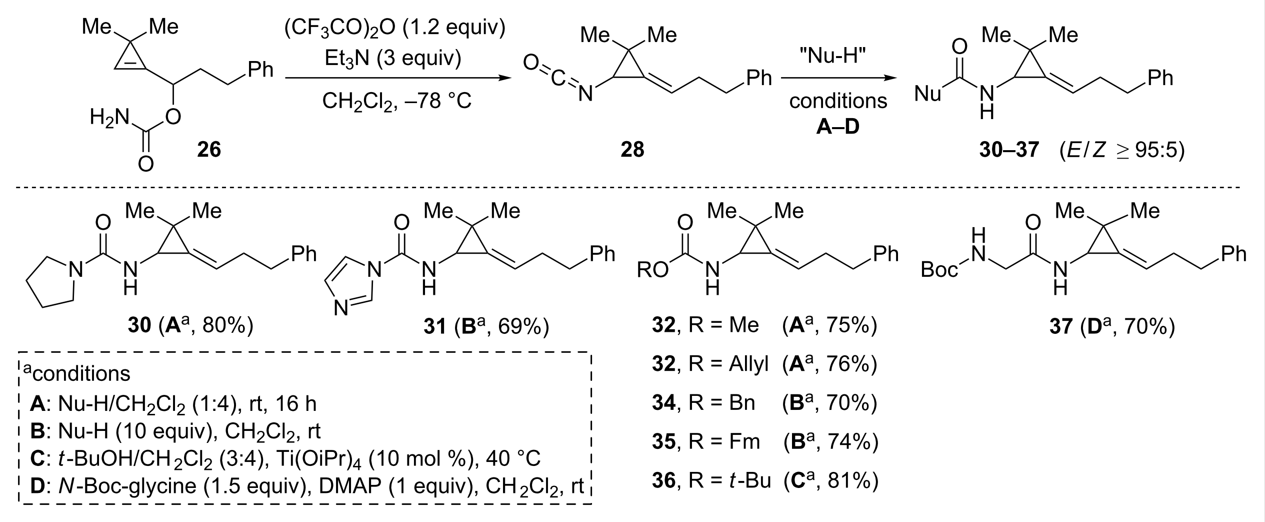
Scheme 15: [3,3]-Sigmatropic rearrangement of cyanate **27** generated from cyclopropenylcarbinyl carbamate **26**.

All attempts to isolate isocyanate **28** were unsuccessful but derivatization of this latter reactive intermediate could be achieved in situ by addition of a broad range of nucleophiles, which were either used as co-solvents or added in excess. Thus, reaction with pyrrolidine, imidazole, methanol, allyl alcohol, benzyl alcohol and 9-fluorenemethanol (FmOH) provided the corresponding urea **30**, *N*-carbamoyl imidazole **31** and carbamates **32**–**35**, respectively, in good yields (69–80%). The reaction of isocyanate **28** with *tert*-butanol was sluggish even by heating at 40 °C but could be accelerated by addition of $Ti(OiPr)_4$ (10 mol %) to deliver the corresponding *N*-Boc-carbamate **36** (81%). The condensation of isocyanate **28** with *N*-Boc-glycine in the presence of DMAP (Goldschmidt–Wick coupling) [57] provided amide **37** in 70% yield (Scheme 16) [53].

The examination of the substrate scope indicated that a broad range of alkyl chains, possibly incorporating heteroatoms, were compatible with the dehydration–[3,3]-sigmatropic sequence, as illustrated with the isolation of compounds **38**–**40** (72–79%) after nucleophilic trapping of the generated isocyanate intermediates with allyl alcohol. Benzylidenecyclopropane **41** was also obtained in good yield (70%) but the efficiency of the sigmatropic rearrangement dropped for carbamates in which the aromatic group at C4 is substituted by an electron-withdrawing group at the *para*-position. Indeed, *N*-Alloc (arylmethylene)(aminocyclopropanes) **42** and **43**, substituted by a *p*-fluorophenyl and a *p*-(trifluoromethyl)phenyl group, respectively, were isolated in moderate yield (53%). Moreover, (*p*-nitrophenylmethylene)cyclopropane **44** could not be obtained under these conditions [53]. These results indicate that the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl cyanates, as previously reported for their allylic counterparts [56], does not involve a synchronous process because dissociation of the C4–O bond is more advanced in the transition state **TS5** than the formation of the C2–N bond (Scheme 15). The rearrangement of cyclopropenylcarbinyl cyanates accommodates various substituents at C3, as well as the presence of a substituent at C2 or even a fully substituted cyclopropene ring, as shown with the successful formation of alkylidenecyclopropanes **45**–**48** (58–86%, Scheme 17) [53].

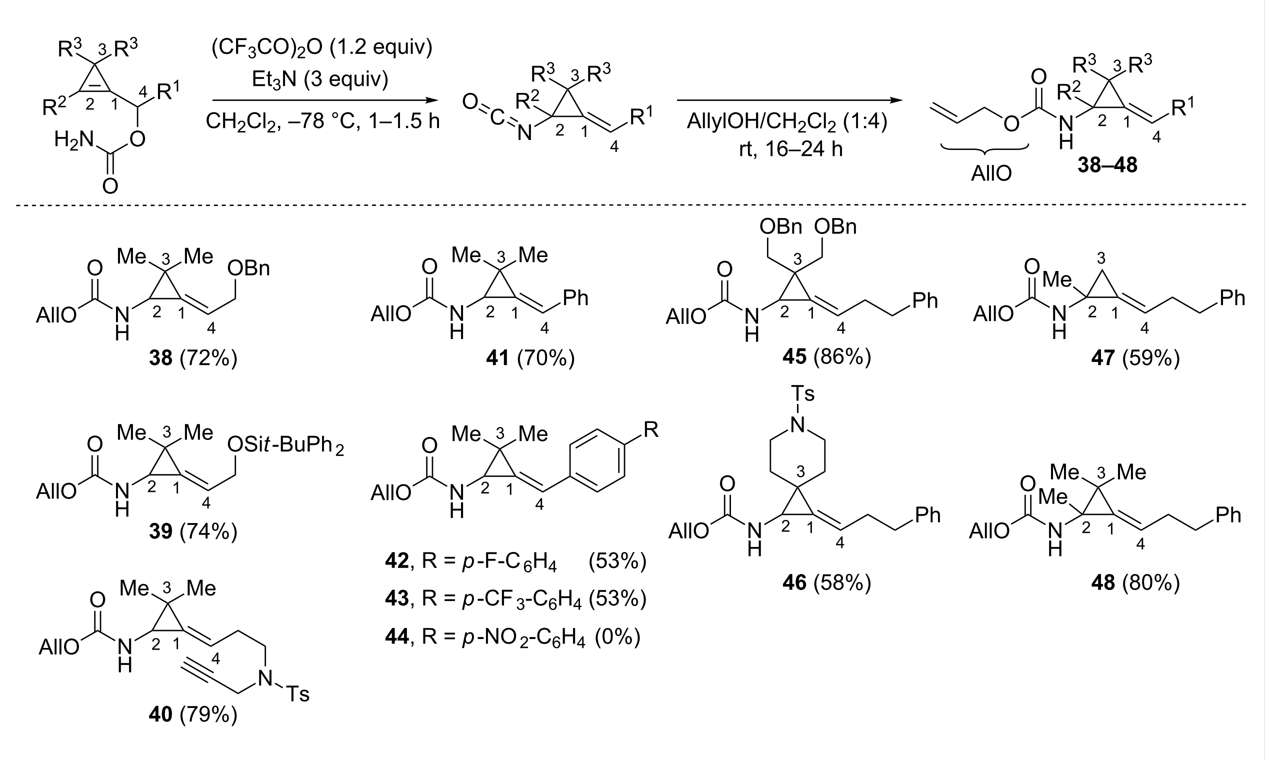
Interestingly, alkylidene(isocyanatocyclopropanes) arising from the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl cyanates could also be derivatized into trifluoroacetamides. This transformation was discovered fortuitously when carbamate **49** was treated with an excess of trifluoroacetic anhydride (2 equiv) in the presence of Et_3N (3 equiv) to achieve the dehydration–sigmatropic rearrangement sequence. Trifluoroacetamide **50** (67%) was the product directly formed under these conditions and the Lewis basic character of the pyridine ring was suspected to be responsible for the observed reactivity (Scheme 18).

With the aim of achieving the same derivatization in the case of other substrates devoid of a pyridine ring, several 3,3-dimethylcyclopropenylcarbinyl carbamates were engaged in the dehydration–[3,3]-sigmatropic rearrangement sequence under the previously used conditions but trifluoroacetic anhydride (1.5 equiv) and pyridine (1.5 equiv) were then subsequently added to the reaction mixture. Under these conditions, the corresponding trifluoroacetamides **51**–**54** could be effectively isolated in good yields (73–85%). The addition of pyridine to the isocyanates **J** arising from the [3,3]-sigmatropic rearrangement would probably generate the zwitterionic intermediates **K** which would then react with trifluoroacetic anhydride to

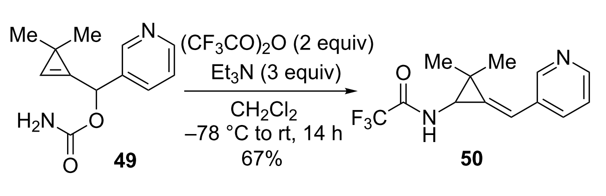


[a]conditions
A: Nu-H/CH_2Cl_2 (1:4), rt, 16 h
B: Nu-H (10 equiv), CH_2Cl_2, rt
C: *t*-BuOH/CH_2Cl_2 (3:4), $Ti(OiPr)_4$ (10 mol %), 40 °C
D: *N*-Boc-glycine (1.5 equiv), DMAP (1 equiv), CH_2Cl_2, rt

Scheme 16: Synthesis of alkylidene(aminocyclopropane) derivatives **30**–**37** from carbamate **26**.



Scheme 17: Scope of the dehydration–[3,3]-sigmatropic rearrangement sequence of cyclopropenylcarbinyl carbamates.



Scheme 18: Formation of trifluoroacetamide **50** from carbamate **49**.

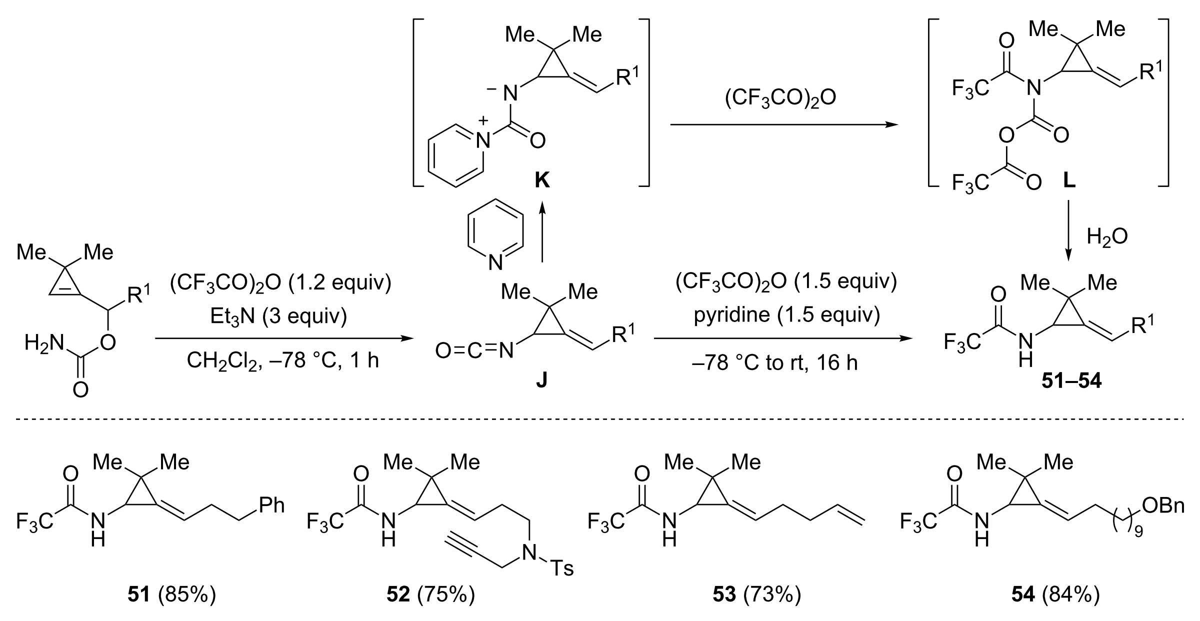
produce *N*,*O*-bis(trifluoroacetyl)carbamates **L**. Trifluoroacetamides **51**–**54** would be generated from adducts **L** after hydrolysis of the reaction mixture (Scheme 19) [53].

To control the diastereoselectivity of the hydrogenation of alkylidene[(*N*-acylamino)cyclopropanes] possessing a single substituent at C2, it is possible to rely either on the steric hindrance or on the coordinating ability of the amide group. Thus, the hydrogenation of trifluoroacetamide **51** catalyzed by Pd/C afforded *N*-trifluoroacetylaminocyclopropane **55** as the major diastereomer (**55**/**55'** = 92:8) because of the preferential addition of hydrogen on the less hindered face of the trisubstituted alkene opposite to the trifluoroacetamide moiety. A reversal of face selectivity can be observed by performing a directed iridium(I)-catalyzed hydrogenation in the presence of Crabtree's catalyst [58] which afforded aminocyclopropane **55'** as the major diastereomer (**55'**/**55** = 90:10, Scheme 20) [53].

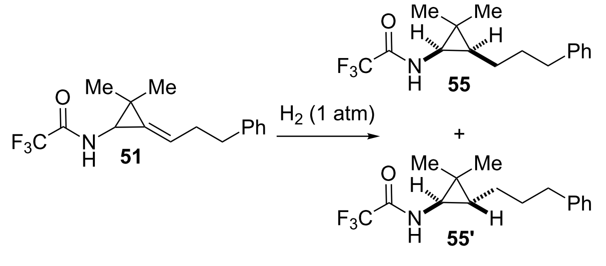
The potential of [3,3]-sigmatropic rearrangements involving cyclopropenylcarbinol derivatives is not restricted to the synthesis of heterosubstituted alkylidenecyclopropanes and was also exploited to access functionalized alkylidenecyclopropanes, with creation of a new carbon–carbon bond on the three-membered ring with the control of two contiguous stereocenters.

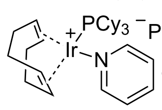
Ireland–Claisen rearrangement of cyclopropenylcarbinyl esters

The Ireland–Claisen rearrangement of silyl ketene acetals generated from allylic (or propargylic) esters is arguably one of the most useful variant of the Claisen rearrangement that has found countless applications in organic synthesis [59]. The feasibility of the Ireland–Claisen rearrangement of cyclopropenylcarbinyl esters was investigated in the case of glycolates **56a**–**l** which were readily prepared by coupling of the corresponding cyclopropenylcarbinols with (4-methoxybenzyloxy)acetic acid. Enolization of glycolates **56a**–**l** was carried out by treatment with Me_3SiCl (4 equiv) followed by addition of KHMDS (usually 4 equiv) in THF at −78 °C. The resulting silyl ketene acetals of (*Z*)-configuration **57a**–**l**, arising from O-silylation of the corresponding chelated potassium enolates [60], underwent an efficient [3,3]-sigmatropic rearrangement upon warming to room temperature. After an acidic work-up and treatment of the crude carboxylic acids with trimethylsilyldiazomethane, the resulting α-alkoxy methyl esters



Scheme 19: Formation of alkylidene[(*N*-trifluoroacetylamino)cyclopropanes] **51**–**54**.

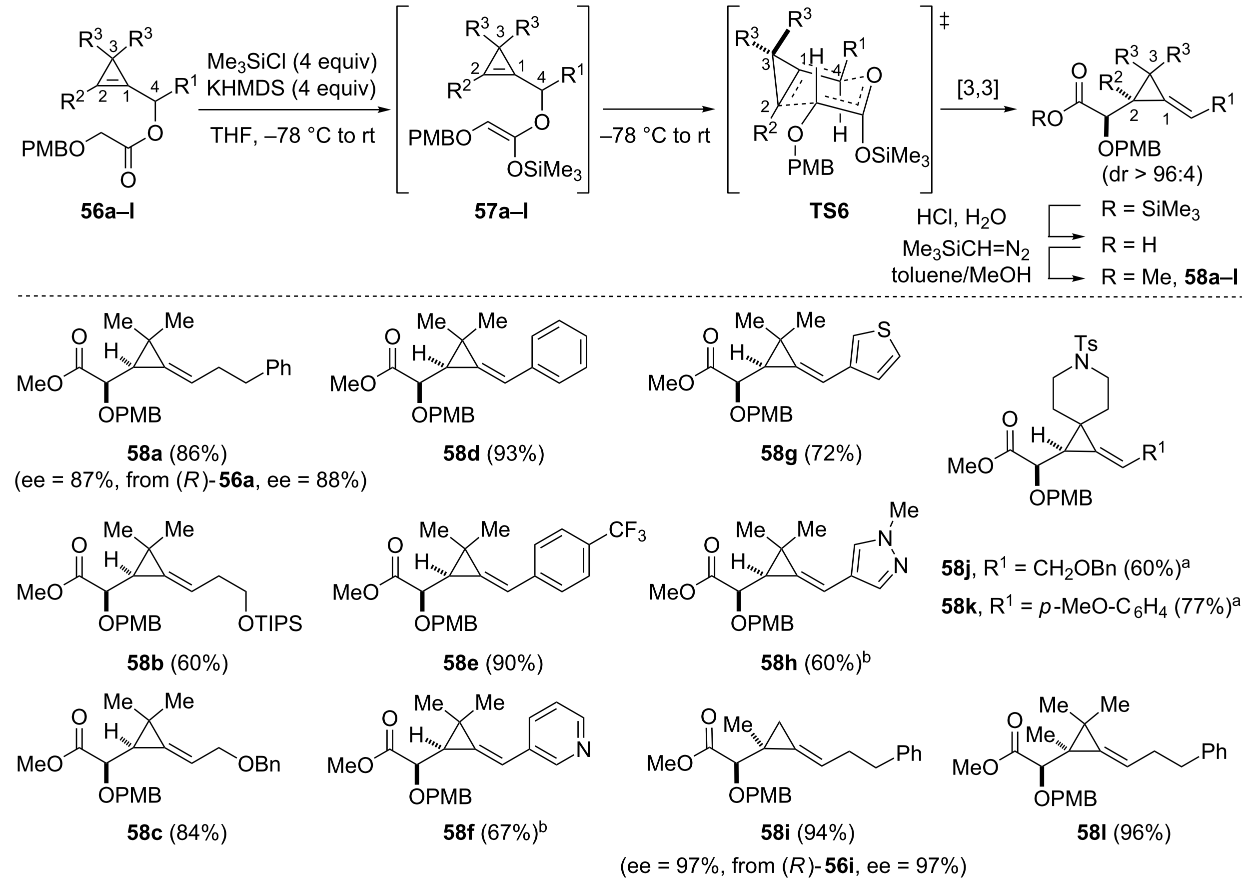


conditions	55/55'	yield
Pd(10%)/C (5 mol %) MeOH, rt, 2 h	92:8	97%
 (6 mol %) CH₂Cl₂, rt, 16 h	10:90	92%

Scheme 20: Diastereoselective hydrogenation of alkylidenecyclopropane **51**.

58a–**l**, incorporating an alkylidenecyclopropane moiety, were obtained as single detectable diastereomers [61]. As in the previously discussed [3,3]-sigmatropic rearrangements, the observed stereochemical outcome was in agreement with a six-membered chair-like transition state model **TS6** in which the substituent at the α-position of the oxygen atom (C4) preferentially occupies a pseudo-equatorial position. The scope of the reaction is rather broad as the substituent at C4 can be an alkyl chain, possibly incorporating a protected alcohol, as illustrated with the formation of alkylidenecyclopropanes **58a** (86%), **58b** (60%) and **58c** (84%). It is worth mentioning that despite the use of a strong base (KHMDS) and the acidity of the "vinylic" protons of cyclopropenes which is comparable to that of a terminal alkyne [62], cyclopropenylcarbinyl glycolates devoid of substituents at C2 were viable substrates. The sequence allowed access to benzylidenecyclopropane **58d** (93%) and to (arylmethylene)cyclopropane **58e** in excellent yield (90%), despite the presence of the electron-withdrawing trifluoromethyl substituent at the *para*-position of the aromatic ring. Some heteroaromatic groups were also tolerated at C4, as shown with the synthesis of (heteroarylmethylene) cyclopropanes **58f**–**h** (60–72%). The *gem*-dimethyl substitution at C3 which was common to the previous cyclopropenylcarbinyl glycolates **56a**–**h**, could be suppressed and the corresponding alkylidenecyclopropane **58i** was produced in excellent yield (94%). More sterically hindered substituents were tolerated at C3, as illustrated with the isolation of the spirocyclic compounds **58j** (60%) and **58k** (77%), and alkylidenecyclopropane **58l** possessing a fully substituted three-membered ring was also formed in excellent yield (96%). That the Ireland–Claisen rearrangement of cyclopropenylcarbinyl glycolates proceeded with chirality transfer was also verified in the case of alkylidenecyclopropanes **58a** and **58i** which were obtained with optical purities (ee = 87% and ee = 97%, respectively) identical to those of the corresponding enantioenriched precursors (*R*)-**56a** and (*R*)-**56i** (Scheme 21) [61].

The addition of a cyclopropenyllithium to an aldehyde is arguably the most widely used method to access cyclopropenylcarbinols but Gevorgyan et al. disclosed an interesting organocatalytic route to cyclopropenylcarbinols possessing *gem*-diester substitution at C3 [63]. As illustrated with the

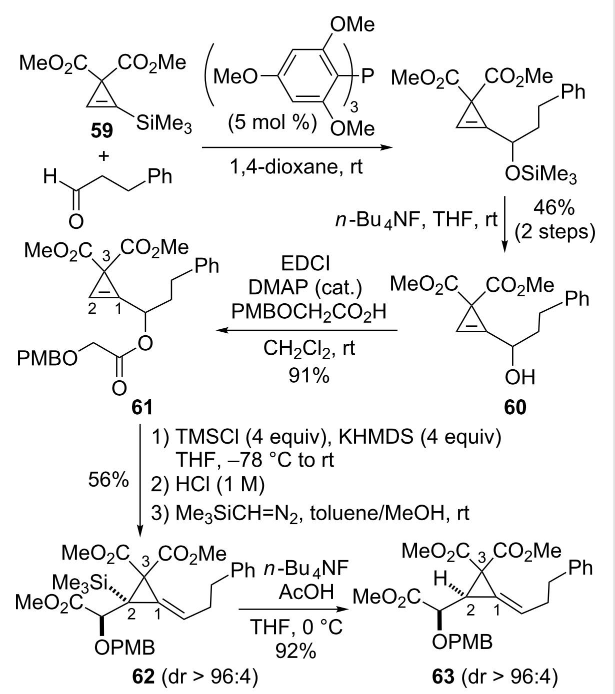


[a]overall yield from the corresponding cyclopropenylcarbinol;
[b]enolization carried out with KHMDS (2 equiv) and Me_3SiCl (2 equiv)

Scheme 21: Ireland–Claisen rearrangement of cyclopropenylcarbinyl glycolates **56a–l**.

preparation of alcohol **60**, the strategy relies on a sila-Morita–Baylis–Hillman reaction between cyclopropenylsilane **59** and 3-phenylpropanal catalyzed by electron-rich tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) [63]. After desilylation, cyclopropenylcarbinol **60** was converted into glycolate **61** under standard conditions and the latter ester was engaged in the Ireland–Claisen rearrangement. Because the *gem*-diester substitution at C3 increased the acidity of the proton at C2 in substrate **61** [64], silylation of that position took place under the reaction conditions prior to the Ireland–Claisen rearrangement which eventually produced alkylidenecyclopropane **62** (56%) with high diastereoselectivity. The trimethylsilyl substituent at C2 could then be easily removed by treatment of **62** with tetrabutylammonium fluoride under buffered conditions (AcOH, THF, 0 °C) to afford alkylidenecyclopropane **63** (92%, Scheme 22) [61].

The Ireland–Claisen rearrangement was then extended to a challenging class of cyclopropylcarbinyl glycolates possessing *gem*-difluoro substitution at C3 [65]. *Gem*-difluorocyclopropenes are accessible by difluorocyclopropenation of alkynes with difluorocarbene but these compounds display poor stability in most cases and readily undergo hydrolysis into cyclopropenones which possess an aromatic character [66,67]. *Gem*-difluorocyclopropenylcarbinyl glycolates **65a**–**n** were prepared by slow addition of an excess of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) [68] to a solution of propargyl glycolates **64a**–**n** containing NaF in diglyme at 120 °C. Difluorocyclopropene **65a** could be purified by flash chromatography on silica gel and was isolated in 86% yield but this compound rapidly underwent decomposition upon storage. The instability of glycolates **65a**–**n** was a critical issue which was solved by carrying those intermediate compounds directly in the sigmatropic rearrangement. By-products arising from the difluorocyclopropenation reaction (CO_2, SO_2 and Me_3SiF) were simply removed by argon sparging of the reaction mixture and the Ireland–Claisen rearrangement was then triggered by addition of Me_3SiCl (4 equiv) and KHMDS (4 equiv), (THF, −78 °C to rt). Subsequent hydrolysis and treatment with trimethylsilyldiazomethane afforded the corresponding α-alkoxy methyl esters **66a**–**h**, and **66k**–**n**



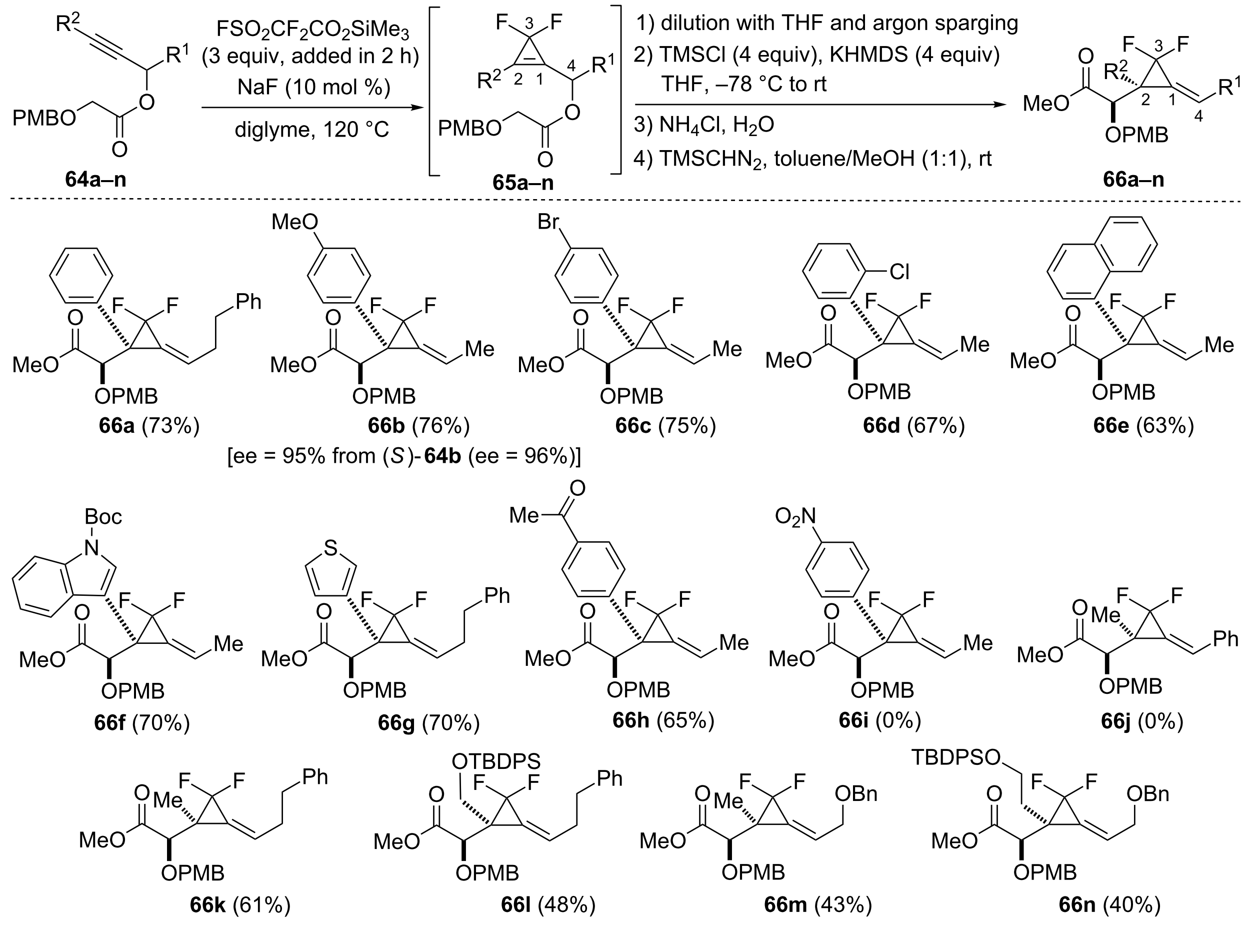
Scheme 22: Synthesis and Ireland–Claisen rearrangement of glycolate **61** possessing *gem*-diester substitution at C3.

possessing a 3,3-difluoroalkylidenecyclopropane scaffold. This two-step difluorocyclopropenation–Ireland–Claisen rearrangement sequence was applied to propargyl glycolates **64a**–**e** possessing a phenyl, a *p*-methoxyphenyl, a *p*-bromophenyl, an *o*-chlorophenyl or a 1-naphthyl substituent at the acetylenic position, as illustrated with the formation of compounds **66a**–**e** (63–76%, two steps from the corresponding propargylic glycolates). Not surprisingly, chirality transfer (from C4 to C2) also occurred in the Ireland–Claisen rearrangement, as demonstrated by the formation of (−)-**66b** (ee = 95%) from optically enriched (*S*)-**64b** (ee = 96%). Heteroaromatic groups (indol-3-yl and 3-thienyl) were tolerated at the acetylenic position and the corresponding glycolates **64f** and **64g** led to compounds **66f** and **66g** in 70% yield. A *p*-acetylphenyl group was compatible as shown with the isolation of alkylidenecyclopropane **66h** (65%) but it should be noted that the electron-withdrawing methyl ketone was converted to a trimethylsilyl enol ether upon treatment with KHMDS/Me_3SiCl. By contrast, an electron-withdrawing *p*-nitrophenyl group was not tolerated because the intermediate cyclopropene **65i** underwent decomposition under the reaction conditions of the Ireland–Claisen rearrangement, presumably because of competitive deprotonation at C4. A phenyl substituent was incompatible at C4 as the corresponding substrate **65j** decomposed upon treatment with KHMDS/Me_3SiCl. This was explained by a competitive abstraction of the hydrogen at C4 by the base thereby resulting in side reactions. However, various alkyl substituents could be present at the propargylic position in glycolates **64k**–**n** which afforded the corresponding rearranged compounds **66k**–**n** in moderate yields (40–61%, Scheme 23) [65].

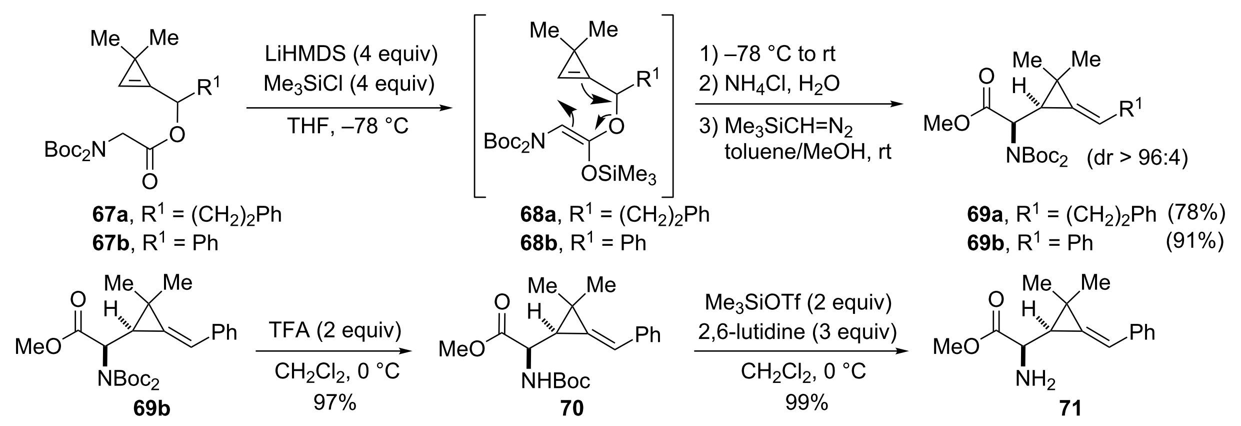
With the goal of accessing α-amino acid derivatives incorporating an alkylidenecyclopropane, the Ireland–Claisen rearrangement of *N*,*N*-diBoc glycinates **67a** and **67b** was explored. The reaction conditions were essentially the same as those described previously with glycolates **56a**–**l** except that LiHMDS was used as the base in the enolization step [69]. The (*Z*)-silyl ketene acetals **68a** and **68b** were generated, in agreement with previous results disclosed by Carbery et al. with allylic *N*,*N*-diBoc glycinates [69], and underwent a Ireland–Claisen rearrangement to afford *N*,*N*-diBoc α-amino esters **69a** (78%) and **69b** (91%) in good yields and with high diastereoselectivity [61]. Although cleavage of the two Boc groups could not be achieved cleanly upon exposure of **69b** to a large excess of trifluoroacetic acid, this operation could be accomplished in a sequential manner by addition of trifluoroacetic acid (2 equiv, CH_2Cl_2, 0 °C) and then by treatment of the resulting *N*-Boc carbamate **70** (97%) with trimethylsilyl triflate in the presence of 2,6-lutidine to generate α-amino ester **71** (99%, Scheme 24) [61].

Alkylidenecyclopropanes resulting from the Ireland–Claisen rearrangement of cyclopropenylcarbinyl glycolates and glycinates can serve as useful precursors of other classes of functionalized cyclopropanes. As shown previously with alkylidene(aminocyclopropane) derivatives, diastereoselective hydrogenation reactions of alkylidenecyclopropanes possessing a single substituent at C2 can be carried out with complementary face selectivities, depending on the conditions and substrates. Thus, the hydrogenation of **58a** catalyzed by Rh/C occurred on the less hindered face of the alkene and gave rise to cyclopropyl α-alkoxy ester **72** as a single detectable diastereomer. When Pd/C was used as the catalyst, cleavage of the PMB group took place concomitantly and the α-hydroxy ester **73** arising from addition of hydrogen on the less-hindered face of the olefin was obtained predominantly (**73**/**73’** = 90:10) albeit with lower diastereocontrol compared to the protected alcohol **58a**. Cleavage of the PMB ether in **58a** was achieved purposely with DDQ so that a hydroxy-directed hydrogenation of the resulting α-hydroxy ester **74** could be carried out in the presence of Crabtree’s catalyst [58], thereby allowing access to cyclopropylcarbinol **73’** with high diastereoselectivity (**73’**/**73** = 97:3, Scheme 25).

By taking advantage of the directing effect of a hydroxy group, diastereoselective hydrogenations of alkylidenecyclopropanes possessing two substituents at C2 could be achieved. As illustrated for alkylidene(*gem*-difluorocyclopropane) **66a**, cleavage

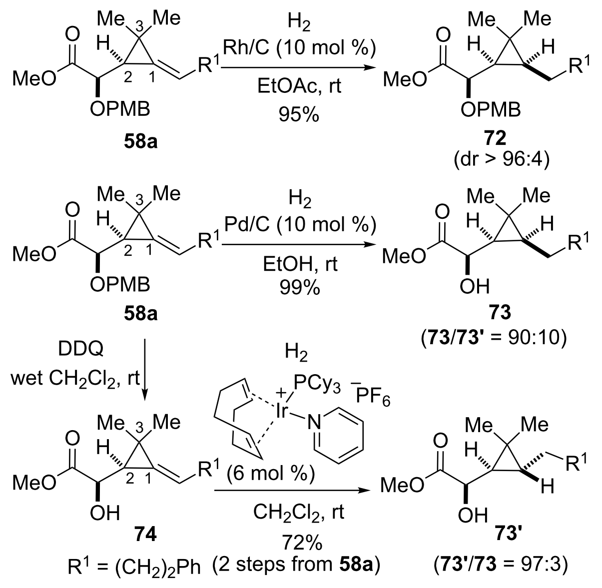


Scheme 23: Synthesis of alkylidene(*gem*-difluorocyclopropanes) **66a**–**h**, and **66k**–**n** from propargyl glycolates **64a**–**n**.

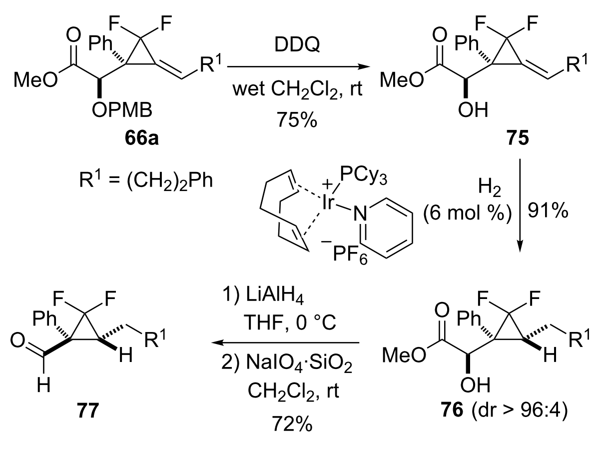


Scheme 24: Ireland–Claisen rearrangement of *N*,*N*-diBoc glycinates **67a** and **67b**.

of the PMB group and subsequent hydrogenation of the resulting α-hydroxy ester **75** (75%) in the presence of Crabtree's catalyst delivered the *gem*-difluorocyclopropane **76** (91%) as a single diastereomer. The reduction of ester **76** with $LiAlH_4$ and oxidative cleavage of the resulting 1,2-diol with $NaIO_4$ delivered the highly substituted *gem*-difluorocyclopropanecarboxaldehyde **77** (72%) possessing a quaternary stereocenter (Scheme 26) [65].



Scheme 25: Diastereoselective hydrogenation of alkylidenecyclopropanes **58a** and **74**.

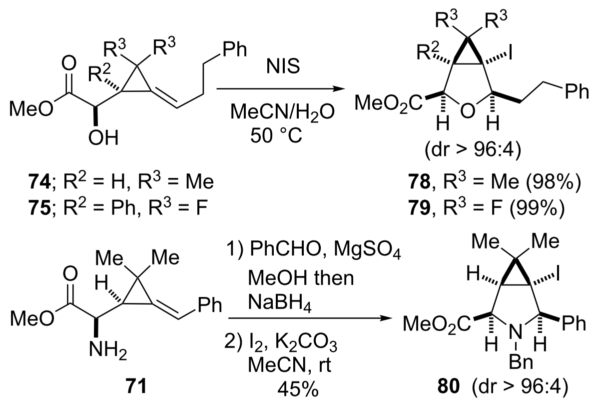


Scheme 26: Synthesis of functionalized *gem*-difluorocyclopropanes **76** and **77** from alkylidenecyclopropane **66a**.

Other examples of post-functionalization involve iodolactonization reactions which were applied to α-hydroxy esters **74** and **75** using *N*-iodosuccinimide (MeCN/H_2O, 50 °C) [70], or to the *N*-benzylamine generated from α-amino ester **71** (by reductive animation with benzaldehyde) in the presence of I_2 and K_2CO_3 (MeCN, rt) [71]. These iodocyclizations led to the oxabicyclic compounds **78** (98%) and **79** (99%), and to the azabicyclic product **80** (45%), respectively, with high diastereoselectivities (Scheme 27) [61,65].

Conclusion

In recent years, [2,3]- and [3,3]-sigmatropic rearrangements of cyclopropenylcarbinol derivatives have emerged as useful tools for the stereoselective synthesis of a wide variety of alkylidenecyclopropanes, substituted by heteroatoms (P, O, N, F) and/or incorporating valuable functional groups (α-alkoxy or α-amino acid derivatives) which are potentially useful for further functionalization. The reactivity of heterosubstituted/ functionalized alkylidenecyclopropanes arising from those sigmatropic rearrangements, which are not easily accessible by other strategies, has only been sparingly investigated to date but the results summarized in this short review, in conjunction with the very rich chemistry of alkylidenecyclopropanes, may stimulate further investigations in this particular area.



Scheme 27: Access to oxa- and azabicyclic compounds **78**–**80**.

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Reusable and highly enantioselective water-soluble Ru(II)-*Amm*-Pheox catalyst for intramolecular cyclopropanation of diazo compounds

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Letter

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Abstract

A reusable and highly enantioselective catalyst for the intramolecular cyclopropanation of various diazo ester and Weinreb amide derivatives was developed. The reactions catalyzed by a water-soluble Ru(II)-*Amm*-Pheox catalyst proceeded smoothly at room temperature, affording the corresponding bicyclic cyclopropane ring-fused lactones and lactams in high yields (up to 99%) with excellent enantioselectivities (up to 99% ee). After screening of various catalysts, the Ru(II)-*Amm*-Pheox complex having an ammonium group proved to be crucial for the intramolecular cyclopropanation reaction in a water/ether biphasic medium. The water-soluble catalyst could be reused at least six times with little loss in yield and enantioselectivity.

Introduction

Water-soluble transition metal complexes have been attracting increasing interest for catalytic applications because of their many advantages such as simple product separation, low cost, safety, and environmentally friendly processing [1-13]. Thus, the study of organic reactions in water is an important area of research [14-21]. Nevertheless, only a few catalytic cyclopropanation reactions were carried out in aqueous media [22-28]. In our previous work, we developed Ru(II)-Pheox catalysts for the intramolecular cyclopropanation of *trans*-allylic diazoacetates in a biphasic medium [29-31]. During the course of our continuous study on the development of a series of Ru(II)-Pheox catalysts, we found the introduction of an ammonium group on the aromatic ring connected with Ru gave high solubility in the water phase compared to a normal Ru(II)-Pheox complex as shown below (Figure 1) [32,33].

Then, Ru(II)-*Amm*-Pheox (**cat. 2**) was found to be soluble in water but not in diethyl ether. This fact prompted us to explore the asymmetric intramolecular cyclopropanation of a variety of diazo compounds such as diazoacetates and diazoacetamides in a biphasic medium. Diazoacetates were tested in our catalytic system because they are widely used for intramolecular cyclopropanation reactions and also the resulted lactones are widely distributed in nature and have excellent biological activity, including strong antibiotic, antihelmetic, antifungal, antitumor, antiviral and anti-inflammatory, which make them interesting lead structures for new drugs [34]. That is why a great deal of attention has been paid to the synthesis of the lactone ring [35,36]. Diazoacetamides, in particular, diazo Weireb amides were tested in our catalytic system because the resulting cyclopropane products can be easily converted into the corresponding aldehydes, ketones, and alcohols [37-48].

Results and Discussion

Asymmetric cyclopropanation using various diazo compounds with Ru(II)-*Amm*-Pheox

Several diazoacetates and diazoacetamides were tested for asymmetric intramolecular cyclopropanation reactions using Ru(II)-*Amm*-Pheox catalyst (**cat. 2**) in H_2O/ether biphasic medium as shown in Table 1. A diazo compound derived from allyl diazoacetate could be cyclopropanated affording the corresponding lactone with low yield and good enantioselectivity (Table 1, entry 1).

In case of the diazo compound derived from cinnamyl diazoacetate the corresponding lactone was obtained in high yield with high enantioselectivity (Table 1, entry 2). A spirocyclopropanation product and a functionalized cyclopropane were obtained with high enantioselectivities (Table 1, entries 3 and 4). *N*-Benzyl-diazoacetamide underwent the asymmetric cyclopropanation reaction affording the corresponding lactam in moderate yield and moderate enantioselectivity (Table 1, entry 5). Interestingly, Ru(II)-*Amm*-Pheox complex (**cat. 2**) catalyzes the asymmetric intramolecular cyclopropanation of diazo Weinreb amide (*N*-cinnamyl-2-diazo-*N*-methoxyacetamide) in a

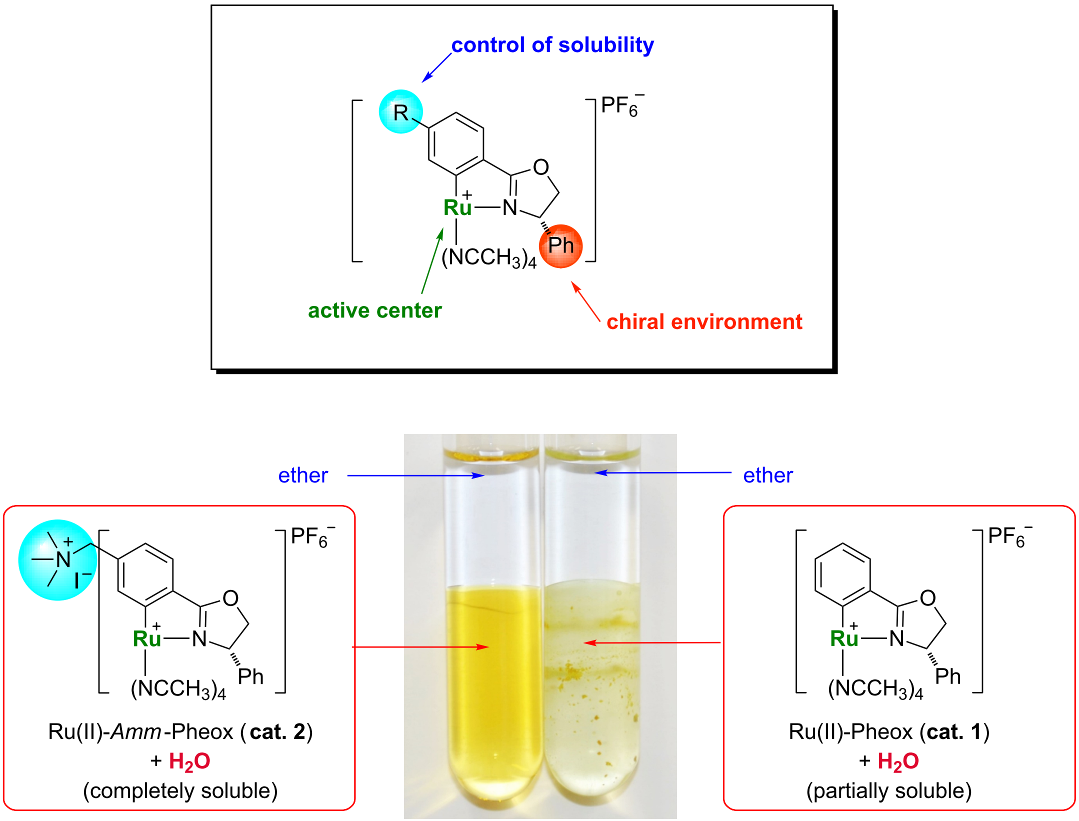
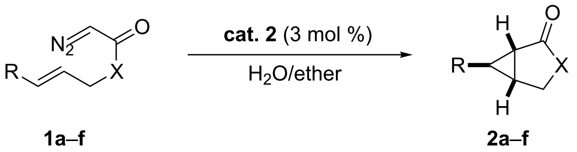
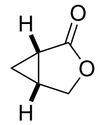
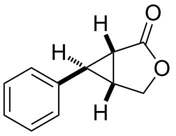
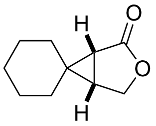
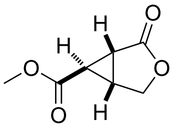
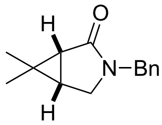
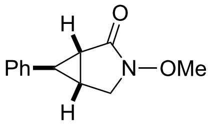


Figure 1: A comparison of the solubility of Ru(II)-Pheox (**cat. 1**) and Ru(II)-*Amm*-Pheox (**cat. 2**).

Table 1: Asymmetric intramolecular cyclopropanation using various substrates.[a]



1a–f **2a–f**

entry	product		yield [%][b]	ee [%][c]
1		**2a**	18	88
2		**2b**	93	93
3		**2c**	56	97
4		**2d**	38	96
5		**2e**	50	43
6		**2f**	99	99

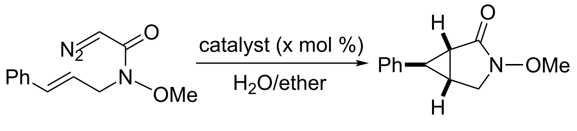
[a]Reaction conditions: 3 mol % of the catalyst was dissolved in water (1 mL) and a solution of the diazo compound in ether (1 mL) was added. The reaction was stirred until the reaction was finished at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

water/ether mixture, giving the corresponding lactam in high yield with high enantioselectivity (99% yield, 99% ee, Table 1, entry 6). These results encouraged us to explore the asymmetric intramolecular cyclopropanation of diazo Weinreb amides in a biphasic medium.

Asymmetric cyclopropanation using diazo Weinreb amide with Ru(II)-*Amm*-Pheox

Ru(II)-Pheox (**cat. 1**) was slightly soluble in water, and afforded only a 53% yield of product in 5 h (Table 2, entry 1). On the other hand, hydroxymethyl Ru(II)-Pheox (**cat. 3**), which is completely soluble in water, catalyzed the cyclization of **1f** affording chiral cyclopropylamide **2f** in 97% yield with a high enantioselectivity of 96% in 5 h (Table 2, entry 5) [49].

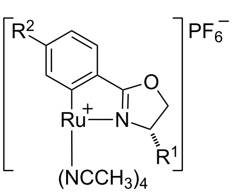
Table 2: Catalyst screening.[a]



1f **2f**

entry	catalyst	X mol [%]	yield [%][b]	ee [%][c]
1	**cat. 1**	3	53	91
2	**cat. 2**	3	99	99
3	**cat. 2**	2	99	99
4	**cat. 2**	1	99	99
5	**cat. 3**	3	97	96
6	**cat. 4**	5	41	95
7	**cat. 5**	5	37	88
8	**cat. 6**	5	61	96

[a]Reaction conditions: (3 mol %) of the catalyst was dissolved in water (1 mL) and a solution of diazo compound **1f** in ether was added. The reaction was stirred until the reaction was finished at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis.



cat. 1 $R^1 = C_6H_5$, $R^2 = H$
cat. 2 $R^1 = C_6H_5$, $R^2 = CH_2N^+(CH_3)_3I^-$
cat. 3 $R^1 = C_6H_5$, $R^2 = CH_2OH$
cat. 4 $R^1 = C_6H_5$, $R^2 = OCH_3$
cat. 5 R^1 = *t*-Bu, $R^2 = H$
cat. 6 $R^1 = C_6H_5$, $R^2 = CH_2Cl$

Next, the intramolecular cyclization of *trans*-allylic diazo Weinreb amide **1f** catalyzed by Ru(II)-*Amm*-Pheox (**cat. 2**) was examined in various solvents, as shown in Table S1 (Supporting Information File 1). Notably, the catalytic reaction proceeded in a variety of solvents, including aromatic, aliphatic, polar, non-polar, and halogenated solvents (Table S1, entries 1–8). In non-polar solvents (Table S1, entries 1−4), in which Ru(II)-*Amm*-Pheox (**cat. 2**) was poorly soluble, low yields and moderate enantioselectivities were obtained. On the other hand, the reaction in halogenated solvents proceeded in moderate yields with high enantioselectivities (Table S1, entries 5−7).

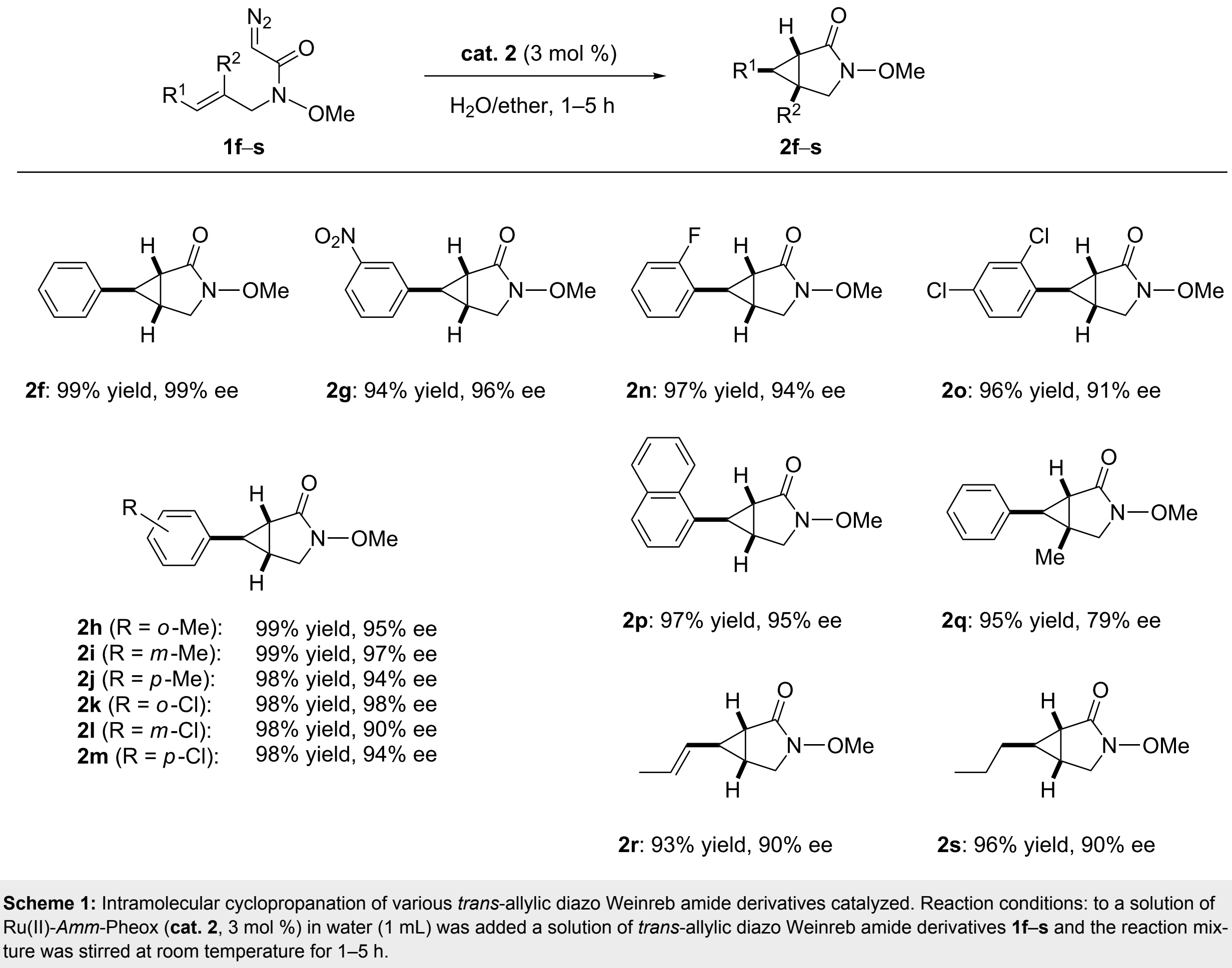
Among the solvents examined, water/diethyl ether was identified as the solvent system of choice because it afforded the desired product in the highest yield and enantioselectivity at room temperature.

With the optimal conditions in hand, various *trans*-allylic diazo Weinreb amide derivatives, prepared from the corresponding allylic alcohols by the Fukuyama method [50] were investigated as shown in Scheme 1. The catalytic system was applicable to a wide variety of substrates, which reacted smoothly to give the corresponding bicyclic products. For example, diazo Weinreb amide derivatives bearing electron-donating or electron-withdrawing groups at the *ortho*, *meta*, or *para* positions could be converted to the corresponding bicyclic products in excellent yields (up to 99%) and enantioselectivities (up to 98% ee, Scheme 1, **2g**–**m**).

A diazo compound with two chlorine substituents on the aromatic ring also underwent the cyclopropanation reaction affording the desired bicyclic compound in high yield and enantioselectivity (Scheme 1, **2o**). Remarkably, the derivative featuring the bulky naphthyl group instead of the phenyl group was also well tolerated and afforded the corresponding bicyclic product in excellent yield with high enantioselectivity (Scheme 1, **2p**).

Even the sterically demanding trisubstituted olefin-based allyl diazo Weinreb amide was found to be an effective substrate for the intramolecular cyclopropanation in this catalytic system, providing the corresponding product in high yield with moderate enantioselectivity (Scheme 1, **2q**). Similar results were obtained with *trans*-allylic diazo Weinreb amide derivatives bearing aliphatic substituents (Scheme 1, **2r** and **2s**). As shown in Figure S1 (Supporting Information File 1), the absolute configuration of product **2g** was determined to be (1*S*,5*R*,6*R*) by single-crystal X-ray diffraction analysis (Supporting Information File 1) [51]. Since the stereoselectivity of products depends on the *cis*/*trans* geometry of the reactants, other stereoisomers such as the (1*S*,5*R*,6*S*) product was not formed in this catalytic cyclopropanation. During the reaction process, no other stereoisomers were obtained.

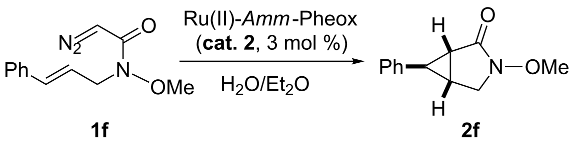
Next, the reusability of water-soluble catalyst **cat. 2** was examined. After separation of the ether layer, the aqueous phase was extracted with diethyl ether several times until no product remained. A new solution of *trans*-allylic diazo Weinreb amide **1f** in ether was added, and the mixture was stirred until completion of the reaction. Interestingly, Ru(II)-*Amm*-Pheox catalyst (**cat. 2**) could be reused at least six times with little loss of reac-



Scheme 1: Intramolecular cyclopropanation of various *trans*-allylic diazo Weinreb amide derivatives catalyzed. Reaction conditions: to a solution of Ru(II)-*Amm*-Pheox (**cat. 2**, 3 mol %) in water (1 mL) was added a solution of *trans*-allylic diazo Weinreb amide derivatives **1f–s** and the reaction mixture was stirred at room temperature for 1–5 h.

tivity and enantioselectivity (Table 3). It is expected that the decreasing activity depended on the catalyst leakage during the work-up.

Table 3: Reusability of Ru(II)-*Amm*-Pheox (**cat. 2**).[a]



entry	run	time [h]	yield [%][b]	ee [%][c]
1	1	50 min	99	99
2	2	2	97	99
3	3	16	95	97
4	4	24	94	95
5	5	24	96	92
6	6	36	93	90

[a]Reaction conditions: After the use of the catalyst in the first run, the ether layer was separated and the aqueous layer was washed 3 times with ether. A new amount of *trans*-allylic diazo Weinreb amide **1f** dissolved in Et_2O (2.0 mL) was added and the reaction mixture was stirred until the end of the reaction. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Synthetic transformations of **2d** and **2f**

In order to demonstrate the advantages of products, further synthetic transformations of the cyclopropane products were investigated. A ring opening and direct amidation of the chiral cyclopropane-fused γ-lacton **2d** using DIBAL-H with benzylamine afforded the desired product **3** in 44% yield with 95% ee (Scheme 2, reaction 1) [52]. We then investigated the arylation of chiral cyclopropylamide **2f** with Grignard reagent PhMgBr (Scheme 2, reaction 2). Only 37% of cyclopropyl ketone **4** were observed at room temperature with unaltered enantioselectivity (98% ee).

Conclusion

In conclusion, we have developed an efficient water-soluble Ru(II)-*Amm*-Pheox (**cat. 2**) for the intramolecular cyclopropanation of *trans*-allylic diazo Weinreb amide derivatives. The water-soluble catalyst provided excellent yields of the bicyclic products (up to 99%) with excellent enantioselectivities (up to 99% ee). The easy separation of the ether layer containing the cyclopropane product allowed for simple reuse of the catalyst in the water phase for at least six times with little loss of reactivity and enantioselectivity.

Supporting Information

Supporting Information File 1

Full experimental details and analytical data (reaction method, ^{1}H NMR, ^{13}C NMR, HPLC, X-ray analysis).
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-31-S1.pdf]

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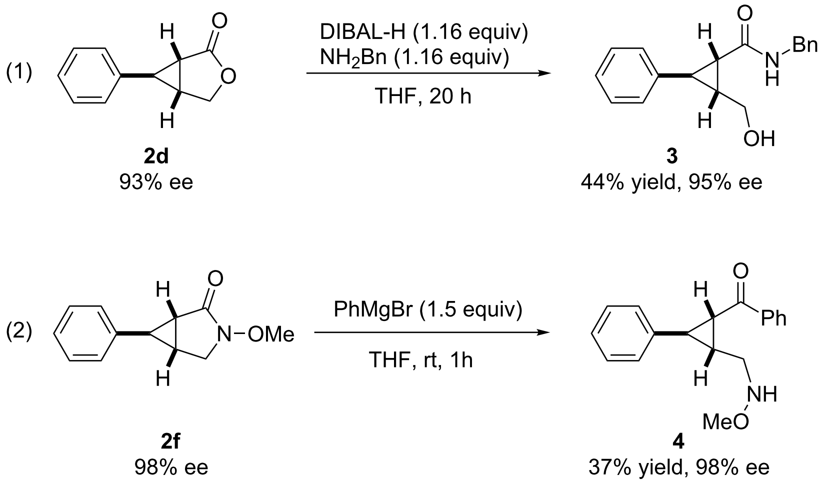

Scheme 2: Synthetic transformation of cyclopropane products **2d** and **2f**.

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Dirhodium(II)-catalyzed [3 + 2] cycloaddition of *N*-arylaminocyclopropane with alkyne derivatives

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Full Research Paper

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[3 + 2]; alkyne; cycloaddition; cyclopropanes; dirhodium catalysis; *N*-arylaminocyclopropanes

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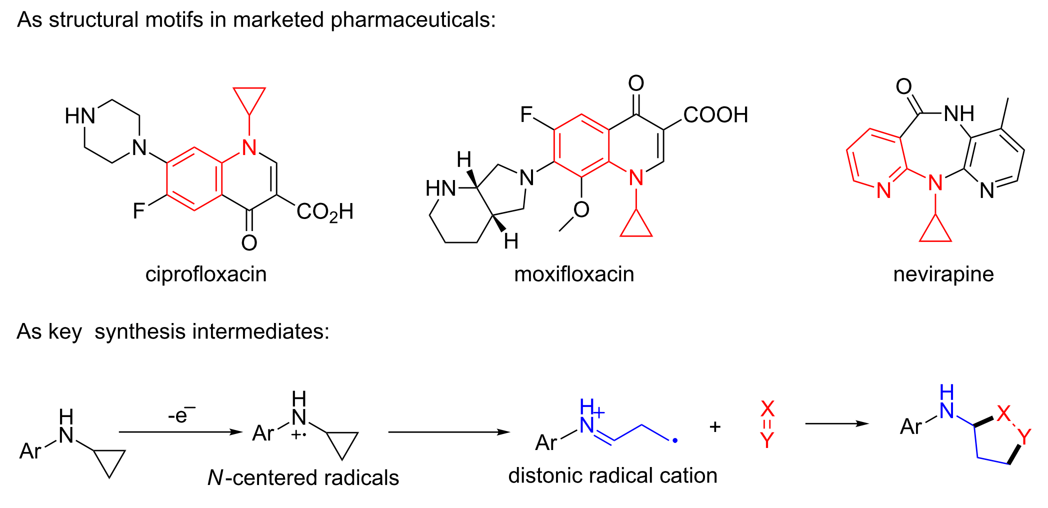
Abstract

Dirhodium(II) complex-catalyzed [3 + 2] reactions between *N*-arylaminocyclopropanes and alkyne derivatives are described. The cycloaddition products proved to be versatile synthetic intermediates. *trans*-Cyclic β-amino acids and derivatives thereof can be conveniently synthesized using this cycloaddition protocol.

Introduction

N-Arylaminocyclopropanes **1** are important structural motifs for pharmaceuticals and are found especially in marketed fluoroquinolone antibiotics [1], such as ciprofloxacin and moxifloxacin (Scheme 1), and reverse transcriptase inhibitors [2], such as nevirapine. Meanwhile, since **1** contains a three-membered ring with high tension [3-6] and a nitrogen prone to single-electron oxidation, ring opening readily occurs followed by *N*-centered radical formation. The generated distonic radical cation can be further trapped by an alkene, alkyne, or triplet oxygen to initiate radical cyclization (Scheme 1) [7-15]. Thus, as key synthons, this class of molecules may play an important role in organic synthesis during construction of a series of aminocyclic compounds. In fact, the synthesis of **1** has always been a challenge [16,17]. Only recently an efficient synthesis method by arylation of cyclopropylamine has been developed and documented by Colacot et al. [16] and Stradiotto et al. [17], which has provided opportunities for further development of cycloaddition chemistry based on compound **1**. Zheng et al. [7] first reported on the [3 + 2] cycloaddition reaction of **1** with an alkene or alkyne mediated by visible light by the aid of the photocatalyst $[Ru(bpz)_3](PF_6)_2$. Our group reported the metal catalyst itself, particularly the dinuclear rhodium complex (Rh_2(II,II)), that efficiently catalyzes the ring opening of **1** to achieve cycloaddition with alkene substrates under an argon atmosphere [18]. During the reaction, no metal valence changes were observed. We proposed that Rh_2(II,II) may coordinate



Scheme 1: Applications of *N*-arylaminocyclopropanes.

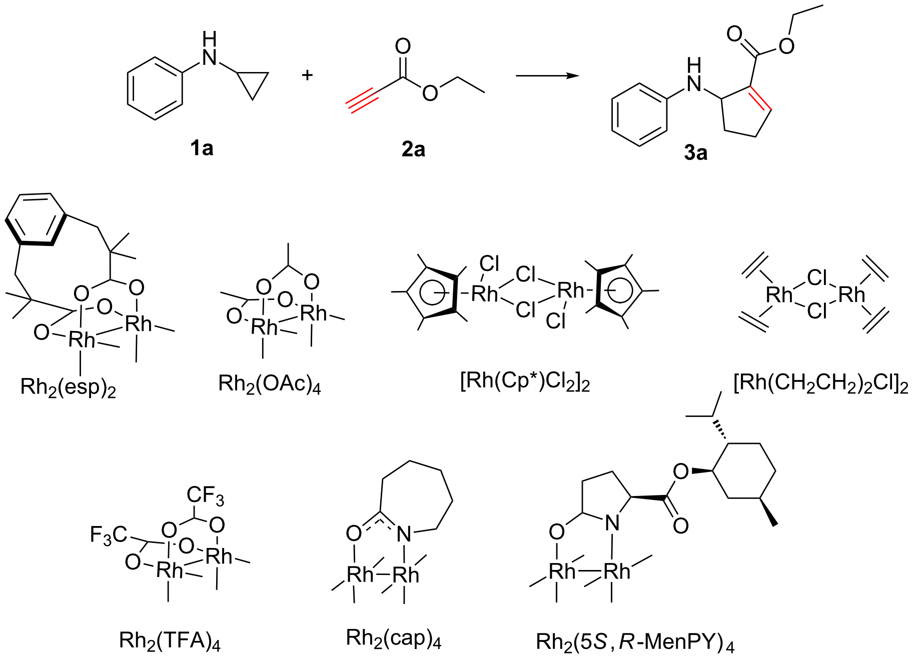
with the nitrogen in **1** to decrease the bond dissociation energy of N–H bonds, which may be beneficial to N-centered radical formation. However, due to the characteristics of the radical reaction, the resulting cycloaddition product mixtures have a low diastereoisomeric ratio, which increases the difficulty of separation and limits applications. In view of this, we applied alkyne derivatives as cycloaddition partners to make the developed methodology more applicable, as well as to investigate the possibility of chiral ring construction.

Results and Discussion

Initially, phenylcyclopropylamine (**1a**) and ethyl propiolate (**2a**) were selected as substrates to study the cycloaddition in dichloromethane (DCM) with 1 mol % starting catalyst loading under the previously reported conditions [18]. In the absence of a catalyst, no cycloaddition product **3a** formed (Table 1, entry 1). We then studied the effect of common rhodium catalysts on the reactions. When 1 mol % Rh(I) catalyst $[Rh(CH_2CH_2)_2Cl]_2$ was used (Table 1, entry 2), product **3a** was not detected. The commonly used Rh(III) catalyst $[Rh(Cp^*)Cl_2]_2$ lead to a 72% yield of product **3a** (Table 1, entry 3). Next, the representative dirhodium(II) carboxylate such as $Rh_2(OAc)_4$, $Rh_2(TFA)_4$, $Rh_2(esp)_2$ and dirhodium(II) carboxamidate catalysts such as $Rh_2(cap)_4$, Rh_2(5*S*, *R*-MenPY)$_4$ were evaluated in the reaction. $Rh_2(OAc)_4$ created **3a** with a yield of 45% (Table 1, entry 4) and $Rh_2(TFA)_4$ improved the yield of **3a** to 52% (Table 1, entry 5). With the chelating catalyst $Rh_2(esp)_2$, the yield further increased to 68% (Table 1, entry 6). Although the carboxamidate type $Rh_2(cap)_4$ resulted in a lower yield (Table 1, entry 7), the yield raised to 61% when Rh_2(5*S*, *R*-MenPY)$_4$ [19,20] was applied as the catalyst (Table 1, entry 8). Next, 0.1 mol % catalytic loading was tested in the reactions to investigate the efficiency of the catalysts. Compared to the 1 mol % catalyst loading, the yield of **3a** dropped to 39 and 44% when $Rh_2(esp)_2$ and $[Rh(Cp^*)Cl_2]_2$, respectively, were used (Table 1, entries 9, 10), and kept practically consistent with Rh_2(5*S*, *R*-MenPY)$_4$ (Table 1, entry 11). These results indicate that the catalytic efficiency of Rh_2(5*S*, *R*-MenPY)$_4$ was the best of all the screened catalysts. Further solvent screening studies found the yields of **3a** obtained in non-coordinating solvents, such as DCM, hexane, toluene, and 1,2-dichloroethane (DCE), and weak coordinating solvents, such as 1,2-dimethoxyethane (DME), were similar (Table 1, entries 11–15). DCE was the best solvent, leading to a 67% yield of **3a**. Due to axial coordination of dirhodium(II) for a strong coordination solvent, the yield of the resulting cycloaddition product in *N*,*N*-dimethylformamide decreased to only 33% (Table 1, entry 16). Regrettably, though Rh_2(5*S*,*R*-MenPY)$_4$ is a chiral catalyst, the obtained cycloaddition products are racemic.

According to previous reports [16], after a series of arylcyclopropylamines **1** with different substituents were synthesized, the scope of **1** was then explored and the results are shown in Table 2. The data suggest that the electronic effect on the aromatic ring of **1** influences the results of the reactions. Compound **1** with electron-donating groups, such as methoxy, *tert*-butyl, and methyl groups, all reacted smoothly to produce products with good yields (Table 2, entries 1–3). The cyclization of substrate **1** containing electron-withdrawing groups at the aromatic substituent proceeded slowly, producing considerably lower yields of the corresponding products. For instance, multiple-substituted compound **1** (with a 3,5-disubstitued trifluoromethyl **1f**) generated product **3f** with a yield of 36% (88% brsm) after 24 h (Table 2, entry 5), but 3,5-dimethyl compound

Table 1: Catalyst screening and optimization of reaction conditions[a].



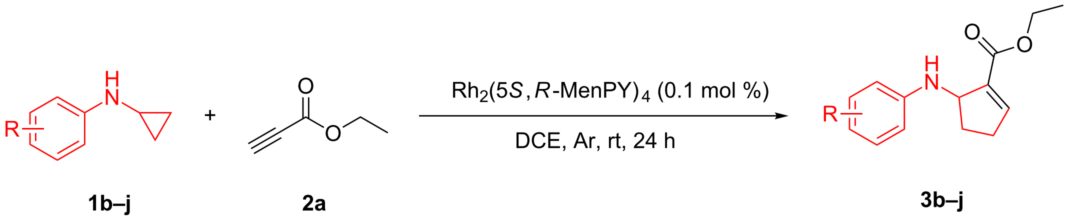
Entry	Conditions	Solvent	Yield[b] (%)
1	no catalyst	DCM	NR
2	$[Rh(CH_2CH_2)_2Cl]_2$	DCM	ND
3	$[Rh(Cp^*)Cl_2]_2$	DCM	72
4	$Rh_2(OAc)_4$	DCM	45
5	$Rh_2(TFA)_4$	DCM	52
6	$Rh_2(esp)_2$	DCM	68
7	$Rh_2(cap)_4$	DCM	40
8	$Rh_2(5S,R\text{-MenPY})_4$	DCM	61
9[c]	$Rh_2(esp)_2$	DCM	39
10[c]	$[Rh(Cp^*)Cl_2]_2$	DCM	44
11[c]	$Rh_2(5S,R\text{-MenPY})_4$	DCM	58
12[c]	$Rh_2(5S,R\text{-MenPY})_4$	DCE	67
13[c]	$Rh_2(5S,R\text{-MenPY})_4$	hexane	59
14[c]	$Rh_2(5S,R\text{-MenPY})_4$	toluene	59
15[c]	$Rh_2(5S,R\text{-MenPY})_4$	DME	60
16[c]	$Rh_2(5S,R\text{-MenPY})_4$	DMF	33

[a] Reaction conditions: **1a** (0.5 mmol, 0.2 M in degassed solvent), **2a** (2.5 mmol), catalyst (1 mol %) under argon at room temperature for 24 h unless otherwise noted. [b] Isolated yield. [c] 0.1 mol % of catalyst. esp = α,α,α’,α’-tetramethyl-1,3-benzenedipropionate, cap = caprolactamate, 5*S*,*R*-MenPY = (*S*)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-oxopyrrolidine-5-carboxylate, NR = no reaction, ND = not detected.

1d afforded the desired product **3d** with an excellent yield of 91% (Table 2, entry 3). We reasoned the electron-withdrawing groups on the arene increased the nitrogen–hydrogen bond dissociation energy ($BDE_{N–H}$) of compound **1** [21], decreasing the rate of ring opening. Substrates **1i**,**j** containing hindered substituents lead to low conversion of the substrates, producing only poor yields of products **3i**,**j** (Table 2, entries 8 and 9), which implied that steric hindrance greatly influenced the reactions.

Next, we surveyed the different alkyne substrates **2** for cycloaddition under optimized reaction conditions. The terminal alkynes with electron-withdrawing groups reacted smoothly to produce the desired products, while alkyl-substituted terminal aldehydes, such as pent-1-yne (**2b**, Table 3, entry 1), did not produce the cycloaddition product [22-24]. *tert*-Butyldimethylsilyl-protected propargyl alcohol **2c** had a greatly reduced reactivity (Table 3, entry 2) and the obtained yield was less than 10%. For aromatic terminal alkynes, moderate yields

Table 2: Substrate scope of *N*-arylaminocyclopropanes[a].



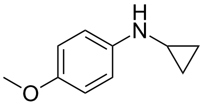
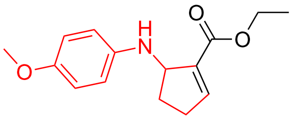
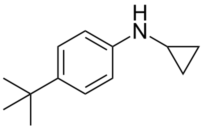
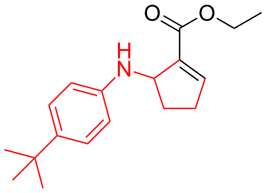
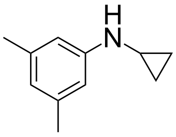
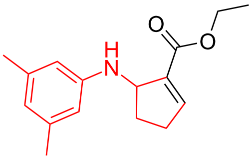
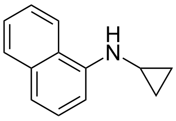
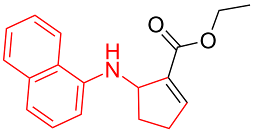
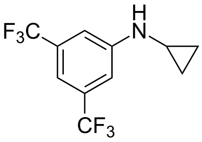
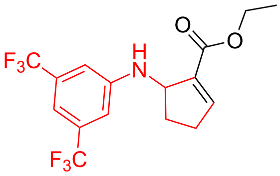
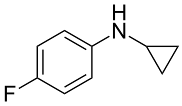
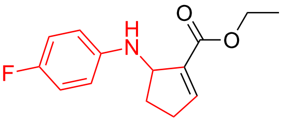
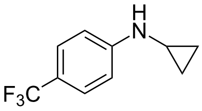
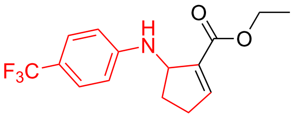
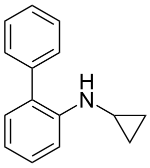
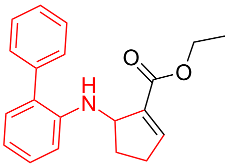
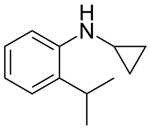
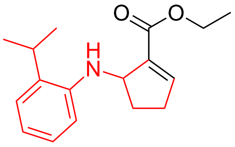
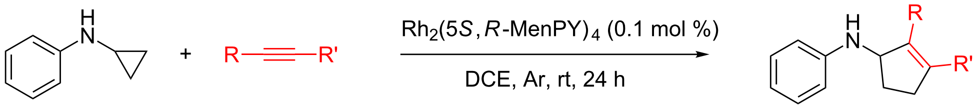
Entry	Substrate		Product		Yield[b]
1		**1b**		**3b**	59%
2		**1c**		**3c**	78%
3		**1d**		**3d**	91%
4		**1e**		**3e**	85%
5		**1f**		**3f**	36% (88% brsm)
6		**1g**		**3g**	67%
7		**1h**		**3h**	24% (52% brsm)
8		**1i**		**3i**	20% (67% brsm)

Table 2: Substrate scope of *N*-arylaminocyclopropanes[a]. (continued)

9		**1j**		**3j**	37% (65% brsm)

[a]Reaction conditions: **1b–j** (1 mmol, 0.2 M in degassed solvent), **2a** (5 mmol), catalyst (0.1 mol %) at room temperature for 24 h unless otherwise noted. [b]Isolated yield; brsm = based on recovered starting material.

Table 3: Substrate scope of alkyne derivatives[a].



1a **2b–l** **4b–l**

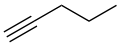
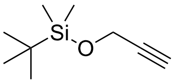
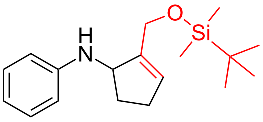
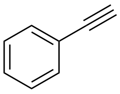
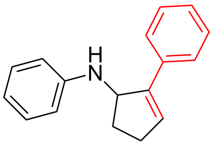
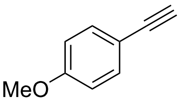
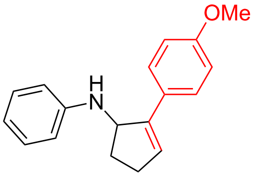
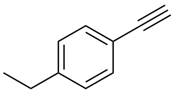
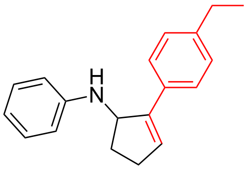
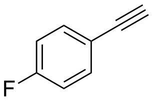
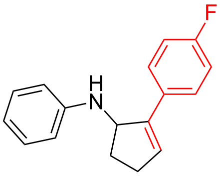
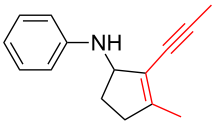
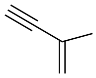
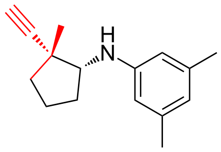
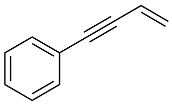
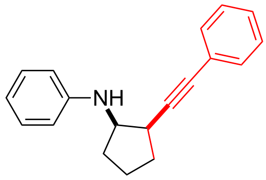
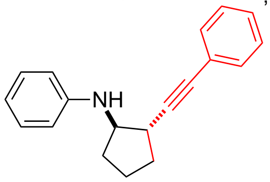
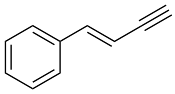
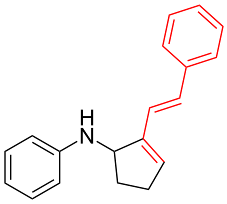
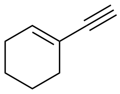
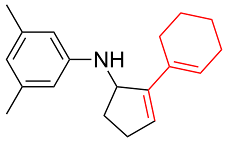
Entry	Substrate		Product		Yield[b](%)
1		**2b**	N.D.	**4b**	N.R.
2		**2c**		**4c**	<10
3		**2d**		**4d**	65
4		**2e**		**4e**	64
5		**2f**		**4f**	65
6		**2g**		**4g**	64
7	$Me-C\equiv C-C\equiv C-Me$	**2h**		**4h**	31

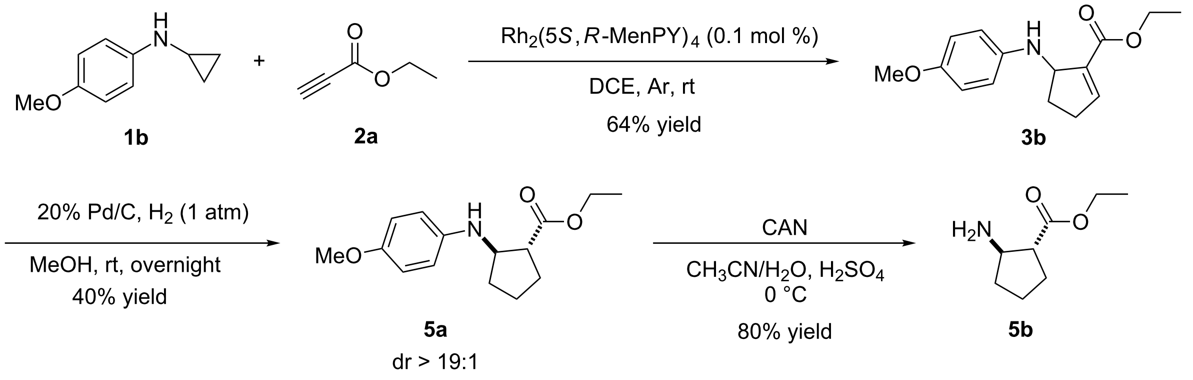
Table 3: Substrate scope of alkyne derivatives[a]. (continued)

8[c]		**2i**		**4i**[d,e]	45 (17:83)[f]
9		**2j**	 , 	**4j**	41 (30:70)[f]
10		**2k**		**4k**	44
11[c]		**2l**		**4l**[d]	40

[a]Reaction conditions: **1a** (1 mmol, 0.2 M in degassed solvent), **2b–l** (5 mmol), catalyst (0.1 mol %) at room temperature for 24 h unless otherwise noted. [b]Isolated yield. [c]*N*-Arylaminocyclopropane **1d** was used instead of **1a**. [d]Major isomer shown. [e]Isomer ratio 89:11. [f]Diastereoisomeric ratios (*cis/trans*) were determined by ^{1}H NMR spectroscopy of the crude products.

(Table 3, entries 3–6) were obtained regardless of the electron-donating or electron-withdrawing groups, indicating the electronic effect on the aromatic ring of **2** had little effect on the results of the reactions. Due to the decrease in the activity of the alkyne, the conjugated 2,4-hexadiyne (**2h**) produced a poor yield of only 31% (Table 3, entry 7). To study the chemical selectivity of the reaction, we examined conjugated alkyne substrates. For 2-methylbut-1-en-3-yne (**2i**) containing both terminal alkenes and alkynes, the activity of the olefin was greater than that of the alkyne, which favors alkene cycloaddition products with a ratio of 89:11. The observed selectivity of product **4i** is similar to that previously reported [11] (Table 3, entry 8), indicating the results of this type of reaction are mainly determined by the stability of the free radical intermediate during the reaction. Further investigation revealed cycloaddition preferentially proceeded with the terminal alkene or alkyne. Product **4j** was obtained with a 41% yield due to cycloaddition with an olefin group in **2j** (Table 3, entry 9). When **2k** was applied in the reaction, the addition product was obtained with a yield of 44% with the alkyne group being involved in the reaction (Table 3, entry 10). The reaction with **2l** mainly produced 1,3-diene product **4l** with a yield of 40% (Table 3, entry 11). In addition, we also examined some alkynes containing heterocycles, such as 3-ethynylpyridine and 2-ethynylthiophene. Because the heteroatoms were axially tightly coordinated to the dirhodium(II) catalyst, coordination of the cyclopropylamine with the dirhodium(II) catalyst was inhibited, resulting in no cycloaddition reaction occurring.

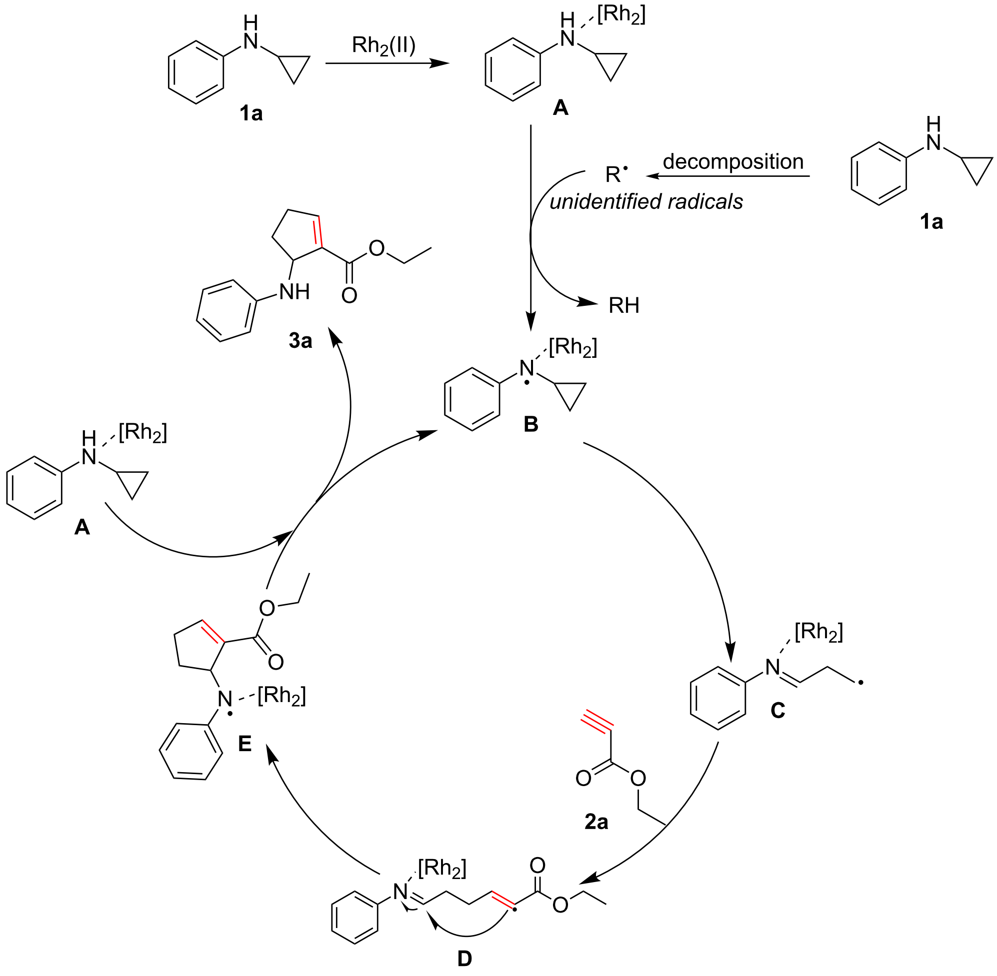
To explore the synthetic practicality of this transformation, racemic compound **3b** resulting from **1b** and **2a** was reduced using hydrogen and palladium on carbon (Scheme 2). It is interesting to note that only *trans*-**5a** was obtained and no *cis* product formed. After further removal of the *para*-methoxyphenyl (PMP) group using ammonium cerium nitrate (CAN), the cyclic β-amino acid ester **5b** was obtained with a yield of 80%. Cyclic β-amino acids and derivatives have good bioactivity and are widely used as key synthetic intermediates in biomedical



Scheme 2: Synthesis of *trans*-ethyl 2-aminocyclopentanecarboxylate.

research [25-29]. Thus, based on this cycloaddition protocol, a convenient strategy can be established to synthesize *trans*-cyclic β-amino acids.

The mechanism of the [3 + 2] cycloaddition reaction of **1a** and **2a** is similar to that previously reported [18] (Scheme 3). The distonic radical cation **C** resulting from cyclopropane ring



Scheme 3: Proposed mechanism.

opening reacts with alkyne substrate **2a** generating radical **D**. The intermediate radical **D** yielded **E** through intramolecular radical addition. After hydrogen atom transfer (HAT) from complex **A**, the desired product is obtained with regeneration of the N-centered radical **B**, which continues to catalyzing the reaction.

Conclusion

In conclusion, we report on the [3 + 2] cycloaddition reaction catalyzed by dirhodium(II) based on arylcyclopropylamine, which broadens the scope of this method to the alkynyl group. This study demonstrated that this cycloaddition method has potential synthetic practicality by providing a convenient way to synthesize *trans*-cyclic β-amino acid derivatives. Further application of this method with other cycloaddition partners and asymmetric synthesis of the chiral ring with the help of chiral auxiliaries are currently underway.

Experimental

General procedure for the [3 + 2] annulation of cyclopropylanilines: An oven-dried Schlenk tube equipped with a stirring bar was charged with $Rh_2(5S,R\text{-MenPY})_4$ (0.1 mol %), alkyne (5.0 mmol), and dry DCE (5 mL). The tube was degassed through three freeze–pump–thaw cycles. After evacuating and backfilling the tube with argon three times, cyclopropylamine (1 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours. After the reaction was complete, the mixture was concentrated and the residue was purified by flash chromatography to obtain the desired allylic amine.

Supporting Information

Supporting Information File 1

Experimental procedures, compound characterization, and NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-48-S1.pdf]

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Cyclopropene derivatives of aminosugars for metabolic glycoengineering

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Full Research Paper

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Abstract

Cyclopropenes have been proven valuable chemical reporter groups for metabolic glycoengineering (MGE). They readily react with tetrazines in an inverse electron-demand Diels–Alder (DAinv) reaction, a prime example of a bioorthogonal ligation reaction, allowing their visualization in biological systems. Here, we present a comparative study of six cyclopropene-modified hexosamine derivatives and their suitability for MGE. Three mannosamine derivatives in which the cyclopropene moiety is attached to the sugar by either an amide or a carbamate linkage and that differ by the presence or absence of a stabilizing methyl group at the double bond have been examined. We determined their DAinv reaction kinetics and their labeling intensities after metabolic incorporation. To determine the efficiencies by which the derivatives are metabolized to sialic acids, we synthesized and investigated the corresponding cyclopropane derivatives because cyclopropenes are not stable under the analysis conditions. From these experiments, it became obvious that *N*-(cycloprop-2-en-1-ylcarbonyl)-modified (Cp-modified) mannosamine has the highest metabolic acceptance. However, carbamate-linked *N*-(2-methylcycloprop-2-en-1-ylmethyloxycarbonyl)-modified (Cyoc-modified) mannosamine despite its lower metabolic acceptance results in the same cell-surface labeling intensity due to its superior reactivity in the DAinv reaction. Based on the high incorporation efficiency of the Cp derivative we synthesized and investigated two new Cp-modified glucosamine and galactosamine derivatives. Both compounds lead to comparable, distinct cell-surface staining after MGE. We further found that the amide-linked Cp-modified glucosamine derivative but not the Cyoc-modified glucosamine is metabolically converted to the corresponding sialic acid.

Introduction

Carbohydrates are an important class of biological molecules involved in many fundamental biological processes [1]. An important tool to visualize glycoconjugates in vitro and in vivo is metabolic glycoengineering (MGE) [2-4]. In this approach, cells are cultivated with an unnatural carbohydrate derivative carrying a chemical reporter group. After cellular uptake, the derivative is deacetylated, metabolized by the biosynthetic machinery and incorporated into glycoconjugates. The chemical reporter group can then be visualized using a bioorthogonal ligation reaction [5,6]. Mannosamine derivatives are of special interest because they are metabolized to sialic acids and then displayed as terminal structures on the cell surface [7]. Various carbohydrate derivatives with different reporter groups have been applied for MGE [2-4]. For example, azides and alkynes can be visualized by the Staudinger ligation [8] or the azide–alkyne cycloaddition, that can be performed either copper-catalyzed [9,10] or strain-promoted [11,12]. Another type of reporter group that has been proven to be a valuable tool are electron-rich or strained alkenes, that can be ligated through the inverse electron-demand Diels–Alder (DAinv) reaction with 1,2,4,5-tetrazines [13-17]. This reaction is advantageous since it is fast, irreversible, and does not require a toxic heavy metal catalyst. Different terminal alkenes that are connected to sugars by an amide [18], carbamate [19], or most recently a urea linkage [20] have been reported. Terminal alkenes are small which is beneficial for being accepted by the enzymes involved in glycan biosynthesis. However, they react only slowly in the DAinv reaction [20]. In contrast, ring-strained alkenes, such as norbornenes, have high DAinv reaction kinetics, but suffer from low incorporation efficiencies [21]. Cyclopropenes, that combine fast reaction kinetics and small size, turned out to be excellent reporters for application in MGE [22-27]. Three cyclopropene-derivatized mannosamine derivatives have been reported: Ac$_4$ManNCyc [23], Ac$_4$ManNCyoc [24,25], and Ac$_4$ManNCp [27] (Figure 1). They differ in their type of linkage (amide or carbamate) and the presence/absence of a stabilizing methyl group at the double bond. Kinetic studies using model compounds revealed that a carbamate-linked cyclopropene reacts two orders of magnitude faster than an amide-linked [28] and that removal of the stabilizing methyl group results in a 9-fold second-order rate constant [27]. However, these studies have been performed with different model compounds and under different reaction conditions and, therefore, are not comparable. Additionally, the influence of the sugar derivative on the reaction rate has not been taken into account. Ac$_4$ManNCyoc as well as Ac$_4$ManNCp were shown to give after MGE a better membrane staining than Ac$_4$ManNCyc [25,27]. A direct comparison of Ac$_4$ManNCyoc and Ac$_4$ManNCp in one biological experiment, however, is still unexplored.

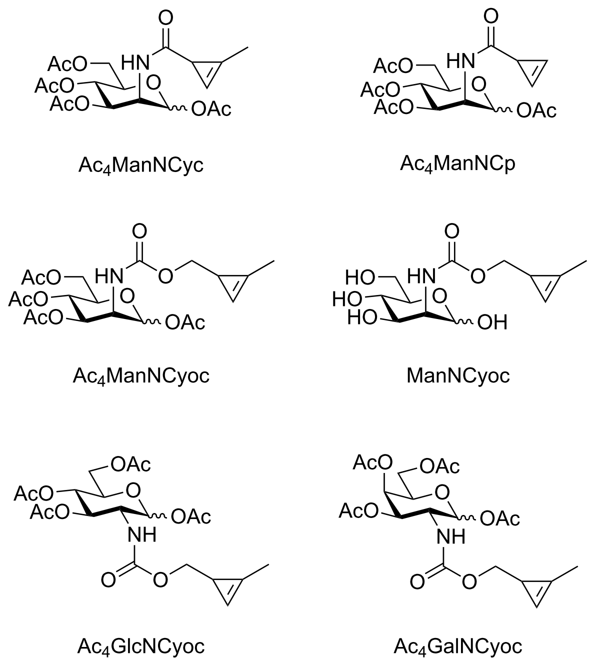


Figure 1: Cyclopropene-modified mannosamine, glucosamine and galactosamine derivatives employed for MGE.

Here we present a comparative study with all three derivatives Ac$_4$ManNCyc, Ac$_4$ManNCyoc, and Ac$_4$ManNCp under the same conditions allowing a direct comparison of Ac$_4$ManNCyoc and Ac$_4$ManNCp. Our study includes the determination of second-order rate constants of the deacetylated (water-soluble) sugars, the performance of the sugars in MGE, and the assessment of their metabolic acceptance. The studies uncovered that Ac$_4$ManNCp is much better accepted than Ac$_4$ManNCyoc although their membrane staining intensity after MGE is comparable. The high metabolic acceptance of the Cp-modified sugar inspired us to develop novel derivatives of glucosamine and galactosamine containing this cyclopropene modification and to explore their behavior in MGE both for membrane-bound and intracellular glycoproteins.

Results and Discussion

Kinetic studies

The second-order rate constant k_2 of ManNCyoc has previously been reported to be $k_2 = 0.99\ \mathrm{M^{-1}s^{-1}}$ [24]. To determine k_2 of Cyc- and Cp-modified mannosamine, we synthesized ManNCyc and ManNCp according to published protocols [23,27], omitting the final peracetylation step. In this way, water-soluble compounds were obtained that allowed the determination of rate constants in aqueous solution. As reported for ManNCyoc, an excess of ManNCyc and ManNCp, respectively, was reacted with water-soluble tetrazine Tz-PEG-OH in acetate buffer (pH 4.7, Figure 2A). The decrease of absorption of Tz-PEG-OH at $\lambda_{\mathrm{max}} = 522$ nm was measured and pseudo-first-order rate constants k_{obs} were determined. From these values second-order rate constants k_2 were determined to be $0.03\ \mathrm{M^{-1}s^{-1}}$ (ManNCyc) and $0.09\ \mathrm{M^{-1}s^{-1}}$ (ManNCp) (Figure 2B). These numbers illustrate that the removal of the stabilizing methyl group results in a triplication of the rate con-

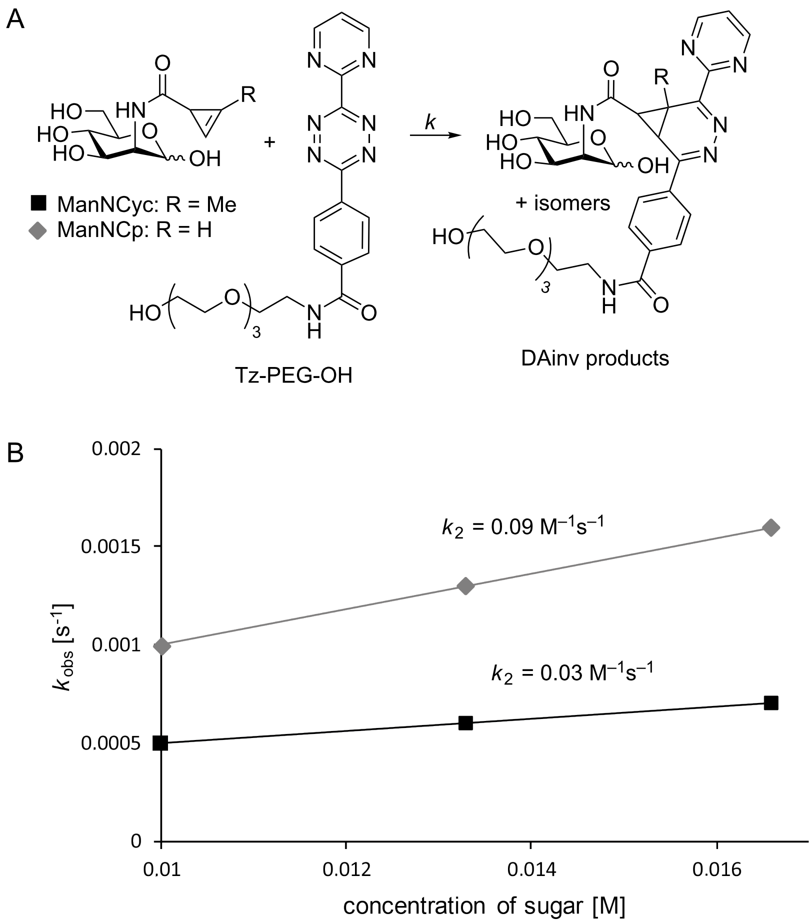


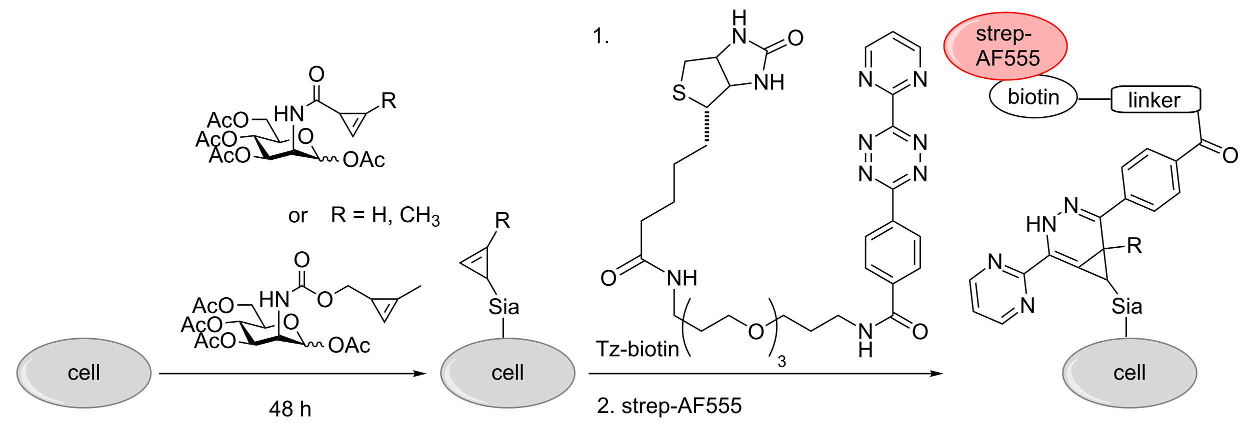
Figure 2: A) Reaction of ManNCyc and ManNCp, respectively, with Tz-PEG-OH to determine second-order rate constants k_2. B) Plot of k_{obs} against the sugar concentrations. The slopes equal the second-order rate constants k_2.

stant. Comparison of the rate constant of ManNCyc with the published one of ManNCyoc (0.99 M^{-1}s^{-1} [24]), which was determined under the same conditions, shows that the carbamate linkage instead of the amide linkage results in a 33-fold second-order rate constant. Obviously, the presence of the carbamate linkage has a higher impact on the reaction rate than the removal of the methyl group; k_2 of ManNCyoc is eleven times higher than that of ManNCp. In conclusion, the three cyclopropene-modified sugars rank in the order ManNCyc, ManNCp, and ManNCyoc with the latter being the fastest.

Metabolic glycoengineering with mannosamine derivatives

All three mannosamine derivatives Ac_4ManNCyc, Ac_4ManNCp, and Ac_4ManNCyoc were employed in metabolic glycoengineering. To this end, HEK 293T cells were cultivated for 48 h in the presence of the respective sugar or DMSO only as negative control. Subsequently, the cells were incubated with Tz-biotin, followed by incubation with streptavidin-AlexaFluor 555 (strep-AF555) for visualization (Scheme 1). In confocal fluorescence microscopy experiments, all sugars showed a distinct cell membrane staining in comparison to the negative control (Figure 3A). As expected [25,27], the staining intensity obtained with Ac_4ManNCyc was much lower than that of Ac_4ManNCyoc and Ac_4ManNCp and required different microscope settings to become clearly visible (Figure S1, Supporting Information File 1). Surprisingly, Ac_4ManNCp and Ac_4ManNCyoc resulted in a similar staining intensity although Ac_4ManNCyoc reacts significantly faster in the DAinv reaction.

To verify and to quantify these findings, we also analyzed the labeled cells by flow cytometry. We used the same conditions for MGE as described above (Scheme 1), but after incubation with strep-AF555, cells were released with trypsin, resuspended in buffer, and then subjected to flow cytometry analysis. The obtained results coincided with those of the fluorescence microscopy experiments (Figure 3B,C). Ac_4ManNCyc gave a significantly higher fluorescence intensity than the negative control, which, however, is exceeded by far from that of Ac_4ManNCp and Ac_4ManNCyoc. The experiments further



Scheme 1: MGE with cyclopropene-modified mannosamines. Cells were grown with sugar for 48 hours and then incubated with Tz-biotin, followed by strep-AF555.

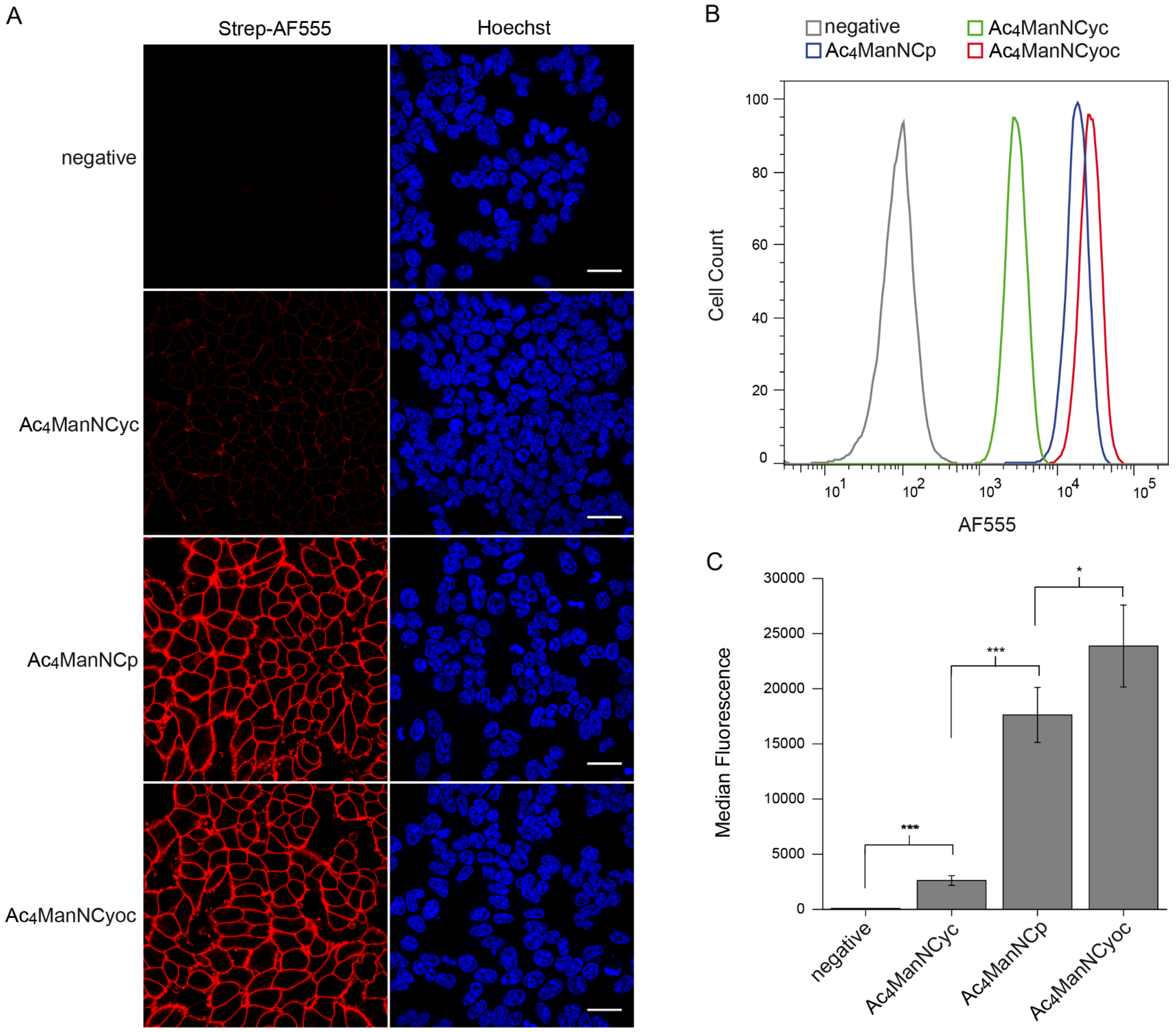


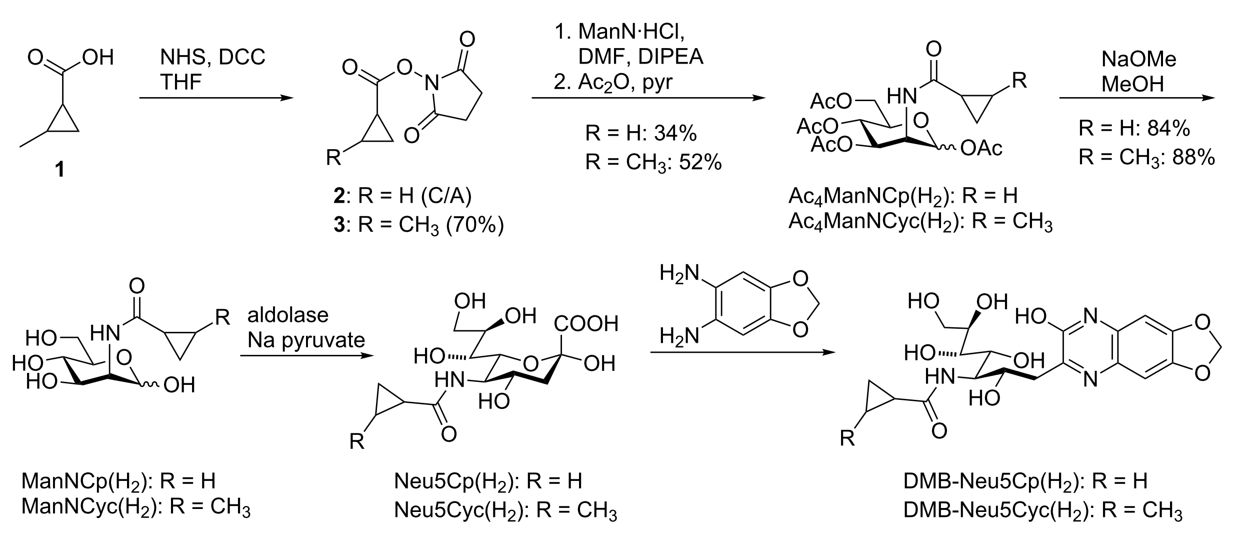
Figure 3: HEK 293T cells were grown with 100 µM $Ac_4ManNCyc$, $Ac_4ManNCp$, $Ac_4ManNCyoc$ or DMSO only (negative control) for 48 h. Cells were incubated with Tz-biotin (100 µM) for 1 h (A) or 30 min (B,C) at 37 °C followed by incubation with strep-AF555. A) Results from confocal fluorescence microscopy. Nuclei were stained with Hoechst 33342. Scale bar: 30 µm. B) Histogram from flow cytometry experiments. C) Median fluorescence from five independent flow cytometry experiments.

revealed that Ac_4ManNCyoc results in a slightly though significantly brighter staining than Ac_4ManNCp. The similar fluorescence intensity of cells engineered with either Ac_4ManNCp or Ac_4ManNCyoc suggests that Ac_4ManNCp with its much lower DAinv reactivity is much more efficiently metabolized and converted to the corresponding sialic acid than Ac_4ManNCyoc.

Determination of incorporation efficiencies

To confirm the hypothesis of different metabolization efficiencies of the mannosamine derivatives, we intended to quantify the proportion of cellular sialic acids that are labeled with a cyclopropene residue after MGE (i.e., the incorporation efficiency, *IE*). After the MGE experiments, we released the sialic acids from the cells by acetic acid treatment at elevated temperature and labeled them by addition of 1,2-diamino-4,5-methylenedioxybenzene (DMB) [29-31]. As described earlier [20], DMB selectively reacts with α-keto acids such as *N*-acetylneuraminic acid (Neu5Ac), the most abundant natural sialic acid in human cells [1], forming a fluorophore. Analysis by RP-HPLC equipped with a fluorescence detector allows the detection of natural and modified sialic acids. The incorporation efficiency *IE* can be calculated from the integrals *I* of the RP-HPLC signals of DMB-labeled Neu5Ac (I_{Neu5Ac}) and the respective DMB-labeled modified sialic acid (I_{Neu5R}) according to the formula $IE = I_{\mathrm{Neu5R}}\,(I_{\mathrm{Neu5R}} + I_{\mathrm{Neu5Ac}})^{-1}\ 100\%$. Unfortunately, it turned out that cyclopropene derivatives were not stable under these conditions, an observation that has also been made by Ye and co-workers [27]. Therefore, we decided to investigate the corresponding cyclopropane derivatives instead. We expected them to be stable under the DMB labeling conditions and during the preparation of reference compounds. Furthermore, their structure was expected to resemble that of the cyclopropenes as close as possible providing valuable information on the metabolic acceptance although it has to be kept in mind that (methyl)cyclopropanes are not plane in contrast to cyclopropenes.

Scheme 2 shows the synthesis of the mannosamine derivatives $Ac_4ManNCp(H_2)$ and $Ac_4ManNCyc(H_2)$ (H_2 indicates the cyclopropane moiety, i.e., the formal hydrogenation of the corresponding cyclopropene) as well as their transformation into the DMB-labeled sialic acids that served as reference compounds for the DMB labeling experiments. For the synthesis of $Ac_4ManNCyc(H_2)$, we activated the free acid **1** with *N*-hydroxysuccinimide (NHS) and *N,N'*-dicyclohexylcarbodiimide (DCC) to obtain active ester **3**. The synthesis of $Ac_4ManNCp(H_2)$ started from the commercially available activated cyclopropane **2**. In the next step, mannosamine hydrochloride (ManN·HCl) was neutralized with Hünig's base (diisopropylethylamine, DIPEA) in DMF and reacted with the activated cyclopropene derivatives, followed by peracetylation with acetic anhydride in pyridine. $Ac_4ManNCp(H_2)$ could be obtained in 34% yield and $Ac_4ManNCyc(H_2)$ in 52% yield. Since the stereoisomers resulting from the chiral centers at the methylcyclopropyl (and also methylcyclopropenyl) residues were not readily separable, we always used mixtures of isomers. Small amounts of the ManN derivatives were deacetylated with sodium methoxide in methanol and a subsequent sialic acid aldolase reaction delivered the corresponding sialic acids. After RP-HPLC purification, they were labeled with DMB and the final reference compounds were analyzed by RP-HPLC-MS (Figures S2 and S3, Supporting Information File 1).



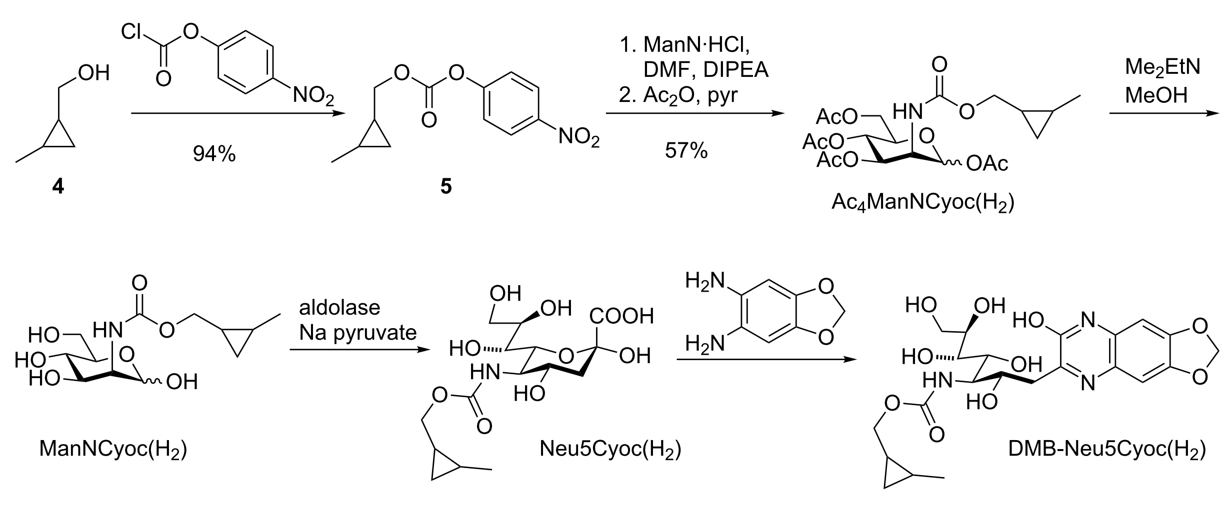
Scheme 2: Synthesis of $Ac_4ManNCp(H_2)$ and $Ac_4ManNCyc(H_2)$ and the corresponding DMB-labeled sialic acids. C/A = commercially available.

The synthesis of cyclopropane derivative $Ac_4ManNCyoc(H_2)$ is shown in Scheme 3. Alcohol **4** was activated with 4-nitrophenyl chloroformate, and the obtained carbonate **5** reacted with neutralized mannosamine and peracetylated as described above to give $Ac_4ManNCyoc(H_2)$ in a yield of 57%. Deacetylation with *N*,*N*-ethyldimethylamine in methanol and further aldolase reaction and DMB labeling gave reference compound DMB-Neu5Cyoc(H_2) that was analyzed by RP-HPLC-MS (Figure S4, Supporting Information File 1). Additionally, we synthesized the literature known DMB derivatives of the natural sialic acid Neu5Ac [29] and of sodium pyruvate [30] as reference compounds to determine their retention times with the chosen gradients (Figures S5–S8, Supporting Information File 1).

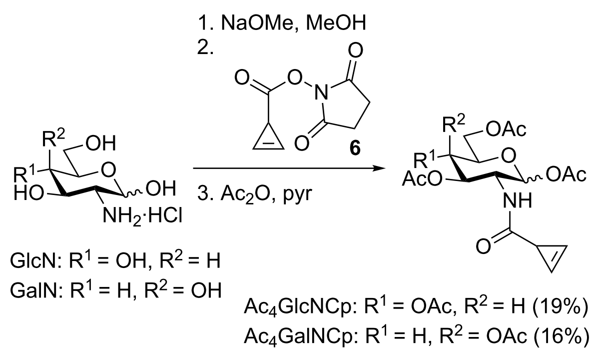
We next performed MGE experiments with cyclopropane derivatives. HEK 293T cells were grown with $Ac_4ManNCyc(H_2)$, $Ac_4ManNCp(H_2)$, $Ac_4ManNCyoc(H_2)$, or DMSO only (solvent control) for two days. Subsequently, cells were harvested and treated with acetic acid to cleave the sialic acids. These were then labeled with DMB and analyzed by RP-HPLC using a fluorescence detector (λ_{ex} = 372 nm, λ_{em} = 456 nm) (for solvent control see Figures S9 and S10, Supporting Information File 1). Both amide-linked derivatives were efficiently incorporated into cellular sialic acids ($Ac_4ManNCyc(H_2)$: $IE = (50.0 \pm 2.1)\%$, $Ac_4ManNCp(H_2)$: $IE = (71.7 \pm 12.8)\%$) (Figures S11 and S12, Supporting Information File 1). This demonstrates that the additional methyl group has a significant impact on the incorporation efficiency although that of $Ac_4ManNCyc(H_2)$ is still very high. However, as indicated above, it has to be kept in mind that a methylcyclopropane has an angled structure in contrast to methylcyclopropene. For $Ac_4ManNCyoc(H_2)$ an incorporation efficiency of only $(4.9 \pm 1.9)\%$ was determined (Figure S13, Supporting Information File 1) showing that this larger modification is much less well accepted by the enzymatic machinery. The different incorporation efficiencies of $Ac_4ManNCp(H_2)$ and $Ac_4ManNCyoc(H_2)$ readily explain our observation that the corresponding cyclopropene derivatives result is a similar staining intensity (Figure 3). Obviously, the lower DAinv reactivity of $Ac_4ManNCp$ is compensated by its higher incorporation efficiency.

MGE with $Ac_4GlcNCp$ and $Ac_4GalNCp$

Recently, the investigation of intracellular glycoproteins gained increasing attention. Therefore, the development of glucosamine and galactosamine derivatives suitable for MGE is of high importance. Until now, the carbamate-linked methylcyclopropenes $Ac_4GlcNCyoc$ and $Ac_4GalNCyoc$ are the only cyclopropene derivatives that were examined in this context [25,26]. $Ac_4GlcNCyoc$ was used to visualize protein-specific glycosylation inside living cells [32]. However, this compound is cytotoxic when applied in higher concentrations. Thus, novel glucosamine derivatives with improved properties would be beneficial. Based on the findings described above, especially the excellent incorporation efficiency of $Ac_4ManNCp(H_2)$, we hypothesized, that also the corresponding glucosamine derivative $Ac_4GlcNCp$ might be better incorporated than $Ac_4GlcNCyoc$. Consequently, we synthesized $Ac_4GlcNCp$ and $Ac_4GalNCp$ (Scheme 4). Glucosamine hydrochloride and galactosamine hydrochloride, respectively, were neutralized with sodium methoxide and then reacted with activated cyclopropene **6** followed by peracetylation. $Ac_4GlcNCp$ was obtained in 19% yield and $Ac_4GalNCp$ in 16% yield over two steps.



Scheme 3: Synthesis of $Ac_4ManNCyoc(H_2)$ and the corresponding DMB-labeled sialic acid.



Scheme 4: Synthesis of Ac_4GlcNCp and Ac_4GalNCp.

We next explored the suitability of Ac_4GlcNCp and Ac_4GalNCp in MGE. Applying the same protocol used for the mannosamine derivatives, we first performed fluorescence microscopy experiments after MGE. As a positive control, we included Ac_4ManNCp to enable comparison studies. The microscopy images showed a distinct membrane staining for Ac_4GlcNCp and Ac_4GalNCp, that was clearly weaker than that for Ac_4ManNCp (Figure 4). These results are similar to those obtained with the Cyoc-sugars [25,26]. Adjustment of the reaction conditions and microscopy settings resulted in a bright staining for Ac_4GlcNCp and Ac_4GalNCp well over that of the negative control (Figure 5). These results were confirmed by flow cytometry (Figure 4 and Figure 5). Interestingly, we did

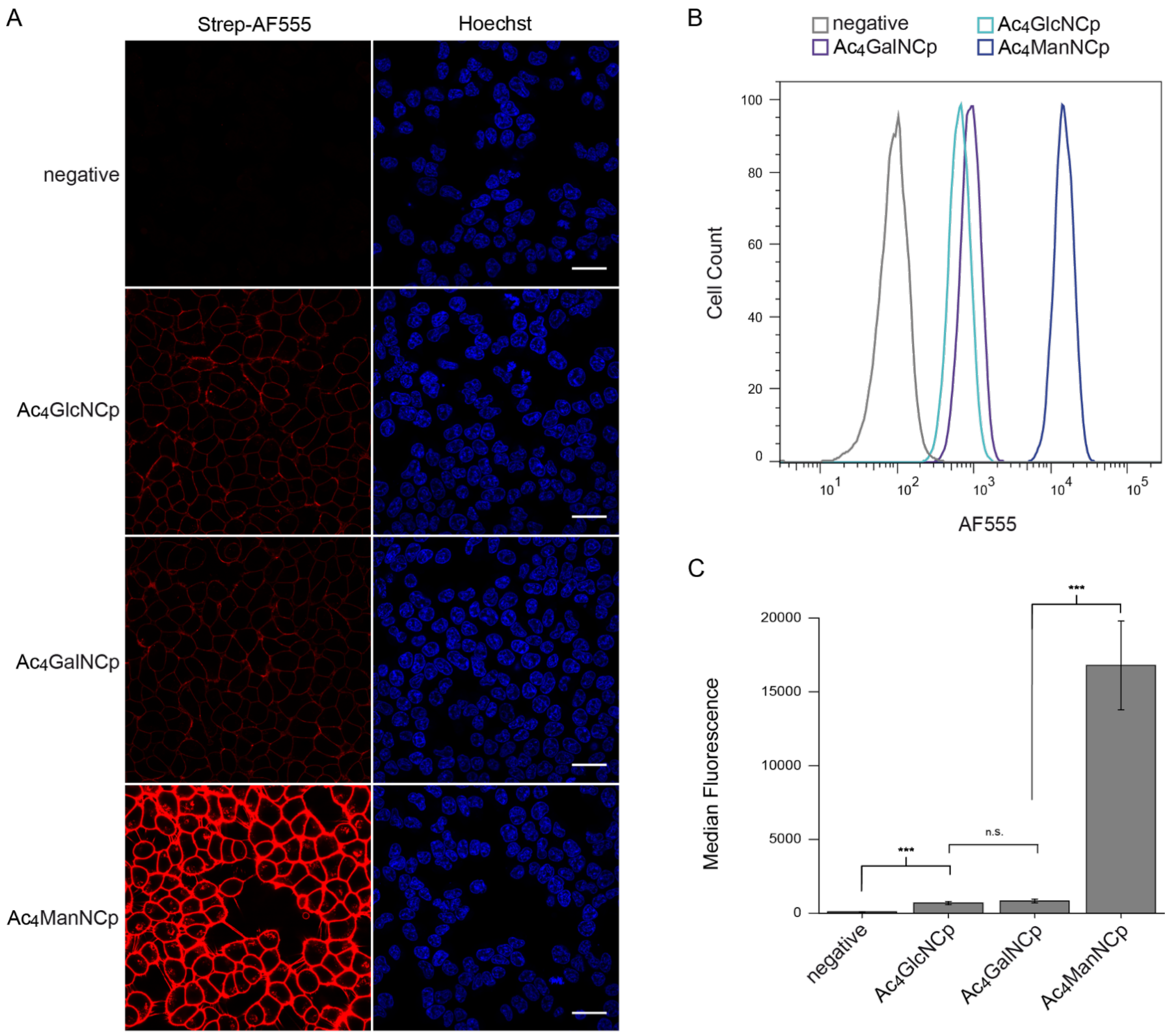


Figure 4: HEK 293T cells were grown with 100 µM Ac_4ManNCp, Ac_4GlcNCp, Ac_4GalNCp or DMSO only (negative control) for 48 h. Cells were incubated with Tz-biotin (A: 500 µM, B/C: 100 µM) for 3 h (A) or 30 min (B/C) at 37 °C followed by incubation with strep-AF555. A) Results from confocal fluorescence microscopy. Nuclei were stained with Hoechst 33342. Scale bar: 30 µm. B) Histogram from flow cytometry experiments. C) Median fluorescence from three independent flow cytometry experiments.

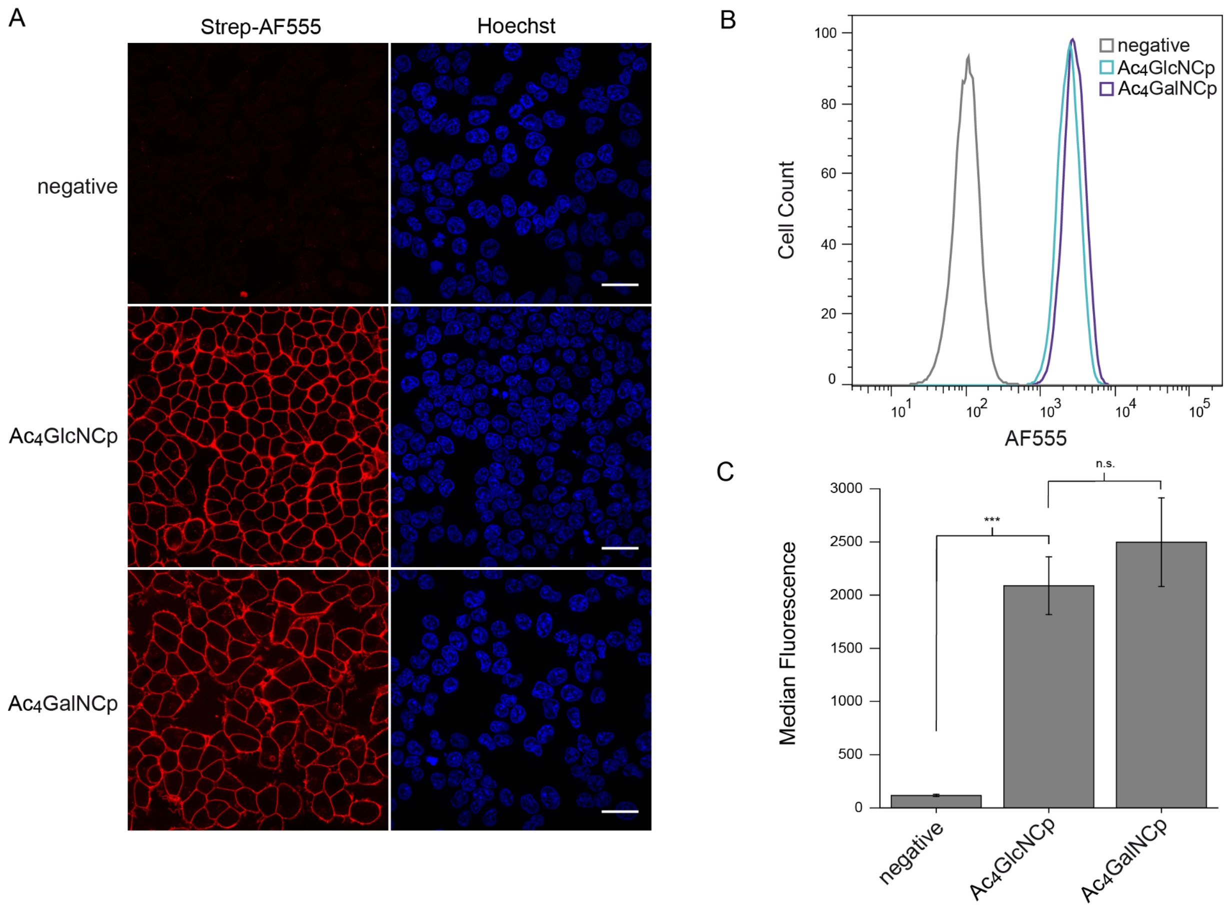


Figure 5: HEK 293T cells were grown with 100 µM Ac_4GlcNCp, Ac_4GalNCp or DMSO only (negative control) for 48 h. Cells were incubated with Tz-biotin (500 µM) for 3 h (A) or 1 h (B/C) at 37 °C followed by incubation with strep-AF555. A) Results from confocal fluorescence microscopy. Nuclei were stained with Hoechst 33342. Scale bar: 30 µm. B) Histogram from flow cytometry experiments. C) Median fluorescence from three independent flow cytometry experiments.

not observe cytotoxicity of Ac_4GlcNCp up to a concentration of 100 µM.

Comparison of glucosamine and galactosamine derivatives

Having proven the suitability of Ac_4GlcNCp for MGE, we next compared it with Ac_4GlcNCyoc. First, we investigated the staining intensity on the cell surface by confocal fluorescence microscopy. Owing to the cytotoxicity of Ac_4GlcNCyoc, a concentration of 50 µM was used for both sugars. In contrast to the corresponding mannosamine derivatives, Ac_4GlcNCp resulted in a much brighter staining compared to Ac_4GlcNCyoc (Figure 6A). Flow cytometry experiments confirmed these results and revealed that the median fluorescence of Ac_4GlcNCp is three times that of Ac_4GlcNCyoc (Figure 6B,C).

MGE with glucosamine and galactosamine derivatives is of interest to investigate O-GlcNAcylation of intracellular glycoproteins [32-35]. To include intracellular proteins in our analysis, we performed Western blot analysis of cell lysates. HEK 293T cells were cultivated with Ac_4ManNCp, Ac_4GlcNCp, Ac_4GalNCp, or Ac_4GlcNCyoc for 48 h. Subsequently, cells were harvested, lysed and the lysate was cleared by centrifugation resulting in an enrichment of soluble proteins. After labeling with Tz-Cy3 the proteins were separated by gel electrophoresis and blotted. Equal protein loading was verified by Ponceau S staining. As observed earlier [26], Ac_4GlcNCyoc resulted in a significant staining of proteins (Figure 7). In contrast, Ac_4GlcNCp as well as the mannosamine and galactosamine derivatives showed only weakly labeled protein bands. The observation that Ac_4GlcNCyoc results in stronger staining of soluble proteins than Ac_4GlcNCp whereas Ac_4GlcNCp gives a stronger cell surface staining suggests that Ac_4GlcNCyoc is better accepted by the enzymes producing intracellular glycoproteins while Ac_4GlcNCp is better accepted by the enzymes involved in the biosynthesis of membrane glycoconjugates.

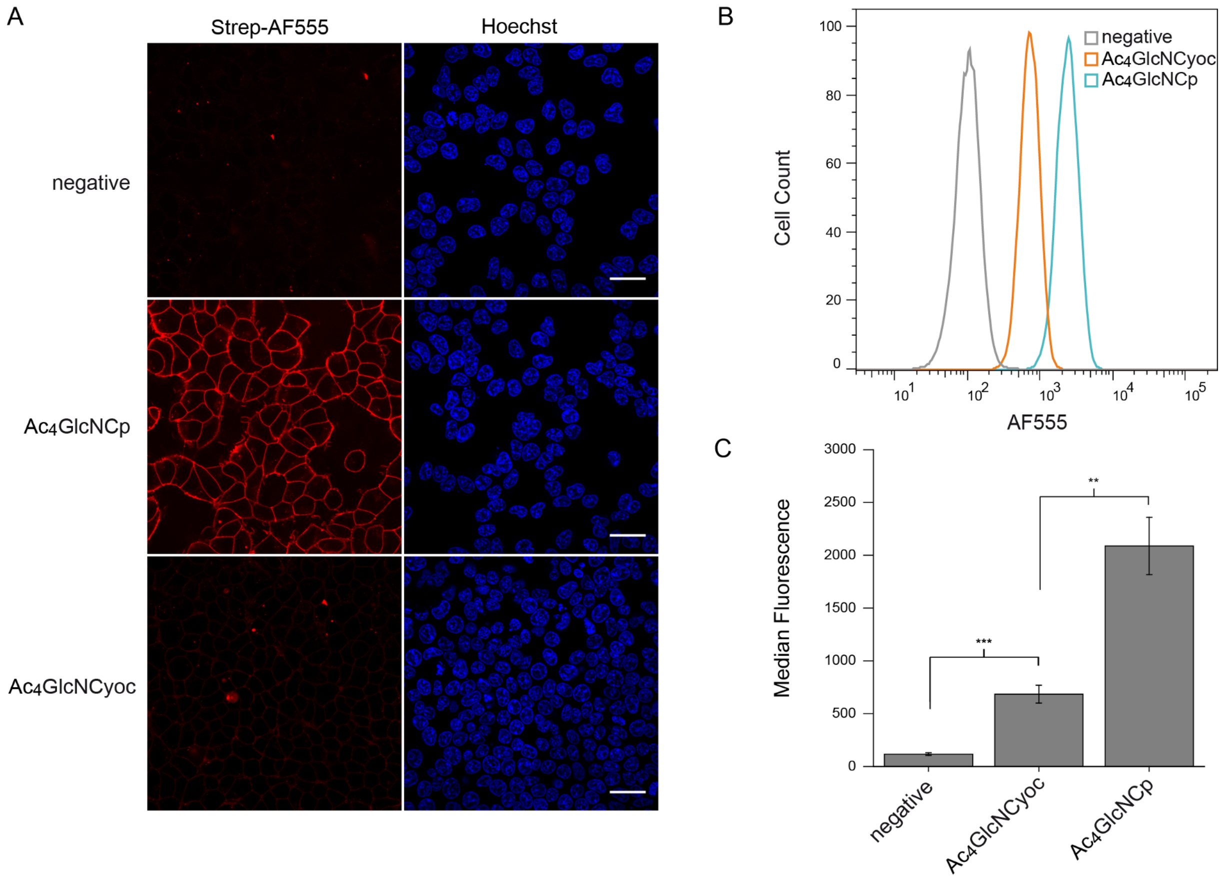


Figure 6: HEK 293T cells were grown with 50 µM (A) or 100 µM (B) Ac$_4$GlcNCp, Ac$_4$GlcNCyoc or DMSO only (negative control) for 48 h. Cells were incubated with Tz-biotin (500 µM) for 3 h (A) or 1 h (B/C) at 37 °C followed by incubation with strep-AF555. A) Results from confocal fluorescence microscopy. Nuclei were stained with Hoechst 33342. Scale bar: 30 µm. B) Histogram from flow cytometry experiments. C) Median fluorescence from three independent flow cytometry experiments.

However, many processes are responsible for the staining intensity of either intracellular or cell-surface proteins including cellular uptake of the carbohydrate derivative used for MGE, its metabolization, transport, speed of the ligation reaction, and the occurrence of alternative glycosylation pathways [36]. Since the elucidation of the exact background of our observation requires an in-depth analysis far beyond the scope of this article, we focus here on one of these aspects, i.e., the conversion of glucosamine into mannosamine derivatives resulting in a possible increase of the staining intensity on the cell surface.

Are Ac$_4$GlcNCyoc and Ac$_4$GlcNCp converted into sialic acids during MGE?

It is well established that carbohydrate derivatives can be interconverted into each other by epimerases. For example, both GlcNAc and UDP-GlcNAc can be converted to ManNAc [37,38] thereby joining the sialic acid biosynthesis pathway. Thus, a possible explanation of the staining of cell surfaces after MGE with glucosamine derivatives is their conversion into sialic acid derivatives and further into sialo glycoconjugates. To investigate this possibility, we carried out MGE experiments with the cyclopropane derivatives Ac$_4$GlcNCp(H$_2$) and Ac$_4$GlcNCyoc(H$_2$) followed by DMB labeling of sialic acids. Their synthesis started from glucosamine hydrochloride (Scheme 5) as described for the mannosamine analogues. After MGE with Ac$_4$GlcNCp(H$_2$) followed by DMB labeling we found that (3.5 ± 0.4)% of the sialic acids are modified as Neu5Cp(H$_2$) (Figure S14, Supporting Information File 1). After MGE with Ac$_4$GlcNCyoc(H$_2$) on the other hand we could not detect the corresponding sialic acid on the cell surface (Figure S15, Supporting Information File 1). Thus, the cell surface staining observed after MGE with Ac$_4$GlcNCp could at least in part be caused by the corresponding sialic acid Neu5Cp being a possible explanation for the higher staining intensity obtained with Ac$_4$GlcNCp compared to Ac$_4$GlcNCyoc.

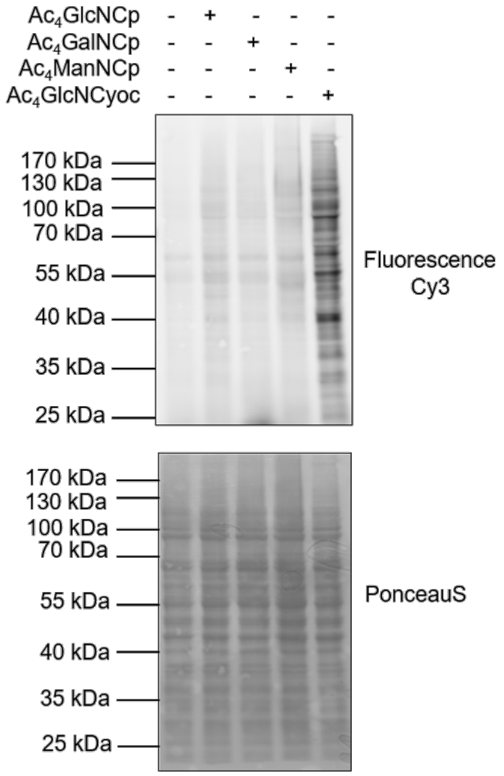
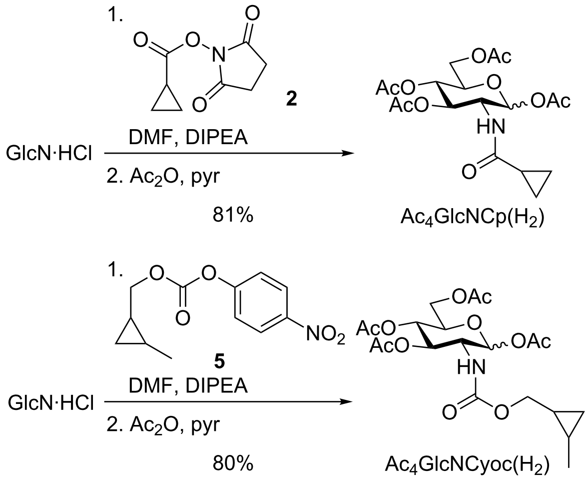


Figure 7: Western blot analysis of soluble glycoproteins. HEK 293T cells were grown for 48 h with 100 µM $Ac_4ManNCp$, $Ac_4GlcNCp$, $Ac_4GalNCp$, $Ac_4GlcNCyoc$ or DMSO only (negative control), lysed, and the cleared lysate was reacted with Tz-Cy3 (10 µM, 90 min, 24 °C). Ponceau S staining was used as loading control.



Scheme 5: Synthesis of $Ac_4GlcNCp(H_2)$ and $Ac_4GlcNCyoc(H_2)$.

Conclusion

Cyclopropene derivatives have proven to be suitable chemical reporter groups for MGE. In this investigation, we compared various aminosugar derivatives carrying three different cyclopropene moieties for this purpose. The Cyc and Cp residues, which differ by the presence or absence of a methyl group at the double bond, are connected by an amide-linkage to the aminosugar. The Cyoc moiety is connected by a carbamate-linkage. All three cyclopropene derivatives easily undergo DAinv reactions. Kinetic studies revealed that the carbamate derivative ManNCyoc has the highest reaction rate, followed by ManNCp and finally ManNCyc with the slowest reaction kinetics. Performing MGE experiments with the mannosamine derivatives followed by visualization of cell-surface labeling using the DAinv reaction demonstrated that $Ac_4ManNCyc$ produced only a weak staining, whereas $Ac_4ManNCp$ and $Ac_4ManNCyoc$ yielded in a comparably strong staining. Obviously, the lower DAinv reactivity of the Cp derivative in comparison to the Cyoc derivative is compensated by its high metabolic acceptance as suggested by investigation of the corresponding cyclopropane derivatives. Previously, it was speculated that the lower staining intensity obtained with $Ac_4ManNCyc$ in comparison to $Ac_4ManNCyoc$ is caused in part by its low incorporation efficiency due to branching in the α-position of the carbonyl group [25]. Our results with the corresponding cyclopropane derivatives, however, indicate that the main reason for the low labeling intensity is the sluggish DAinv reactivity of the Cyc reporter.

Based on the high incorporation efficiency of $Ac_4ManNCp$, we synthesized two new derivatives, $Ac_4GlcNCp$ and $Ac_4GalNCp$, which are both suitable for MGE resulting in cell-surface staining of comparable intensity. Interestingly, $Ac_4GlcNCp$ – in contrast to $Ac_4GlcNCyoc$ – showed only weakly labeled protein bands in a Western blot whereas its staining intensity on the cell surface was considerably stronger. MGE experiments with the cyclopropane analogs and subsequent DMB labeling of cellular sialic acids suggest that the amide-linked $Ac_4GlcNCp$ but not the carbamate-linked $Ac_4GlcNCyoc$ is converted to the corresponding sialic acid thus contributing to cell-surface labeling. In conclusion, we expanded the MGE toolbox by novel cyclopropene-modified glucosamine and galactosamine derivatives that offer interesting options for metabolic labeling.

Experimental

General methods

$Ac_4ManNCyc$ [23], $Ac_4ManNCp$ [27], $Ac_4ManNCyoc$ [24,25], and $Ac_4GlcNCyoc$ [25,26] were synthesized according to published procedures. AlexaFluor 555-labeled streptavidin and Hoechst 33342 were purchased from Invitrogen. Reactions were monitored by TLC using aluminum sheets pre-coated with silica gel 60 F254 (Merck) with detection by UV light (λ = 254 nm). Additionally, acidic ethanolic *p*-anisaldehyde solution or basic

$KMnO_4$ solution, followed by gentle heating, were used for visualization. Preparative column chromatography was performed by flash column chromatography using silica gel 60 M from Macherey-Nagel or with an MPLC-Reveleris X2 system (Büchi). NMR spectra were recorded at room temperature with an Avance III 400 or an Avance III 600 instrument from Bruker. Chemical shifts are reported in ppm relative to solvent signals ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Signal assignments were carried out by two-dimensional $^1H,^1H$ and $^1H,^{13}C$ correlation spectroscopy (COSY, HSQC, and HMBC). Analytical RP-HPLC-MS was performed on an LCMS2020 prominence system (pumps LC-20AD, column oven CTO-20AC, UV–vis detector SPD-20A, RF-20A Prominence fluorescence detector (λ_{ex} = 372 nm, λ_{em} = 456 nm), controller CBM-20A, ESI detector, software LC-solution) from Shimadzu under the following conditions. Column: EC125/4 Nucleodur C_{18} from Macherey-Nagel, flow: 0.4 mL min^{-1}; mobile phase: gradient of acetonitrile with 0.1% formic acid (solvent B) in water with 0.1% formic acid (solvent A). Semi-preparative HPLC was performed on a LC20A Prominence system (high-pressure pumps LC-20AT, auto sampler SIL-20A, column oven CTO-20AC, diode array detector SPDM20A, controller CBM-20A, software LC-solution) from Shimadzu under the following conditions. Column: Nucleodur 100-5 C18ec from Macherey Nagel (21.1 × 250 mm), flow: 9 mL min^{-1}, mobile phase: gradient of acetonitrile with 0.1% formic acid (solvent B) in water with 0.1% formic acid (solvent A). UV–vis absorption for kinetic measurements was measured with a Cary 50 instrument from Varian and Cary WinUV scanning kinetics software. High-resolution mass spectra (HRMS) were recorded on a micrOTOF II instrument from Bruker in positive and negative mode. The ionization method was electrospray (ESI) and for detection the time of flight (TOF) method was used. Analysis of recorded mass spectra was performed using the software Xcalibur by Thermo Fischer Scientific.

2,5-Dioxopyrrolidin-1-yl 2-methylcyclopropane-1-carboxylate (3): *N*-Hydroxysuccinimide (16.09 g, 139.83 mmol) and *N,N'*-dicyclohexylcarbodiimide (24.73 g, 119.86 mmol) were dissolved under nitrogen atmosphere in dry THF (300 mL). 2-Methylcyclopropanecarboxylic acid (**1**, 10.0 g, 99.88 mmol) was added and the milky reaction mixture was stirred overnight. The precipitate was filtered off and the filtrate evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 2:1) to obtain **3** as a white solid (13.75 g, 70%) as a mixture of isomers (indicated as a and b). R_f = 0.39 (petroleum ether/ethyl acetate 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 4H, CH_2CH_2), 1.99–1.90 (m, 1H, C(O)CH-b), 1.68–1.52 (m, 2H, C*H*CH_3, C(O)CH-a), 1.42–1.35 (m, 1H, CH_2-a), 1.32–1.26 (m, 1H, CH_2-b), 1.23 (d, *J* = 6.2 Hz, 3H, CH_3-b), 1.19 (d, *J* = 5.7 Hz, 3H, CH_3-a), 1.09–1.00 (m, 1H, CH_2-b), 1.00–0.91 (m, 1H, CH_2-a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (C=O), 169.3 (C=O), 168.1 (C=O), 25.6 (CH_2CH_2), 19.8 (CH_2-a), 18.8 (*C*HCH_3), 18.4 (CH_2-b), 18.1 (CH_3-a), 17.7 (C(O)*C*H-a), 16.6 (CH_2-b), 15.7 (C(O)*C*H-b), 12.0 (CH_3-b).

$Ac_4ManNCp(H_2)$: Mannosamine hydrochloride (500 mg, 2.32 mmol) was suspended under a nitrogen atmosphere in dry DMF (10 mL) and diisopropylethylamine (1.1 mL, 6.33 mmol) was added. After 1 h, 2,5-dioxopyrrolidin-1-yl cyclopropanecarboxylate (386 mg, 2.11 mmol) was added and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue dissolved in pyridine (2 mL) and acetic anhydride (2 mL). After two days at room temperature, the solvents were removed under reduced pressure and coevaporated with ethanol. The brown residue was dissolved in dichloromethane (20 mL) and washed with 10% aq $KHSO_4$ (1 × 20 mL), sat. aq $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 1:1) to yield $Ac_4ManNCp(H_2)$ (302 mg, 34%) as a mixture of anomers as a colorless solid. Whereas the α-anomer could be partially separated by column chromatography, semi-preparative RP-HPLC (50–65% B over 20 min) was required to obtain pure β-anomer (t_R = 10.0 min). R_f = 0.50 (petroleum ether/ethyl acetate 1:2); α-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (d, *J* = 1.9 Hz, 1H, H-1), 5.87 (d, *J* = 9.2 Hz, 1H, NH), 5.32 (dd, *J* = 10.2, 4.5 Hz, 1H, H-3), 5.21 (‘t‘, *J* = 10.2 Hz, 1H, H-4), 4.67 (ddd, *J* = 9.2, 4.5, 1.9 Hz, 1H, H-2), 4.29 (dd, *J* = 12.6, 5.0 Hz, 1H, H-6), 4.14–3.97 (m, 2H, H-5, H-6), 2.17 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.49–1.36 (m, 1H, CH), 1.06–0.89 (m, 2H, CH_2), 0.91–0.74 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C=O), 170.7 (C=O), 170.1 (C=O), 169.9 (C=O), 168.3 (C=O), 92.0 (C-1), 70.3 (C-5), 69.1 (C-3), 65.7 (C-4), 62.3 (C-6), 49.5 (C-2), 21.0 (OAc), 20.9 (OAc), 20.8 (OAc), 20.8 (OAc), 14.9 (CH), 8.2 (CH_2), 8.1 (CH_2); β-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, *J* = 9.1 Hz, 1H, NH), 5.90–5.77 (m, 1H, H-1), 5.15 (“t“, *J* = 9.8 Hz, 1H, H-4), 5.03 (ddd, *J* = 9.9, 4.1, 1.3 Hz, 1H, H-3), 4.85–4.73 (m, 1H, H-2), 4.29 (dd, *J* = 12.4, 5.3 Hz, 1H, H-6), 4.10 (dd, *J* = 12.6, 2.0 Hz, 1H, H-6), 3.86–3.72 (m, 1H, H-5), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.96 (s, 3H, OAc), 1.54–1.39 (m, 1H, CH), 1.04–0.90 (m, 2H, CH_2), 0.90–0.67 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (C=O), 170.7 (C=O), 170.2 (C=O), 169.9 (C=O), 168.5 (C=O), 90.9 (C-1), 73.6 (C-5), 71.5 (C-3), 65.6 (C-4), 62.1 (C-6), 49.6 (C-2), 20.9 (OAc), 20.9 (OAc), 20.8 (OAc), 20.8 (OAc), 15.0 (CH), 8.1 (CH_2), 7.9 (CH_2); HRMS *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{25}NO_{10}$, 438.1371; found, 438.1366.

Ac$_4$ManNCyc(H$_2$): Mannosamine hydrochloride (500 mg, 2.32 mmol) was suspended under nitrogen atmosphere in dry *N*,*N*-dimethylformamide (10 mL) and diisopropylethylamine (1.1 mL, 6.33 mmol) was added. After 1 h the activated cyclopropane **3** (416 mg, 2.11 mmol) was added and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue dissolved in pyridine (2 mL) and acetic anhydride (2 mL). After two days at room temperature, the solvents were removed under reduced pressure and coevaporated with ethanol. The brown residue was dissolved in dichloromethane (20 mL) and washed with 10% aq KHSO$_4$ (1 × 20 mL), sat. aq NaHCO$_3$ (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 1:1) to yield Ac$_4$ManNCyc(H$_2$) (473 mg, 52%) as a mixture of isomers (anomers as well as cyclopropane isomers indicated as a and b) as a colorless solid. Whereas the α-anomers could be partially separated by column chromatography, semi-preparative RP-HPLC (50–55% B over 20 min) was required to obtain β-anomers (t_R = 12.3 min). R_f = 0.54 (petroleum ether/ethyl acetate 1:2); α-isomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.07 (d, *J* = 1.8 Hz, 1H, H-1a), 6.04 (d, *J* = 1.9 Hz, 1H, H-1b), 5.86–5.72 (m, 1H, NH), 5.36–5.28 (m, 1H, H-3), 5.28–5.12 (m, 1H, H-4), 4.69–4.57 (m, 1H, H-2), 4.36–4.25 (m, 1H, H-6), 4.12–3.94 (m, 2H, H-5, H-6), 2.17 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.99 (s, 3H, OAc-b), 1.97 (s, 3H, OAc-a), 1.47–1.27 (m, 1H, C(O)CH), 1.20–1.06 (m, 5H, CHC*H*$_3$,CH$_2$), 0.74–0.53 (m, 1H, C*H*CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.59 (C=O), 173.56 (C=O), 170.7 (C=O), 170.1 (C=O), 169.94 (C=O), 169.88 (C=O), 168.3 (C=O), 92.0 (C-1a), 91.97 (C-1b), 70.3 (C-5), 69.05 (C-3a), 69.02 (C-3b), 65.8 (C-4b), 65.7 (C-4a), 62.30 (C-6b), 62.26 (C-6a), 49.52 (C-2b), 49.45 (C-2a), 23.6 (CH$_2$-a), 23.50 (CH$_2$-b), 21.0 (OAc), 20.89 (OAc), 20.9 (OAc), 20.82 (OAc), 20.80 (OAc), 18.03 (CH*C*H$_3$-a), 18.01 (CH*C*H$_3$-b), 16.8 (*C*HCH$_3$-b), 16.59 (*C*HCH$_3$-a), 16.56 (C(O)*C*H-a), 16.52 (C(O)*C*H-b); β-isomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.96–5.87 (m, 1H, NH), 5.87–5.79 (m, 1H, H-1), 5.18–5.09 (m, 1H, H-4), 5.08–4.97 (m, 1H, H-3), 4.80–4.70 (m, 1H, H-2), 4.33–4.17 (m, 1H, H-6), 4.15–4.05 (m, 1H, H-6), 3.83–3.71 (m, 1H, H-5), 2.12–2.08 (m, 6H, OAc), 2.06–2.03 (m, 3H, OAc), 1.97 (s, 3H, OAc-a), 1.95 (s, 3H, OAc-b), 1.39–1.27 (m, 1H, C(O)CH), 1.24–1.06 (m, 5H, CHC*H*$_3$,CH$_2$), 0.68–0.53 (m, 1H, C*H*CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.13 (C=O), 174.09 (C=O), 170.6 (C=O), 170.2 (C=O), 168.5 (C=O), 90.9 (C-1), 73.6 (C-5), 71.5 (C-3b), 71.4 (C-3a), 65.65 (C-4a), 65.57 (C-4b), 62.2 (C-6a), 62.1 (C-6b), 49.6 (C-2a), 49.5 (C-2b), 23.6 (CH$_2$-b), 23.5 (CH$_2$-a), 20.92 (OAc), 20.89 (OAc), 20.84 (OAc), 20.79 (OAc), 20.75 (OAc), 18.05 (CH*C*H$_3$-a), 17.99 (CH*C*H$_3$-b), 16.5, 16.4, 16.2 (C(O)*C*H, *C*HCH$_3$); HRMS *m/z*: [M + Na]$^+$ calcd for $C_{19}H_{27}NO_{10}$, 452.1527; found, 452.1522.

(2-Methylcyclopropyl)methyl (4-nitrophenyl) carbonate (5): 2-Methylcyclopropanemethanol (**4**, 0.57 mL, 5.81 mmol) was dissolved under nitrogen atmosphere in dry dichloromethane (80 mL) and dry pyridine (2.8 mL). The solution was cooled to 4 °C and 4-nitrophenyl chloroformate (2.57 g, 12.77 mmol) was added. After 18 h at room temperature, the reaction mixture was diluted with water until complete solution of the precipitate. The aqueous phase was extracted with dichloromethane, the organic phases were combined, dried over MgSO$_4$ and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate 5:1) and **5** (1.37 g, 94%) was obtained as a mixture of isomers (indicated as a and b) as a colorless liquid. R_f = 0.70 (petroleum ether/ethyl acetate 5:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.32–8.12 (m, 2H, H$_{ar}$), 7.53–7.28 (m, 2H, H$_{ar}$), 4.52–4.39 (m, 2H, OCH$_2$-b), 4.21–3.96 (m, 2H, OCH$_2$-a), 1.30–1.19 (m, 1H, CH$_2$C*H*-b), 1.14 (d, *J* = 6.2 Hz, 3H, CH$_3$-b), 1.09 (d, *J* = 6.0 Hz, 1H, CH$_3$-a), 1.07–1.02 (m, 1H, CH$_2$-b), 1.01–0.91 (m, 1H, CH$_2$C*H*-a), 0.89–0.72 (m, 1H, CH$_3$C*H*), 0.59–0.50 (m, 1H, CH$_2$-a), 0.49–0.36 (m, 1H, CH$_2$-a), 0.16–0.08 (m, 1H, CH$_2$-b); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.7 (C$_{quart}$), 152.6 (C$_{quart}$), 145.3 (C$_{quart}$), 125.3 (C$_{ar}$), 121.8 (C$_{ar}$), 74.0 (OCH$_2$), 70.7 (OCH$_2$), 18.2 (CH$_3$-a), 17.9 (CH$_2$*C*H-a), 14.0 (CH$_2$*C*H-b), 13.3 (CH$_3$-b), 12.0 (CH$_2$-a), 11.7 (CH$_3$*C*H-a), 11.2 (CH$_3$*C*H-b), 10.3 (CH$_2$-b).

Ac$_4$ManNCyoc(H$_2$): Mannosamine hydrochloride (500 mg, 2.32 mmol) was suspended under nitrogen atmosphere in dry *N*,*N*-dimethylformamide (10 mL) and diisopropylethylamine (1.1 mL, 6.33 mmol) was added. After 20 min the activated cyclopropane **5** (530 mg, 2.11 mmol) was added and the reaction mixture was stirred at room temperature for 4 days. The solvent was removed under reduced pressure and the residue dissolved in pyridine (2 mL) and acetic anhydride (2 mL). After 2 days at room temperature, the solvents were removed under reduced pressure and coevaporated with ethanol. The brown residue was dissolved in dichloromethane (25 mL) and washed with 10% aq KHSO$_4$ (1 × 25 mL), sat. aq NaHCO$_3$ (1 × 25 mL) and brine (1 × 25 mL). The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 2:1) to yield Ac$_4$ManNCyoc(H$_2$) (550 mg, 57%) as a colorless solid. Anomers could be separated by column chromatography and were obtained as isomeric mixtures (indicated as a and b). R_f = 0.38 (petroleum ether/ethyl acetate 3:2); α-isomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.14–6.02 (m, 1H, H-1), 5.29 (dd, *J* = 10.3, 4.3 Hz, 1H, H-3), 5.19 (‘t‘, *J* = 10.1 Hz, 1H, H-4), 5.10 (d, *J* = 9.2 Hz, 1H, NH), 4.36–4.29 (m, 1H, H-2), 4.24 (dd, *J* = 12.3, 4.5 Hz, 1H, H-6), 4.09–3.99 (m, 2H, H-6, H-5), 3.97–3.79 (m, 2H, OCH$_2$), 2.16 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.12–0.96 (m, 4H, CHC*H*$_3$, OCH$_2$C*H*-b), 0.99–0.90 (m, 1H, C*H*CH$_3$-b), 0.89–0.78 (m, 1H, OCH$_2$C*H*-a), 0.78–0.73 (m, 1H, CH$_2$-b), 0.72–0.64 (m, 1H, C*H*CH$_3$-a), 0.49–0.39 (m, 1H, CH$_2$-a), 0.37–0.24 (m, 1H, CH$_2$-a), 0.02–0.04 (m, 1H, CH$_2$-b); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.6 (C=O), 170.1 (C=O), 169.6 (C=O), 168.1 (C=O), 156.2 (C=O), 91.9 (C-1), 70.2, 70.0 (C-5 and OCH$_2$), 69.2 (C-3), 65.4 (C-4), 62.0 (C-6), 51.1 (C-2), 20.9 (OAc), 20.7 (OAc), 20.6 (OAc), 18.4, 18.3 (CH*C*H$_3$-a and OCH$_2$*C*H),13.2 (CH*C*H$_3$-b), 11.63, 11.61, 11.55, 11.48 (*C*HCH$_3$-a and CH$_2$), 10.0 (CHCH$_3$-b). β-isomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 5.84 (d, *J* = 1.9 Hz, 1H, H-1), 5.21–5.08 (m, 2H, NH, H-4), 5.02 (dd, *J* = 9.8, 3.8 Hz, 1H, H-3), 4.51–4.43 (m, 1H, H-2), 4.29–4.19 (m, 1H, H-6, OCH$_2$-b), 4.10 (dd, *J* = 12.4, 2.5 Hz, 1H, H-6), 4.04–3.84 (m, 2H, OCH$_2$-a), 3.78 (ddd, *J* = 9.6, 5.0, 2.6 Hz, 1H, H-5), 2.13–2.11 (m, 3H, OAc), 2.10 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04–2.01 (m, 3H, OAc), 1.17–1.02 (m, 3H, CHC*H*$_3$, OCH$_2$C*H*-b), 1.00–0.92 (m, 1H, C*H*CH$_3$-b), 0.89–0.80 (m, 1H, OCH$_2$C*H*-a), 0.80–0.66 (m, 1H, CH$_2$-b, CHCH$_3$-a), 0.52–0.40 (m, 1H, CH$_2$-a), 0.36–0.22 (m, 1H, CH$_2$-a), 0.05–0.00 (m, 1H, CH$_2$-b); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.6 (C=O), 170.1 (C=O), 169.6 (C=O), 168.5 (C=O), 156.8 (C=O), 90.7 (C-1), 73.3 C-5), 71.5 (C-3), 69.8 (OCH$_2$), 65.3 (C-3), 61.9 (C-6), 51.2 (C-2), 20.78 (OAc), 20.76 (OAc), 20.71 (OAc), 20.68 (OAc), 20.64 (OAc), 18.4 (CH*C*H$_3$-a), 18.3 (OCH$_2$*C*H-a), 14.3 (OCH$_2$*C*H-b), 13.2 (CH*C*H$_3$-b), 11.6, 11.5, 11.4 (CH*C*H$_2$), 11.0 (CHCH$_3$-a), 9.9 (CHCH$_3$-b); HRMS *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{29}NO_{11}$, 482.1633; found, 482.1623.

Ac$_4$GlcNCp: Glucosamine hydrochloride (0.50 g, 2.32 mmol) was suspended under argon atmosphere in dry methanol (40 mL) and sodium methoxide in methanol (0.5 M, 4.7 mL, 2.34 mmol) was added. After 20 min, 2,5-dioxopyrrolidin-1-yl cycloprop-2-ene-1-carboxylate (**6**, 0.63 g, 3.48 mmol) was added and the reaction was stirred at room temperature for 16 h, turning the solution from colorless to yellow. The solvent was removed under reduced pressure and the residue dissolved in pyridine (30 mL) and acetic anhydride (6 mL). After 18 h at room temperature, the solvents were removed under reduced pressure, the brown residue was dissolved in dichloromethane (100 mL) and washed with 10 % aq KHSO$_4$ (1 × 75 mL), sat. aq NaHCO$_3$ (1 × 75 mL) and brine (1 × 75 mL). The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 1:2) to yield Ac$_4$GlcNCp (183 mg, 19%) as a colorless solid. R_f = 0.48 (ethyl acetate); α-isomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.96–6.93 (m, 2H, HC=C*H*), 6.14 (d, *J* = 3.6 Hz, 1H, H-1), 5.48 (d, *J* = 9.1 Hz, 1H, NH), 5.28–5.16 (m, 2H, H-3, H-4), 4.56–4.45 (m, 1H, H-2), 4.25 (dd, *J* = 12.5, 4.2 Hz, 1H, H-6), 4.06 (dd, *J* = 12.5, 2.4 Hz, 1H, H-6), 4.02–3.94 (m, 1H, H-5), 2.18 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.05–2.03 (m, 7H, OAc, CH); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.5 (C=O), 171.8 (C=O), 170.8 (C=O), 169.2 (C=O), 168.7 (C=O), 105.3 (H*C*=CH), 105.1 (HC=*C*H), 91.0 (C-1), 70.9 (C-3), 69.9 (C-5), 67.6 (C-4), 61.7 (C-6), 51.3 (C-2), 21.18 (OAc), 21.02 (OAc), 20.99 (OAc), 20.86 (OAc), 19.0 (*C*H); HRMS *m/z*: [M + Na]$^+$calcd for $C_{18}H_{23}NO_{10}$, 436.1214; found, 436.1212.

Ac$_4$GalNCp: Galactosamine hydrochloride (0.50 g, 2.32 mmol) was suspended under argon atmosphere in dry methanol (40 mL) and sodium methoxide in methanol (0.5 M, 4.7 mL, 2.34 mmol) was added. After 20 min, 2,5-dioxopyrrolidin-1-yl cycloprop-2-ene-1-carboxylate (**6**, 0.63 g, 3.48 mmol) was added and the reaction was stirred at room temperature for 27 h turning the solution from colorless to yellow. The solvent was removed under reduced pressure and the residue dissolved in pyridine (30 mL) and acetic anhydride (6 mL). After 16 h at room temperature, the solvents were removed under reduced pressure, the brown residue was dissolved in dichloromethane (100 mL), and washed with 10 % aq KHSO$_4$ (1 × 100 mL), sat. aq NaHCO$_3$ (1 × 100 mL) and brine (1 × 100 mL). The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 1:2 to pure ethyl acetate) to yield Ac$_4$GalNCp (157 mg, 16%) as a colorless solid. R_f = 0.44 (ethyl acetate); α-isomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.95 (s, 1H, *H*C=CH), 6.93 (s, 1H, HC=C*H*), 6.18 (d, *J* = 3.6 Hz, 1H, H-1), 5.41 (m, 1H, H-4), 5.38 (d, *J* = 9.3 Hz, 1H, NH), 5.22 (dd, *J* = 11.6, 3.2 Hz, 1H, H-3), 4.75 (ddd, *J* = 11.6, 9.2, 3.7 Hz, 1H, H-2), 4.23 (t, *J* = 6.8 Hz, 1H, H-5), 4.16–4.02 (m, 2H, H-6), 2.16 (s, 6H, 2 x OAc), 2.04 (s, 1H, CH-C=C), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.9 (C=O), 171.5 (C=O), 170.7 (C=O), 170.5 (C=O), 169.1 (C=O), 105.3 (H*C*=CH), 105.1 (HC=*C*H), 91.7 (C-1), 68.75 (C-5), 68.1 (C-3), 66.9 (C-4), 61.5 (C-6), 47.2 (C-2), 21.2 (OAc), 21.1 (OAc), 20.98 (OAc), 20.95 (OAc), 19.2 (*C*H). HRMS *m*/*z*: [M + Na]$^+$ calcd for $C_{18}H_{23}NO_{10}$, 436.1214; found, 436.1210.

Ac$_4$GlcNCp(H$_2$): Glucosamine hydrochloride (500 mg, 2.32 mmol) was suspended under nitrogen atmosphere in dry *N*,*N*-dimethylformamide (10 mL) and diisopropylethylamine (1.1 mL, 6.33 mmol) was added. After 45 min, 2,5-dioxopyrrolidin-1-yl cyclopropanecarboxylate (**2**, 386 mg, 2.11 mmol) was added and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue dissolved in pyridine (4 mL) and acetic anhydride (4 mL). After 1 day at room temperature, the solvents were removed under reduced pressure and coevaporated with ethanol. The brown residue was dissolved in dichloromethane (20 mL) and washed with 10% aq $KHSO_4$ (1 × 20 mL), sat. aq $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 1:1) to yield Ac_4GlcNCp(H_2) (712 mg, 81%) as a mixture of anomers as a colorless solid. Whereas the α-anomer could be partially separated by column chromatography, semi-preparative RP-HPLC (50–55% B over 20 min) was required to obtain the pure β-anomer (t_R = 9.5 min). R_f = 0.41 (petroleum ether/ethyl acetate 1:2); α-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, *J* = 3.6 Hz, 1H, H-1), 5.70 (d, *J* = 9.1 Hz, 1H, NH), 5.36–5.07 (m, 2H, H-3, H-4)), 4.49 (ddd, *J* = 10.7, 9.1, 3.7 Hz, 1H, H-2), 4.24 (dd, *J* = 12.4, 4.2 Hz, 1H, H-6), 4.05 (dd, *J* = 12.4, 2.4 Hz, 1H, H-6), 3.99 (ddd, *J* = 9.9, 4.2, 2.4 Hz, 1H, H-5), 2.19 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (d, *J* = 1.2 Hz, 6H, OAc), 1.33–1.21 (m, 1H, CH), 1.00–0.87 (m, 2H, CH_2), 0.79–0.68 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C=O), 171.8 (C=O), 170.8 (C=O), 169.2 (C=O), 168.7 (C=O), 90.9 (C-1), 70.9 (C-3), 69.8 (C-5), 67.6 (C-4), 61.7 (C-6), 51.2 (C-2), 21.0 (OAc), 20.8 (OAc), 20.7 (OAc), 14.6 (CH), 7.8 (CH_2), 7.7 (CH_2); β-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, *J* = 9.6 Hz, 1H, NH), 5.70 (d, *J* = 8.7 Hz, 1H, H-1), 5.24–5.03 (m, 2H, H-3, H-4), 4.38–4.22 (m, 2H, H-2, H-6), 4.12 (dd, *J* = 12.5, 2.2 Hz, 1H, H-6), 3.89–3.71 (m, 1H, H-5), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.04 (s, 6H, OAc), 1.33–1.22 (m, 1H, CH), 0.98–0.85 (m, 2H, CH_2), 0.82–0.62 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C=O), 171.4 (C=O), 170.8 (C=O), 169.7 (C=O), 169.4 (C=O), 92.9 (C-1), 73.2 (C-5), 72.8 (C-3), 68.0 (C-4), 61.9 (C-6), 53.2 (C-2), 21.0 (OAc), 20.9 (OAc), 20.8 (OAc), 20.7 (OAc), 14.8 (CH), 7.64 (CH_2), 7.58 (CH_2); HRMS *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{25}NO_{10}$, 438.1371; found, 438.1366.

Ac_4GlcNCyoc(H_2): Glucosamine hydrochloride (500 mg, 2.32 mmol) was suspended under nitrogen atmosphere in dry *N*,*N*-dimethylformamide (10 mL) and diisopropylethylamine (1.1 mL, 6.33 mmol) was added. After 45 min, the activated cyclopropane **5** (530 mg, 2.11 mmol) was added and the reaction mixture was stirred at room temperature for 4 days. The solvent was removed under reduced pressure and the residue dissolved in pyridine (2 mL) and acetic anhydride (2 mL). After 3 days at room temperature, the solvents were removed under reduced pressure and coevaporated with ethanol. The brown residue was dissolved in dichloromethane (20 mL) and washed with 10% aq $KHSO_4$ (1 × 20 mL), sat. aq $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 2:1) to yield Ac_4GlcNCyoc(H_2) (771 mg, 80%) as a colorless solid. Anomers were separated by RP-HPLC (60–70% B over 20 min) and obtained as mixture of isomers. Retention time β-anomer: 12.6 min, α-anomer: 13.4 min. R_f = 0.30 (petroleum ether/ethyl acetate 3:2); α-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (d, *J* = 3.7 Hz, 1H, H-1), 5.36–5.12 (m, 2H, H-3, H-4), 4.77 (d, *J* = 9.5 Hz, 1H, NH), 4.26 (dd, *J* = 12.5, 4.1 Hz, 1H, H-6), 4.23–4.13 (m, 1H, H-2), 4.05 (dd, *J* = 12.6, 2.2 Hz, 1H, H-6), 4.02–3.95 (m, 1H, H-5), 3.96–3.73 (m, 2H, OCH_2), 2.18 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.03 (d, *J* = 6.0 Hz, 3H, CHC*H*$_3$), 0.83–0.73 (m, 1H, OCH_2C*H*), 0.73–0.59 (m, 1H, C*H*CH_3), 0.53–0.34 (m, 1H, CH_2), 0.34–0.23 (m, 1H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C=O), 170.6 (C=O), 169.2 (C=O), 168.6 (C=O), 155.9 (C=O), 90.9 (C-1), 70.7 (C-3), 69.9 (OCH_2), 69.7 (C-5), 67.7 (C-4), 61.6 (C-6), 52.7 (C-2), 20.9 (OAc), 20.7 (OAc), 20.5 (OAc), 18.4 (CH*C*H_3), 18.3 (OCH_2*C*H), 11.6 (CH_2), 11.4 (*C*HCH_3); β-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (d, *J* = 8.7 Hz, 1H, H-1), 5.18 (‘t‘, *J* = 9.9 Hz, 1H, H-3), 5.11 (‘t‘, *J* = 9.6 Hz, 1H, H-4), 4.76–4.61 (m, 1H, NH), 4.29 (dd, *J* = 12.5, 4.6 Hz, 1H, H-6), 4.11 (dd, *J* = 12.5, 2.3 Hz, 1H, H-6), 3.97–3.84 (m, 3H, H-2, OCH_2), 3.84–3.76 (m, 1H, H-5), 2.12 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.03 (d, *J* = 6.0 Hz, 3H, CH_3), 0.84–0.75 (m, 1H, OCH_2C*H*), 0.72–.64 (m, 1H, C*H*CH_3), 0.49–0.37 (m, 1H, CH_2), 0.31–0.21 (m, 1H, CH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8 (C=O), 169.5 (C=O), 169.5 (C=O), 156.2 (C=O), 92.8 (C-1), 92.7 (C-1), 73.0 (C-5), 72.5 (C-3), 72.4 (C-3), 69.9 (OCH_2), 68.1 (C-4), 61.8 (C-6), 55.0 (C-2), 21.0 (OAc), 20.9 (OAc), 20.8 (OAc), 20.7 (OAc), 18.6 (CH*C*H_3), 18.5 (OCH_2*C*H), 11.71, 11.68, 11.6 (CH_2, *C*HCH_3); HRMS *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{29}NO_{11}$, 482.1633; found, 482.1624.

ManNCp(H_2): Ac_4ManNCp(H_2) (80 mg, 0.19 mmol) was dissolved under nitrogen atmosphere in dry methanol (5 mL) and sodium methoxide (0.5 M, 0.06 mL) was added. After stirring overnight, Amberlite IR 120 was added for neutralization. The resin was filtered off and the solvent was removed under reduced pressure to obtain ManNCp(H_2) as slightly yellow solid (40 mg, 84%) which was used without further purification for the aldolase reaction.

ManNCyc(H_2): Ac_4ManNCyc(H_2) (67 mg, 0.16 mmol) was dissolved under nitrogen atmosphere in dry methanol (4.5 mL) and sodium methoxide (0.5 M, 0.05 mL) was added. After stirring overnight, Amberlite IR 120 was added for neutralization. The resin was filtered off and the solvent was removed under reduced pressure to obtain ManNCyc(H_2) as slightly colorless solid (37 mg, 88%) which was used without further purification for the aldolase reaction.

ManNCyoc(H_2): Ac_4ManNCyoc(H_2) (70.9 mg, 0.16 mmol) was dissolved in methanol (3.2 mL) and *N*,*N*-dimethylethylamine (0.7 mL, 6.82 mmol) was added. After stirring for eight days, the solvents were removed under reduced pressure and ManNCyoc(H_2) was obtained as colorless solid (45 mg, quant.) which was used without further purification for the aldolase reaction.

Sialic acid aldolase reaction: In a polypropylene vial, the sugar derivatives ManNCp(H_2), ManNCyc(H_2) and ManNCyoc(H_2), respectively, were dissolved in phosphate buffer (100 mM, pH 7.16) to a final concentration of 0.1 M. Sodium pyruvate (15 equiv.) and sialic acid aldolase (a spatula tip) were added. After stirring for 17 days the mixture was concentrated under reduced pressure, diluted with ethanol and filtered through cotton. The solvents were removed under reduced pressure and the crude product purified via RP-HPLC.

Neu5Cp(H_2): RP-HPLC (5–10% over 20 min): t_R = 9.1 min, HRMS *m/z*: $[M - H]^-$ calcd for $C_{13}H_{21}NO_9$, 334.1144; found, 334.1219.

Neu5Cyc(H_2): RP-HPLC (5–10% over 20 min): t_R = 15.0 min, HRMS *m/z*: $[M - H]^-$ calcd for $C_{14}H_{23}NO_9$, 348.1300; found, 348.1381.

Neu5Cyoc(H_2): RP-HPLC (5–20% over 20 min): t_R = 13.4 min, HRMS *m/z*: $[M - H]^-$ calcd for $C_{15}H_{25}NO_{10}$, 378.1405; found, 378.1492.

Preparation of DMB labeling solution: The stock solution for DMB labeling was prepared with $Na_2S_2O_4$ (18 mM), 2-mercaptoethanol (1 M) and TFA (40 mM) in Milli-Q water and was stored at 8 °C. 1,2-Diamino-4,5-methylenedioxybenzene dihydrochloride (DMB·2HCl) was added on the day of the experiment to a final concentration of 5.3 mM.

DMB labeling of reference compounds: The sialic acid derivatives Neu5Cp(H_2), Neu5Cyc(H_2), Neu5Cyoc(H_2) (0.1–0.2 mg), respectively, were dissolved in DMB labeling solution (265 µL) and incubated for 2.5 h at 56 °C in a thermomixer (300 rpm). The mixture was cooled on ice for 10 minutes and neutralized with sodium hydroxide (0.5 M, 25 µL). The solutions were analyzed via RP-HPLC-MS. For fluorescence detection (λ_{ex} = 372 nm, λ_{em} = 456 nm), they were diluted with Milli-Q water (1:400).

To determine their retention times, the literature known compounds DMB-Neu5Ac and DMB-Sodium pyruvate were synthesized following the above-mentioned protocol as well.

DMB-Neu5Cp(H_2): Analytical RP-HPLC (10–25% over 40 min): t_R = 17.2 min, MS *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}N_3O_9$, 452.17; found, 452.10.

DMB-Neu5Cyc(H_2): Analytical RP-HPLC (10–25% over 40 min): t_R = 24.0; 24,4, MS *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_3O_9$, 466.18; found, 466.15.

DMB-Neu5Cyoc(H_2): Analytical RP-HPLC (10–40% over 40 min): t_R = 24.9; 25.2; 25.7, MS *m/z*: $[M + H]^+$ calcd for $C_{22}H_{29}N_3O_{10}$, 496.19; found, 496.20.

Kinetic measurements: For kinetic studies, ManNCyc [23] and ManNCp [27] were synthesized according to the literature excluding the peracetylation step. Stock solutions of Tz-PEG-OH and sugar were prepared in acetate buffer (pH 4.8) and mixed in a quartz cuvette to give final concentrations of 1 mM Tz-PEG-OH and 10 mM, 13.3 mM and 16.6 mM, respectively, of ManCyc or ManCp. The reaction was monitored by measuring the absorption of the tetrazine at 522 nm. Pseudo-first-order rate constants were determined for every concentration of ManNCyc and ManNCp, respectively, by plotting $\ln(A_0/A_t)$ versus time. For the determination of A_0, a 1 mM solution of Tz-PEG-OH was used. A_t is the absorption of the reaction at time point *t*. Analysis by linear regression provided pseudo-first-order rate constants. Second-order-rate constants were determined by plotting the pseudo-first-order rate constants versus the corresponding sugar concentration, followed by linear regression and determination of the slope. All measurements were carried out in triplicate.

Cell growth conditions: HEK 293T (human embryonic kidney) cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) containing fetal bovine serum (FBS, 10%) and penicillin and streptomycin (each 100 U mL^{-1}). Cells were incubated under carbon dioxide (5%) in a water-saturated incubator at 37 °C. The cells were diluted every 3 to 4 days by washing with PBS buffer and detaching with trypsin and EDTA.

Sugar stock solutions: The sugars were prepared as stock solutions (100 mM) in DMSO and stored at −20 °C. They were freshly diluted into media on the day of the experiment.

Fluorescence microscopy: In an approach similar to that used in previously described experiments [24], HEK 293T cells (18000 cells cm^{-1}) were seeded in a 4-well ibiTreat µ-Slides (ibidi) Ph+ coated with poly-L-lysine (0.0025%, 1 h at 37 °C or overnight at 4 °C) and allowed to attach for 20 h. Cells were then incubated with Ac_4ManNCyc (100 µM), Ac_4ManNCp (100 µM), Ac_4ManNCyoc (100 µM), Ac_4GlcNCyoc (50 µM),

$Ac_4GlcNCp$ (100 µM or 50 µM), and $Ac_4GalNCp$ (100 µM) for 48 h. DMSO only was added as solvent control. Cells were washed twice with PBS and then treated with Tz-biotin (100 µM or 500 µM) for 1–3 h at 37 °C. After two washes with PBS, cells were incubated with streptavidin-AlexaFluor 555 (6.6 µL mL^{-1}) and Hoechst 33342 (10 µg mL^{-1}) for 20 min at 37 °C in the dark. Cells were washed thrice with PBS and DMEM was added for microscopy. Confocal fluorescence microscopy was performed with a Zeiss LSM 880 instrument equipped with a 40×1.4 NA Plan-Apochromat oil immersion objective and a GaAsP-detector array for spectral imaging. The obtained data were analyzed with image J software version 1.51.

Western blot analysis: Western Blot analysis was performed by a modified version of the previously described protocol [26,32]. HEK 293T cells were seeded (800000 cells/10 cm dish), and allowed to attach for 20 h. Cells were then incubated with $Ac_4ManNCp$ (100 µM), $Ac_4GalNCp$ (100 µM), $Ac_4GlcNCp$ (100 µM), and $Ac_4GlcNCyoc$ (100 µM) for 48 h. DMSO only was added as solvent control. Cells were trypsinated, resuspended in PBS (10 mL), and pelleted by centrifugation (5 min, 400*g*). The supernatant was discarded, and the pellet was resuspended in PBS (1 mL) and pelleted by centrifugation (5 min, 400*g*). The cells were lysed in lysis buffer (180 µL) containing Triton X-100 (0.5%), DNase (30 µg mL^{-1}), RNase (30 µg mL^{-1}), β-glycerophophate (20 mM), sodium fluoride (20 mM), sodium orthovanadate (0.3 mM), complete X protease inhibitor (Roche; 1×), NaCl (300 mM), Tris·HCl (pH 7.4, 25 mM), EDTA (5 mM), and 2-acetamido-2-deoxy-D-glucopyranosylidenamino *N*-phenylcarbamate [PUGNAc (*O*-GlcNAc-β-*N*-acetylglucosaminidase inhibitor to maintain *O*-GlcNAcylation during lysis), Sigma-Aldrich, 100 µM], and incubation was carried out at 4 °C for 30 min. The lysate was cleared by centrifugation (20000*g*, 30 min, 4 °C). Tz-Cy3 (3-(*p*-Benzylamino)-1,2,4,5-tetrazine-Cy3, Jena Bioscience) was added to the sample to afford a final concentration of 10 µM. The samples were incubated for 90 min at 24 °C, SDS-sample buffer (4×) was added and the sample was heated at 95 °C for 10 min. Proteins were separated by SDS-polyacrylamide gel electrophoresis with 10% polyacrylamide gels and transferred to nitrocellulose membranes (BioRad). Transfer efficiency and equal loading was analyzed by Ponceau S staining. The Cy3 fluorescence was detected with an Amersham Imager 600 using a 520 nm long pass filter.

Flow cytometry analysis: For flow cytometry analysis, the previously described protocol [21] was modified. HEK 293T cells were seeded in 12-well plates (150000 cells/well) coated with poly-L-lysine (0.0025%, 1 h at 37 °C or overnight at 4 °C). After 20 h cells were incubated with $Ac_4ManNCyc$ (100 µM), $Ac_4ManNCp$ (100 µM), $Ac_4ManNCyoc$ (100 µM), $Ac_4GlcNCyoc$ (50 µM), $Ac_4GlcNCp$ (100 µM or 50 µM), or $Ac_4GalNCp$ (100 µM) for 48 h. DMSO only was added as solvent control. Cells were washed twice with PBS and then treated with Tz-biotin (100 or 500 µM) for 30 min or 1 h at 37 °C. After two washes with PBS, cells were incubated with streptavidin-Alexa Fluor 555 (6.6 µL mL^{-1}) for 20 min at 37 °C in the dark. Cells were washed twice with PBS, released with trypsin-EDTA (200 µL/well), and resuspended in flow cytometry staining buffer (thermo fisher scientific) (600 µL/well). 10000 cells were counted per measurement. For flow cytometry analysis, BD LSRFortessa was used and the obtained data were evaluated with FlowJo Software version 8.8.7. Experiments were performed in triplicate.

DMB labeling of sialic acids released from engineered cells: In an approach similar to that described previously [20], HEK 293T cells were seeded in 6 cm dishes (400000 cells/dish). After 20 h cells were incubated with $Ac_4ManNCp(H_2)$ (100 µM), $Ac_4ManNCyc(H_2)$ (100 µM), $Ac_4ManNCyoc(H_2)$ (100 µM), $Ac_4GlcNCp(H_2)$ (100 µM), or $Ac_4GlcNCyoc(H_2)$ (100 µM). DMSO was added as solvent control. After 2 days, the media, except for 1 mL, was discarded. The cells were harvested in the leftover media, transferred to an Eppendorf tube and pelleted by centrifugation (5 min, 500*g*). The supernatant was discarded and the pellet was washed twice by resuspension in PBS (800 µL) and centrifugation (5 min, 500*g*). Cells were resuspended in PBS (1 mL), counted and transferred in a new Eppendorf tube (400000 cells/tube). The cells were pelleted again and the supernatant discarded. The pellet was resuspended in AcOH (3 M, 300 µL) and incubated for 90 min at 80 °C. The mixture was diluted with Milli-Q water and neutralized with aq. NH_3 (25%, 20 µL). The solvents were removed under reduced pressure using a SpeedVac and the residue was coevaporated with ethanol (3×) to obtain a colorless solid. At this point, the samples could be stored for a few days at −20 °C. For DMB labeling, the pellets were dissolved in DMB labeling solution (265 µL) and incubated for 2.5 h at 56 °C in a thermomixer (300 rpm). The mixture was cooled on ice for 10 min and neutralized with sodium hydroxide (0.5 M, 25 µL). Analysis was performed by analytical RP-HPLC using a fluorescence detector (λ_{ex} = 372 nm, λ_{em} = 456 nm).

Supporting Information

Supporting Information File 1

Additional figures and ^1H and ^{13}C NMR spectra of new compounds.

[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-54-S1.pdf]

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Diastereo- and enantioselective preparation of cyclopropanol derivatives

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Full Research Paper

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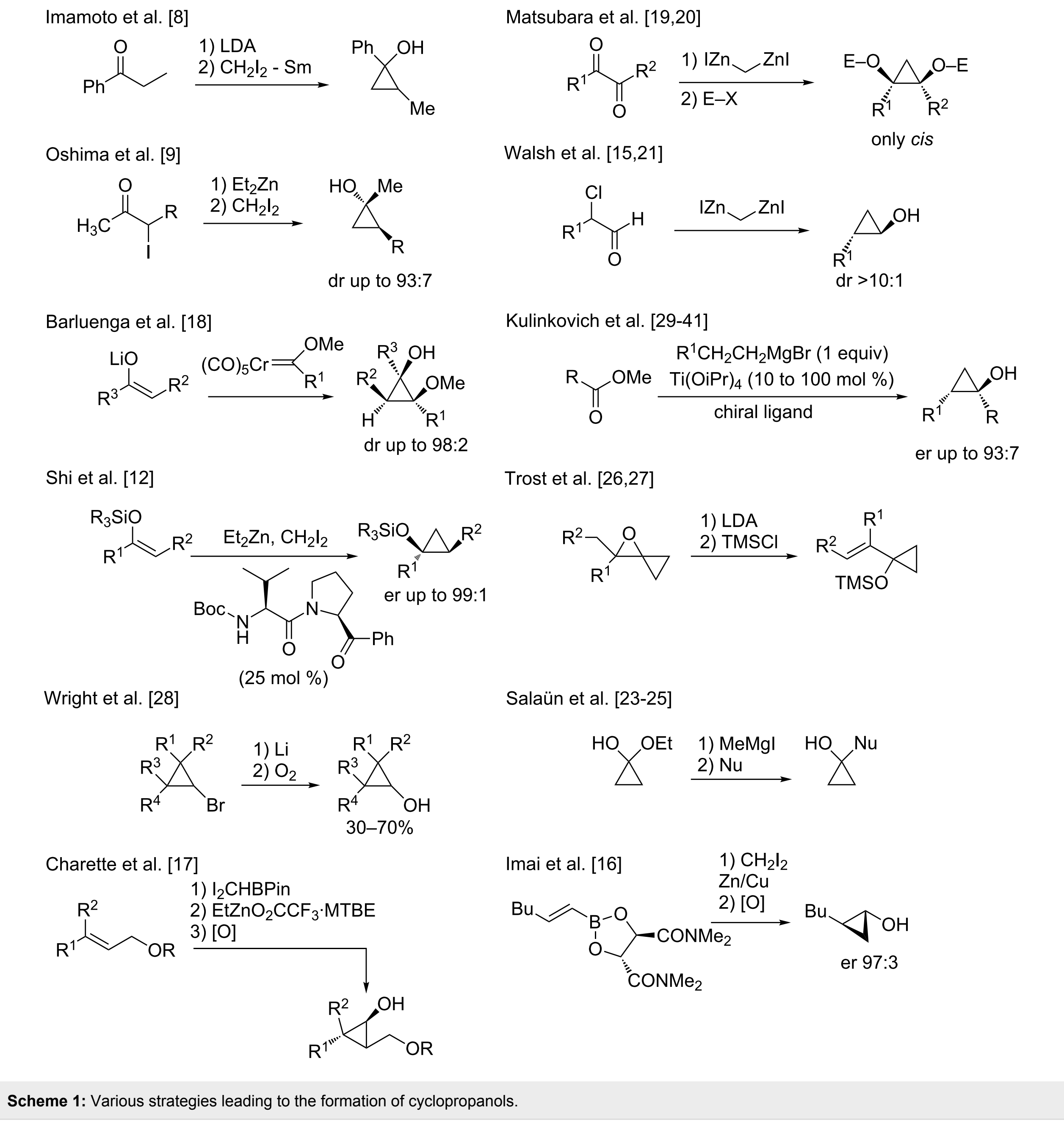
Abstract

The diastereoselective carbocupration reaction of alkoxy-functionalized cyclopropene derivatives, followed by a subsequent trapping of the resulting cyclopropylmetal species with an electrophilic source of oxygen (oxenoid) afforded various tetrasubstituted cyclopropanol derivatives in high diastereo- and enantiomeric ratios. Similarly, the enantioselective copper-catalyzed carbomagnesiation/oxidation (or amination) sequence on achiral nonfunctionalized cyclopropenes provided the desired cyclopropanol (and cyclopropylamine) derivatives in excellent diastereo- and enantiomeric excesses.

Introduction

The highly strained structure and bonding properties of cyclopropyl rings have constantly fascinated successive generations of chemists. These small carbocycles are known to have high ring strain (27.5 kcal/mol) and limited degrees of freedom, making them very attractive substrates for various chemical transformations [1]. The cyclopropane subunit is also present in many biologically important compounds such as pheromones, fatty acid metabolites, unusual amino acids and possess interesting herbicidal, insecticidal, antibiotic, antibacterial, antifungal, antiviral and antitumor activities [2]. For these reasons, cyclopropanes have been extensively studied and numerous approaches have been described for their preparation [3]. Among all possible three-membered ring subunits that have been reported, cyclopropanols have recently attracted renewed attention as they are not only contained in many natural products but they are also important precursors in the synthesis of various biologically active molecules and pharmaceuticals such as antidepressants, antiviral and antibacterial drugs [4]. Cyclopropanols and their derivatives are considered to be carbocyclic homologues of enols presenting similar chemical properties which are caused by the unsaturated character of the cyclopropyl ring. Although cyclopropanols are usually less reactive than enols and enolates, their chemical properties are somehow more diverse as they undergo useful transformations either with preservation or rupture of the cyclic structure [5]. Several reliable approaches to produce cyclopropanols have been reported in the literature (Scheme 1) [6] but a number of challenges still exist particularly for the stereoselective preparation of cyclopropanols of high structural complexity and substitution pattern. Since the first synthesis of cyclopropanol by Cottle [7], the most popular methods for the preparation of cyclopropanols rely on the transformation of enolates [8,9], silyl enol ether [10-12], vinyl borane [13-17], Fischer carbene addition [18], addition of nucleophiles to carbonyl groups [19-25], elimination [26,27], oxidation [28] or on the Kulinkovich reaction [29-41] as summarized in Scheme 1. However, and despite the increasing and justified popularity of all of these methods, the short summary described in Scheme 1 emphasizes an intrinsic problem: a different strategy is required for every cyclopropanol and cyclopropylamine that one needs to prepare, limiting the rapid structural diversification which is usually essential for biological studies. From this rapid tour d'horizon, it is clear that if one could design a stereoselective synthetic pathway to afford polysubstituted cyclopropanols (or cyclopropylamines) potentially

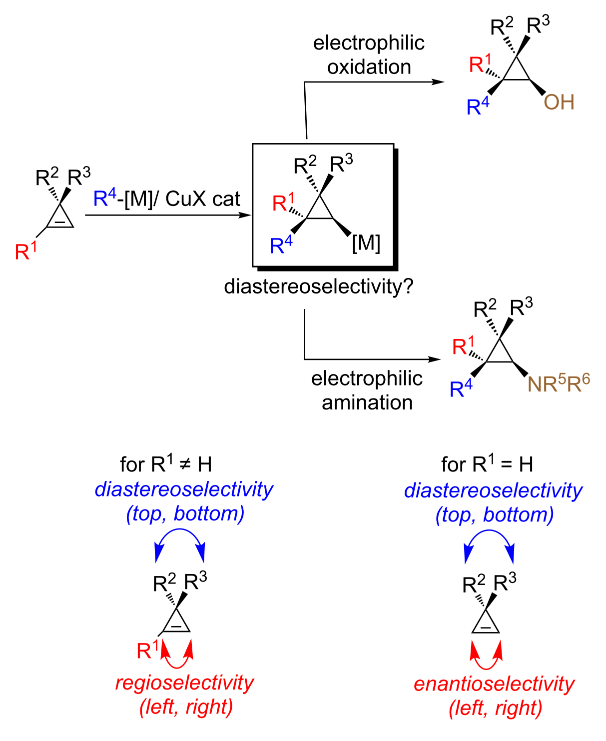


Scheme 1: Various strategies leading to the formation of cyclopropanols.

bearing several diastereo- and enantiomerically enriched adjacent stereogenic centers, including quaternary carbon stereocenters, as single diastereo- and enantiomer from a simple precursor, it would certainly provide an additional and useful entry to the synthesis of these heterosubstituted three-membered rings.

Results and Discussion

To reach these goals, we are describing herein the diastereo- and enantioselective carbometalation reaction of cyclopropenes to provide cyclopropylmetal species. By subsequent stereoselective reactions of the cyclopropylmetal species with an electrophilic source of oxygen (or nitrogen), cyclopropanols (and cyclopropylamines) should be easily accessible (Scheme 2).



Scheme 2: General approach to the preparation of cyclopropanol and cyclopropylamine derivatives.

In order to assemble both cyclopropanols and cyclopropylamines from a single and unique precursor in a single-pot reaction double facial selection by the catalyst is required: (i) regioselectivity when R^1 is different to H and enantioselectivity when R^1 is equal to H (left or right) and (ii) diastereotopic face selection (top or bottom) as described in Scheme 2. Since the pioneering addition of a carbon–metal bond (carbometalation) across the double bond of cyclopropenes [42], a very large number of groups have reported the addition of organometallic species demonstrating the generality of this approach for the preparation of cyclopropanes [43-63]. To achieve good diastereoselectivity during the carbometalation reaction, few conditions needed to be fulfilled in the design of the starting cyclopropenyl ring (Figure 1):

1. The presence of a coordinating group (such as an oxygen) at the C_3 position is crucial for the selective facial addition of the incoming organometallic species.
2. The presence of a bulky substituent (alkyl or aryl) at the opposite face at the C_3 position might equally be important as it might induce an additional steric parameter leading to a potentially more selective carbometalation reaction.
3. The substitution pattern on the double bond needs to be addressed carefully as it plays an important role in the control of the regioselectivity of the reaction pathway. An alkyl group on the C_1 position of the cyclopropene should control the regioselectivity of the addition of the organometallic species to give the more stable secondary cyclopropylmetal species (metal at C_2).

We therefore decided to start our research with cyclopropanes bearing an electron-rich methoxy group on one side of the ring and a phenyl or methyl substituent on the opposite side, respectively. Following reported methods from the literature [64-67], cyclopropenes **3** were easily prepared through the well-known Rh^{II}-catalyzed decomposition of diazo esters in the presence of alkynes to give cyclopropenyl esters **1**. Reduction of **1** using DIBAL-H afforded cyclopropenyl alcohols **2** and subsequent protection of the primary alcohols gave **3** in good yields (Scheme 3).

First, we checked that the carbometalation reaction was regio- and diastereoselective by addition of lower order cyanocuprate, easily obtained from the corresponding organolithium and a stoichiometric amount of CuCN (Scheme 4) [68-70].

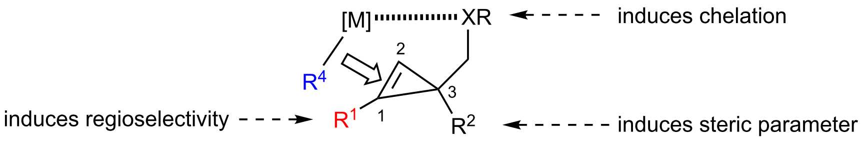
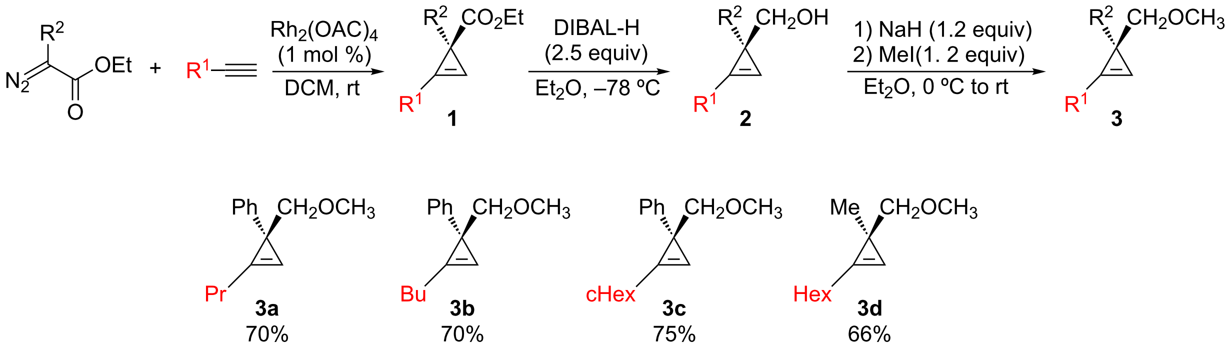
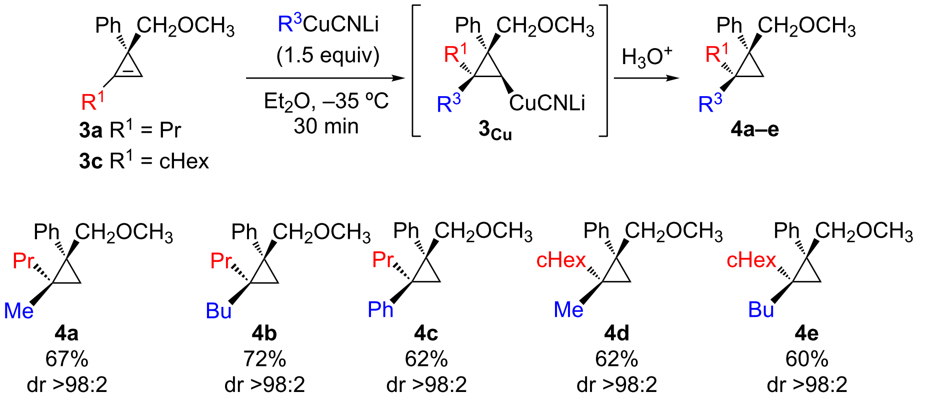


Figure 1: Prerequisite for a regio- and diastereoselective carbometalation.



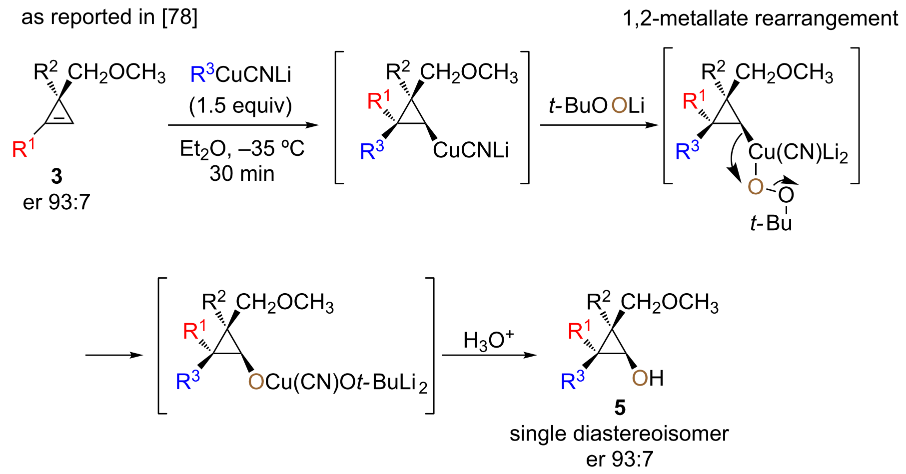
Scheme 3: Preparation of cyclopropenyl methyl ethers **3a–d**.



Scheme 4: Regio- and diastereoselective carbocupration of cyclopropenyl methyl ethers **3a**,**c**.

The addition reaction proceeds similarly for the addition of alkyl- or arylcuprate (**4a**,**b** and **4c**) as well as for the addition on cyclopropene possessing either a primary or secondary alkyl group at the vinylic carbon center (**4a–c** and **4d**,**e**). Having in hand diastereoisomerically pure and configurationally stable cyclopropylcopper species $\mathbf{3_{Cu}}$, we next turned our attention to their stereoselective oxidation reaction (Scheme 5). Considering electrophilic oxidation processes of organometallic species, molecular oxygen seems to be the most obvious choice due to its abundancy and low cost. Nevertheless, the reaction of molecular oxygen with a organocopper species usually proceeds through single-electron transfer to dioxygen, leading to either a loss of stereoselectivity, degradation of the organocopper or to the formation of dimer as major products [71]. Therefore, it was clear that a different approach for the oxidation process was needed. Oxenoid, possessing the general structure M–O–LG, with a metal and a leaving group connected to an oxygen atom, have been shown to be an excellent electrophilic oxygen source for nucleophilic organometallic species [72]. Since the original discovery of Müller and Töpel of lithiated peroxides [73], several studies have been reported on the reactivity of oxenoids [74-77], indicating that the reaction of a nucleophile with oxenoid proceeds through an S_N2 process [74]. Following the carbocupration of cyclopropene **3** into cyclopropylcopper species, the subsequent oxidation with the amphiphilic lithiated hydroperoxide *t*-BuOOLi (oxenoid), simply generated by deprotonation of *t*-BuOOH with *n*-BuLi, led to the copper alkoxide, as anticipated, without the formation of free radical intermediates. As already reported [78], the expected 2,2,3,3-tetrasubstituted cyclopropanols **5** were obtained as single diastereoisomers (Scheme 5).

The reaction proceeded for all R^1 and R^2 groups tested and determination of the stereochemistry confirmed that the oxidation reaction proceeds with pure retention of configuration at the metalated center (intramolecular S_N2 reaction or 1,2-metalate rearrangement) [78-80]. It should be noted that when the same sequence of diastereoselective carbometalation/oxidation was performed on cyclopropenyl ester **1**, the in situ-formed donor–acceptor cyclopropanol undergoes a selective ring-

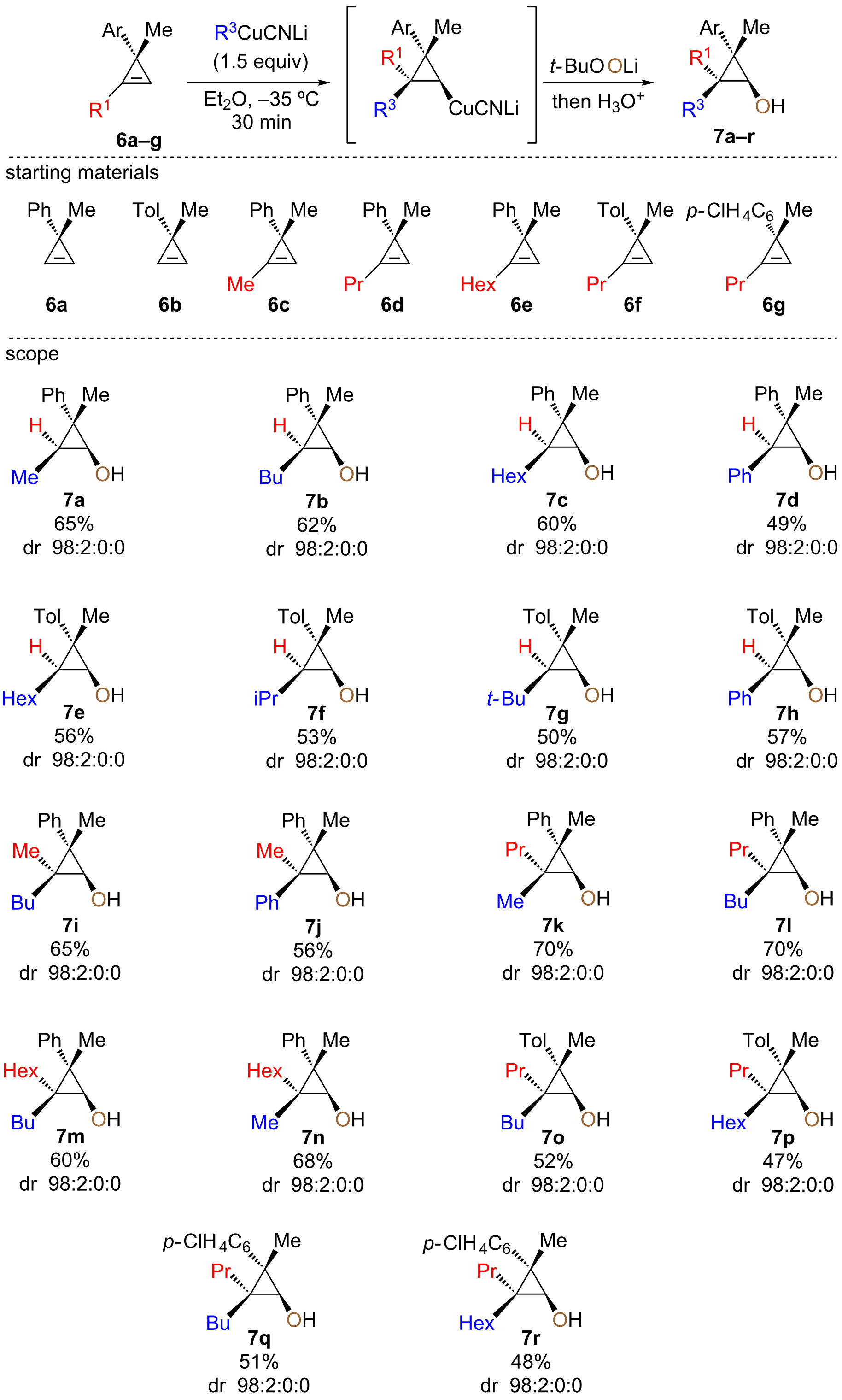


Scheme 5: Diastereoselective formation of cyclopropanols.

opening to provide the acyclic product possessing a quaternary carbon stereocenter [57]. As the enantioselective synthesis of the cyclopropenylmethyl ether **3** was easily achieved in high enantiomeric ratio (er 93:7, Scheme 5 [78,81,82]), the subsequent combined diastereoselective carbometalation reaction and oxidation gave the enantiomerically enriched cyclopropanols **5** as unique diastereoisomer with the same enantiomeric ratio as the starting material (Scheme 5, dr 98:2:0:0, er 93:7). Having established the optimized reaction conditions for the preparation of diastereomerically pure 2,2,3,3-tetrasubstituted cyclopropanol derivatives **5**, we were interested to expand the scope of this transformation and include different types of cyclopropene precursors. We concentrated our efforts on the reaction of diversely substituted 3-methyl-3-arylcyclopropenes **6**. In this case, as there is no coordinating functionality to dictate the facial selectivity, the control of the diastereoselectivity may be more challenging. Performing the same carbocupration/oxidation sequence on 3-methyl-3-phenylcyclopropene **6a**,**b** (R^1 = H), we were pleased to observe that trisubstituted cyclopropanols **7a–h** were obtained in good yields with excellent diastereoselectivities (Scheme 6).

The addition of primary, secondary and tertiary alkylcuprates or arylcuprates proceeded smoothly to give the desired cyclopropanols (**7a–h**) after hydrolysis. In all cases, the easily prepared cyclopropanol derivatives were obtained with the methyl, the incoming organometallic and the alcohol in the *syn*-orientation which was determined through comparison of the hydrolyzed carbometalated products with compounds already described in the literature [83]. To further increase the structural complexity of the final cyclopropanols, we also tested the reaction on nonfunctionalized trisubstituted cyclopropenes (**6c–g**). Addition of primary alkyl- or arylcuprates followed by the oxidation of the cyclopropylcopper species proceeded equally well and gave the corresponding cyclopropanols possessing two adjacent quaternary carbon stereocenters (**7i–r**) in good yields and excellent diastereomeric ratios. Here again, the methyl, the alkyl group from the organometallic and the alcohol in the resulting cyclopropanols are *syn*-oriented as previously observed. As reported in a different context, the nature of the two substituents on the cyclopropene rings could be changed without drastically altering the selectivity of the reaction [83,91].

We were also interested to develop the access to non-racemic unfunctionalized cyclopropanols. Based on the pioneering work of Lautens [62], Nakamura [60], Fox [61], Gevorgyan [51] and Tortosa [84], we anticipated that an enantioselective copper-catalyzed carbometalation reaction [83,85] would be an ideal solution to access the desired polysubstituted enantioenriched cyclopropanols. As reported, the copper-catalyzed diastereo- and enantioselective carbomagnesiation reaction of cyclopropenes **6** was easily achieved in the presence of (*R*,*S*)-Josiphos (2.2 mol %, Scheme 7). Having in hand, diastereoisomerically pure and enantiomerically enriched cyclopropylmagnesium species $\mathbf{6_{MgBr}}$, the selective oxidation reaction of the copper species, resulting from a transmetalation reaction, was similarly achieved by reaction with oxenoid [71,79,80,86-89]. In all cases, cyclopropanols **7** were obtained as single diastereoisomer (dr 98:2:0:0) with excellent enantiomeric ratios (er up to 99:1, Scheme 7). Following the same concept of copper-catalyzed diastereo- and enantioselective carbomagnesiation reaction of cyclopropenes **6** followed now by a selective electrophilic amination reaction, a powerful entry to cyclopropylamines as single diastereoisomer and in excellent enantiomeric ratios could also be achieved (Scheme 7) [89]. However, the enantioselective and catalytic copper-catalyzed carbomagnesiation

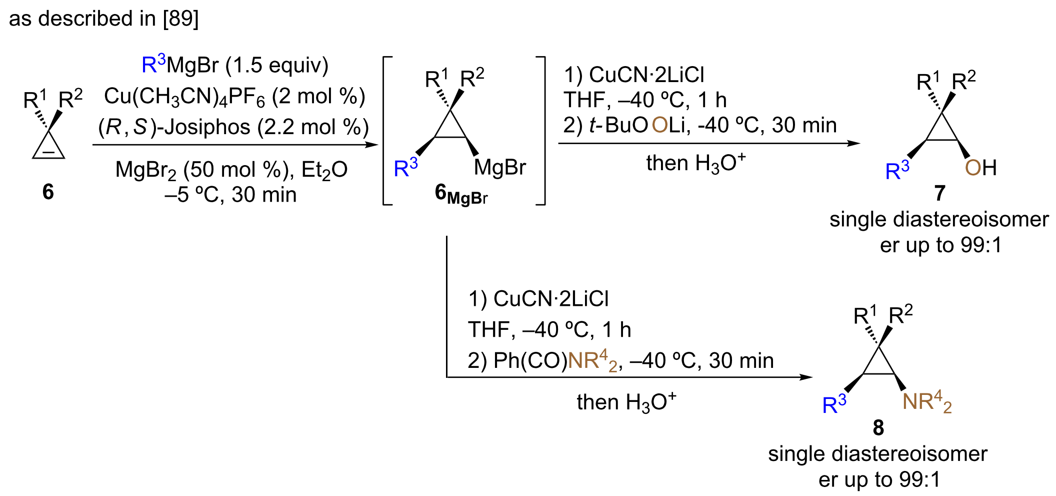


Scheme 6: Diastereoselective carbometalation/oxidation of nonfunctionalized cyclopropenes **6**.

reaction gave poor enantiomeric ratios for the addition of vinyl, aryl and allyl groups and alternative strategies have been recently developed in our research group [90-92].

Conclusion

In conclusion, we have successfully merged the regio- and diastereoselective carbocupration reaction of alkoxy-functionali-



Scheme 7: Preparation of diastereoisomerically pure and enantioenriched cyclopropanols and cyclopropylamines.

zed cyclopropenes with electrophilic oxidation of the resulting cyclopropylcopper species to afford 2,2,3,3-polysubstituted cyclopropanol derivatives bearing two adjacent quaternary stereogenic centers in a single pot operation. The simple preparation of enantiomerically enriched cyclopropene afforded the corresponding cyclopropanols in high enantiomeric excess. This transformation was then applied to unfunctionalized diversely substituted cyclopropenes. Using the catalytic and enantioselective carbometalation reaction of unfunctionalized cyclopropenes followed by an electrophilic oxidation reaction, polysubstituted cyclopropanols were obtained as single diastereoisomer with high enantiomeric ratios. In all cases, the configurationally stable cyclopropylmetal species reacted with retention of configuration with those electrophiles opening a new approach to *O*-heterosubstituted cyclopropyl rings.

Experimental

General procedure for the carbocupration reaction of **3a**,**c** with RCuCNLi

To a suspension of CuCN (1.5 equiv) in 8 mL of Et_2O was added alkyllithium dropwise at −35 °C (2 equiv). The resulting mixture (pale yellow in case of MeLi and PhLi and dark brown in case of *n*-BuLi and *n*-HexLi) was allowed to stir for 30 min. Cyclopropene **3a**,**c** (1 equiv in 2 mL/mmol of Et_2O) was added at that temperature and the reaction mixture was stirred until TLC shows complete consumption of the starting material (eluent hexane/EtOAc 9:1, ca. 30 min). The reaction was then quenched with an aqueous solution of NH_4Cl/NH_4OH (2:1). The aqueous layer was extracted twice with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixtures were then purified by flash chromatography using pentane/diethyl ether as eluent.

General procedure for the combined carbocupration/oxidation sequence

The reaction was performed on a 1 mmol scale. To a suspension of CuCN (2 equiv) in 8 mL of Et_2O was added alkyllithium dropwise at −35 °C (2 equiv/2 mmol). The resulting mixture (pale yellow in case of MeLi and PhLi and dark brown in case of *n*-BuLi and *n*-HexLi) was allowed to stir for 30 min. Cyclopropene **6a–g** (1 equiv/1 mmol in 2 mL of Et_2O) was added at that temperature and the reaction mixture was stirred until TLC shows complete consumption of the starting material (eluent hexane/EtOAc 9:1, ca. 30 min). The oxenoid was prepared in a different flask by slowly adding *n*-BuLi (1.2 equiv) to a solution of *tert*-butyl hydroperoxide (2 equiv) in THF (5 mL/2 mmol) at −80 °C. After 30 min at −80 °C, the resulting *t*-BuOOLi was transferred to the organocopper dropwise at −78 °C via a cannula. The mixture (orange to brown) was stirred at this temperature until disappearance of the cyclopropylcopper species (followed by TLC, eluent hexane/EtOAc 9:1, ca. 30 min). The reaction was then quenched with an aqueous solution of NH_4Cl/NH_4OH (2:1). The aqueous layer was extracted twice with Et_2O and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude mixtures were then purified by flash chromatography using pentane/diethyl ether as eluent.

Supporting Information

Supporting Information File 1

Experimental part.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-71-S1.pdf]

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