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Synthesis of Functionalized Alkylidenecyclopropanes by Ireland–Claisen Rearrangement of Cyclopropenylcarbinyl Esters

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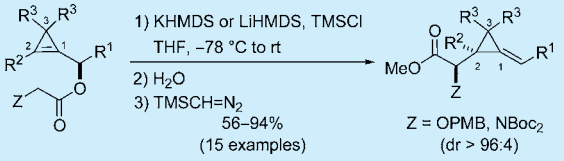
Supporting Information

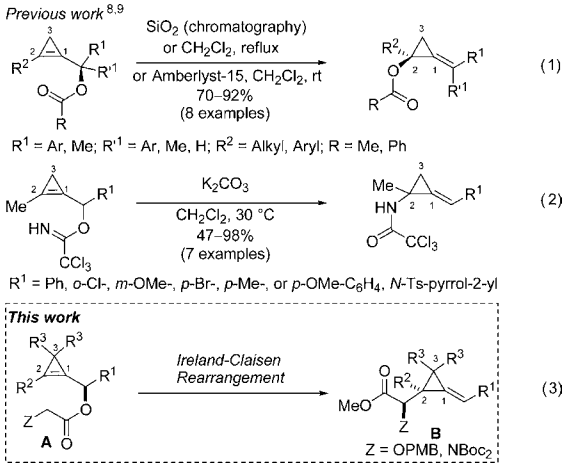
ABSTRACT: Glycolates or glycinates derived from diversely substituted secondary cyclopropenylcarbinols have been involved for the first time in an Ireland–Claisen rearrangement. This reaction allows an efficient and stereoselective access to highly functionalized alkylidenecyclopropanes possessing an α-hydroxy or α-amino acid subunit, which in turn are valuable precursors of substituted cyclopropanes by diastereoselective hydrogenation of the exocyclic alkene.



The fascinating reactivity of alkylidenecyclopropanes continues to elicit considerable interest in organic synthesis,[1] notably in transition-metal-catalyzed processes allowing either the construction of complex molecular architectures by cycloadditions[2] or efficient challenging acyclic stereocontrol.[3] By additions across the C=C bond, alkylidenecyclopropanes can serve as useful precursors of substituted cyclopropanes,[4] which are widely encountered in natural and/or bioactive compounds.[5] Among the different synthetic routes toward alkylidenecyclopropanes, transformations relying on cyclopropenes as precursors are thermodynamically favored owing to the relief of ring strain occurring upon migration of the double bond to the exocyclic position.[1,6] Nucleophilic displacements of cyclopropenylcarbinol derivatives proceeding with allylic shift (S_N2' or addition–elimination mechanisms) are undoubtedly the most documented transformations.[7] Surprisingly, by analogy with allylic alcohols, examples of [3,3]-sigmatropic rearrangements involving cyclopropenylcarbinol derivatives are scarce and restricted to the synthesis of heterosubstituted alkylidenecyclopropanes.[8,9] Marek et al. reported the [3,3]-sigmatropic transposition of cyclopropenylcarbinyl acetates (or a benzoate) which occurs with complete chirality transfer in the case of enantioenriched substrates (Scheme 1, eq 1).[8] Recently, Hyland et al. disclosed the rearrangement of trichloroacetimidates derived from cyclopropenylcarbinols bearing an electron-rich or -neutral aromatic substituent (Scheme 1, eq 2).[9] The substrates involved in these rearrangements were derivatives of cyclopropenylcarbinols lacking substituents at C3, the presence of which may have a dramatic influence on the reactivity by either raising the activation barrier[10] or inducing competitive rearrangement pathways.[9]

Herein, we report our investigations on the reactivity of glycolates or glycinates **A**, derived from secondary cyclopropenylcarbinols, in the Ireland–Claisen rearrangement[11] with the goal of synthesizing highly functionalized and diversely substituted alkylidenecyclopropanes **B**, incorporating an α-hydroxy or α-amino acid subunit (Scheme 1, eq 3).

Scheme 1. [3,3]-Sigmatropic Rearrangements of Cyclopropenylcarbinol Derivatives



The Ireland–Claisen rearrangement of glycolate **3a**, arising from the coupling of cyclopropenylcarbinol **1a** with the glycolic acid derivative **2** (94%), was investigated first. The silyl ketene acetal **4a** was generated by addition of an excess of KHMDS (4 equiv) to a solution of glycolate **3a** and TMSCl (4 equiv) (THF, −78 °C).[12] Upon warming to rt, **4a** underwent a [3,3]-sigmatropic rearrangement leading to the trimethylsilyl ester **5a** (86%). After an acidic aqueous workup, the resulting crude carboxylic acid was treated with trimethylsilyldiazomethane to afford methyl ester **6a**.[13] Analysis of the ^{1}H NMR spectrum of the

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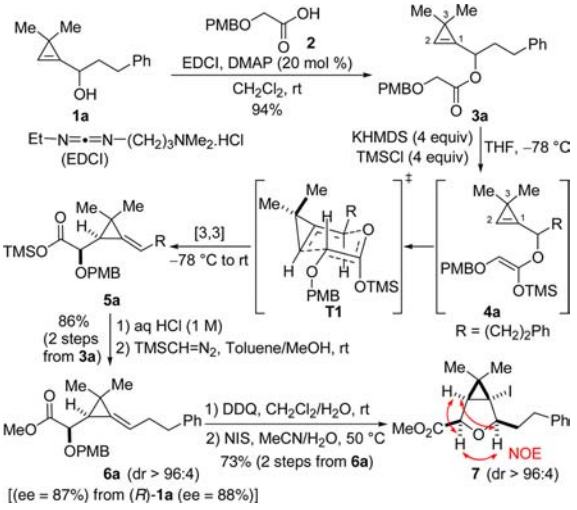
crude reaction product indicated the formation of **6a** as a single detectable diastereomer (dr >96:4). The *Z* configuration of the exocyclic alkene in **6a** was established by NMR (NOESY), whereas the relative configuration of the two newly formed stereocenters was assigned by a chemical correlation. Cleavage of the PMB ether in **6a** and subsequent iodoetherification afforded the oxabicyclic compound **7**,[14] whose relative configuration was readily established by NMR (NOESY). The stereochemical outcome was in agreement with a [3,3]-sigmatropic rearrangement of the *Z* silyl ketene acetal **4a** proceeding through a chairlike transition state **T1** in which the substituent at the α position of the cyclopropene preferentially occupies a pseudoequatorial orientation.[11,12] We checked that the rearrangement of glycolate (*R*)-**3a**, derived from cyclopropenylcarbinol (*R*)-**1a** (ee = 88%), proceeded with chirality transfer and afforded the enantioenriched glycolate **6a** (ee = 87%) (Scheme 2).

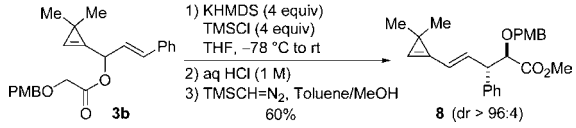
Scheme 2. Ireland−Claisen Rearrangement of Cyclopropenylcarbinyl Glycolate 3a



It is worth noting that an excess of base could be used with no adverse effect despite the substantial acidity of the vinylic C−H bond in cyclopropenes.[15] Moreover, disubstitution at C3, which hampered the thermal [2,3]-sigmatropic shift of cyclopropenylcarbinyl phosphonites,[10] is well accommodated by the Ireland−Claisen rearrangement. It was observed that the rearrangement of **3a**, although favored by the relief of ring strain, did not experience significant rate acceleration compared to regular allylic glycolates.[12,16] For a more meaningful comparison, the Ireland−Claisen rearrangement of glycolate **3b** substituted by a styryl group was studied. After hydrolysis and esterification, analysis of the crude product by ^{1}H NMR spectroscopy indicated the exclusive formation of vinylcyclopropene **8**, which was isolated in 60% yield. This competition experiment indicates the higher reactivity of an α,β-disubstituted alkene, compared to the more sterically hindered 3,3-dimethylcyclopropene, in the Ireland−Claisen rearrangement (Scheme 3).[17]

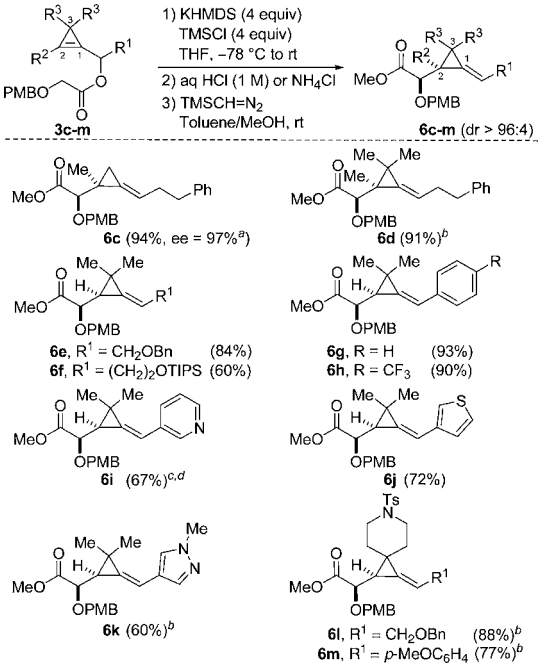
The Ireland−Claisen rearrangement of diversely substituted glycolates **3c−3l** was then investigated to address the scope of this transformation. Not surprisingly, the rearrangement occurs in the absence of *gem*-dimethyl substitution at C3 though the presence of a substituent at C2, such as a methyl group in **3c**, is required to ensure substrate stability. We checked that the rearrangement of the enantioenriched glycolate (*R*)-**3c** (ee = 97%)[7d] afforded the optically active alkylidenecyclopropane **6c**

Scheme 3. Competition between an Alkene and a Cyclopropene in the Ireland−Claisen Rearrangement of 3b



without erosion of the optical purity (ee = 97%). The alkylidenecyclopropane **6d** arising from the Ireland−Claisen rearrangement of the sterically hindered 2,3,3-trimethylcyclopropenylcarbinyl glycolate was also obtained in excellent yield (91%). The Ireland−Claisen rearrangement accommodates a variety of substituents at the α position of the oxygen atom, as illustrated with the formation of **6e** (84%) and **6f** (60%) with alkyl chains containing a protected alcohol, of the benzylidenecyclopropanes **6g** (93%) and **6h** (90%), as well as of compounds **6i** (67%), **6j** (72%), and **6k** (60%) incorporating heteroaryl groups.[18] The *gem*-dimethyl substitution could be varied, in particular by embedding the C3 atom into a nitrogen heterocycle,[19] as illustrated with the formation of the alkylidene-azaspirocycles **6l** (88%) and **6m** (77%) (Scheme 4).

Scheme 4. Ireland−Claisen Rearrangement of Substituted Cyclopropenylcarbinyl Glycolates 3c−l



[a]Obtained from (*R*)-**3c** (ee = 97%). [b]Overall isolated yield from the corresponding cyclopropenylcarbinol (three steps, glycolate precursor not purified). [c]KHMDS (2 equiv) and TMSCl (2 equiv) were used. [d]Workup with H_2O.

The reactivity of glycolate **12** substituted by two methyl esters at C3 deserves particular comments. The requisite cyclopropenylcarbinol precursor **11** was obtained by a sila−Morita−Baylis−Hillman reaction between silylcyclopropene **9** and hydrocinnamaldehyde, catalyzed by tris(2,4,6-trimethyl-phenyl)-phosphine (TTMPP),[20] followed by desilylation (46%). Under the previous conditions, a sigmatropic rearrangement effectively took place and delivered, after workup and esterification, alkylidenecyclopropane **15** (56%) incorporating a TMS group

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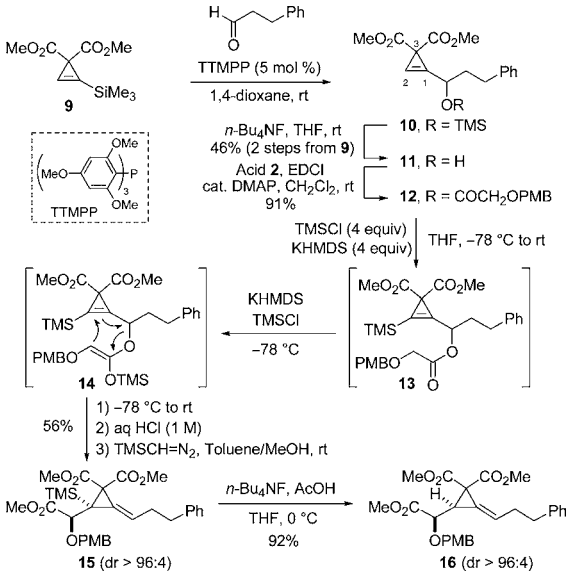
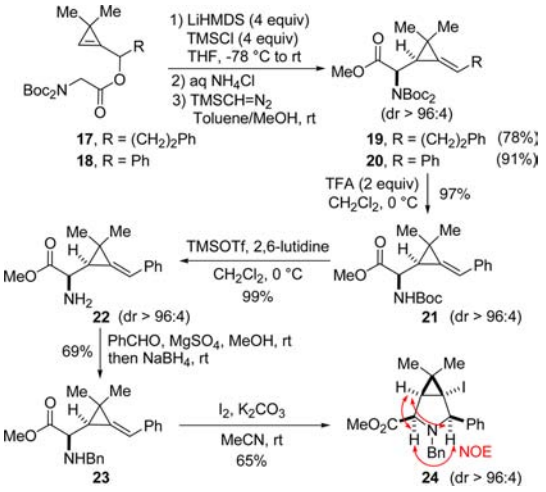
on the three-membered ring. The formation of **15** can be explained by the initial deprotonation of the cyclopropene **12** with KHMDS (4 equiv), due to the increase of acidity provided by the negative inductive effect of the carbomethoxy groups at C3. Related metalated cyclopropenes are known to undergo rapid ring cleavage to the corresponding metalated alkynyl malonates but can be trapped *in situ* with reactive electrophiles such as TMSCl.[21] Thus, the resulting silylcyclopropene **13** would undergo Ireland–Claisen rearrangement, through the silyl ketene acetal intermediate **14**, to provide alkylidene-(silylcyclopropane) **15**. Lowering the quantity of KHMDS (2 equiv) induced quantitative silylation of cyclopropene **12** but resulted in an incomplete Ireland–Claisen rearrangement of **13**, thereby confirming that silylation of **12** precedes the [3,3]-sigmatropic rearrangement. Desilylation of **15** could be accomplished using *n*-Bu_4NF buffered with AcOH to afford alkylidenecyclopropane **16** (92%) (Scheme 5).

Scheme 5. Ireland–Claisen Rearrangement of Glycolate 11 Possessing *gem*-Diester Substitution at C3



Replacement of the glycolate by a glycinate derivative was also briefly examined to further highlight the interest of the [3,3]-Ireland–Claisen rearrangement of cyclopropenylcarbinol derivatives. The *N*,*N*-diBoc glycinates **17** and **18** were selected as substrates for this study.[22,23] The Ireland–Claisen rearrangement was triggered by formation of the corresponding silyl ketene acetals using LiHMDS in the presence of TMSCl (THF, −78 °C to rt).[23] After a mild acidic aqueous workup and esterification ($TMSCHN_2$), alkylidenecyclopropane **19** (78%) and benzylidenecyclopropane **20** (91%) were obtained with high diastereoselectivity (dr >96:4). To elucidate the stereochemical outcome, transformation of compound **20** into a cyclic derivative was considered, which entailed cleavage of the Boc protecting groups. This operation was accomplished in a stepwise manner by treatment with TFA under mild conditions, to avoid jeopardizing the acid-sensitive benzylidene moiety, and subsequent reaction of the *N*-Boc derivative **21** (97%) with TMSOTf in the presence of 2,6-lutidine.[24] The resulting ester **22** (99%) possessing a free amino group underwent reductive amination with benzaldehyde, and the *N*-benzyl amine **23** (69%) was engaged in a stereoselective iodocyclization leading to the azabicyclic compound **24** (65%).[25] The relative configuration of **24**, which was assigned by NMR spectroscopy (NOESY), confirmed that the stereochemical outcome of the Ireland–Claisen rearrangement of cyclopropenylcarbinyl glycolates and glycinates is similar (Scheme 6).[12,23]

Scheme 6. Ireland–Claisen Rearrangement of *N*,*N*-diBoc-Glycinates 17 and 18



To demonstrate the synthetic utility of the functionalized alkylidenecyclopropanes arising from the Ireland–Claisen rearrangement of cyclopropenylcarbinyl esters, the hydrogenation of the exocyclic alkene was investigated to access substituted cyclopropanes. In the presence of Pd/C, hydrogenation of alkylidenecyclopropane **19** proceeded uneventfully and stereoselectively afforded the *cis*-cyclopropane **25** (99%), as a result of hydrogen addition on the less-hindered face of the trisubstituted alkene. By contrast, hydrogenation of alkylidenecyclopropane **6a** led to a 90:10 mixture of *cis*- and *trans*-cyclopropanes **26** and **26′** (99%) and occurred with concomitant cleavage of the PMB group. In this latter case, we reasoned that the diastereoselectivity could be improved if the PMB ether was not cleaved during the reaction. Indeed, by switching to Rh/C as the catalyst, hydrogenolysis of the PMB ether was suppressed and the hydrogenation of **6a** could be achieved with high diastereoselectivity to provide the *cis*-cyclopropane **27** (95%). Conversely, deprotection of the alcohol in **6a** with DDQ enabled a hydroxyl-directed hydrogenation in the presence of Crabtree's catalyst [Ir]-**I**[26] which secured a highly diastereoselective access to the *trans*-cyclopropane **26′** (**26′**/**26** = 97:3) (72%, two steps from **6a**) (Scheme 7).

In summary, we have reported the first examples of Ireland–Claisen rearrangement of esters derived from secondary cyclopropenylcarbinols which complement the repertoire of sigmatropic rearrangements in which these latter substrates have been involved so far. The [3,3]-sigmatropic rearrangement of the silyl ketene acetals generated from cyclopropenylcarbinyl glycolates and *N*,*N*-diBoc glycinates provides a straightforward and diastereoselective access to a wide variety of highly functionalized alkylidenecyclopropanes which are valuable precursors of substituted cyclopropanes. Other functionalizations of the alkylidenecyclopropanes arising from these sigmatropic rearrangements are currently investigated.

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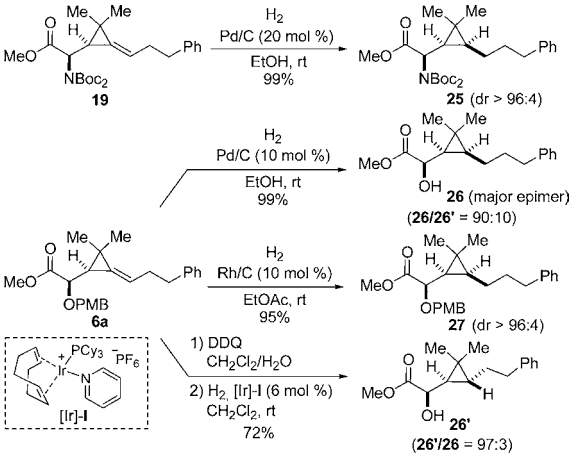
Scheme 7. Diastereoselective Hydrogenation of Alkylidenecyclopropropanes 19 and 6a



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01759.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(17) Competition between styryl and 2-methylcycloprop-1-enyl groups was not studied, as the corresponding carbinol is too unstable.

(18) Substrates with R^1 substituents leading to strongly adjacent C−H bonds (such as the pyridin-2-yl group) cannot be used.

(19) Only cyclopropenes possessing two identical substituents at C3 have been considered as substrates to date.

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(27) The diastereoselective hydrogenation of alkylidenecyclopropane **6c**, lacking the *gem*-dimethyl substitution at C3 and possessing a quaternary stereocenter at C2, is disclosed in the Supporting Information.

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