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Stereospecific and Stereoselective Alkyl and Silylcyclopropanation of α,β-Unsaturated Amides

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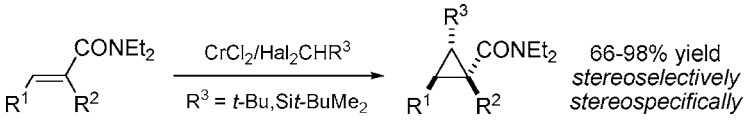
ABSTRACT



A novel chromium-promoted alkyl- and silyl cyclopropanation of (*E*)- or (*Z*)-α,β-unsaturated amides in which the C–C double bond is di-, or trisubstituted is described. This process takes place with total stereospecificity, and the new stereogenic center is generated with high or total stereoselectivity. A mechanism is proposed to explain the cyclopropanation reaction.

The smallest cycloalkane[1] can be found in a wide number of natural products. In addition, the use of cyclopropanes in biological mechanistic studies and their utility as synthetic intermediates warrants interest in these carbocycles from a variety of fields in organic chemistry.[2] Moreover, cyclopropanecarboxylic acids and their derivatives are important building blocks and have been used as starting materials in the synthesis of a range of compounds such as pyrethrins, pyrethroids, and other industrially valuable compounds that are abundant in nature.[3] In general, these cyclopropyl derivatives can be generally accessed through the metal-catalyzed decomposition of diazocompounds or through the cyclopropanation of various unsaturated acceptors. In the case of the synthesis of 2-silylcyclopropanecarboxylic acid derivatives, to the best of our knowledge only three examples[4] have been reported with the 2-silylcyclopropanoates being obtained in low yields, low stereoselectivities, and with poor generality and substitution patterns on the cyclopropane ring. Taking into account the synthetic applications of these compounds,[5] an efficient synthesis of 2-silylcyclopropanecarboxamides, in which a new stereogenic center can be generated to furnish only one diastereoisomer would be desirable.

Very recently, Takai et al. reported an efficient silylcyclopropanation of terminal alkenes by using I_2CHSiR_3 or a LiI/Br_2CHSiR_3 mixture, promoted by $CrCl_2$ in the presence

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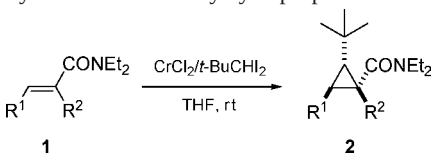
of TMEDA.[6] The *trans/cis* ratios of the obtained silylcyclopropanes ranged between 63/37 and 87/13, the reaction was carried out using nonfunctionalized terminal alkenes, and consequently no information about the conservation of the geometry of the starting olefin has been reported. We have also recently described the stereospecific cyclopropanation of α,*β*-unsaturated amides, in which the C−C double bond was di-, tri-, or tetrasubstituted, using also $CrCl_2$ and chloroiodomethane.[7]

In this communication we describe a novel stereospecific alkyl- and silylcyclopropanation of α,*β*-unsaturated amides with total stereoselectivity promoted by $CrCl_2$. The cyclopropanation process took place with complete stereochemical control of the newly generated stereogenic center, affording a single diastereoisomer of the proposed alkyl- and silylcyclopropanecarboxamide. A mechanism is proposed to explain these results.

Taking into account the difficulty that is presented in the last objective (stereoselective generation of a new stereogenic center during the cyclopropanation), prior to attempting the synthesis of 2-silylcyclopropanecarboxamides, we initially studied the easier $CrCl_2$-mediated alkylcyclopropanation of α,*β*-unsaturated amides[8] using the commercially available *t*-$BuCHI_2$. Thus, the treatment of several α,*β*-enamides **1** with 4.0 equiv of $CrCl_2$ and 3.75 equiv *t*-$BuCHI_2$ at room temperature afforded, after hydrolysis, the corresponding *tert*-butylcyclopropylamides **2** as a single diastereoisomer (dr > 98/2, determined on the crude reaction products by GC−MS and 300 MHz ^{1}H NMR) and in high yields (Table 1).

Table 1. Synthesis of *tert*-Butylcyclopropanecarboxamides **2**



1 **2**

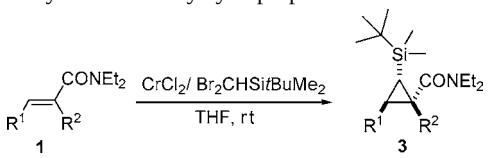
entry	**2**	R^1	R^2	dr[a]	yield (%)[b]
1	**2a**	*n*-Bu	Me	>98/2	79
2	**2b**	Ph	Me	>98/2	98
3	**2c**	*p*-$MeOC_6H_4$	Me	>98/2	80

[a] Diastereoisomeric ratio (dr) was determined by GC−MS and 300 MHz ^{1}H NMR analysis of the crude products **2**. [b] Yields of the isolated products after column chromatography based on compound **1**.

With these preceding results in hand, our following efforts were directed toward the synthesis of 2-silylcyclopropylamides. Hence, this process was carried out with the corresponding commercially available dibromomethylsilane.

Thus, when a mixture of 4.0 equiv of $CrCl_2$ and 3.75 equiv of $Br_2CHSitBuMe_2$ was stirred at room temperature for 18 h in the presence of the corresponding α,*β*-enamides **1**, cyclopropylamides **3** were obtained after hydrolysis in high yields. In all of these cases, only one stereoisomer was obtained (determined by analysis of the crude materials by GC−MS and/or 300 MHz ^{1}H NMR spectroscopy); the new stereogenic center was therefore generated with complete stereoselectivity (Table 2).[9]

Table 2. Synthesis of Silylcyclopropanecarboxamides **3**



1 **3**

entry	**3**	R^1	R^2	dr[a]	yield (%)[b]
1	**3a**	Me	H	>98/2	81
2	**3b**	*n*-C_5H_{11}	H	95/5[c]	66
3	**3c**	*i*-Bu	H	>98/2	78
4	**3d**	*n*-Bu	Me	>98/2	79
5	**3e**	Ph	Me	>98/2	84
6	**3f**	*p*-$MeOC_6H_4$	Me	>98/2	76

[a] Diastereoisomeric ratio (dr) was determined by GC−MS and 300 MHz ^{1}H NMR analysis of the crude products **3**. [b] Yields of the isolated products after column chromatography based on compound **1**. [c] dr of the starting amide 95/5.

The structure and relative configuration of *tert*-butylcyclopropylamides **2**, and silylcyclopropanes **3** (as depicted in Tables 1 and 2) were established by analysis of the ^{1}H NMR coupling constants between the cyclopropane protons of compounds **2a**−**c** and **3b**−**f**, by NOE experiments in the case of compounds **3c** and **3e**, and by single-crystal X-ray analysis of compound **3e**.[10] The NOE experiment in compound **3e** was in accordance with the obtained X-ray structure.

It is worth noting that the relative configuration of the alkene is conserved and that a new stereogenic center has been generated with complete stereoselectivity, affording a cyclopropane ring showing a 1,2,3-subsitution pattern in which the *tert*-butyl or silyl group has a *cis*-disposition relative to the amide functional group.

The stereospecificity of this silylcyclopropanation was unambiguously established starting from (*Z*)-*N*,*N*-dimethyloct-2-enamide (Scheme 1).[11] It was shown that the geometry of the C=C bond was conserved during the cyclopropanation process: **4** was then obtained as a 77/23 mixture from a 78/22 *Z*/*E* mixture of the starting α,*β*-unsaturated amide (GC−

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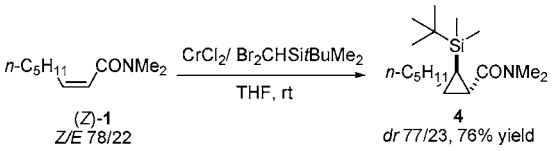
(8) (*E*)-α,*β*-Unsaturated amides **1** were prepared following the methods described in: (a) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 3062−3068. (b) Concellón, J. M.; Rodríguez-Solla, H.; Díaz, P. *J. Org. Chem.* **2007**, *72*, 7974−7979.

(9) In the case of compound **3b** although dr = 95/5 the reaction was also completely stereoselective since the *E*/*Z* ratio of the starting α,*β*-unsaturated amide was 95/5.

(10) CCDC 630875 contains the supplementary crystallographic data for compound **3e**. These data can be obtained free of charge via: www.ccdc.cam.ac.uk/conts/retrieving.html (or the Cambridge Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax (+44)1223-336-033, or e-mail deposit@ccdc.cam.ac.uk).

(11) (*Z*)-*N*,*N*-Dimethyloct-2-enamide was obtained from the catalytic Lindlar's hydrogenation of *N*,*N*-dimethyloct-2-inamide.

Scheme 1. Synthesis of Silylcyclopropylamides Starting from (*Z*)-α,*β*-Enamides



MS and/or 300 MHz ^{1}H NMR) and in 76% yield. In this case, the silyl group adopted a *trans*-relative position with respect to the carboxamide instead of the *cis*-relative position observed when the (*E*)-unsaturated amides were employed as starting material.

The relative configuration of substituents on the cyclopropane ring of compound **4** was again established by NOESY experiments and analysis of the ^{1}H NMR coupling constants between the cyclopropane protons.

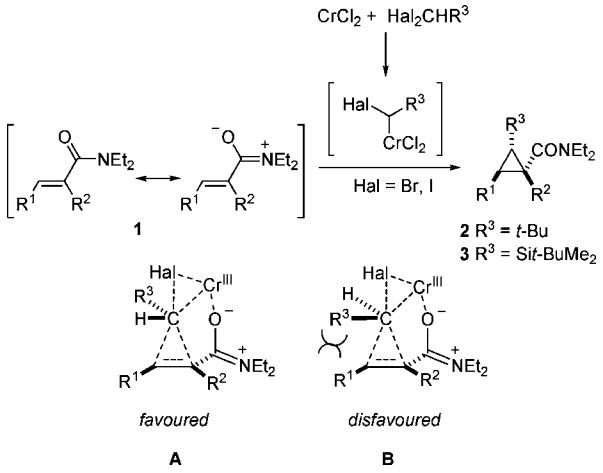
It is worth noting that (1) this alkyl- and silylcyclopropanation reaction seems to be general and aliphatic (linear or branched) and aromatic unsaturated amides **1** can be employed as starting materials; (2) di- and trisubstituted C−C double bonds can be efficiently cyclopropanated, affording mainly only one stereoisomer (Tables 1 and 2); (3) the cyclopropanation takes place in high yields; (4) in contrast with other methods, no employment of diamines or other additives is necessary to promote the cyclopropanation (Indeed, when the reaction was performed in the presence or absence of diamines, no significant differences were detected.[12]); and finally (5) the determination of the structure for compounds **2**, **3**, and **4** has proven that the cyclopropanation process takes place with complete stereospecificity since the geometry of the C=C bond of both (*E*)- or (*Z*)-α,*β*-enamides is conserved during the cyclopropanation process Table 2/Scheme 1).

Mechanism. Synthesis of products **2** and **3** may be rationalized by assuming the formation of chromium (III) carbenoids and using a model similar to that proposed by Houk for the addition of carbenoids to olefins.[13] This staggered model has also been utilized to explain the cyclopropanation of α,*β*-unsaturated amides by using the $CrCl_2$/ICH_2Cl system.[7]

Tentatively, we propose a transition-state model depicted as **A**/**B** in Scheme 2, in which the transition state **A** could be favored when compared with **B** due to the steric hindrance between the R^1 and R^3 groups.

The coordination of the Cr(III) center (from the incipient :CHR^3 carbene) with the oxygen atom of the amide group provides the obtained cyclopropylamides **2** and **3** (R^3 = *t*-Bu and Si*t*-BuMe_2 respectively), while maintaining the C=C bond geometry. In this proposed transition state the C=C bond and the C=O double bonds are not conjugated. Indirect support for this mechanistic proposal could be the fact that

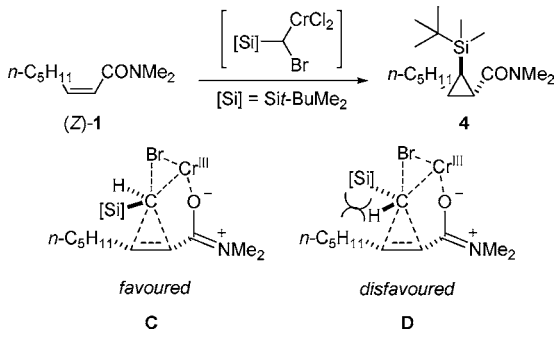
Scheme 2. Proposed Mechanism



no cyclopropanation reaction takes place on α,*β*-unsaturated esters under the same reaction conditions. This experimental result also suggests that the electron-donating character of the nitrogen is decisive in the cyclopropanation of the C−C double bond.

This proposed mechanism also explains the observed stereospecificity of the cyclopropanation. Thus, in cyclopropane **4** obtained from a *Z*-amide (Scheme 1) the silyl group is in an opposite spatial disposition, with respect to those shown by cyclopropanes obtained from *E*-amides (Table 2). Thus, in the reaction of *Z*-amides, the favored transition state could be **C**, since the silyl group would adopt a *trans*-disposition relative to the pentyl group rather than the *cis*-disposition shown in the less favored transition state **D** (Scheme 3).

Scheme 3. Mechanistic Proposal for the Cyclopropanation of (*Z*)-Unsaturated Amides



In conclusion, a $CrCl_2$-promoted stereospecific alkyl- and silylcyclopropanation reaction of α,*β*-unsaturated amides with complete or very high stereoselectivity and in high yields was carried out. This cyclopropanation process is achieved from α,*β*-unsaturated amides in which the C=C bond is di- and trisubstituted. Generalization of this reaction and studies to fully delineate all the factors involved in these transformations are currently under investigation in our laboratory.

(12) The use of diamines, TMEDA or TEEDA, was necessary to carry out the silylcyclopropanation described in reference 6.

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Supporting Information Available: General procedure, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds **2**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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