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Stereospecific Cyclopropanation of Highly Substituted C–C Double Bonds Promoted by $CrCl_2$. Stereoselective Synthesis of Cyclopropanecarboxamides and Cyclopropyl Ketones

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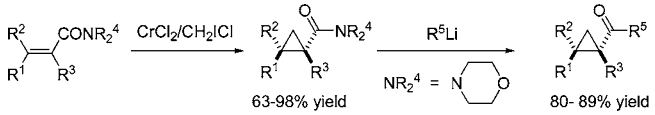
ABSTRACT



We describe herein a $CrCl_2$-promoted cyclopropanation of α,*β*-unsaturated amides. This reaction can be carried out on (*E*)- or (*Z*)-α,*β*-enamides in which the C–C double bond is di-, tri-, or tetrasubstituted. In all cases the process is completely stereospecific and only a single diastereoisomer is obtained. In addition, cyclopropyl ketones were readily prepared by reaction of the cyclopropanecarboxamides (derived from morpholine) obtained with a range of organolithium compounds. A mechanism has been proposed to explain the cyclopropanation reaction.

In general the properties and reactions of cyclopropanes are significantly different in comparison to those of other carbocycles.[1] The smallest cycloalkane is present in an important number of natural products[2] and compounds bearing this moiety are largely used to elucidate biological mechanisms.[3]

Although the Simmons−Smith reaction[4] is considered one of the most widely employed methods for cyclopropanation processes, the two most commonly utilized methodologies to access cyclopropyl esters or amides with high stereoselectivity are the metal-catalyzed decomposition of diazocompounds[2b,5] or through the cyclopropanation of different unsaturated acceptors.[2b,6]

Despite strenuous efforts, the difficulty or impossibility to cyclopropanate highly substituted C=C bonds[5a,b,d,6a−c] or

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C−C double bonds with unsaturated esters or amides having (*Z*)-stereochemistry[6a] remains clear.

In the established case of cyclopropyl ketones, various methods for their preparation have been developed since the cyclopropyl ketone moiety exhibits important properties in mechanistic studies and it is also found in marine organisms conferring important physiological properties.[7] Generally, the cyclopropyl ketone moiety is mostly synthesized by using the cyclopropanation methodology of Michael acceptors;[8] nevertheless some other methods for their preparation are also reported in the literature.[9]

For all of these reasons, an efficient synthesis of cyclopropanecarboxamides and cyclopropyl ketones is desirable.

Very recently, $CrCl_2$-promoted cyclopropanation processes of terminal alkenes, in moderate or good stereoselectivity, were reported.[10] Consequently, no information about the conservation of the olefin geometry during the cyclopropanation reaction can be established. In addition, alkenes in which the olefinic carbons were di-, tri-, or tetrasubstituted could not be cyclopropanated by using these $CrCl_2$-mediated methods. Previously, we have reported the stereospecific cyclopropanation of (*E*)- and (*Z*)-α,*β*-unsaturated amides by using a mixture of samarium and diiodomethane.[11]

Thus, our own results[11] and Takai's fore-mentioned work[10] prompted us to test the possible cyclopropanation reaction of α,*β*-unsaturated amides promoted by $CrCl_2$. Thus, in this Letter we describe the cyclopropanation of α,*β*-unsaturated amides by reaction with chloroiodomethane in the presence of $CrCl_2$. It is noteworthy that this reaction can be carried out from (*E*)- or (*Z*)-enamides in which the C−C double bond is di-, tri-, or tetrasubstituted and takes place with complete stereospecificity and in higher yield than with Sm/CH_2I_2. In addition, cyclopropyl ketones were readily prepared by reaction of the obtained cyclopropanecarboxamides (derived from morpholine) with a range of organolithium compounds. A mechanism has been proposed to explain the cyclopropanation reaction.

Initially the cyclopropanation reaction of α,*β*-unsaturated amides **1**[12] was carried out on *N*,*N*-diethylcinnamamide **1e** at room temperature, with the amount of ICH_2Cl, $CrCl_2$, reaction time, and temperature being varied. The obtained results are shown in Table 1.

Table 1. Study of the Reaction Conditions Based on *N*,*N*-Diethylcinnamamide **1e**

entry	$CrCl_2$ (equiv)	CH_2ICl (equiv)	*T*	*t* (h)	yield (%)[a]
1	2.5	2.5	rt	96	61
2	3.0	3.0	rt	96	75
3	4.0	3.75	rt	96	89
4	4.0	3.75	rt	96	85[b]
5	4.0	3.75	rt	96	76[c]
6	4.0	3.75	reflux	18	98

[a] Yield of the isolated product after column chromatography based on compound **1e**. [b] TMEDA was added (see ref 10). [c] CH_2I_2 was employed instead of CH_2ICl.

After testing the reaction conditions shown in Table 1, the best results were obtained by treatment of the *N*,*N*-diethylcinnamamide **1e** (0.4 mmol, 1 equiv)[13] with a mixture of $CrCl_2$ (4.0 equiv) and CH_2ICl (3.75 equiv) at reflux. These reaction conditions afforded, after hydrolysis, the corresponding cyclopropylamide **2e** with total stereoselectivity and in high yields (Table 2).

After this study, the cyclopropanation reaction was then performed on various α,*β*-unsaturated amides. As is shown in Table 2, the reaction seems to be general and cyclopropanation can be carried out on a variety of aliphatic (linear, cyclic, branched, and unsaturated) and aromatic α,*β*-unsaturated amides **1**. Taking into account the absence of alternative methods to cyclopropanate the highly substituted C−C double bond, the results obtained in the cyclopropanation of enamides in which the C−C double bond is tri- or tetrasubstituted were especially interesting. It is noteworthy that the process took place with total chemoselectivity since only the cyclopropanation reaction of the 2,3-double bond took place in the case of the polyunsaturated amide **1b** (Table 2).

Other significant aspects of the described cyclopropanation were the following: (1) No important differences were observed when the reaction was performed on amides derived from different amines, so no lower stereoselectivity was observed from amides with bulky groups (R^4= *i*-Pr) on the carbonyl amide (Table 2). (2) No additives were necessary to perform the cyclopropanation reaction, in opposition to other previously described methods.[10] (3) Cyclopropylamides were prepared in higher yields (approximately a 20%

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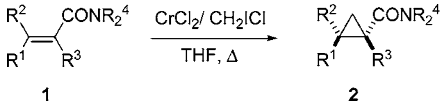
(12) (a) α,*β*-Unsaturated amides **1** were prepared following the method described in: Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 3062−3068. (b) Compounds **1e**−**g** were easily obtained through the amination of cinnamoyl chloride in THF. (c) (*Z*)-Cinnamamide **1h** was obtained from the catalytic Lindlar's hydrogenation of *N*,*N*-diethyl-3-phenylpropiolamide. (d) (*Z*)-Amide **1o** was prepared by using the method described in: Concellón, J. M.; Bardales, E. *J. Org. Chem.* **2003**, *68*, 9492−9495.

(13) Although the reactions were all carried out on a 0.4 mmol scale, when this process was carried out on a 3 mmol scale no differences were observed. However, 4 equiv of $CrCl_2$ were necessary; when a lower amount of $CrCl_2$ was employed (3 equiv) lower yields were obtained (see also Table 1).

Table 2. Synthesis of Cyclopropanecarboxamides **2**



2	R^1	R^2	R^3	R^4	dr[a]	yield (%)[b]
a	Me	H	H	Et	>98/2	68
b	MeCH=CH	H	H	Et	93/7[c]	90
c	*n*-C_7H_{15}	H	H	Et	>98/2	89
d	Cy	H	H	Et	>98/2	92
e	Ph	H	H	Et	>98/2	98
f	Ph	H	H	*i*-Pr	>98/2	89
g	Ph	H	H	d	>98/2	79
h	H	Ph	H	Et	>98/2	98
i	*i*-Bu	H	Me	Et	98/2	89
j	*n*-C_7H_{15}	H	Me	Et	98/2	88
k	Cy	H	Me	Et	>98/2	84
l	Ph	H	Me	Et	>98/2	91
m	Ph	H	Me	*i*-Pr	>98/2	79
n	Ph	H	Me	*d*	>98/2	90
o	H	*p*-ClC_6H_4	Me	*i*-Pr	>98/2	87
p	Et	Et	Me	Et		97
q	*n*-Pr	Me	Me	Et	68/32[e]	63
r	*n*-C_5H_{11}	Me	Me	Et	96/4[f]	79
s	Ph	Me	Me	Et	98/2[g]	86
t	Ph	Et	Me	Et	92/8[h]	85

[a] Diastereoisomeric ratio (dr) of the cyclopropylamides **2** was determined by GC-MS and/or ^{1}H NMR (300 MHz) analysis of the crude reaction products. [b] Yields of the isolated products (major diastereoisomer) after column chromatography based on compounds **1**. [c] dr of the starting amide **1b**, 93/7. [d] From morpholine. [e] dr of the starting amide **1q**, 68/32. [f] dr of the starting amide **1r**, 95/5. [g] dr of the starting amide **1s**, >98/2. [h] dr of the starting amide **1t**, 94/6.

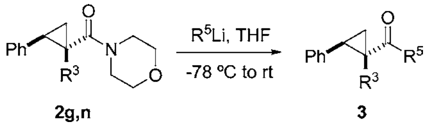
increase) than the previously obtained compounds **2b**, **2e**,**f**, **2h**, **2j**−***l***, and **2t** with the Sm/CH_2I_2 system.[11a]

The relative configuration of the cyclopropane ring was established by comparison with the data previously reported in the literature for products **2b**, **2e**,**f**, **2h**, **2j**−**l**, **2t**,[11a] and **2d**,[11b] by analysis of the ^{1}H NMR coupling constants between the cyclopropane protons of compounds **2a**, **2c**, and **2g**,[14] or by NOESY experiments in the case of tri- and tetrasubstituted cyclopropanes **2i**, **2o**, and **2s**. The structure and relative configuration of the other cyclopropylcarboxamides **2** was assigned by analogy.

After this determination it could be established that the starting enamides **1** and cyclopropanecarboxamides **2** present the same relative configuration. Consequently, the cyclopropanation reaction took place with conservation of the C=C bond geometry of the starting material **1** affording only one diastereoisomer of **2**. This fact together with the synthesis of cyclopropanamides **2b** and **2q**−**t** with the same dr as those shown by the starting unsaturated amides **1** (Table 2) could support the complete stereospecificity of the cyclopropanation reaction. To unambiguously prove the stereospecificity of the reaction, the cyclopropanation of (*E*)-[12b] and (*Z*)-cinnamamide[12c] was carried out (Table 2, starting compounds **1e** and **1h**). In both cases, the geometry of the C=C bond was conserved during the cyclopropanation, each yielding a sole diastereoisomer as the reaction product.

Taking into account the synthetic applications of amides derived from morpholine,[15] α,β-unsaturated amides derived from morpholine were readily prepared from the corresponding α,β-unsaturated acid chloride and morpholine.[12b] Cyclopropanation reactions of these α,β-enamides **1g** and **1n** gave the corresponding cyclopropylamides **2g** and **2n** with total stereoselectivity and in good yields. The reaction of **2g** and **2n** with a range of organolithium compounds at −78 °C for 1 h afforded the corresponding crude cyclopropyl ketones **3a**−**g** without any loss of diastereoselectivity and in high yields (Table 3).

Table 3. Synthesis of Cyclopropyl Ketones **3**



entry	**3**	R^3	R^5	dr[a]	yield (%)[b]
1	**a**	H	Me	>98/2	80
2	**b**	H	*n*-Bu	>98/2	86
3	**c**	H	Ph	>98/2	89
4	**d**	Me	Me	>98/2	91
5	**e**	Me	*n*-Bu	>98/2	88
6	**f**	Me	CH_2SiMe_3	>98/2	82
7	**g**	Me	allyl	>98/2	85[c]

[a] Diastereoisomeric ratio (dr) of the cyclopropylketones **3** was determined by GC-MS and/or ^{1}H NMR (300 MHz) analysis of the crude reaction products. [b] Yields of the isolated products after column chromatography based on compounds **2**. [c] This reaction was carried out by using the corresponding Grignard derivative (under the same conditions) rather than the organolithium compound.

Synthesis of products **2** might be explained 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 (Scheme 1).[16] This staggered model has also been utilized to explain the cyclopropanation of α,β-unsaturated amides by using the Sm/CH_2I_2 system.[11]

Tentatively, we propose a transition state model **A** in which the C−C double bond is not conjugated with the amide carbonyl group[17] and the coordination of the Cr^{III} center (from the incipient :CH_2 carbene) to the oxygen atom of the amide group providing the obtained cyclopropylamides **2**, while maintaining the C=C bond geometry (Scheme 1).

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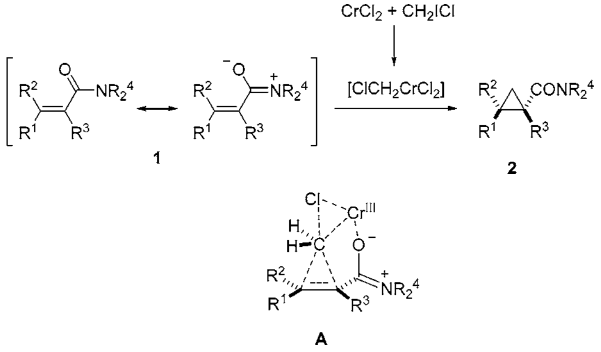
(17) This is based on the well-known resonance of the lone pair electron of the nitrogen atom with the carbonyl group. As a consequence of this conjugation the free rotation through the CO−N bond is restricted, being this CO−N bond is shorter than a C−N bond (*The Chemistry of Acid Derivatives* Patai, S., Ed.; John Wiley and Sons: New York, 1979; Supplement B).

Scheme 1. Proposed Mechanism



Indirect support for this mechanistic proposal is provided by the fact that no cyclopropanation reaction of α,*β*-unsaturated esters is observed under the same reaction conditions. This experimental result suggested that both the electron-donating character of the nitrogen and the lack of conjugation of the C−C double bond with the amide carbonyl group are decisive in the cyclopropanation of the C−C double bond favoring the coordination of the oxygen atom of the amide group with the Cr^{III} center.

In conclusion, a cyclopropanation reaction of α,*β*-unsaturated amides with complete stereospecificity and high yields with use of CrCl$_2$/CH$_2$ICl has been developed. Interestingly, cyclopropanecarboxamides can be accessed from α,*β*-unsaturated amides in which the C−C double bond is di-, tri-, or tetrasubstituted. The reaction of cyclopropanamides derived from morpholine with a range of organolithium reagents readily afforded cyclopropyl ketones, as a single diastereoisomer and in high yields. Other synthetic applications of this CrCl$_2$-promoted cyclopropanation process, including studies directed toward fully delineating the factors involved in these transformations, and the preparation of functionalized and enantiopure cyclopropylamides are currently under investigation within our laboratory.

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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** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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