ORGANIC LETTERS

2002
Vol. 4, No. 24
4273−4276

First Intermolecular Cyclopropanation of Fischer Dialkylaminocarbene Complexes. Synthesis of 1-Aminocyclopropanecarboxylic Acid Derivatives

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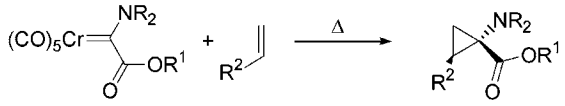
Received September 13, 2002

ABSTRACT



The first cyclopropanation reaction of olefins with Fischer dialkylaminocarbene complexes is presented. The reaction yields 1-aminocyclopropanecarboxylic acid derivatives in a single step, usually with high diastereoselectivity. An approach to the asymmetric version of this reaction is also presented. The synthetic utility of the procedure is exemplified by the synthesis of both cycles of metanoproline in a single step. In addition, the synthesis of the first Fischer carbene containing a halocarbonyl group is reported.

Fischer carbene complexes have become valuable tools for stoichiometric carbon−carbon bond formation over the last three decades.[1] One of the earliest synthetically significant reactions developed for this class of complexes was the thermal cyclopropanation of olefins.[2] Many of the traditional limitations of this reaction have recently been overcome: the lack of diastereoselectivity,[3] the somewhat harsh reaction conditions,[4] the cyclopropanation of nonactivated dienes[3] and, more recently, the cyclopropanation of nonconjugated olefins.[5] Nevertheless, a long-standing limitation has been the cyclopropanation reaction of aminocarbene complexes, which are rather less reactive than their alkoxy counterparts. Apart from the inertness of aminocarbene complexes, the main reason for the failure of the reaction with electron-poor olefins is the low stability of the product, a cyclopropane that bears an amine and an electron acceptor group in

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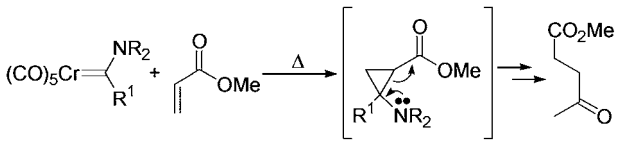
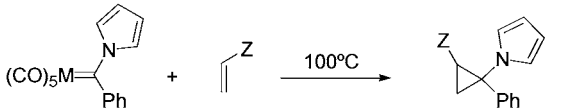
10.1021/ol026896p CCC: $22.00
Published on Web 10/30/2002

adjacent carbons. At the reaction temperature this kind of compound evolves toward the cyclopropane opening products (Scheme 1).[6] We know of only one case where a cyclopropane has been isolated from the reaction of an aminocarbene complex with an alkene.[7] In this elegant approach, Hegedus et al. reduced the electron-donor ability of the nitrogen atom by its inclusion in an aromatic pyrrol ring (Scheme 2), thus making the complex more similar to an alkoxycarbene.

Scheme 1



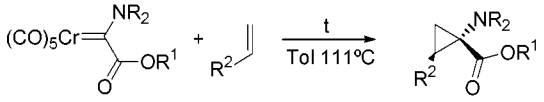
Scheme 2



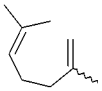
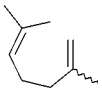
The instability of the resulting aminocyclopropanes can be avoided by reacting the carbene complexes with nonconjugated olefins. We have recently developed a method for the cyclopropanation of this type of olefin, its success being based on the stabilization of reaction intermediate by intramolecular coordination with a suitably placed donor group.[6] With the purpose of generalizing this reaction, we recalled the recent publication of two syntheses of (alkoxycarbonyl)dialkylaminocarbene complexes,[8] in which the ester oxygen may serve for this kind of coordination. Furthermore, the cyclopropanes so formed would be 1-aminocyclopropanecarboxylic acid (ACC) derivatives, which are interesting compounds since they are present in a number of natural and biologically active compounds, and can be used as conformationally restricted analogues of proteinogenic amino acids.[9] We report herein our results in the cyclopropanation of nonconjugated olefins with (alkoxycarbonyl)dialkylaminocarbene complexes, which turns out to be the first successful cyclopropanation reaction of a dialkylaminocarbene.

Aminocarbene complexes **1** were treated with an excess of monosubstituted olefins **2** in refluxing toluene until complete disappearance of the starting complexes was observed. The only product isolated from the reaction was the corresponding cyclopropane **3**, usually as a single diastereomer (Table 1).[10] It was found that the reaction tolerates aryl, alkyl, and alkenyl substituents in the olefin (entries **a**, **b**, and **d**). The diastereoselectivity of the process is in line with that described for the cyclopropanation of nonconjugated olefins with alkoxycarbene complexes. In both cases the substituent of the olefin and the chelating substituent of the carbene carbon (here the alkoxycarbonyl group) end preferentially in the same side of the cyclopropane. It is worth mentioning that the molybdenum analogue of complex **1b** failed in producing these cyclopropanes in a variety of conditions tested. The synthetic potential of this methodology is enhanced by the possibility of forming ACC derivatives suitably substituted for the deprotection of both the amino and the acid functions (Table 1, entry **e**).

Table 1. Cyclopropanation Reactions of Carbene Complexes **1**



1 **2** **(±)-3**

comp.	NR_2	R^1	R^2	t (h)	d.e. (%)	yield (%)
3a	NMe_2	^{t}Bu	Ph	24	>95	47
3b	NMe_2	^{t}Bu	Hx	50	>95	70
3c	NMe_2	^{t}Bu	CH_2OTBS	30	0	45
3d	NMe_2	^{t}Bu		48	30	30
3e	NBn_2	Me	Ph	24	>95	35
3f	Morf.	Me	Ph	30	>95	70
3g	Morf.	Me		20	>95	69

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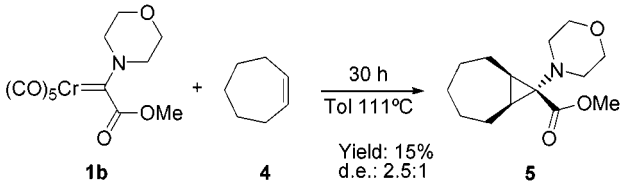
(10) General experimental procedure for the cyclopropanation reaction: A 0.1 M solution of complex **1** or **8** in toluene was treated with 4 equiv of the olefin **2** and deoxygenated (3 freeze−pump−thaw cycles). The mixture was then refluxed while a constant flow of N_2 (g) was bubbled through it. Once all the carbene complex was consumed (as seen by IR monitoring) the reaction mixture was exposed to the air and sunlight. The reaction was then filtered through Celite and chromatographed on silica gel. Selected data: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.31−7.25 (m, 5H, Ph), 2.68 (s, 6H, N(C**H**$_3$)$_2$), 2.62 (dd, 1H, J = 9.5, 7.7 Hz, C**H**Ph), 1.93 (dd, 1H, J = 7.7, 4.6 Hz, 3β-ciclopropane), 1.29 (dd, 1H, J = 9.5, 4.6 Hz, 3α-ciclopropane), 1.10 (s, 9H, C(C**H**$_3$)$_3$). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm) 169.9 (**C**O_2R), 136.8 (**C** ipso), 129.2 (2 × **C**H, Ph), 127.8 (2 × **C**H, Ph), 126.4 (**C**H, *p*-Ph), 80.5 (**C**Me$_3$), 54.0 (**C**NMe$_2$), 41.4 (N(CH_3)$_2$), 35.2 (**C**HPh), 27.7 (C(**C**H$_3$)$_3$), 21.2 (**C**H$_2$). HRMS (IE): calcd 261.1729; found 261.1743.

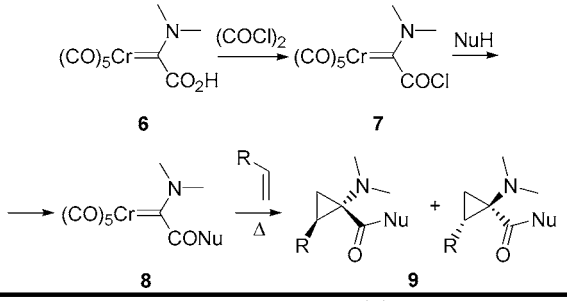
The reaction is quite sensitive to the steric size of the olefin, and trisubstituted substituents are not cyclopropanated in these conditions. The cyclopropanation of disubstituted olefins could not be carried out with carbene complex **1a**, but the reaction of complex **1b** with cycloheptene affords bicyclic cyclopropane **5**, although in low yield (Scheme 3).

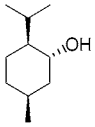
Scheme 3



The extension of this reaction to the preparation of enantiomerically enriched cyclopropanes required the preparation of carbene complexes bearing chiral auxiliaries. The synthetic methods developed by Beck et al.[8b] and Dvorak et al.[8a] proved not to be adequate for the preparation of these complexes. We envisioned a convergent entry to these compounds by activation and derivatization of the ester moiety in carbene complex **1a** (Table 2). We performed the

Table 2. Synthesis and Cyclopropanation Reactions of Carbene Complexes **8**



entry	NuH	yield **8**	R	t (h)	yield **9**	d.r.
a		33 %	Ph	24	45 %	2:1
b		60 %	Hx	28	35 %	1.5:1

first step (deprotection of the ester) according to a previously reported procedure,[8a] and next carried out the activation by reacting carboxylic acid **6** with oxalyl chloride in CH_2Cl_2 at room temperature. Acyl chloride **7** was obtained in nearly quantitative yield as a pale yellow solid. Then, the reaction with an appropriate nucleophile afforded chiral carbene complexes **8**. Treatment of these complexes with terminal olefins in the conditions described above provided the

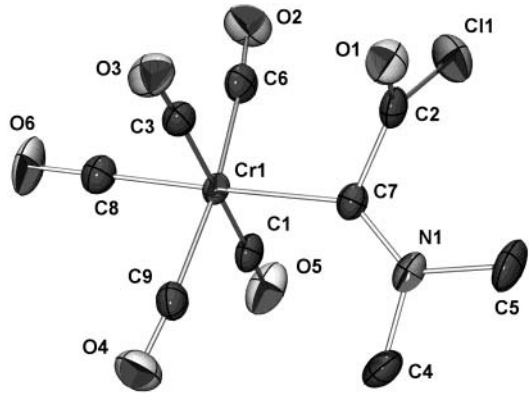


Figure 1. X-ray structure of halocarbonyl carbene complex **7**.

corresponding cyclopropanes **9** as a mixture of both cis diastereoisomers (Table 2).

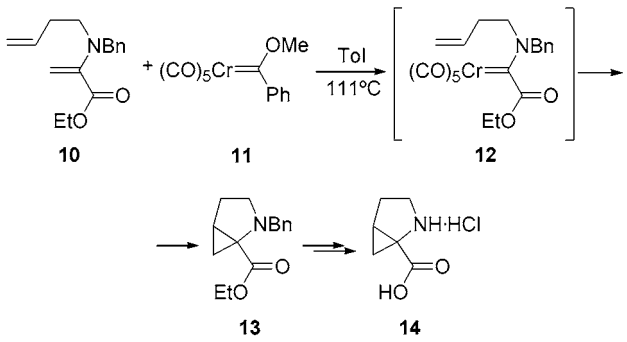
To the extent of our knowledge, complex **7** is the first example of a carbene complex bearing an acyl halide moiety in its structure. To ascertain its structure we carried out an X-ray diffraction experiment (Figure 1, Table 3). The most

Table 3. Bond Lengths and Angles of the X-ray Structure

bond lengths (Å)		bond and dihedral angles (deg)	
Cr1−C9	1.896(4)	C9−Cr1−C7	93.64(13)
Cr1−C1	1.903(4)	C1−Cr1−C7	90.99(10)
Cr1−C6	1.904(4)	C6−Cr1−C7	94.84(13)
Cr1−C3	1.915(4)	C3−Cr1−C7	88.58(10)
Cr1−C7	2.098(3)	C7−N1−C4	122.6(2)
Cl1−C2	1.804(3)	C7−N1−C5	125.0(3)
O1−C2	1.176(4)	C4−N1−C5	112.4(2)
N1−C7	1.295(4)	C9−Cr1−C7−N1	34.4(3)
N1−C4	1.471(4)	C5−N1−C7−Cr1	−175.7(2)
N1−C5	1.474(4)	O1−C2−C7−N1	−92.9(4)
C2−C7	1.494(4)	O1−C2−C7−Cr1	82.9(3)

notable feature is the lack of conjugation between the halocarbonyl and the carbene functions. On the contrary, the latter is fully conjugated with the dialkylamino moiety.

Scheme 4



A further step to increase the synthetic utility of the cyclopropanation reaction would be to carry it out in an intramolecular manner. When we tried to synthesize the homoallylaminocarbene **12** by metathesis reaction of dehydroamino acid **10** and carbene complex **11** the only isolable product was ethyl *N*-benzylhomoprolinate **13** (Scheme 4), which probably arises from the intramolecular cyclopropanation of aminocarbene **12** in the reaction conditions. Homoprolinate **13** was easily deprotected following standard methodology to afford homoproline **14** as chlorhydrate.

In conclusion, we have reported the first cyclopropanation reaction of Fischer dialkylaminocarbene complexes, which represents a novel approach to the skeleton of ACC derivatives. Furthermore, we have prepared and characterized by means of an X-ray diffraction experiment the first example of a Fischer carbene complex bearing an acyl chloride group.

Acknowledgment. This research was supported by the Comisión Ministerial de Ciencia y Tecnología (CICYT) and European Commission (Fondos FEDER) 1FD97-0632.

Supporting Information Available: Experimental procedures and characterization data for all new products described and an X-ray CIF file for complex **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026896P