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Synthetic Approach To Substituted Cyclopropanes Based on the Coupling Reaction of Lithiated Chloroalkyloxazolines with Fischer Carbene Complexes

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Received March 9, 2004

Abstract: Regioselective addition of lithiated oxazoline **2a**, easily available from 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline **1a** (LDA, THF, −98 °C), to α,β-unsaturated Fischer carbene complexes **3** afforded cyclopropylcarbene complexes **4** as sole diastereoisomers. Exposure of carbene complexes **4a**−**c** (M = Cr) to air and sunlight gave cyclopropane carboxylate derivatives **5a**−**c**. A plausible mechanistic explanation is proposed. Moreover, when lithiated oxazoline **2b** was generated from **1b** in the presence of the carbene complex **3a**,**b**, the oxazolinylcyclopropane carboxylates **6a**,**b** formed as a 1:1 mixture of diastereoisomers. Chiral lithiated oxazoline **2c** added regioselectively and diastereoselectively to chromium complexes **3a**,**b** and to tungsten complexes **3d**,**e**, leading, after oxidation of the metal fragment, to esters **7a**,**b** with good diastereoselectivity (dr = 4:1). The reaction of lithiated oxazoline **2d** with chromium complex **3b** and tungsten complex **3e** proceeded less diastereoselectively, furnishing, in both cases, after oxidation, the ester **7c** as a 3:2 diastereoselective mixture.

Chiral cyclopropanes are extremely useful intermediates in synthetic organic chemistry,[1] and the cyclopropane ring is frequently found in the skeletons of many natural products and substances of biological and pharmaceutical interest.[2] Several synthetic procedures have been developed for stereoselective synthesis of disubstituted cyclopropanes, but routes to trisubstituted cyclopropanes are rather rare.[3] In recent publications from our labs, we reported the synthesis of certain trisubstituted cyclopropanes based on the addition of lithiated chloroalkyloxazolines to electron-deficient alkenes[4] and a sort of trimerization of lithiated chloromethyloxazolines.[5]

Fischer carbene complexes are currently attracting a great deal of interest due to their particularly valuable and rich chemistry.[6,7] Specifically, cyclopropyl carbene complexes have been successfully used for the preparation of cyclopentenones,[8] cycloalkadienones,[9,10] cyclopentanes fused with heterocycles,[11] and cyclopropanes containing electron-withdrawing and electron-donating groups.[12] Thermal and photochemical transformations have also been reported.[13,14] Moreover, we have described a versatile methodology for the preparation of different enantiopure 1,2-disubstituted and 1,2,3-trisubstituted cyclopropanes by the reaction of enantiomerically pure (alkenyl)[(−)-8-phenylmenthyloxy]carbene complexes and in situ-generated monohalo- or dibromomethyllithium.[15]

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10.1021/jo049613a CCC: $27.50
Published on Web 07/02/2004

SCHEME 1

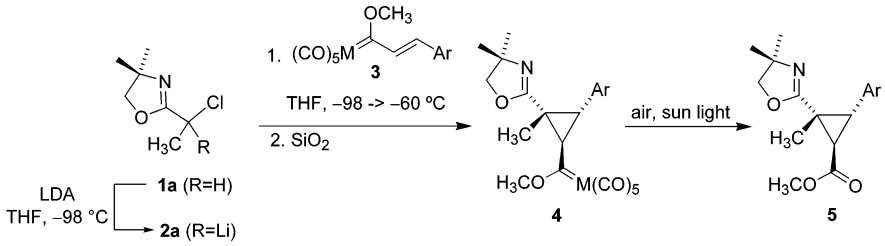


TABLE 1. Cyclopropylcarbene Complexes 4 and Methyl Cyclopropanecarboxylate Derivatives 5 from α,β-Unsaturated Carbene Complexes 3 and Lithiated Oxazoline 2a

carbene complex	M	Ar	**4** (yield%)[a]	**5** (yield%)[a]	dr
3a	Cr	Ph		**5a** (72)	>99/1
3b	Cr	4-MeOC$_6$H$_4$		**5b** (85)	>99/1
3c	Cr	2-Furyl		**5c** (83)	>99/1
3d	W	Ph	**4d** (80)		>99/1
3e	W	4-MeOC$_6$H$_4$	**4e** (85)		>99/1

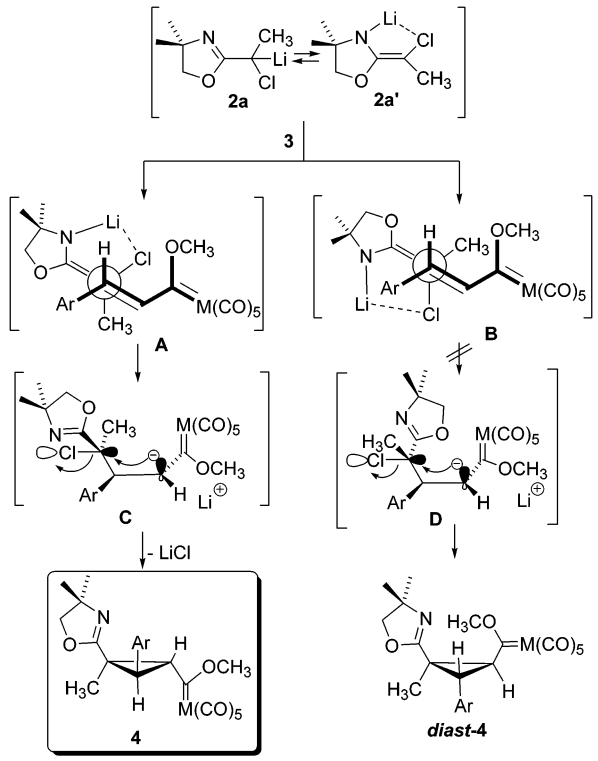
[a] Isolated yield based on starting carbene complex **3**.

Here we present an easy procedure for the synthesis of trisubstituted cyclopropylcarbene complexes or cyclopropanecarboxylates in a diastereoselective manner from chloroalkyloxazolines and α,β-unsaturated Fischer carbene complexes.

Treatment of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline **1a** with LDA in THF at −98 °C led to the formation of the corresponding lithiated oxazoline **2a**.[4] Further reaction of this intermediate with α,β-unsaturated Fischer carbene complexes **3** at temperatures ranging between −98 and −60 °C afforded, after purification on silica gel, the cyclopropylcarbene complexes **4** in good yields and, in each case, as a sole diastereoisomer. Exposure of carbene complexes **4a**−**c** (M = Cr) to air and sunlight gave rise to cyclopropane carboxylate derivatives **5a**−**c**, respectively, in good yield and as sole diastereoisomers (Scheme 1 and Table 1). The structure and relative configurations of the stereogenic centers of compounds **4** and **5** were unequivocally determined by two-dimensional NMR experiments (COSY, HMQC, HMBC, and NOESY).[16]

A plausible mechanistic explanation accounting for the formation of compounds **4** is shown in Scheme 2. Thus, lithiated oxazoline **2a** in its chelated (*E*)-configurated azaenolate form[17] reacts with the unsaturated carbene complex **3** following a model similar to that described by Nakamura for the 1,4-addition of enolates to the same kind of carbene complexes.[18] According to this mechanism, two possible orientations of the azaenolate **2a′** interacting with the carbene complex could be considered.

SCHEME 2



These two orientations, represented as **A** and **B**, would lead to intermediates **C** and **D** and finally to compounds **4** and ***diast*-4**, respectively. However, the steric interactions between the methyl group of the azaenolate and the methoxy group of the carbene complex make approach **B** energetically less favorable than **A**, where the steric interaction between the chlorine and methoxy group is weaker, considering that the chlorine here is to some extent pulled away from the methoxy group by the lithium chelation.

Thus, formation of intermediate **C** should be preferred. Moreover, the appropriate alignment of the orbitals involved in the ongoing ring formation in **C** would lead to diastereomerically pure complexes **4**.

In view of the interesting results obtained in the reaction described above, we decided to extend our study to the oxazoline **1b**. Lithiated oxazoline **2b**, promptly available by deprotonation of chloromethyloxazoline **1b** with LDA at −98 °C, tends, as reported,[5] to trimerize to give the trioxazolinyl cyclopropane. However, when **2b** was generated in the presence of the carbene complex **3a**,**b** (the in situ quenching technique), the oxazolinylcyclopropane carboxylates **6a**,**b** formed in an acceptable yield and as a 1:1 mixture of diastereoisomers. In contrast, the tungsten complex **3d** did not lead to the

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(16) Relative configurations of compounds **4**, **5**, and **7** have been assigned by two-dimensional NOESY experiments and on the basis of the coupling constants between the vicinal hydrogens of the cyclopropane ring: J_{cis} (8−12 Hz) > J_{trans} (4−7 Hz).

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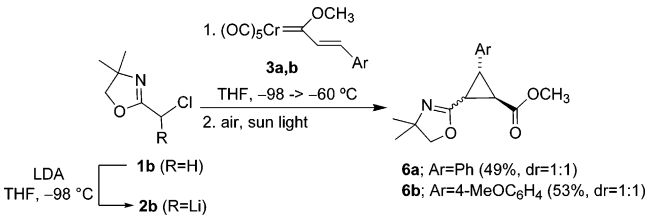
SCHEME 3

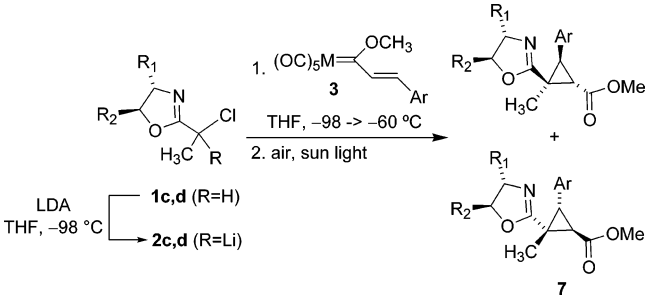


corresponding cyclopropane derivative likely due to the fact that the trimerization reaction of **2b** proceeds faster than its trapping by **3d**. The lack of diastereoselectivity in the reaction of **2b** with carbene complexes **3a** and **3b**, in contrast with the excellent diastereoselectivity of the reactions of **2a**, might be accounted for assuming that lithiated species **2b** could react with the (*E*)- and (*Z*)-azaenolate forms, thus leading to both the diastereomers of **6a** and **6b**, respectively.

The excellent results obtained with the lithiated methyl-substituted oxazoline **2a** led us to start an investigation on the synthesis of enantiopure cyclopropane derivatives. To this end, the chiral nonracemic oxazolines **1c** and **1d** were prepared as reported.[19] With these oxazolines in hand, we decided to study the reaction of their lithiated derivatives **2c** and **2d** with chromium and tungsten carbene complexes **3**. We found that lithiated oxazoline **2c** added regioselectively and diastereoselectively to chromium complexes **3a**,**b** and to tungsten complexes **3d**,**e,** leading, after oxidation of the metal fragment, to the formation of esters **7a**,**b** in acceptable yields and good diastereoselectivity (dr = 4:1 in all cases). Moreover, the reaction of lithiated oxazoline **2d** with chromium carbene complex **3b** and tungsten carbene complex **3e** proceeded less diastereoselectively, furnishing in both cases, after oxidation, the ester **7c** in 50 and 55% yields, respectively, and a 3:2 diastereomeric ratio.

It is worth noting that the metallocarbene complex used does not affect the diastereoselectivity of the reaction of lithiated oxazolines **2a**−**d**, as we obtained the same drs (>99:1 in the case of **2a**, 1:1 in the case of **2b**, 4:1 in the case of **2c**, and 3:2 in the case of **2d**) regardless of the complex used. Thus, it is clear that the diastereoselectivity of the reaction is substantially dictated by the structural feature of the lithiated oxazoline used, particularly by the α-substitution (dr >99:1 for **2a** and 1:1 for **2b**). In conclusion, a simple and useful synthetic methodology for the preparation of functionalized cyclopropanes has been developed that is based on the regioselective addition of lithiated oxazolines to unsaturated chromium and tungsten carbene complexes. The new cyclopropane derivatives look like good building blocks to be used for the preparation of other substances by the viable elaboration of the functionalities (the oxazoline ring and the ester group) tethered to the cyclopropane ring. The chiral version of the coupling reaction described in this paper deserves a deeper investigation. Preliminary results are encouraging. Indeed, the reaction of **2c** with complexes **3** is reasonably diastereoselective so that only two diastereisomers (easily separable by column chromatography) are formed out of the eight possible. Results will be reported in due course.

TABLE 2.



oxazoline	R^1	R^2	carbene complex	M	Ar	product[d]	yield (%)[a]	dr[b]
1c	^{i}Pr	H	**3a**	Cr	Ph	**7a**	55	4:1[c]
1c	^{i}Pr	H	**3b**	Cr	4-MeOC$_6$H$_4$	**7b**	60	4:1[c]
1c	^{i}Pr	H	**3d**	W	Ph	**7a**	51	4:1[c]
1c	^{i}Pr	H	**3e**	W	4-MeOC$_6$H$_4$	**7b**	52	4:1[c]
1d	MeOCH$_2$	Ph	**3b**	Cr	4-MeOC$_6$H$_4$	**7c**	50	3:2
1d	MeOCH$_2$	Ph	**3e**	W	4-MeOC$_6$H$_4$	**7c**	55	3:2

[a] Global isolated yields based on the starting carbene complex **3**. [b] Diastereomeric ratio calculated on the basis of ^{1}H NMR spectrum of the crude reaction mixture. The absolute configuration of the major diastereoisomer was not determined. [c] Diastereoisomers easily separated by flash column chromatography. [d] As in compounds **4**, the oxazolinyl and aryl groups are both trans to the ester group.

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni" and the FIRB Project "Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi" supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Rome), by the University of Bari, and by C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi). We also thank Principado de Asturias (Grant PR-01-GE-9) and Spanish DGI (Grant BQU-2001-3853).

Supporting Information Available: General procedures for the preparation of cyclopropanecarbene complexes **4d**,**e**, cyclopropanecarboxylate **5a**−**c**, **6a**,**b**, and **7a**−**c** and spectroscopic and physical data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049613A

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