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Cyclopropanation with Fischer Acyloxycarbene Complexes: Preparation of Cyclopropane and Cycloheptane-Fused γ-Lactones

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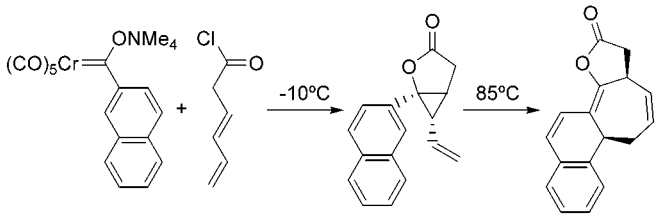
ABSTRACT



A sequential acylation–intramolecular cyclopropanation reaction takes place upon treatment of a series of tetraalkylammonium acylchromates with β,γ-unsaturated acyl chlorides at −10 °C. The reaction leads to 2-oxabicyclo[3.1.0]hexan-3-ones with exo selectivity in good yields. The diastereoselectivity of the reaction allows the preparation of *cis*-divinyl cyclopropanes, which evolve via Cope sigmatropic reaction toward cycloheptadiene derivatives. Furthermore, the aromatic Cope rearrangement of a series of *cis*-aryl vinyl cyclopropanes prepared by means of this methodology has been studied.

Since the fundamental discovery of carbene complexes by Fischer and co-workers,[1] these interesting compounds have been applied in various organic syntheses.[2] More than 30 years ago, Fischer reported the first reaction of carbene complexes leading to organic structures, namely, the cyclopropanation of olefins, which include electron-deficient[3] and electron-rich olefins[4] and, more recently, nonconjugated double bonds.[5]

A well-known paradigm in the chemistry of Fischer carbene complexes is the influence of the electronic properties of the substituents in both the reactivity and the thermal stability: the greater the electron-donating ability of the heteroatom, the lower the reactivity of the carbene complex, and vice versa. This trend is reflected in the lower reactivity of aminocarbene versus alkoxycarbene complexes, while acyloxycarbene complexes are more reactive and thermally unstable due to the electron-withdrawing effect of the acyl group. Although this increased reactivity has been exploited in the preparation of carbene complexes by addition−elimination reactions,[6] it has been scarcely applied to organic

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(1) Maasböl, A.; Fischer, E. O. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580.

(2) Recent reviews: (a) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 5, pp 1065−1113. (b) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds; Pergamon: Oxford, 1995; Vol. 12, pp 470−547. (c) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105−4128. (d) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999. (e) Weyershausen, B.; Dötz, K. H. *Eur. J. Inorg. Chem.* **1999**, 1057−1066. (f) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964−4002.

(3) (a) Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1970**, *103*, 1273−1278. (b) Dötz, K. H.; Fischer, E. O. *Chem. Ber.* **1972**, *105*, 1356−1278.

(4) Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1972**, *105*, 3966−3973.

(5) (a) Barluenga, J.; Férnandez-Acebes, A.; Trabanco, A. A.; Flórez, J. *J. Am. Chem. Soc.* **1997**, *119*, 7591−7592. (b) Barluenga, J.; López, S.; Trabanco, A. A.; Férnandez-Acebes, A.; Flórez, J. *J. Am. Chem. Soc.* **2000**, *122*, 8145−8154.

(6) (a) Connor, J. A.; Jones, E. M. *J. Chem. Soc. A* **1971**, 3368−3372. (b) Fischer, E. O.; Leupold, M. *Chem. Ber.* **1972**, *105*, 599−608. (c) Fischer, E. O.; Leupold, M.; Kreiter, C. G.; Müller, J. *Chem. Ber.* **1972**, *105*, 150−161.

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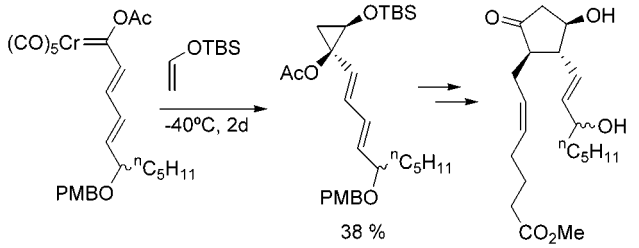
synthesis. To the best of our knowledge, there is only one example of a cyclopropanation of olefins with acyloxycarbene complexes by Wulff et al. (Scheme 1).[7]

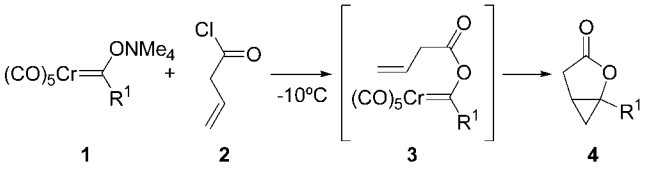
Scheme 1. Wulff's Synthesis of Prostaglandin E_2



We envisioned that one possibility of taking advantage of the enhanced reactivity of the acyloxycarbene complexes despite their thermal instability would be to carry out the reactions in an intramolecular fashion at a low temperature. We describe herein the successful application of this strategy to the olefin cyclopropanation reaction.

Previous studies on the intramolecular cyclopropanation of alkoxy- and aminocarbenes showed that the optimal length of the tether between the carbene carbon and the double bond is three atoms.[8] Therefore, we decided to test the reaction of benzoylchromate **1a**[9] and 3-butenoyl chloride **2**. Acylation took place at −40 °C in less than 20 min. The acyloxycarbene complex evolved after prolonged stirring at this temperature (6 h). After oxidative workup and chromatography, the only isolable product was cyclopropane **4a**. In an optimized procedure, reactions were carried out at −10 °C. Next, the scope and limitations of the reaction were explored. It was found that the reaction tolerates aromatic, heteroaromatic, and olefinic substituents in the carbene complex (Table 1). The length of the tether was also varied, but neither acryloyl chloride nor 4-pentenoyl chloride gave any isolable product upon treatment with **1a**.[10]

Table 1. Cyclopropanation via Acyloxycarbene Complexes

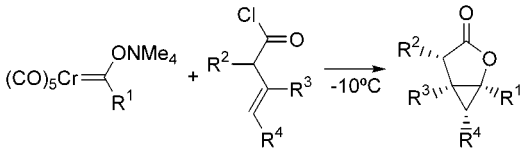


1 2 3 4

entry	R^1	yield (%)
a	Ph	73
b	2-Fu	20
c		22
d		39

The extension of this reaction to substituted β,γ-unsaturated acyl chlorides was also attempted. Reactions of (*E*)-alkenes proceeded with complete retention of the double-bond stereochemistry, whereas (*Z*)-olefins were not cyclopropanated (Table 2). When a substituent was placed into the

Table 2. Variation of the Olefinic Moiety



1 5 (±)-6

entry	R^1	R^2	R^3	R^4	yield
a	Ph	Me	H	H	53%[a]
b	Ph	Bn	H	H	73%[b]
c	Ph	H	Me	H	85%
d	Ph	H	H	(*E*)-Me	23%
e	Ph	H	H	(*E*)-CH=CH_2	75%
f	Ph	H	H	(*Z*)-Et	c
g	c-C_3H_5[d]	H	H	(*E*)-CH=CH_2	54%

[a] de = 5:1. [b] de = 4:1. [c] No identifiable product was isolated. [d] c-C_3H_5 = cyclopropyl.

α-position of the acid chloride, the cyclopropanes were obtained as a separable mixture of diastereomers in ratios of 4:1 and 5:1. The major isomers were identified as exo by comparison of the observed coupling constants between the α-H and the bridgehead-H with those calculated with the Karplus equation[11] for the corresponding dihedral angles seen in the PM3[12] minimized structures.[13]

In order to propose a mechanism for the reaction, it was necessary to take into account that the extremely mild

(7) Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660−5662. The methodology developed by these authors has been recently applied by Takeda et al.: Takeda, K.; Sakumura, K.; Yoshii, E. *Tetrahedron Lett.* **1997**, *38*, 3257−3260.

(8) Söderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 3113−3121.

(9) Tetraalkylammonium chromates are readily available from the corresponding lithium chromates and tetraalkylammonium bromide. For several examples, see: (a) Semmelhack, M. F.; Bozell, J. J. *Tetrahedron Lett.* **1982**, *23*, 2931−2934. (b) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*, 5803−5812. (c) Hegedus, L. S.; Schwindt, M. A.; Delombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264−2273. (d) Soderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364. Vernier, J. M.; Hegedus, L. S.; Miller, D. B. *J. Org. Chem.* **1992**, *57*, 6914−6920. (e) Hoye, T. R.; Chen, K. J.; Vyvyan, J. R. *Organometallics* **1993**, *12*, 2806−2809. (f) Barluenga, J.; López, S.; Trabanco, A. A.; Flórez, J. *Chem. Eur. J.* **2001**, *7*, 4723−4730.

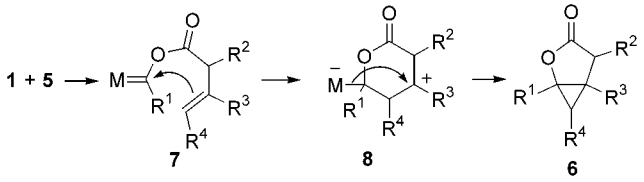
(10) **General Experimental Procedure for the Cyclopropanation Reaction.** A 0.05 M solution of chromate **1** in CH_2Cl_2 was cooled to −10 °C and treated with 1.5 equiv of acyl chloride **2** or **5**. The reaction was allowed to reach room temperature over 2 h. The reaction crude was then diluted 2-fold with hexanes and exposed to air and sunlight until all chromium species were oxidized. The reaction was then filtered through Celite and chromatographed on silica gel to obtain the corresponding cyclopropane **4** or **6** as an oil. **Selected Data for 4a.** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40−7.20 (m, 5H, Ph), 3.09 (dd, J = 19, 6.5 Hz, *exo*-COC*H*), 2.61 (d, J = 19 Hz, *endo*-COC*H*), 2.00 (m, 1H, C*H*), 1.57 (m, 1H, cyclopropane), 1.13 (m, 1H, cyclopropane). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm) 175.6 (*C*O_2R), 136.5 (*C ipso*), 128.3 (2 × *C*H, Ph), 127.3 (*C*H, *p*-Ph), 124.2 (2 × *C*H, Ph), 68.0 (*C*), 33.9 (CO*C*H_2), 22.3 (*C*H_2), 19.4 (*C*H). HRMS (IE): calcd, 174.0681; found, 174.0682

(11) Günter, H. *NMR Spectroscopy*, 2nd ed; Wiley & Sons: Chichester, UK, 1994; p 115.

(12) PM3 implemented in MOPAC V6.

conditions employed (temperatures as low as −40 °C) are not compatible with the usually proposed preliminary decarbonylation step. Therefore, we postulate an initial acylation step of the anionic organometallic species **1** that would give rise to the acyloxycarbene complex **7**. An intramolecular nucleophilic attack of the double bond to the (extremely electrophilic) carbene carbon would lead to zwitterion **8**, which would cyclize to the cyclopropane by elimination of the neutral chromium pentacarbonyl moiety.

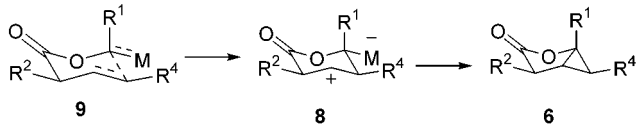
Scheme 2. Mechanistic Proposal



Although only a postulate at this stage, this mechanistic proposal seems to be in agreement with all the experimental observations. Thus, the highest yield observed with the *β*-methyl-substituted acyl chloride **5c** could be rationalized on the basis of the formation of a tertiary carbocation upon nucleophilic attack of the double bond. Furthermore, both acryloyl chloride and 4-pentenoyl chloride would fail to undergo this reaction as the initial attack would be disfavored due to the formation of carbocations either α to a carbonyl group (in the first case) or primary (in the latter case).

The stereochemical outcome of the reaction can be explained by assuming a six-membered chairlike cyclic transition state for the nucleophilic attack (Scheme 3). The

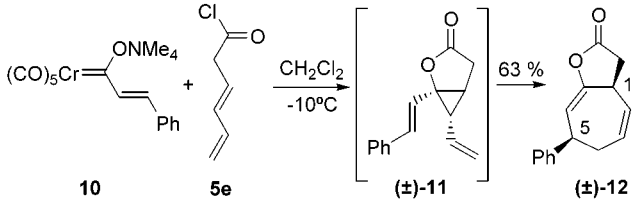
Scheme 3. Proposed Origin of the Diastereoselectivity



α-substituent R^2 would tend to occupy the equatorial rather than axial position, leading preferentially to the exo products. The failure of the reaction of the substrate with a (*Z*)-olefin (Table 2, entry f) is likely to be a consequence of the axial disposition of the ethyl group in the proposed transition state, which would hamper the approach of the reactive centers.

It is well-known that *cis*-divinyl cyclopropanes undergo Cope rearrangements at room temperature. We envisioned that the aforementioned cyclopropanation methodology could be adapted for the synthesis of this kind of system. When propenoylchromate **10** was treated with diene **5e**, the only isolable product was cycloheptadiene **12**, which presumably results from a ring enlargement of the initially formed cyclopropane **11** (Scheme 4). It is worth mentioning that both

Scheme 4. Cyclopropane Expansion by Cope Rearrangement

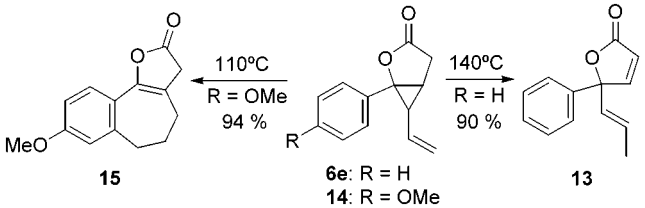


the cyclopropanation and the sigmatropic reaction are diastereoselective, and therefore the cycloheptadiene derivative is obtained as a single isomer. NOESY experiments carried out on the product showed a cross-peak between protons 1 and 5, thus indicating that they are cis-positioned. Therefore, the bicycle possesses an endo disposition of the phenyl sustituent, arising from the boatlike transition state imposed by the presence of the cyclopropane.

A long-standing problem of the Cope reaction is its extension to the rearrangement of homoallylarenes, where one of the double bonds is part of an aromatic system.[14] Only the anionic oxy-Cope version has found application, giving rise to dearomatized carbonyl compounds.[15] The versatility and diastereoselectivity of the intramolecular cyclopropanation of acyloxycarbene complexes appeared to be especially suitable for the preparation of starting products for the study of this interesting reaction.

Our studies started with compound **6e**, which was found to be unreactive until heated to 140 °C. However, when **6e** was heated in toluene-d_8 in a sealed tube at that temperature for 30 h, neither the corresponding cycloheptadiene derivative nor any product derived from it was observed. Instead, butenolide **13**, which arises from a formal intramolecular retro-ene reaction, was obtained. It is well-known that the presence of electron-donor groups accelerates the rate of Cope-type rearrangements, so we synthesized *p*-methoxyphenylcyclopropane **14** (Scheme 5, R = OMe) by the

Scheme 5. Thermolysis of Arylvinylcyclopropanes

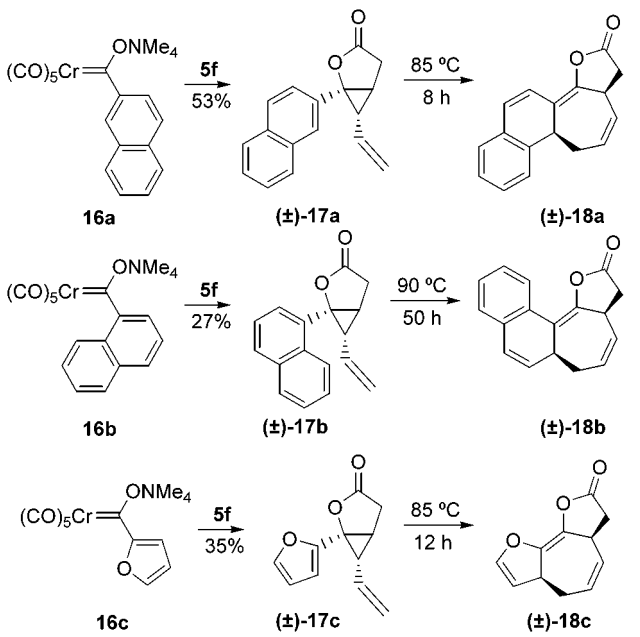


methodology presented above. In this case, cycloheptadiene derivative **15** was obtained upon heating **14** at 110 °C for

(13) For example, data for **6a** are as follows: calculated dihedral angle for the exo isomer = 100°; ^3J (H,H) calcd = 0.1 Hz, observed for the major isomer = 0.6 Hz. Calculated dihedral angle for the endo isomer = 30°; ^3J (H,H) calcd = 5.9 Hz, observed for the minor isomer = 6.9 Hz.

(14) For leading references: Kawasaky, T.; Nonaka, Y.; Watanabe, K.; Ogawa, A.; Higuchi, K.; Terashima, R.; Masuda, K.; Sakamoto, M. *J. Org. Chem.* **2001**, *66*, 1200−1204.

Scheme 6. Synthesis and Dearomatization of Aryl Vinyl Cyclopropanes



80 h, thus revealing that the rearrangement had taken place. Nevertheless, the high energy of aromatization promotes the migration of the double bonds of the initially formed compound to furnish the aromatized final product.

The desired dearomatization could be more easily achieved with systems of reduced aromaticity. For this purpose, we synthesized naphthyl- and furyl-substituted cyclopropanes **17** (Scheme 6). We found that when these compounds were subjected to thermolysis in a sealed tube, they underwent a clean and complete conversion to the ring expansion products at temperatures lower than those of the previous examples shown in Scheme 5. Furthermore, products **18** were obtained as the initial rearranged dearomatized dienes, probably due to the lower aromatization energy of these systems.

In conclusion, we have presented a versatile and diastereoselective method for the synthesis of cyclopropyl fused γ-lactones. This method constitutes the first intramolecular cyclopropanation of acyloxycarbene complexes and can be easily adapted for the preparation of *cis*-divinyl and *cis*-arylvinyl cyclopropanes. The ring expansion of these systems furnishes, in most cases, the corresponding cycloheptane derivatives.

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Supporting Information Available: Experimental procedures and characterization data for all new products described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For some examples, see: (a) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4309−4311. (b) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 2463−2464. (c) Martin, D.; Wurster, J. A.; Boylan, M. J.; Borzilleri, R. M.; Engel, G. T.; Walsh, E. J. *Tetrahedron Lett.* **1993**, *39*, 8395−8398. (d) Santora, V. J.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 7976−7977. (e) Seki, K.; Tooya, M.; Sato, T.; Masako, U.; Uyehara, T. *Tetrahedron Lett.* **1998**, *39*, 8673−8676.