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Carbocupration of Cyclopropene. A Novel Synthon of Cyclopropanone Enolate and Its Application to [3 + 2] and [3 + 2 + 2] Annulation

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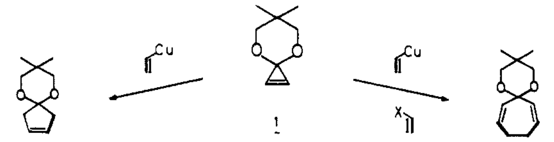
We report here that organocuprates undergo extremely rapid addition across the double bond of the cyclopropenone ketal **1**[1] to produce a previously inaccessible synthon of cyclopropanone enolate **2**. The resultant cuprio cyclopropane **2** then reacts with various electrophiles to produce substituted cyclopropanone ketals **3**. The virtue of this carbocupration/trapping reaction, besides its novelty,[2] stems from its ability to quickly assemble functional groups on the cyclopropane ring[2c] that are useful for further transformation. Thus, the reaction has been developed into a two-step transformation of **1** to a five-membered ring in a [3 + 2] manner as well as to a remarkably efficient single-pot [3 + 2 + 2] constructuion of a seven-membered ring (Scheme I).

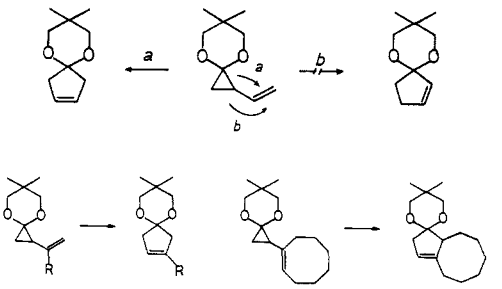
Success of such an addition/trapping sequence primarily depends on the efficiency of the addition of the organometallics to the cyclopropene double bond. Of various species examined,[3a] organocuprates were found suitable for the desired reaction scheme.[3b] For instance, quantitative addition of Me_2CuLi (1.1 equiv) to the cyclopropene **1** occurred at −70 °C in 1 min (in ether, terminated by addition of MeOH) to afford the 2-methylcyclopropanone ketal **3a** (96% yield by quantitative GLC analysis; 71% isolated yield). When the reaction was quenched by D_2O, a deuteriated cyclopropane **3b** was obtained. A characteristic high field ^1H NMR signal of the protio 2-methylcyclopropane **3a** (0.30 ppm), assigned to the C-3 proton cis to the C-2 methyl group,[4] was absent in the deuteriated product **3b**, indicating the cis disposition of the metal and the methyl group (i.e., R^1) in the cuprio cyclopropane **2**.

Given the evidence of clean cis addition of the cuprate, we examined the trapping of the cuprio cyclopropane with carbon electrophiles. Thus, treatment of **1** with Me_2CuLi (1.0 equiv) followed by addition of MeI (2.1 equiv)/HMPA (1.05 equiv) gave, after warming to 0 °C, cis-2,3-disubstituted cyclopropane **3c** in 88% yield as a single product. Symmetry elements in the product, established by NMR spectroscopy,[5] unambiguously demonstrated the cis dimethyl structure. These experiments showed that the overall reaction (eq 1) involves the cis addition followed by the trapping with retention of the configuration.

Scheme I



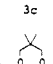
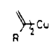
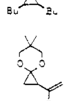
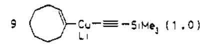
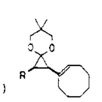
Scheme II[a]



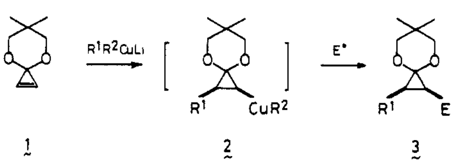
4 R = H 57%
5 R = n-C_7H_{15} 51%
6 R = Ph 56%
7 78%
240–290 °C 1–5h

[a] Carried out in toluene containing 1 equiv of bis(trimethylsilyl) acetamide.

Table I. Carbocupration/Electrophilic Trapping of the Cyclopropenone **1**[a]

entry	cuprate (equiv)	electrophile (equiv)	product		%yield[b]
1	Me_2CuLi (1.10)	MeOH	3a		71, 96[c]
2	(1.0)	MeI (2.1)/HMPA (1.05)	3c		88[c]
3	(1.05)	$CH_2{=}CHCH_2Br$ (2.1)	3d		81[d]
4	$MeCu(Li)-{\equiv}-SiMe_3$ (1.05)	$CH_2{=}CHCH_2Br$ (1.05)	3d		76[d]
5	$MeCu(Li)SPh$ (1.1)	MeI (1.0)/HMPA (1.1)	3c		78[c]
6	Bu_2CuLi (1.0)	BuI (2.1)/HMPA (1.05)			72
7	 R = H (1.3)	H_2O		R = H	54
8	R = Ph (1.3)	H_2O		R = Ph	78
9	 (1.0)	H_2O		R = H	72
10	 (1.1)	MeI (5) /HMPA (1.1)		R = Me	79

[a] See footnote 14 for experimental procedure. [b] Isolated yield except in entries 1–5. [c] Determined by GLC by using an internal standard. [d] Determined by ^1H NMR by using an internal standard.



	R^1	E
3a	CH_3	H
3b	CH_3	D
3c	CH_3	CH_3
3d	CH_3	$CH_2CH{=}CH_2$

(1)

The reaction proceeded smoothly for several combinations of cuprates and alkylating reagents. Table I summarizes the results of the addition/trapping sequence. Addition of Bu_2CuLi followed by trapping with BuI afforded *cis*-dibutylcyclopropanone ketal (entry 6).[5] Allyl bromide reacted with the intermediary cuprio

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[1] Albert, R. M.; Butler, G. B. *J. Org. Chem.* **1977**, *42*, 674. Breslow, R.; Pecoraro, J.; Sugimoto, T. *Org. Synth.* **1977**, *57*, 41. For recent work on the thermal reaction of **1**, see: Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.

[2] (a) Carbometalation of simple olefins leading to stable organometallics has not been reported: Cf. Yamamoto, Y.; Yamada, J.-i.; Uyehara, T. *J. Am. Chem. Soc.* **1987**, *109*, 5820. (b) There have been reported a few examples of carbometalation of simple cyclopropenes by main group organometallics around or above room temperature: Grignard reagent: Lukina, M. Yu.; Rudashevskaya, T. Yu.; Nesmeyanova, O. A. *Dokl. Akad. Nauk SSSR* **1970**, *190*, 1109. Rudashevskaya, T. Yu.; Nesmeyanova, O. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1983**, 1821. Lehmkuhl, H.; Mehler, K. *Liebigs Ann. Chem.* **1978**, 1841. Allylic metals: Köster, R.; Arora, S.; Binger, P. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 205. Stoll, A. T.; Negishi, E.-i. *Tetrahedron Lett.* **1985**, *26*, 5671. (c) Elaborate preparation of substituted cyclopropanes directed toward synthesis of complex molecules has been achieved with low level of stereocontrol: cf. Piers, E.; Morton, H. E.; Nagakura, I.; Thies, R. W. *Can. J. Chem.* **1983**, *61*, 1226. Wender, P. A.; Essenstat, M. A.; Filosa, M. P. *J. Am. Chem. Soc.* **1979**, *101*, 2196. Yamamoto, H.; Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 5816.

[3] (a) Reaction of alkyllithium, alkylmagnesium halide, and alkylcopper resulted either in recovery of **1** at low temperatures or in total decomposition at higher temperatures. (b) The cuprio cyclopropane **2** starts to decompose above −50 to −20 °C.

[4] The assignment was based on the characteristically high chemical shift and the coupling constant (200 MHz ^1H NMR/$CDCl_3$ 0.30 ppm, dd, $J = 5.4$, 5.9 Hz): Cf. Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; pp 227 and 286.

[5] The appearance of only seven ^{13}C signals (equivalent ketal methyl groups as well as nonequivalent ketal methylene carbons) excluded the trans structure (C_2 symmetry). Same argument also proved the stereochemistry of the *cis*-dibutylcyclopropanone ketal. Further evidence of the cis addition/trapping is provided in the Supplementary Material. Cyclopropyl cuprates generally react with electrophiles with retention of configuration (ref 2c).

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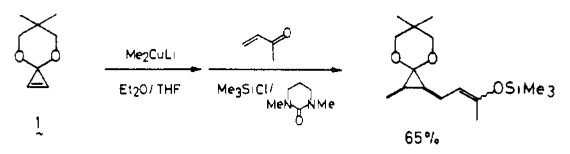
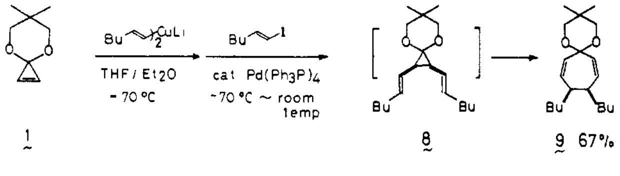
cyclopropane **2** much faster than alkyl iodides (without HMPA, −70 °C, 10 min) to give cis-allylated product **3d** in 81% yield (entry 3). Cuprates with nontransferrable "dummy" ligands, e.g., silylethynyl[6] (entries 4 and 9) and phenylthio[7] (entry 5) ligands, underwent smooth addition, and the resulting copper species cleanly reacted with 1 equiv of electrophiles (entries 4 and 5). The Me_3SiCl-accelerated conjugate addition[8] of the cuprio cyclopropane also proceeded in good yield (eq 2).



(2)

Thermal rearrangement of the vinylcyclopropanone ketals, prepared by addition of vinyl cuprates, proceeded with great facility due to the accelerating effect[9] of the ketal moiety (Scheme II). Thus, heating of the cyclopropanes **4**–**6** at 240–290 °C in toluene resulted in the formation of substituted 3-cyclopentenone ketals in 50–80% yield. The rearrangement proceeded with exclusive migration of the electronically favored ketal carbon (Scheme II, path a) rather than the sterically favored methylene carbon (path b). The net carbocupration rearrangement provides a powerful [3 + 2] annulation method. The rearrangement of **7** illustrates the utility of the reaction sequence for attachment of a five-membered ring to an existing ring system.

The stereoselective formation of cis-disubstituted cyclopropanes led to the development of a novel *single-pot* assembly of seven-membered rings in a [3 + 2 + 2] fashion via divinylcyclopropane[10] (**8**). Namely, addition of *trans*-hexenyl cuprate (1.1 equiv) followed by trapping of the intermediate with *trans*-hexenyl iodide (3.0 equiv) *in the presence of Pd(0)*[11] at −70 to 25 °C (5 h) directly afforded the 4,5-*cis*-dibutylcycloheptadienone ketal **9** in 67% yield.[12] The formation of the cis isomer **9** is due to the boat transition state in the rearrangement of **8**.[10]



(3)

Works to explore the generality of the carbometalation reaction of cyclopropenes as well as the utility of the cyclopropanone ketals in homoenolate chemistry[13] are in progress.[14]

Supplementary Material Available: Physical data for **3a**,**c**,**d** and other new compounds (6 pages). Ordering information is given on any current masthead page.

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(8) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662.

(9) Monoalkoxy substitution lowers the activation energy of the vinylcyclopropane rearrangement: Simpson, J. M.; Richey, H. G., Jr. *Tetrahedron Lett.* **1973**, 2545.

(10) Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 1.

(11) Substitution reaction of the vinyl iodide did not proceed in the absence of $Pd(Ph_3P)_4$.

(12) The ^{13}C NMR spectrum revealed the C_s symmetry of the product, which in turn supported the expected cis dibutyl structure.

(13) Cf. Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

(14) Typical procedure: cuparate addition/MVK trapping (eq 2). To a solution of Me_2CuLi (2.2 mmol) in a 2:3 ether/THF mixture (5 mL) at −70 °C was added during 30 s a solution of the cyclopropene **1** (2.0 mmol). After 1 min were added sequentially THF solutions of *N,N*-dimethylpropylene urea (5 mmol), Me_3SiCl (5 mmol), and methyl vinyl ketone (4.4 mmol). After 2 h at −70 to −30 °C, triethylamine (6 mmol) and hexane (6 mL) were added. Workup as reported (ref 6a) followed by silica gel chromatography gave the conjugate adduct as enol silyl ether (387 mg, 65%).

Generation and Trapping of an Alkynyl Cation

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Disubstituted cations, vinyl and phenyl cations, are accepted organic intermediates.[1] They have been generated, e.g., by solvolytic processes, and some stabilized vinyl cations have even been observed by ^1H and ^{13}C NMR spectroscopy under non-nucleophilic conditions.[2] We report here for the first time on the generation in solution of the alkynyl cation **1**, which has been previously observed only in mass spectrometry.[3]

Satisfactory agreement exists between the calculated and the experimental value (ca. 390 kcal mol^{-1}) of the heat of formation of the alkynyl ion **1** (R = H).[4] Accordingly, ion **1** (R = H) is ca. 130 kcal mol^{-1} less stable than a methyl cation and ca. 120 kcal mol^{-1} less stable than a primary vinyl and phenyl cation.[1] Owing to its exceedingly low stability, solvolytic procedures to generate an alkynyl cation **1** met with no success,[5] even by resorting to very good leaving groups, i.e., N_2, as in the decomposition of alkynyldiazonium salts **2** (R = C_6H_5, $p\text{-}ClC_6H_4$; X^- = $SbCl_5Ts^-$).[6] This is explained by recent ab initio calculations,[7] showing that the dissociation energy of the alkynyl diazonium ion **2** (R = H) to form a singlet alkynyl cation **1** (R = H) and an N_2 molecule amounts to ~150 kcal mol^{-1}. Even considering that the energy of a singlet alkynyl cation **1** (R = H) lies between 64 and 69 kcal mol^{-1} above that of the triplet ground state,[4,7] one must conclude that dediazonation of an alkynyl diazonium ion **2** under solvolytic conditions is hardly a suitable procedure to generate an alkynyl cation **1**.

$$R-C\equiv C^{\oplus} \qquad R-C\equiv C-\overset{\oplus}{N}\equiv N \quad X^{\ominus}$$

1 **2**

Spontaneous nuclear decay of a tritium atom in a tritiated organic molecule represents a well-established method to generate highly unstable carbocations of defined structure under all experimental conditions (Scheme I).[8] By this method, both singlet primary vinyl and aryl cations were readily generated from multitritiated ethylene[9] and arenes,[10] respectively under conditions

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