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Macrocarbocycle Synthesis by Copper- and Silver-Mediated Cyclization of Tethered Cyclopropenone Acetals. Electronic Tuning of Metal Vinylcarbene Complex into Vinylmetallic Species

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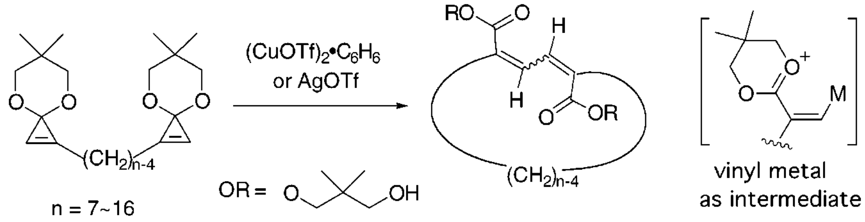
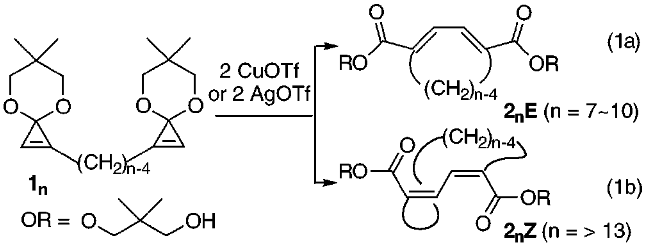
ABSTRACT



Synthesis of *n*-membered medium and macrocarbocycles through intramolecular sp^2–sp^2 C–C bond formation was achieved with the aid of CuOTf or AgOTf by intramolecular coupling reaction of cyclopropenone acetals tethered by a methylene chain of (n − 4) carbon atoms. The reaction has proved to be useful for the synthesis of large carbocycles (n > 13) in yields as high as 78%, and most notably also for an eight-membered carbocycle in 88% yield.

We report herein a new reaction for the construction of medium and macrocyclic dienyl diesters $\mathbf{2}_n$ through intramolecular sp^2−sp^2 C−C bond formation starting with a polymethylene-tethered bis-cyclopropenone acetal $\mathbf{1}_n$ (eqs 1a,b).



The synthetic utility of the method is highlighted by the high-yield formation of an eight-membered carbocycle ($\mathbf{2_8E}$), which is among the most difficult ring sizes to form by direct cyclization of an acyclic precursor.[1] The new cyclization method thus adds to the repertoire for macrocarbocycle formation, which is still limited in its variety.[2,3] Note that the formation of the vinylmetal **3** of a zwitterionic character leading to the diene **4** (Scheme 1) is unique since the usual pathway of a transition metal mediated cyclopropene ring opening would have generated a vinyl carbene intermediate **5**, which might be an isolable complex[4] or a transient species

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(1) (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. (b) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609 and references therein.

(2) Roxburgh, C. *Tetrahedron* **1995**, *51*, 9767−9822.

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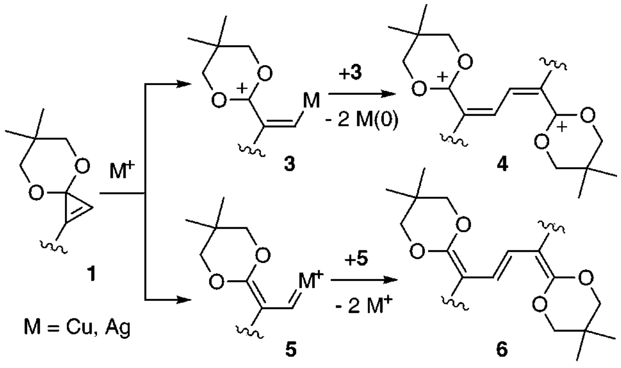
Scheme 1



dimerizing to give a triene **6**[5] or undergoing other carbene reactions.[6] Quantum mechanical calculations revealed that the acetal moiety plays a decisive role in determining the nature of the reactive intermediate.

The new synthetic route to macrocycles rests on the ready availability of $\mathbf{1}_n$, which can be prepared (70−85% isolated yield) through double alkylation of a 1,ω-diiodide or dibromide ($X(CH_2)_{n-4}X$) with the corresponding 2-lithiocyclopropenone acetal (2.2 equiv) in THF.[7] Initial screening of various metal complexes revealed that Cu(I) and Ag(I) triflates effect the desired cyclization reaction. Other compounds are often quite inert.[8] Thus, we found that $(CuOTf)_2\cdot C_6H_6$ effects the cyclization of $\mathbf{1}_n$ to medium- and large-size carbocycles $\mathbf{2_n}$ (and copper metal precipitate) under dilution conditions (eq 1 and Figure 1a). The bond cleavage took place exclusively at the less substituted side of the cyclopropenone acetal moiety in **1**.

The formation of the medium-size ring was rather low yielding under various conditions examined, and attempted cyclization of 10- to 12-membered rings gave a mixture of polar products without formation of the desired product. However, rings larger than 13-membered ones ($\mathbf{2_nZ}$) cyclized under the conditions mediated by 2 equiv (stoichiometric) of $(CuOTf)_2\cdot C_6H_6$ (33−66%, Figure 1a). We noted further that the presence of 0.3 equiv of $PdCl_2$ along with 2 equiv of $(CuOTf)_2\cdot C_6H_6$ in THF at 0 °C improves the yield by 10−25%. Under these conditions, $\mathbf{1_{16}}$ was cyclized to $\mathbf{2_{16}Z}$ in 78% yield as well as 14- and 15-rings which formed in 67% and 56% yields, respectively (Figure 1b).

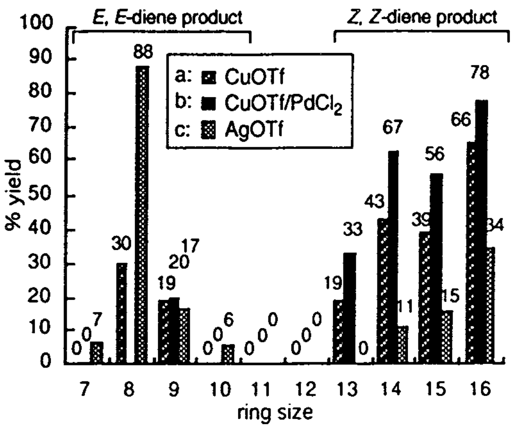
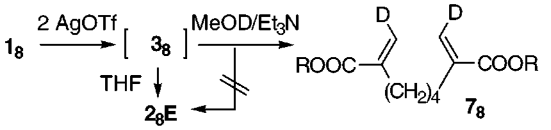


Figure 1. Synthesis of macrocycles by Cu(I)- and Ag(I)-mediated ring opening of tethered cyclopropenone acetals. The yields of pure isolated products are shown both in bar representation and in numbers from left to right in the order of (a) CuOTf, (b) CuOTf/$PdCl_2$, and (c) AgOTf. All the reactions gave a single isomer of carbocycle with (*E*,*E*) geometry for 7-, 8-, 9-, and 10-membered carbocycles and (*Z*,*Z*) geometry for 13-, 14-, 15-, and 16-membered carbocycles.

Interestingly, the medium rings were formed with exclusive *E*,*E*-configuration (eq 1a) and the larger ones with exclusive *Z*,*Z*-configuration (eq 1b). The different product selectivity was apparent from the ^1H NMR shift of the vinylic proton: $\mathbf{2}_7$ to $\mathbf{2}_{10}$ exhibited only one signal at δ 7.2−7.25 ppm, characteristic of *E*,*E*-dienyl diesters, and $\mathbf{2}_{13}$ to $\mathbf{2}_{16}$ at δ 7.55−7.59 ppm, characteristic of *Z*,*Z*-diene diesters.[9] Obviously, the smaller ring size only allows the presence of an *E*,*E*-diene within the ring. The *Z*,*Z*-geometry reflects the geometry of the vinylmetal **3**, whose intermediacy has been identified (vide infra).

In search of conditions suitable for cyclizing medium rings in better yield, we found that 2 equiv of AgOTf cyclizes $\mathbf{1_8}$ to the cyclooctadiene $\mathbf{2_8E}$ in 88% yield.[10] Examination AgOTf for 7- to 16-membered ring formation (Figure 1c) not only revealed the same reactivity trend but also the stereoselectivity trend as observed with CuOTf (i.e., formation of 7- to 10-membered rings with *E*,*E*-diene and 13- to 16-membered rings with *Z*,*Z*-diene). Thus, the AgOTf cyclized most effectively an 8-membered ring, which can be achieved much less efficiently with CuOTf.[11]

As mentioned at the outset, the vinylmetal intermediate **3** is unusual as the product of copper- or silver-mediated cyclopropene opening. This vinylmetal intermediate was not stable enough for characterization but was detected by in situ deuteration (eq 2). Thus, treatment of $\mathbf{1_8}$ with 2 equiv of AgOTf in MeOD in the presence of triethylamine at 0 °C afforded the diester $\mathbf{7_8}$ in 91% yield instead of the cyclized product $\mathbf{2_8}$. The olefin was deuterated 100% *Z*-specifically,



(2)

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(6) Müller, P.; Granicher, C. *Gazz. Chim. Ital.* **1995**, *125*, 459−463.

(7) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045−2057.

(8) Most of the ineffective compounds caused simple hydrolysis of the acetal: $AgNO_3$, $AgBF_4$, CuBr, CuCN, $Cu(CH_3CN)_4BF_4$, $Pd(OAc)_2$, $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$, $CoCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$, $FeCl_3$, $Zn(OTf)_2$, $Rh_2(OAc)_4$, $Rh_2(OOCCF_3)_4$, $PtCl_2(PPh_3)_2$, Cp_2TiCl_2, Cp_2ZrCl_2, $W(CO)_6$.

(9) Elvidge, J. A.; Ralph, P. D. *J. Chem. Soc. C* **1966**, 387−389.

(10) **Typical Procedure**, $\mathbf{2_8E}$. A solution of $\mathbf{1_4}$ (300 mg, 0.90 mmol) in THF (3 mL) was added to a solution of AgOTf (462 mg, 1.80 mmol) in THF (3 mL) at a rate of 0.66 mL/h. After addition, the mixture was stirred at 0 °C for 1 h. K_2CO_3 (0.3 g) and saturated NaCl (5 mL) were added, and then the solution was filtered though Celite. Purification with flash chromatography gave $\mathbf{2_8E}$ as a white solid (290 mg, 88% yield), mp 87−88 °C.

(11) Conditions for achieving effective bimolecular coupling reaction were found to need further optimization, which is under current investigations.

indicating the generation of a *Z*-vinylsilver intermediate (**3_8**). The stereochemistry agrees with that of the Hg(II)-mediated ring opening of cyclopropenone acetals,[12] where the strained σ-bond was cleaved with retention the olefin geometry. Since a vinylsilver(I) or vinylcopper(I) species is known to be thermally unstable to dimerize to a diene with retention of configuration,[13] we consider, for larger rings, that a transient *Z*-vinylmetallic species **3** forms and couples intramolecularly with retention of stereochemistry to produce **2_nZ.** The mechanism for the *E*,*E*-diene formation in medium-size rings is unclear at this time.

What is responsible for the change of the ordinary metal carbene pathway to the present vinylmetal pathway? To explore this crucial mechanistic question we examined **A** as a theoretical model of the vinylcopper(I) species **3** and **B** as a model of the parent copper vinylcarbene complex with the B3LYP density functional theory.[14,15] As shown in Figure 2, the geometries of the carbon/copper backbones in **A** and **B** are essentially the same, giving us no clue to understand the difference of their reactivities. Charge distributions in **A** and **B**, however, are meaningfully different from each other. In agreement with the formation of **3**, the acetal carbon (C3) is highly positive in **A**. The most clear-cut indication of the difference of the nature of **A** and **B** was provided by the analysis of the occupied localized Kohn−Sham molecular orbitals (LMOs)[16] shown in Figure 2 (bottom boxes). LMO of **A** (**LMO_A1**) reveals allylic π-conjugation. The filled 3d Cu orbital is seen simply as a lone pair (**LMO_A2**). The LMOs of **B** show a very different picture for the copper orbital. Thus, we clearly see that **LMO_B1** represents a π-type interaction characteristic of a metal carbene complex. The π-allylic resonance is seen in **LMO_B2**. The reactive species **3** can be therefore best regarded as the predominant limiting structure **C** in the resonance between **C** and **D**.[17]

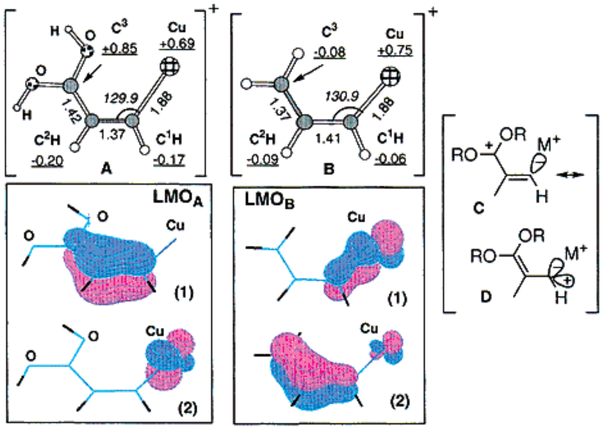

Figure 2. Optimized structures of cationic vinylcopper(I) complex **A** and cationic copper vinylcarbene complex **B** and their localized Kohn−Sham orbitals of π-character obtained by B3LYP/631A as well as two limiting structures representing the electronic character of **3**. Bond lengths are in Å, bond angles are in deg, and natural charges of C^1H, C^2H, C^3, and Cu moieties are underlined.

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Supporting Information Available: Experimental details of all reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] All calculations were performed at the B3LYP levels with assumption of C_s symmetry. The 6-31G* basis set was used for C, H, and O and all electron Ahlrichs-SVP (Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571−2577) for Cu: Nakamura, E.; Mori, S.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4887−4899.

[15] 3D pictures and coordinates of **A** and **B** are available on: http://www.chem.s.u-tokyo.ac.jp/∼common/Theo/macro/title.html.

[16] Boys, S. F. In *Quantum Theory of Atoms, Molecules, and the Solid State*; Lowdin, P. O., Ed.; Academic Press: New York, 1968; pp 253−262.

[17] Strong perturbation effects of the acetal group have been observed also for free vinyl carbene species (Boger, D. L.; Brotherton, C. E. In *Advances in Cycloaddition, volume 2*; Curran, D. P., Ed.; JAI Press: Greenwich, 1990; p 147. Tokuyama, H.; Isaka, M.; and Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 5523) and trimethylenemethane species (Nakamura, E.; Yamago, S.; Ejiri, S.; Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 3183−3184. Nakamura, E. In *Organic Synthesis in Japan. Past, Present and Future*; Noyori, R., Ed.; Kagaku Dojin: Tokyo, 1992).