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8-*Endo* selective Friedel–Crafts cyclization of vinyloxiranes with $Co_2(CO)_6$-complexed acetylene

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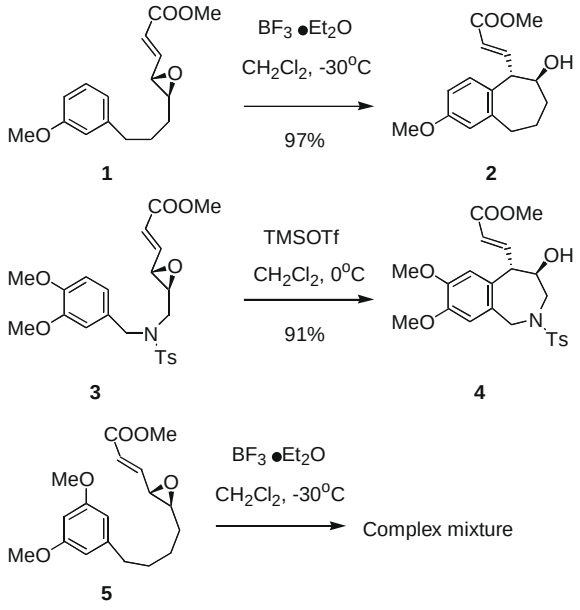
ABSTRACT

An 8-*endo* selective Friedel–Crafts cyclization of vinyloxirane **8** with $Co_2(CO)_6$-complexed benzeneacetylene was found to give poly-functional eight-membered cyclic compound **9** in high yields.

Stereoselective construction of medium-sized poly-functional rings is an important subject because these structures are found in a number of natural products. Our group previously reported a Lewis acid assisted intramolecular Friedel–Crafts (FC) reaction of vinyloxirane **1**.[1] The reaction proceeded stereospecifically to afford seven-membered poly-functional carbocycle **2** in excellent yield. It is also noteworthy that it showed high selectivity for the unusual 7-*endo* mode. The novel cyclization has been extended to the construction of poly-functional hydrobenzazepine **4**.[2] The high reactivity observed in these FC reactions prompted our efforts to attempt a more difficult 8-*endo* cyclization of **5**. Contrary to our expectations, treatment of **5** with $BF_3{\cdot}Et_2O$ resulted in significant decomposition. More recently, we developed a novel cyclization of eight- and nine-membered iminium ions using a $Co_2(CO)_6$-complexed acetylene unit.[3] The cyclization was achieved due to the bent conformation of the complex, which facilitates access of the aromatic ring to the iminium ion generated from **6**.[4] Suzuki et al. reported ene reaction of $Co_2(CO)_6$-complexed eneyne with aldehydes in the presence of a Lewis acid.[5] Interestingly, the corresponding non-complexed eneyne did not give any ene product under similar reaction conditions. We consider that the *ortho* position of the aromatic ring in **6** is also activated by the adjacent $Co_2(CO)_6$-complexed acetylene. Both electronic and structural properties of $Co_2(CO)_6$-complexed acetylene are also expected to induce cyclization of an eight-membered ring using a vinyloxirane as an electrophile. Herein, we report an 8-*endo* FC cyclization of vinyloxirane **8** based on the installation of $Co_2(CO)_6$-complexed acetylene unit in the linker between the two reacting sites (Schemes 1 and 2).



Scheme 1.

Vinyloxiranes **8a–e**[6] were synthesized as shown in Scheme 3. Sonogashira coupling[7] of bromobenzenes **10a–e** with 4-pentyn-1-ol afforded alcohols **11a–e**, which were converted into **12a–e**[6] by Dess–Martin oxidation and subsequent Wittig reaction. Reduction of **12a–e** using DIBAL-H and subsequent epoxidation with MCPBA gave epoxyalcohol **13a–e**.[6] Oxidation of **13a–e** followed by Wittig reaction furnished **14a–e**,[6] which was easily transformed to **8a–e** upon treatment with $Co_2(CO)_8$.

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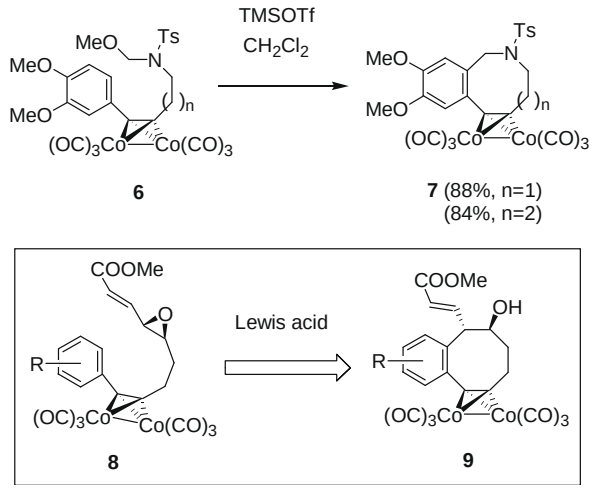
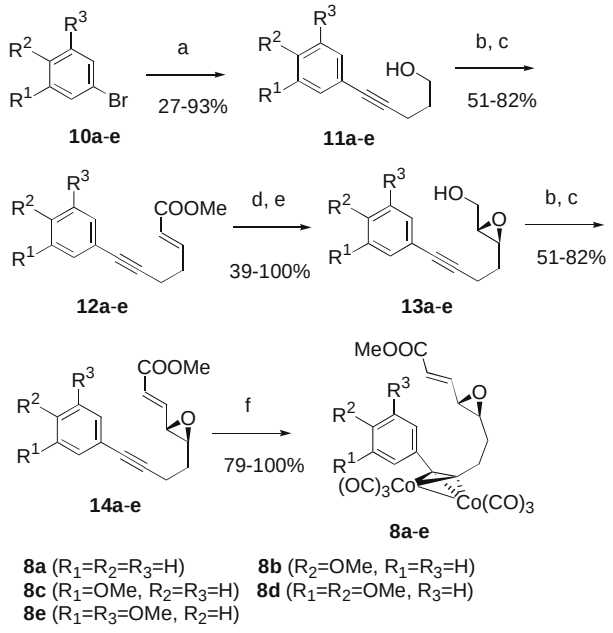
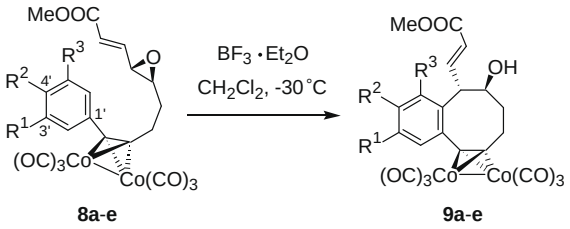


Scheme 2.

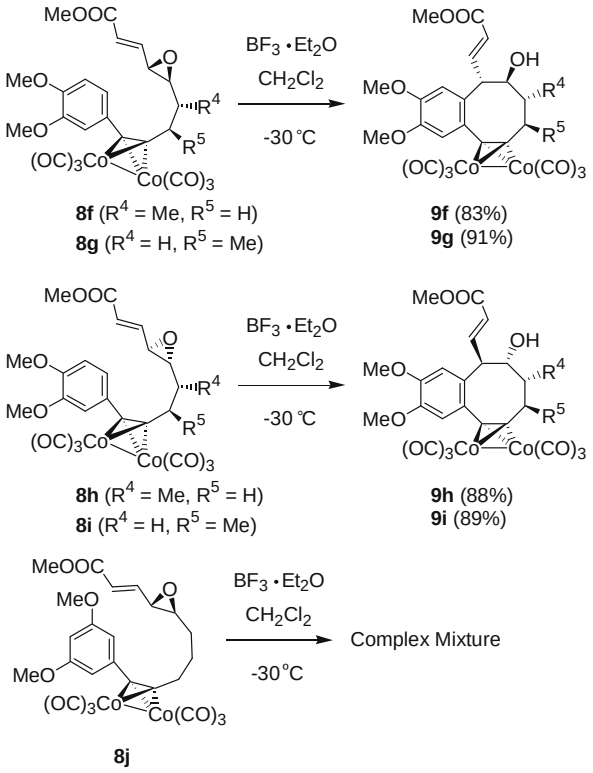


Scheme 3. Reagents and conditions: (a) 4-Pentyn-1-ol, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 70 °C; (b) Dess–Martin periodinane; (c) Ph_3P=CHCOOMe; (d) DIBAL-H, −78 °C; (e) MCPBA; (f) $Co_2(CO)_8$.

Table 1



Entry	Substrates	R^1	R^2	R^3	Products	Yield (%)
1	**8a**	H	H	H	**9a**	–
2	**8b**	H	OMe	H	**9b**	–
3	**8c**	OMe	H	H	**9c**	39
4	**8d**	OMe	OMe	H	**9d**	95
5	**8e**	OMe	H	OMe	**9e**	99

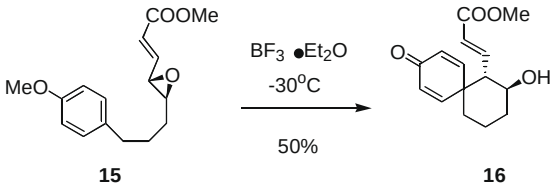


Scheme 4.

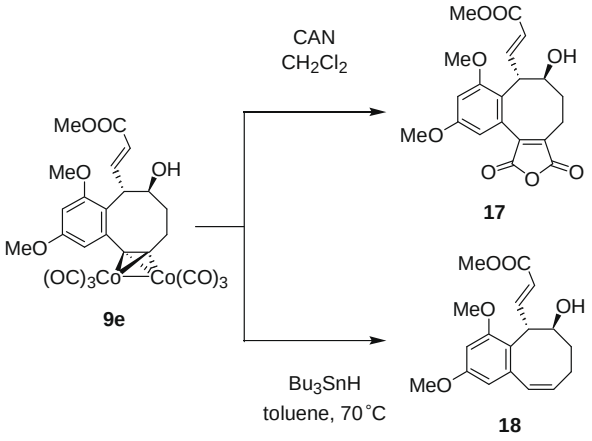
Intramolecular FC reaction of the vinyloxirane **8a–e** with $Co_2(CO)_6$-complexed benzeneacetylene was performed as shown in Table 1. Vinyloxirane **8a** with no electron-donating group could not be cyclized upon treatment with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −30 °C, and only degradation products were observed. The effect of a methoxy group on the cyclization was thus examined in order to achieve an 8-*endo* selective cyclization of vinyloxirane. Compound **8b**, which bears a methoxy group at the C4′ position of the benzene ring, was decomposed, whereas **8c** with methoxy group at the C3′ position underwent selective 8-*endo* cyclization in a stereospecific fashion to afford **9c** in 39% yield. Moreover, the efficiency of the reaction was increased by introducing another methoxy group on the benzene ring.[8] The cyclization of **8d–e** proceeded smoothly with an 8-*endo* mode to afford **9d–e** in excellent yields.

In addition, cyclization of vinyloxiranes **8f–i**[6,9] having a methyl substituent on the alkyl chain tether was performed (Scheme 4). In all cases, eight-membered carbocycles **9f–i** were generated in high yields. Unfortunately, construction of nine-membered carbocycle has not been achieved using this method. Treatment of **8j**[6] with $BF_3 \cdot Et_2O$ gave only degradation products. In all cases, 8-*endo* cyclization was preferred over the 7-*exo* one. This selectivity was attributed to the resonance effect of the vinyl group in stabilizing the partial positive charge of a transition state. Furthermore, all cyclizations proceeded stereospecifically to give the cyclized products as single stereoisomers. An ester group can be considered to make the resonance effect mild and prevent generation of an open-cation.[10]

We recently found that vinyloxirane **15** bearing a methoxy group only at the C4′ position underwent *ipso*-cyclization and elimination of the methyl group to produce spiro-cyclic product **16** (Scheme 5).[11] This result was in contrast to that observed for **8b**, which also had a methoxy group at the C4′ position. The $Co_2(CO)_6$-complexed acetylene unit increases nucleophilicity at



Scheme 5.



Scheme 6.

the *ortho* position of the benzene ring by stabilizing the developing positive charge at the *ipso* position. Such a property of the complex may prevent the *ipso*-cyclization of **8b**. However, activation by the cobalt complex is not strong enough to induce cyclization of an eight-membered ring at the *ortho* position with an *endo* mode. The methoxy group at the C3′ position on the benzene ring is essential for the eight-membered cyclization. Decomplexation was performed under either oxidizing or reducing conditions. Treatment of cyclic molecule **9e** with ceric ammonium nitrate afforded **17**[6] in 72% yield.[12] On the other hand, **9e** was transformed into poly-functional cyclooctene **18** in high yields upon treatment with tributyltin hydride in toluene at 70 °C (Scheme 6).[13]

In conclusion, a novel route for constructing poly-functional eight-membered carbocycles was developed based on the *endo*-selective Friedel–Crafts reaction of vinyloxiranes with $Co_2(CO)_6$-complexed benzeneacetylene. The cyclization showed high stereoselectivity and regioselectivity for the opening of the epoxide. Furthermore, decomplexation of the cyclization product proceeded smoothly. The present reaction is expected to provide a useful method for the synthesis of natural products with eight-membered carbocycles.

Acknowledgement

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6. All newly synthesized compounds gave spectroscopic data in agreement with the assigned structures. Representative data are shown below. *Compound* **9e**: IR ($CHCl_3$) 3468, 2092, 2036, 1717 cm^{-1}; Anal. Calcd for $C_{24}H_{20}O_{11}Co_2$: C, 47.86; H, 3.35. Found: C, 47.57; H, 3.49; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 16.0, 8.3 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.41 (d, J = 2.0 Hz, 1H), 5.76 (d, J = 16.0 Hz, 1H), 4.37 (dd, J = 10.7, 2.4 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (m, 1H), 3.70 (s, 3H), 3,50 (dd, J = 18.0, 11.0 Hz, 1H), 3.20 (dd, J = 18.0, 6.3 Hz, 1H), 1.96 (ddd, J = 14.0, 6.3, 2.4 Hz, 1H), 1.84 (d, J = 2.4 Hz, 1H), 1.80 (d, J = 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.64 (s), 167.09 (s), 159.84 (s), 158.27 (s), 150.55 (d), 139.66 (s), 121.85 (d), 119.89 (s), 110.44 (d), 102.59 (s), 99.60 (d), 92.07 (s), 71.08 (d), 55.67 (q), 55.34 (q), 51.41 (q), 48.33 (d), 33.44 (t), 28.86 (t). *Compound* **17**: IR ($CHCl_3$) 3486, 1769, 1736 cm^{-1}; EI-MS m/z 388 (M^+); HR-MS m/z 388.1146 (Calcd for $C_{20}H_{20}O_8$: 388.1157); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 16.1, 7.8 Hz, 1H), 6.68 (s, 1H), 6.57 (s, 1H), 5.83 (d, J = 16.1 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.59 (dd, J = 10.3, 7.8 Hz, 1H), 3.16 (m, 1H), 2.64 (m, 1H), 2.13 (br s, 1H), 1.87–1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.98 (s), 165.4 (s), 164.85 (s), 159.62 (s), 158.47 (s), 149.01 (d), 145.45 (s), 137.79 (s), 128.53 (s), 123.03 (d), 120.56 (s), 106.47 (d), 102.25 (d), 68.50 (d), 55.78 (q), 55.63 (q), 51.54 (q), 48.24 (d), 27.05 (t), 20.91 (t). *Compound* **18**: IR ($CHCl_3$) 3482, 1717 cm^{-1}; EI-MS m/z 318 (M^+); HR-MS m/z 318.1479 (Calcd for $C_{18}H_{22}O_5$: 318.1466); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 15.9, 10.0 Hz, 1H), 6.47–6.30 (m, 2H), 6.32 (s, 1H), 6.31 (m, 1H), 5.84 (d, J = 15.9 Hz, 1H), 4.21 (d, J = 10.0 Hz, 1H), 4.07 (t, J = 10.0 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 2.68 (d, J = 15.0 Hz, 1H), 2.29–2.13 (m, 2H), 1.73 (t, J = 15.0 Hz, 1H), 1.50 (br d, J = 15.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.30 (s), 158.84 (s), 158.18 (s), 151.59 (d), 139.45 (s), 134.53 (d), 126.84 (d), 121.61 (d), 119.26 (s), 105.02 (d), 98.23 (d), 69.63 (d), 55.39 (q), 55.18 (q), 51.24 (q), 48.10 (d), 29.09 (t), 24.80 (t).
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8. The *meta* methoxy group to the reacting site generally exerts an electron-withdrawing inductive effect. It was thus interesting that the cyclization of **8d** proceeded smoothly in spite of the presence of the methoxy group at the C4′ position. A previously reported 7-*endo* cyclization of 3′,4′-dimethoxyphenylpropyl vinyloxirane (see Ref. 1) can be explained to proceed via an *ipso*-cyclization and the subsequent migration. Such a mechanism might be inadequate in the case of **8d** because the neighbouring effect of the cobalt complex might inhibit an *ipso*-cyclization.
9. These vinyloxiranes were prepared as optically active compounds.
10. A previously reported 7-*endo* cyclization of 3′-methoxyphenylpropyl vinyloxirane having no adjacent ester group yielded a mixture of stereoisomers (see Ref. 1). However, the corresponding vinyloxirane having an adjacent ester group proceeded stereospecifically to give only *trans*-isomer.
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