An Organometallic Diradical Cycloaromatization Reaction

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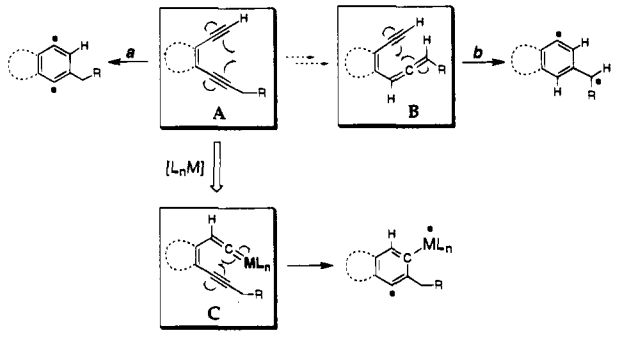
The intriguing structure and reactivity of the enediyne antitumor antibiotics has captured the intense attention of chemists and biochemists for the past several years.[1] Two reaction classes have been found to be important for the generation of highly reactive intermediates under mild conditions: the cycloaromatization of 1,5-diyne-3-enes (**A**) giving 1,4-dehydrobenzene diradical intermediates (Scheme 1, reaction **a**, first studied by Bergman[2] and employed by such agents as calicheamicin) and the cycloaromatization of 1-yne-3-ene-5-cumulenes (such as **B**) giving α,3-dehydrotoluene species (reaction **b**, studied by Myers and others[3] and occuring in neocarzinostatin).

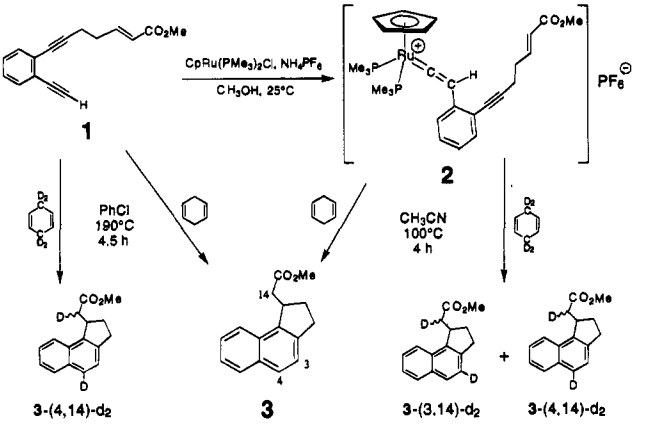
Unless packaged in a strained cyclic structure, enediynes require substantial heating to effect cycloaromatization at a rapid rate,[1,4] whereas simple allene-ene-ynes often undergo σ,π-diradical generating ring closure more rapidly.[3,5] The well-known synthesis of vinylidene complexes from terminal alkynes[6] (**C**, Scheme 1) offers an interesting means for transforming the former type of reaction into the latter. Here we report the first example of such a process. The rate of cycloaromatization of a vinylidene-ene-yne is found to be substantially faster than that of its precursor enediyne and is sensitive to the size of the metal fragment.

Diyne **1**, prepared by the method of Grissom and co-workers,[7] was easily converted to the air-stable vinylidene complex **2** by treatment with $CpRu(PMe_3)_2Cl$[8] and NH_4PF_6 in methanol solution (Scheme 2).[9] Saturation of the PMe_3 NMR resonances of **2** resulted in strong NOE enhancement of the vinylidene and aromatic C−H signals and not those of the methylene bridge between olefin and alkyne functionalities.[9] Thus, it is likely that the molecule preferentially adopts conformations in which the alkyne moiety points away from the large ruthenium center.

Scheme 1



Scheme 2



When complex **2** is heated to 100 °C for 4−6 h in a 1:3 (v/v) mixture of 1,4-cyclohexadiene and acetonitrile, or in THF without cyclohexadiene, followed by evaporation of volatile components and chromatography, **3** is isolated in 50−70% yield (Scheme 2).[9] Naphthalene **3** is the same molecule[10] obtained by Grissom and co-workers in high yield upon the thermolysis of **1** at 190 °C for 4.5 h in the presence of 1,4-cyclohexadiene, resulting from tandem bis− and mono-radical cyclizations.[7] In the absence of 1,4-cyclohexadiene, both **1** (at 190 °C)[7,12a] and **2** (at 100 °C) decompose to uncharacterized products that do not include substantial quantities of **3**.

The reactions of **1** and **2** in the presence of 15 equiv of 1,4-cyclohexadiene-3,3,6,6-d_4 were examined by ^1H and ^2H NMR to probe the cycloaromatization mechanism. As shown in Scheme 2, in the absence of ruthenium, **1** provides incorporation of deuterium at positions 4 (7.71 ppm, ≈80% D) and 14 (2.81 and 2.40 ppm, ≈50% each), as expected. Complex **2** gives the same labeling at C14, but shows approximately equal (and incomplete) deuterium incorporation at aromatic positions 3 and 4 (≈30% each).[9,11]

A mechanism that is consistent with the incorporation of deuterium at C3 is shown in Scheme 3. Heating of complex **2**

(1) Reviews: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387−1416. (b) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191−198. (c) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172−1178. (d) Gleiter, R.; Kratz, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 842−845.

(2) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−661. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25−32. (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082−4090.

(3) (a) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369−9386. (b) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057−8059. (c) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 7021−7022. (d) Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907−2910. (e) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995−4998. (f) Fujiwara, K.; Kurisaki, A.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4329−4332. (g) Hirama, M.; Tokuda, M.; Fujiwara, K. *Synlett* **1991**, 651−653. (h) Mikami, K.; Matsueda, H.; Nakai, T. *Synlett* **1993**, *23*, 25.

(4) (a) Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367−5369. (b) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986−4987. (c) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866−4868.

(5) Dopico, P. G.; Finn, M. G. Manuscript in preparation.

(6) (a) Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59−128. (b) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197−257. (c) Bruce, M. I.; Wallis, R. C. *Aust. J. Chem.* **1979**, *32*, 1471−1485. (d) LeBozec, H.; Touchard, D.; Dixneuf, P. H. *Adv. Organomet. Chem.* **1989**, *29*, 163−247. (e) Selegue, J. P.; Young, B. A.; Logan, S. L. *Organometallics* **1991**, *10*, 1972−1980. (f) Abbott, S.; Davies, S. G.; Warner, P. *J. Organomet. Chem.* **1983**, *246*, C65−C68.

(7) Grissom, J. W.; Calkins, T. L.; Egan, M. *J. Am. Chem. Soc.* **1993**, *115*, 11744−11752.

(8) (a) Treichel, P. M.; Komar, D. A.; Vincenti, P. J. *Synth. React. Inorg. Met.-Org. Chem.* **1984**, *14*, 383−400. (b) Bruce, M. I.; Wong, F. S. *J. Chem. Soc., Dalton Trans.* **1981**, 1398−1404. (c) For preparation of $CpRu(PPh_3)_2Cl$, a required starting material, see: Bruce, M. I.; Hameister, C.; Swincer, A. G.; Wallis, R. C. *Inorg. Synth.* **1990**, *28*, 270−272.

(9) See supporting information for details.

(10) All data for **3** (^1H and ^{13}C NMR, IR, TLC) match those previously reported.[7]

(11) Peak assignments were confirmed by analysis of $^1H-^1H$ coupling constants and the $^1H,^1H$-correlated (COSY) spectra. Interestingly, cycloaromatization of **2** in the presence of thiophenol-*d* (PhSD), a much faster radical trapping agent, gives deuterium incorporation at both aromatic positions as before (C3 and C4), but at only one (2.35 ppm) of the two H14 sites.

(12) (a) Grissom, J. W.; Calkins, T. L. *Tetrahedron Lett.* **1992**, *33*, 2315−2318. (b) Grissom, J. W.; Calkins, T. L.; Huang, D.; McMillen, H. *Tetrahedron* **1994**, *50*, 4635−4650. (c) Grissom, J. W.; Calkins, T. L. *J. Org. Chem.* **1993**, *58*, 5422−5427. (d) Grissom, J. W.; Calkins, T. L.; McMillen, H. A. *J. Org. Chem.* **1993**, *58*, 6556−6558. (e) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559−6564. (f) Grissom, J. W.; Klingberg, D.; Meyenburg, S.; Stallman, B. L. *J. Org. Chem.* **1994**, *59*, 7876−7888.

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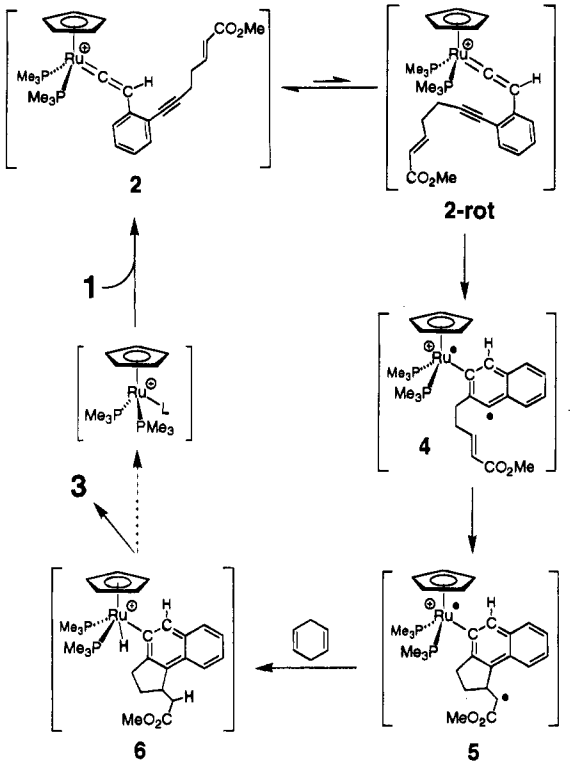
Scheme 3



allows the desired rotameric conformation (**2**-rot) to be achieved for cycloaromatization to diradical **4**. This step appears to be rate-limiting, as the sterically less encumbered 1,2-bis(dimethylphosphino)ethane (dmpe) analogue undergoes cycloaromatization in the same manner (and affording the same deuterated products) as **2**, but at 60 °C (8−12 h) instead of 100 °C.[9]

Radical cyclization of **4** to give the five-membered ring of **5** should be fast.[7,12] Trapping of both carbon- and metal-centered radicals of **5** can occur (in either order) to give ruthenium(IV) hydride **6**, which is expected to undergo reductive elimination to give **3** and $[CpRu(PMe_3)_2(CH_3CN)]^+$.[13] The putative liberation of the same cationic ruthenium complex that is used to prepare **2** from **1** suggests that a catalytic cycle should be feasible, but this has not yet been accomplished.[14]

Incorporation of deuterium at C4 in the thermal decomposition of **2** could arise from the liberation of enediyne **1** upon heating, since vinylidene formation is known to be reversible.[15] However, in the absence of ruthenium, as expected,[7,12] **1** is unchanged under conditions identical to those in which **2** was found to undergo complete reaction (CD_3CN at 100 °C). Therefore, if **1** is an intermediate in the formation of **3**-4,14-d_2 from **2**, its cycloaromatization may be mediated by a ruthenium species in a way that does not involve the vinylidene moiety.

These observations document the first case of participation of a metal fragment in a radical-generating cycloaromatization process, offering new opportunities for control of reaction rates and product structures, which are issues of both mechanistic and practical interest.[1−5]

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Supporting Information Available: Full experimental details (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access intstructions.

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(13) (a) Bruce, M. I.; Wong, F. S. *J. Chem. Soc., Dalton Trans.* **1981**, 1398−1404. (b) Indeed, the formation of **3** in CD_3CN in the presence of an excess of 1,4-cyclohexadiene is accompanied by the appearance of new Cp resonances at 4.7 ppm (major) and 5.0 ppm (minor) in the NMR spectrum of the reaction mixture, both of which are in the range characteristic of $[CpRu(PMe_3)_2(L)]^+$ species.

(14) Incubation of **2** with a 4-fold excess of **1** and a 20-fold excess of 1,4-cyclohexadiene gives **3** in improved isolated yield (88% with respect to complex **2**), but not at a level conclusively indicating catalysis. A related ruthenium vinylidene intermediate participates in a different catalytic process: Trost, B. M.; Flygare, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 5476−5477.

(15) Bullock, R. M. *J. Chem. Soc., Chem. Commun.* **1989**, 165−166.