

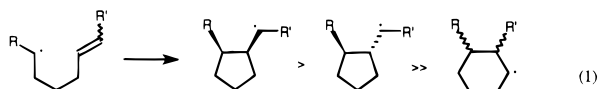
## Novel Cobalt-Mediated Regio- and Stereoselective Radical Cyclizations

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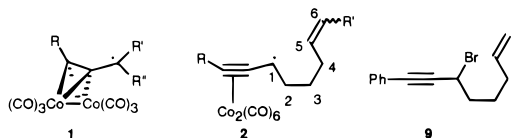
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The discovery of efficient, radical-based carbon–carbon bond-forming reactions has provided a powerful new array of tools for organic synthesis.<sup>1</sup> Especially valuable are intramolecular radical additions to carbon–carbon double bonds as typified by the 5-hexenyl radical cyclization (eq 1).<sup>2</sup> A distinctive and useful feature of this reaction is the kinetically-controlled, highly regioselective formation of five-membered rings. The levels of stereoselectivity for such reactions, however, are less useful, e.g., 1-substituted 5-hexenyl radicals undergo cyclization generally with only a modest preference for *cis*-1,2-disubstituted cyclopentanes.<sup>3</sup>



We recently initiated a program to investigate the chemistry of carbon-centered organotransition metal radicals, wondering whether sterically and electronically influential organometallic units, which have powerful effects on carbocation<sup>5</sup> and carbanion reactivity,<sup>6</sup> can induce extraordinary radical reactivity. Indeed, initial studies of (propargyl)Co<sub>2</sub>(CO)<sub>6</sub>-radicals (**1**)<sup>4</sup> have uncovered some of the highest diastereoselectivities known for radical dimerizations.<sup>4b</sup> We now report that cyclizations of 1-(alkynyl)Co<sub>2</sub>(CO)<sub>6</sub>-5-hexenyl radicals (**2**) not only proceed with exceptionally high *trans*-1,2-stereoselectivity in the 5-*exo* mode but also exhibit novel regioselectivity that is remarkably sensitive to the 6-position substituent.



Initially, we sought to generate the radicals **2** by reduction of the cobalt-stabilized cations, e.g., **3a** (Scheme 1). Thus,

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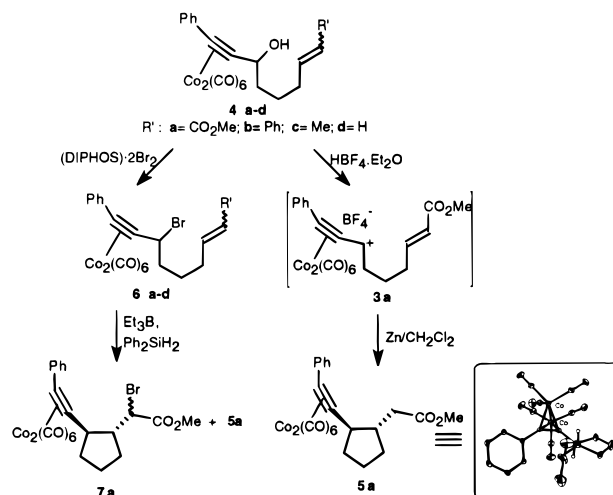
(3) Curran, D. P.; Porter, N. A.; Geise, B. In *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; pp 30–76, and references therein.

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(6) Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon: Oxford, 1982; pp 209–214.

## Scheme 1



treatment of alcohol **4a**<sup>7,8</sup> with excess HBF<sub>4</sub>·Et<sub>2</sub>O at –30 °C in ether precipitated salt **3a** which reacted with Zn powder in CH<sub>2</sub>Cl<sub>2</sub> to produce a single cyclized product **5a** (38%). NMR analysis of **5a** indicated the presence of only one isomer, established as the *trans* cyclopentane derivative by X-ray diffraction (Scheme 1).<sup>8,9</sup>

The unusual *trans* stereoselectivity of this reaction, coupled with its modest yield, prompted us to seek a more efficient and general method for cyclization. Accordingly, little known, labile propargyl bromide–Co<sub>2</sub>(CO)<sub>6</sub> complexes,<sup>10</sup> i.e., **6a–d**, were prepared by treatment of the alcohols **4a–d** (CH<sub>2</sub>Cl<sub>2</sub>, 0 °C) with 2Br<sub>2</sub>·(Ph<sub>2</sub>PCH<sub>2</sub>CH<sub>2</sub>PPh<sub>2</sub>)<sup>11</sup> (Scheme 1).<sup>8</sup> A CH<sub>2</sub>Cl<sub>2</sub> solution of **6a** (R = CO<sub>2</sub>Me) reacted with Et<sub>3</sub>B and Bu<sub>3</sub>SnH or Ph<sub>2</sub>SiH<sub>2</sub> at 20 °C, producing a 1.0:1.8 separable mixture (70% yield from **4a**) of the expected *trans* **5a** and a compound suspected to be the Br-atom transfer product **7a** based on its spectroscopic properties (*vide infra*).

Serendipitously, it was discovered that *neat samples* (or a benzene solution) of oily *cis/trans*-**6b** (R = Ph) left in laboratory sunlight or briefly irradiated with a 300 W sunlamp were converted exclusively to the atom transfer product *trans*-**7b** (76% from **4b**; Scheme 2).<sup>9</sup> This remarkably facile photocyclization appears to be quite general as the bromides **6a**, **c**, and **d** (R' = CO<sub>2</sub>Me, Me, and H) also underwent ready conversion to cycloisomerized products.<sup>12</sup> The regiochemical course of these reactions depends dramatically on the C-6 substituent. Irradiation of the ester *trans*-**6a**, like the phenyl derivative **6b**, caused its smooth conversion to *trans* **7a** (56% from **4a**). However, the bromide **6c** (R = Me) afforded a

(7) Complexes **4** were prepared in good yield by addition of lithium phenylacetylide to glutaraldehyde, reaction of the resulting hemiacetal with Ph<sub>3</sub>PCHR' (R = CO<sub>2</sub>Me, Ph, Me, H) and complexation of the en-yn-ol with Co<sub>2</sub>(CO)<sub>8</sub>.

(8) Preparative procedures and spectroscopic and analytical data for new compounds are provided in the Supporting Information.

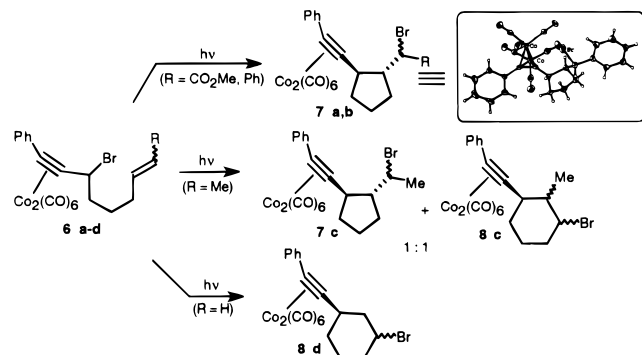
(9) The structures of **5a**, **7b**, and **8d** were established by X-ray diffraction; crystal data and collection details are provided in the Supporting Information.

(10) Examples of (propargyl halide)Co<sub>2</sub>(CO)<sub>6</sub> are few and poorly characterized. (a) Tirpak, M. R.; Hollingsworth, C. A.; Wotiz, J. H. *J. Org. Chem.* **1960**, *25*, 687. (b) Melikyan, G. G.; Mkrtchyan, V. M.; Atanesyan, K. A.; Asaryan, G. K.; Badanyan, S. O. *Bioorg. Khim.* **1990**, *16*, 1000. (c) Vizniowski, C. S.; Green, J.; Breen, T. L.; Dalacu, A. V. *J. Org. Chem.* **1995**, *60*, 7496.

(11) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *28*, 767.

(12) General procedure for **4** → **6** → **7**, **8**: Under N<sub>2</sub> 0.21 mmol of Ph<sub>2</sub>PCH<sub>2</sub>CH<sub>2</sub>PPh<sub>2</sub> dissolved in 14 mL of CH<sub>2</sub>Cl<sub>2</sub> was treated with bromine (0.24 mmol) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0 °C followed by 0.21 mmol of the alcohol **4** in 3 mL of CH<sub>2</sub>Cl<sub>2</sub>; the mixture was stirred for an hour. Addition of pentane and diethyl ether (1:2:4 CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O:pentane) produced a white precipitate. The mixture was filtered through Celite under N<sub>2</sub> and concentrated under vacuum, and crude **6** was then placed under a 300 W GE Halogen Floodlight (ca. 0.5 m) for an hour. The products **7** and **8** were purified by column chromatography over silica gel or deactivated alumina.

## Scheme 2



mixture of isomeric products (60% from **4c**), comprised of the *trans* cyclopentyl compound **7c** (2:1 stereoisomeric at C-6) and a comparable amount of the cyclohexyl derivative **8c** (isomeric mixture). This rare *6-endo-trig* pathway became the exclusive one when the parent complexed bromide **6d** was irradiated, the stereoisomeric cyclohexyl derivatives **8d** being the sole products (2:1 *trans/cis*, 73% from **4d**).<sup>9</sup>

The ready cyclization of **6** having either electron-rich or -deficient double bonds is both synthetically promising and consistent with an intervening radical process. That the special reactivity of the radicals **2** derives from the  $-\text{Co}_2(\text{CO})_6$  unit is apparent since the uncomplexed bromide **9d** was unchanged after being irradiated neat for 3 h or 24 h in the presence of  $\text{Sn}_2\text{Bu}_6$  (cf. reaction of **6** in Scheme 2).<sup>13</sup> The exclusive *trans* stereoselectivity observed in the cyclizations of **6** stands in contrast to the moderate *cis* preference typical of most 1-substituted hexenyl substrates.<sup>3,14</sup> Even more striking, however, is the extent to which the ring size depends on the 6-substituent, ranging from exclusively *5-exo* (when  $\text{R} = \text{Ph}, \text{CO}_2\text{Me}$ ) to *6-endo* (with  $\text{R} = \text{H}$ ).<sup>15</sup>

The distinctive regio- and stereoselectivity of the reactions of **6** can be rationalized in terms of an atom transfer mechanism having a late, product-like, transition state for cyclization (Scheme 3). This process is presumably initiated by cobalt-assisted photoinduced homolysis of the C–Br bond to generate radical **2** which may be stabilized by metal coordination.<sup>17</sup> As such, the transition states for the cyclization of **2** (**A** vs **B**) would involve significant C–C bond making (and breaking) as well as the development of radical character at the original olefinic carbons. With a strongly radical-stabilizing group at C-6 (e.g., Ph or  $\text{CO}_2\text{R}$ ) the *5-exo* transition state **A** is favored because it allows delocalization of the developing radical at C-6. Moreover, steric interactions between the bulky (alkyne) $\text{Co}_2(\text{CO})_6$  unit and the  $-\text{CHR}$  group would be amplified in this later,

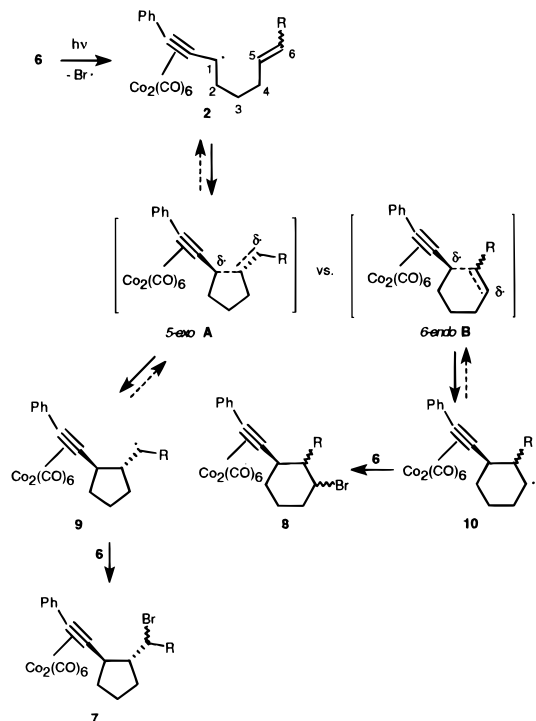
(13) Atom transfer cyclizations of typical hexenyl halides require radical initiators and bromides react inefficiently. (a) Curran, D. P. *Synthesis* **1988**, 489. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489. (c) Giese, B.; Horler, H.; Leising, M. *Chem. Ber.* **1986**, *119*, 444. (d) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477. (e) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (f) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(14) The *trans* stereoselectivity exceeds that of substrates with bulky or heteroatomic groups. (a) Beckwith, A. L. J.; Cliff, M. D.; Schiesser, C. H. *Tetrahedron* **1992**, *48*, 4641. (b) Keck, G. E.; Tafesh, A. M. *Synlett* **1990**, 257. (c) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (d) Ueno, Y.; Khare, R. K.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2637.

(15) Substrates which previously have exhibited appreciable *6-endo* selectivity either have been 5-substituted (sterically blocking the *5-exo* mode, ref 13f) or conformationally biased (e.g.,  $\alpha$ -halo carbonyl compounds, ref 13f) or produce radicals which cyclize reversibly (under thermodynamic control, ref 16).

(16) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.

## Scheme 3



probably “boat-like” transition state,<sup>3</sup> which could account for the high *trans* stereoselectivity. The *6-endo* transition state **B** may be preferred for  $\text{R} = \text{H}$  since it develops secondary radical character at C-5 (vs primary C-6 radical character as in **A**). When  $\text{R} = \text{Me}$ , the choice (**A** vs **B**) is between two incipient (and similarly energetic) secondary radicals.<sup>18</sup>

Our studies to date of the propargyl–cobalt radicals **1** and **2** presage that new and unusual reaction selectivity will be associated with carbon-centered organometallic radicals. Efforts to further elucidate the origin of this selectivity and to exploit it in organic synthesis are underway.

**Acknowledgment.** We are grateful for partial financial support by the Petroleum Research Fund of the American Chemical Society (27375AC) and a Patricia Roberts-Harris Fellowship to K.L.S.

**Supporting Information Available:** Characterizational data for **4–8** and details of crystal structure determinations, diagrams, listings of bond distances, bond angles, hydrogen atom coordinates, and thermal parameters for **5a**, **7b**, and **8d** (54 pages). See any current masthead page for ordering and Internet access instructions.

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(17) There are scattered reports of dimerizations presumed to involve metal-complexed organic radicals, but the stability and structure of these species are essentially unknown. (a) Baker, C.; Horspool, W. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1862, 2294, 2298. (b) Forrester, A. R.; Hepburn, S. P.; Dunlop, R. S.; Mills, H. H. *J. Chem. Soc., Chem. Commun.* **1969**, 698. (c) Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S. *J. Org. Chem.* **1989**, *54*, 2904. (d) Top, S.; Jaouen, G. *J. Organomet. Chem.* **1987**, *336*, 143. (e) Schmalz, H.-G.; Siegel, S.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2383. (f) Le Berre-Cosquer, N.; Kergoat, R.; L’Haridon, P. *Organometallics* **1992**, *11*, 721. (g) Meyer, A.; McCabe, D. J.; Curtis, M. D. *Organometallics* **1987**, *6*, 1491. (h) Sapienza, R. S.; Riley, P. E.; Davis, R. E.; Pettit, R. *J. Organomet. Chem.* **1976**, *121*, C35. (i) Pearson, A. J.; Chen, Y.-S.; Daroux, M. L.; Tanaka, A. A.; Zettler, M. *J. Chem. Soc., Chem. Commun.* **1987**, 155. (j) Casty, G. L.; Stryker, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 7814.

(18) We cannot exclude the possibility that the product distribution is determined by a thermodynamically controlled (i.e., reversibly formed) ratio of the radicals **9** and **10**. However, product formation from **9** or **10** apparently is not reversible since irradiation of **7c** in the presence of a trace of **6c** as initiator gave no NMR-detectable amount of the isomeric **8c**.