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Carbon tether rigidity as a stereochemical tool directing intramolecular radical cyclizations

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ABSTRACT

The phenyl group incorporated into a carbon tether provides for the synthesis of 1,5-cyclodecadiynes with 95–100% *d*,*l*-diastereoselectivity due to intrinsic conformational constraints and preorganization of the $Co_2(CO)_6$-complexed propargyl intermediates.

The 1,5-cyclodecadiyne carbon framework remains one of the hot targets in organic chemistry given its immediate structural relevance to enediyne-based cancer therapeutics.[1] The current degree of exploration of 1,5-cyclodecadiyne chemistry[2] is not commensurate to the synthetic and practical significance presented by this class of organic compounds. Available synthetic strategies are inherently limited in scope providing the parent 1,5-cyclodecadiyne,[2a,b] or its 3,4-dihydroxy derivative,[2c–g] via multistep schemes, in low overall yields. To partially fill the void, as a part of the systematic studies on the chemistry of transition metal-complexed organic radicals,[3,4] we recently reported on the diastereoselectivity of the intramolecular coupling of cobalt-complexed propargyl alcohols **1**, yielding *d*,*l*- and *meso*-3,4-diaryl-1,5-cyclodecadiynes **2** (Scheme 1).[5] While a four-step synthetic strategy represents a viable synthetic approach to otherwise hardly accessible organic molecules, the diastereoselectivity—*d*,*l*:*meso* ratio—remained relatively low varying in the range of 54:46 to 80:20.[5] In this account, we report that the phenyl group incorporated into the carbon tether—due to limiting the conformational flexibilities—is an effective stereochemical tool, providing for a nearly exclusive formation of *d*,*l*-1,5-cyclodecadiynes.

To synthesize the requisite $Co_2(CO)_6$-complexed propargyl alcohols **3**–**5**, benzyl dibromide **6** interacted with two equivalents of the lithiated derivatives of the propargyl alcohols **7**–**9**,[6] followed by the protection of the triple bonds[7] with dicobaltoctacarbonyl (Scheme 2). Treatment with tetrafluoroboric acid[8] (12 equiv) afforded bis-cationic species **10**–**12** that could be isolated as dark-red solids. The subsequent reduction with a 100-fold excess of zinc[5] generated, in situ, the respective propargyl diradicals **13**–**15** and, upon intramolecular cyclization, *d*,*l*-1,5-cyclodecadiynes **16**–**18**. Thus, the parent alcohol **3** ($R^1 = R^2 = H$) was converted to *d*,*l*-**16** in 85.3% yield, as a single diastereomer. For comparison, in the absence of the aromatic ring incorporated into the carbon tether, the respective 1,5-cyclodecadiyne was obtained in 41.2% yield, as a diastereomeric mixture (*d*,*l*:*meso*, 67:33; Table 1, entry 1).[5] The favorable impact of the rigid tether is not unique to the unsubstituted aromatic derivative **3** ($R^1 = R^2 = H$): in the presence of 4-isopropyl group, the cyclization also occurred with an excellent diastereoselectivity, producing *d*,*l*-**17** as a single stereoisomer ($R^1 = i\text{-Pr}$, $R^2 = H$). This outcome represents a significant improvement over the level of diastereocontrol observed with the flexible, all-saturated carbon tether (*d*,*l*:*meso*, 80:20;[5] Table 1; entry 2). A higher degree of substitution, and the presence of multiple methoxy groups (**5**, $R^1 = R^2 = OMe$), did not compromise the stereochemical outcome: 1,5-cyclodecadiyne **18** was obtained as a mixture of *d*,*l*:*meso* diastereomers in the ratio of 95:5. For comparison, in the case of the flexible tether, cyclization occurred stereorandomly producing comparable quantities of both diastereoisomers (*d*,*l*:*meso*, 54:46;[5] Table 1, entry 3). Bis-complexes **16**–**18** can be released from metal bondage by conventional means[5,8]—under either oxidative or reductive conditions—giving rise to bicyclic *d*,*l*-1,5-cyclodecadiynes **19** and their derivatives.

The relative configuration of *d*,*l*-**16** was determined by X-ray crystallography[9] (Fig. 1; Supplementary data, Tables 1–6). The disposition of substituents around the central C_8–C_9 bond confirms

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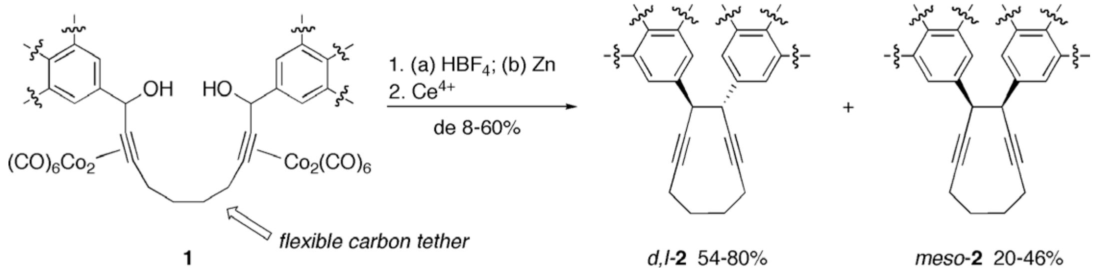
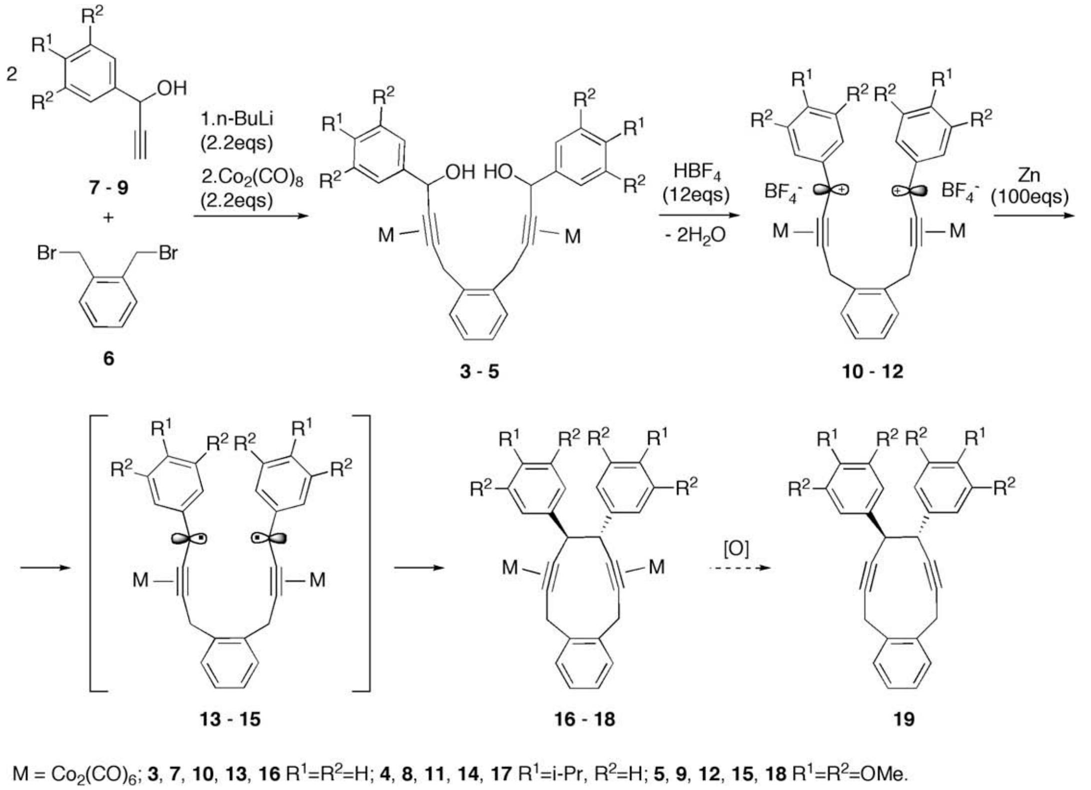


Scheme 1. Intramolecular cyclization of bis-propargyl diols with a flexible tether.



Scheme 2. Intramolecular cyclization of bis-propargyl diols with a rigid tether.

Table 1
Diastereoselectivity as a function of the tether rigidity

Substrates	Substitution pattern	Products	Diastereoselectivity			
			With rigid tether		With flexible tether[5]	
			d,l:meso	de	*d,l:meso*	de
3	0-	**16**	100:0	100	67:33	34
4	4-	**17**	100:0	100	80:20	60
5	3,4,5-	**18**	95:5	90	54:46	8

the stereochemical assignment and allows to assess how strained the ring system is bearing the bulky $Co_2(CO)_6$ cores. The dihedral angle between propargyl H-atoms is equal to 134.8° (H_8–C_8–C_9–H_9), representing a significant deviation from the typical anti-disposed H-atoms in acyclic *d,l*-isomers (171°).[4a] All three pairs of substituents around the internal C_8–C_9 bond are nearly eclipsed. The dihedral angle between aromatic rings—C_{11}–C_9–C_8–C_{17}—is only 9.7°, instead of anticipated staggered gauche arrangement**.** Analogously, both propargyl bonds are nearly eclipsed with respective C–H bonds (C_{10}–C_9–C_8–H_8 19.2°, C_7–C_8–C_9–H_9 20.1°) further contributing to the torsional strain of the molecule. Metal cores—Co_2C_2—represent the tetrahedrons with a skew geometry where the angles between Co–Co and C–C triple bonds are slightly deviated from the perpendicular arrangement (83.6°; 83.9°).[8] Other noteworthy structural features of *d,l*-**16** include: (a) a distorted planarity of alkyne moieties (C_9–C_{10}–C_1–C_2 5.0°, C_5–C_6–C_7–C_8 14.0°) which is less emphasized in acyclic *d,l*-1,5-alkadiynes (0.6–7.7°)[4a,d]; (b) a lengthened coordinated C–C triple bond (1.31–1.33 Å vs 1.21 Å for the free ligand) reflective of the nature of bonding between unsaturated ligand and transition metal;[8] (c)

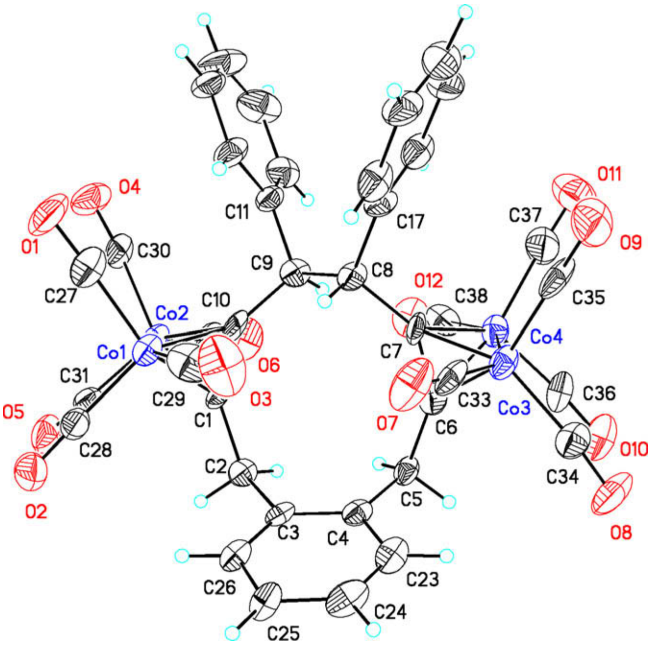


Figure 1. ORTEP diagram of the molecular structure of complex *d*,*l*-**16** with 30% probability ellipsoids. Selected bond distances (Å) and angles (deg): C(1)–C(10) 1.313(10); C(6)–C(7) 1.330(11); C(8)–C(9) 1.554(9); C(1)–C(10)–C(9) 143.0(7); C(6)–C(7)–C(8) 143.8(7); C(2)–C(1)–C(10) 148.4(7); C(5)–C(6)–C(7) 147.3(7); C(2)–C(1)–C(10)–C(9) 5.0; C(5)–C(6)–C(7)–C(8) 14.0; C(2)–C(3)–C(4)–C(5) 1.1; H(8)–C(8)–C(9)–H(9) 134.8; C(10)–C(9)–C(8)–H(8) 19.2; C(7)–C(8)–C(9)–H(9) 20.1; C(7)–C(8)–C(9)–C(10) 95.5; C(7)–C(8)–C(9)–C(11) 137.2; C(11)–C(9)–C(8)–C(17) 9.7.

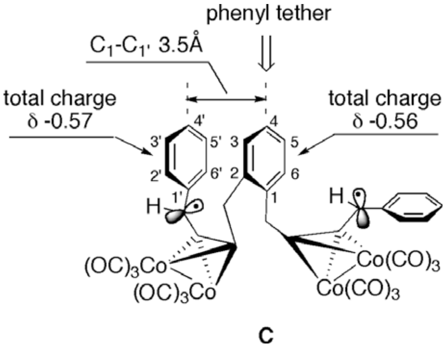


Figure 3. The least stable conformation in diradical **B** with repulsing aromatic rings.

a bent geometry for coordinated alkyne units (143–148°) attendant with coordination to the transition metal and consequent decrease in bond order;[8] and (d) unequivalency of alkyne units with one side of the triple bond being flatter than the other (C_{10}–C_1–C_2 148.4°, C_1–C_{10}–C_9 143.0°; C_7–C_6–C_5 147.3°, C_6–C_7–C_8 143.8°).

The exclusive formation of *d*,*l*-diastereomers **16**–**18** stands in sharp contrast with the moderate level of diastereoselection observed in the absence of a phenyl group (de 8–34%).[5] We hypothesized that a tether rigidity introduced by the sp^2-hydridized carbon atoms might affect the conformational freedoms in diradicals **13**–**15**, in particular, the rotation around the propargylic bonds. The rotational barriers were calculated for diradicals **A** and **B**, featuring flexible and rigid tethers, respectively (Fig. 2). The computation data revealed (PM3; Spartan'06) that the barrier of rotation is equal to 11.58 kcal/mol for diradical **A**, and it is much higher, by 6.1 kcal/mol, for its more 'rigid' counterpart, diradical **B** (17.68 kcal/mol). Detailed analysis of the least stable conformation of diradical **B** showed that a destabilizing factor is the repulsion between phenyl groups (Fig. 3). Thus, in conformation **C** ($\theta_{C\equiv C-C-H}$ 170.5°), the α-Ph group and disubstituted aromatic ring, a rigid tether, come into proximity to each other: the shortest distance between aromatic carbon atoms is equal to 3.5 Å (C_1–$C_{1'}$), nearly the sum of van der Waals radii for carbon atoms (3.40 Å).[10] The total charge of both aromatic rings is negative (−0.56; −0.57), creating a significant resistance to rotation that manifests itself in an increased rotational barrier (17.68 kcal/mol). To further understand why an inhibited rotation around the propargylic bond would translate into a nearly exclusive formation of thermodynamically more stable *d*,*l*-diastereomers (**16** $\Delta E_{d,l\text{-}meso}$ = 8.83 kcal/mol), single point calculations (MMFF) were carried out for converging diradicals **D** and **E** (Fig. 4). The former would give rise to *d*,*l*-stereoisomer with an anti-disposition of propargylic hydrogen atoms and gauche-disposed phenyl groups; the latter would afford an opposite, *meso*-diastereomer. Calculation data indicated that pre-*d*,*l*-conformation **D** is by far lower in energy (ΔE = 15.63kcal/mol) than pre-*meso* conformation **E**, thus explaining the observed preference for *d*,*l*-configuration. As confirmed by X-ray crystallographic studies (Fig. 1), in *d*,*l*-**16**, hydrogen atoms are placed anti- to each other with phenyl groups occupying the 'lower-energy' equatorial positions. To the contrary, pre-*meso* conformation **E** could be destabilized by an axially oriented phenyl group, resulting in an increased number of gauche interactions between the bulky cobalt-alkyne and phenyl rings (*meso*- 3 vs *d*,*l*- 2).

A high level of *d*,*l*-stereocontrol observed by us in intramolecular radical cyclizations is another demonstration of the idea of preorganization of reactive termini in order to enhance the reaction characteristics. The concept has been widely used in organic and bioorganic chemistries for the study of the reaction rates leading to the development of the phenomenon coined 'effective molarity'.[11] In particular, it is established that by conformationally 'locking' two reaction centers in a proximity to each other, more efficient and accelerated reactions could be effected.[11] The method developed by us could be further expanded by controlling the flexibility of the carbon tether with alternative configurationally rigid moieties, such as a naphthalene ring, heterocycles, a double bond, and a cyclic acetal group.

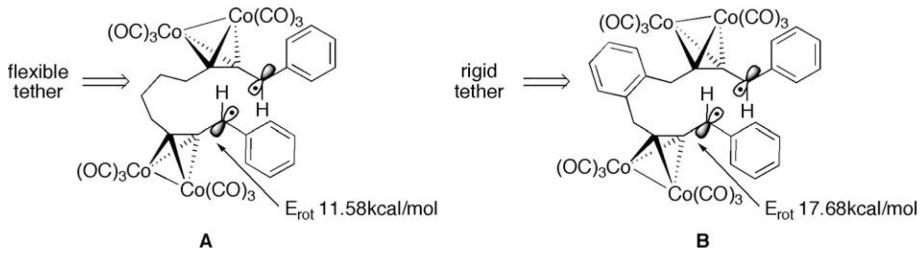


Figure 2. Rotational energy barriers around propargylic bonds.

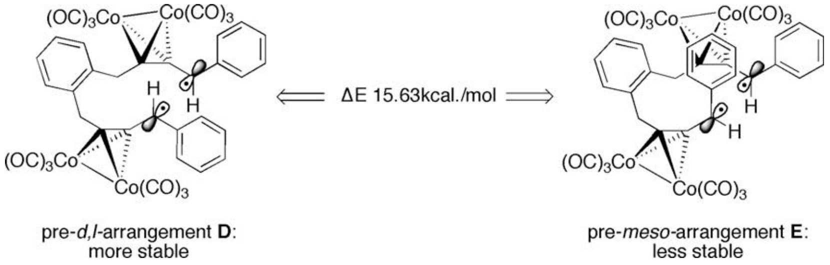


Figure 4. Single point calculation of converging diradicals **D** and **E** giving rise to *d*,*l*- and *meso*-diastereomers **16**, respectively.

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Supplementary data

Experimental procedures and full characterization of compounds **3** – **5**, **16** – **18**, as well as tables of crystallographic details, bond distances, angles, atomic coordinates, equivalent isotropic displacement parameters, and torsion angles for *d*,*l*-**16** can be found, in the online version, at doi: 10.1016/j.tetlet.2010.02.117. Crystallographic data (excluding structure factors) for *d*,*l*-**16** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 761732. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).

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