

# Propargyl Radical Chemistry: Renaissance Instigated by Metal Coordination

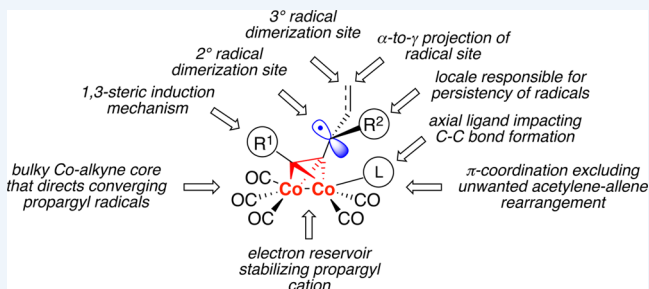
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**CONSPECTUS:** Over the last two decades, radical chemistry of propargyl systems was developed into a potent synthetic field providing access to classes of organic compounds that are otherwise hardly accessible. The levels of diastereoselection thus achieved (up to 100%) are unprecedented for free propargyl radicals, as well as for organic radicals  $\pi$ -bonded to transition metals. These advances were enabled by the coordination of the triple bond to a  $\text{Co}_2(\text{CO})_6$  core that precluded an acetylene–allene rearrangement, stabilized requisite propargyl cations, created conformational constraints at the carbon–carbon bond formation site, configurationally altered the acetylenic moiety allowing for 1,3-steric induction upon the newly formed stereocenters, increased bulkiness of propargyl triads thus controlling the spatial orientation of converging radicals, and allowed for  $\alpha$ -to- $\gamma$  projection of the reaction site and alteration of the transiency of radical intermediates.

In the course of these studies, a number of popular “beliefs” were proven to be untrue. First, cobalt-complexed propargyl cations, which have long been considered to be thermally labile species, were engaged in synthetically meaningful transformation at temperatures as high as 147 °C. Second, in radical dimerization reactions, higher reaction temperatures did not adversely impact the yields and levels of *d,l*-diastereoselectivity. Third,  $\pi$ -bonded organometallic radicals, deemed unruly, were effectively controlled with complementary mechanistic tools, thus achieving the highest levels of stereoselectivity (up to 100%) in inter- and intramolecular reactions. Fourth, *meso* stereoisomers, being thermally labile and kinetically disfavored, were discovered to be major products in intramolecular cyclizations induced by cobaltocene. Fifth, propargyl cations were synthesized *in the absence of strong acids*, thus increasing the functional tolerance and achieving a long sought after compatibility with acid-sensitive functionalities. A concept of *sequestered* propargyl radicals was introduced to explain disparity in diastereoselectivity data: heterogeneous reducing agents allegedly produce “free” radicals, while homogeneous reductants generate “sequestered” radicals associated with reductant-derived oxidized species. Among mechanistic tools, a 1,3-steric induction was found to be most efficient for controlling the stereoselectivity of radical reactions (up to 100% *d,l*). In intramolecular reactions, a *d,l*-to-*meso* reversal of stereoselectivity was discovered with zinc being replaced with cobaltocene as a reductant. Among efficient tools for controlling the stereoselectivity in intramolecular cyclizations is a *rigidity of the carbon tether* that provides for an exclusive formation of *d,l*-diastereomers.

Two novel reactions that belong to a new field of *unorthodox organometallic radical chemistry* were discovered: the spontaneous conversion of cobalt-complexed propargyl cations to radicals and the THF-mediated process wherein a THF molecule assumes a new role of an initiator in radical reactions. A multistep mechanism involves a THF-induced alteration of propargyl cations that facilitates a redox process between metal clusters. Novel stereoselective methods provide access to topologically and functionally diverse 3,4-diaryl and 3,4-dialkyl-1,5-alkadiynes, 3,4-disubstituted 1,5-cycloalkadiynes (C8–C12), 3,4-dialkoxy-1,5-(cyclo)-alkadiynes, and 3,7-diene-1,9-alkadiynes, which can be used in targeted syntheses of organic assemblies of relevance to medicinal chemistry, materials science, and natural product syntheses. Novel mechanistic tools and methodologies for controlling stereoselectivity in radical reactions can be expanded toward new types of  $\pi$ -bonded unsaturated units (dienes, arenes, diynes, and enynes) and transition metals other than cobalt (Fe, Cr, Mo, W, and Mn).



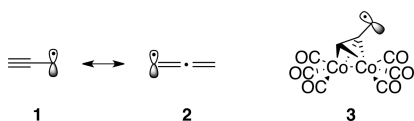
## 1. INTRODUCTION

Propargyl radicals are challenging species to study given the limited synthetic arsenal for their generation, an intrinsic ability to undergo an acetylene–allene rearrangement, a small molecular size that restricts possibilities for exploiting a steric factor, a linear geometry that precludes using conformational constraints for selectivity gains, and the absence of built-in mechanistic tools that could potentially improve the selectivity parameters. For example, the classical azo route for generating

$\alpha,\alpha$ -dimethyl propargyl radicals produces an inseparable mixture of head-to-head (33%), head-to-tail (57%), and tail-to-tail (10%) dimers due to rearrangement of propargyl radical **1** to allenic counterpart **2** (Figure 1).<sup>1</sup> These are the reasons why propargyl radicals are not intermediates of choice for synthetic chemists, who tend to use more reliable and

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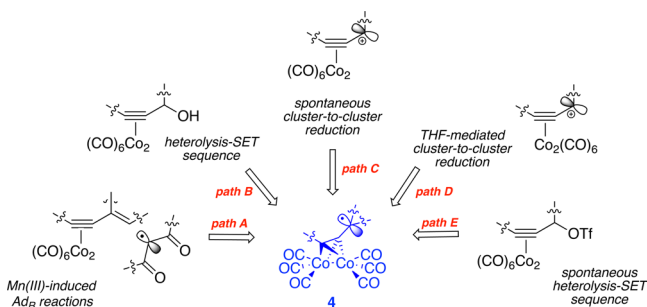


**Figure 1.** Two states of propargyl radical: free and  $\pi$ -bonded to a cobalt core.

predictable ionic counterparts. Over the last two decades, our main goal was to rehabilitate the propargyl radical by creating novel approaches for its generation and by developing mechanistic tools and methodologies that would allow for controlling its behavior and achieving levels of chemo-, regio-, and stereoselectivities that could rival those in ionic reactions. The complexation with a dicobalthexacarbonyl moiety<sup>2</sup> was selected in order to preclude an unwanted acetylene–allene rearrangement, to bend the triple bond thus avoiding an undesirable linearity, and to increase bulkiness due to a sizable metal core. The combination thereof fundamentally alters the stereoelectronic nature of propargyl triad in metal-bonded radical **3** thus creating favorable conditions for exploiting steric factors and conformational restraints, as well as acquiring an ability to predict the most preferable spatial arrangements for converging radical species.

## 2. GENERATION OF COBALT-COMPLEXED PROPARGYL RADICALS

In the early 1990s, at the inception of this project, the chemistry of organic radicals  $\pi$ -bonded to transition metals was in a rudimentary state.<sup>2,3</sup> Sporadic reports involved a handful of unsaturated radicals (pentadienyl, propargyl, benzyl, ferrocenyl, and cycloheptatrienyl) with all of them dimerizing stereorandomly despite the presence of  $\pi$ -bonded metal cores (Fe, Mo, Cr, and Co).<sup>3</sup> As a generation method, zinc reduction of the respective metal-stabilized carbocations was the one routinely used.<sup>3</sup> No systematic studies on the diastereoselectivity of the radical C–C bond formation in  $\pi$ -bonded organic ligands,  $\alpha$  to a metal core, have ever been conducted. Also, the steric, electronic, and structural parameters that control the course of the radical reactions remained mostly unknown. Our interest in developing the chemistry of  $\pi$ -bonded organometallic radicals stemmed from prior research on manganese-initiated radical reactions of 1,3-enynes wherein a propargyl radical was a key reactive intermediate.<sup>4–6</sup> Chronologically, the first method<sup>7</sup> for generation of the  $\text{Co}_2(\text{CO})_6$ -complexed propargyl radical **4** became the radical addition across the double bond in 1,3-enynes (path A, Figure 2). Requisite species were generated from  $\beta$ -dicarbonyl compounds by the oxidation with trivalent manganese, followed by the radical attack upon



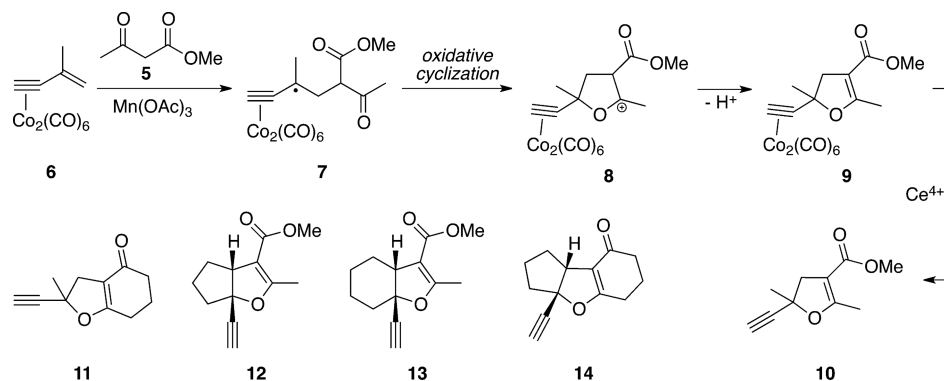
**Figure 2.** Generation of cobalt-complexed propargyl radicals.

the  $\beta$ -carbon atom and positioning an unpaired electron  $\alpha$  to a metal core. Path B represents a two-step approach<sup>8</sup> with the first one being the classical generation of the Nicholas cation<sup>2</sup> from propargyl alcohols, followed by the reduction of isolated cationic salts with various single electron donors. In 2003, we discovered<sup>9</sup> that the cobalt-complexed propargyl cations can undergo a spontaneous, albeit slow, conversion to respective radicals (path C). The metal cores act as an electron reservoir reducing the neighboring cobalt–alkyne complex and facilitating the transfer of a single electron from the metal core onto a  $\pi$ -bonded organic ligand. In 2006, the mechanism of novel THF-mediated generation of propargyl radicals was reported<sup>10</sup> (path D); the redox process is conceptually related to the spontaneous generation reaction<sup>9</sup> but occurs at a much higher rate and involves a THF-modified metal complex as a reductant. The most recent method,<sup>11</sup> utilizing propargyl triflates as substrates, has a number of advantages over the alternatives, avoiding the laborious isolation of the propargyl cation and carrying out the whole process under neutral conditions compatible with acid-sensitive functional groups (path E, Figure 2). The paths C and D belong to *unorthodox organometallic radical chemistry*<sup>3</sup> wherein the methodologies applied do not belong to the traditional methods of radical generation commonly used in organic chemistry.

## 3. 1,3-ENYNES AS SUBSTRATES: RADICAL CYCLOADDITION REACTIONS MEDIATED BY TRIVALENT MANGANESE

$\beta$ -Dicarbonyl compounds were chosen as radical precursors due to their demonstrated ability to undergo oxidation at an  $\alpha$  position, generating  $\alpha$ -mono- and  $\alpha,\alpha$ -dicarbonyl radicals.<sup>4–6</sup> Thus, methyl acetoacetate (**5**) interacts with  $\text{Mn}(\text{OAc})_3$  by converting to the respective radical, which in turn attacks the  $\beta$ -carbon atom in cobalt–enynes complex **6** (Scheme 1). Adduct-radical **7**, with an unpaired electron located  $\alpha$  to the metal core, undergoes an intramolecular cyclization upon the carbonyl group, generating heterocyclic cation **8**.<sup>7,12</sup> The latter can effectively be trapped with methanol, if present, but in acetic acid, it undergoes  $\beta$ -deprotonation to form dihydrofuran **9** (72%). An organic product can be readily released from metal bondage affording heterocycle **10** (59%). The very formation of the cycloaddition product **9** is quite remarkable given the inherent incompatibility between cobalt–alkyne complexes susceptible to oxidative decomplexation<sup>2</sup> and trivalent manganese, a strong oxidizing agent. Fine-tuning of experimental conditions allowed for optimization of the process wherein an *in situ* decomplexation was minimized to the extent possible (6–10%).<sup>12</sup> The scope of the reaction was expanded to involve cyclic enynes and  $\beta$ -dicarbonyl compounds, thus gaining access to fused di- and tricyclic derivatives **11–14** (Scheme 1). It is worth mentioning that with cyclic enynes (cyclopentenyl and cyclohexenyl acetylenes) as substrates, the formation of the fused [4.3.0] and [3.3.0] systems occurred in a *cis*-stereoselective manner. An exclusive participation of the double bonds in cycloaddition reactions stands in sharp contrast with the analogous reaction of uncomplexed enynes wherein both multiple bonds are involved to a comparable degree.<sup>5</sup> Not only does a  $\text{Co}_2(\text{CO})_6$  group provide for excellent regioselectivity by “tying” a triple bond, but it also facilitates the formation of the intermediate propargyl cation and stereodirects the ring formation step. Overall, a three-step, cobalt-assisted method for assembling topologically diverse furanoid derivatives can be

Scheme 1. Cobalt-Complexed 1,3-Enynes: Radical Cycloaddition Mediated by Trivalent Manganese

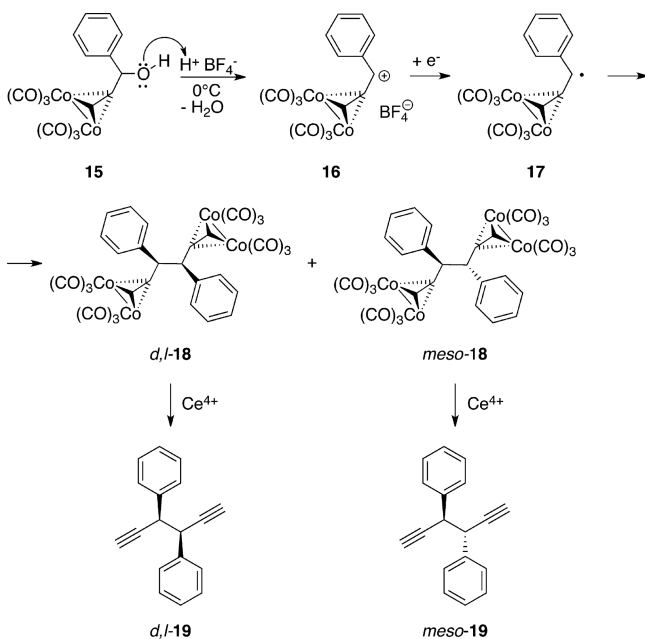


used, as a key step, in the targeted syntheses of heterocyclic compounds of biological relevance.

#### 4. INTERMOLECULAR RADICAL DIMERIZATION: HOMO- AND CROSS-COUPLING REACTIONS

The cobalt-complexed propargyl cation was first isolated in 1977 by the treatment of a propargyl alcohol with a strong acid in the presence of propionic anhydride.<sup>2</sup> An X-ray crystallographic study<sup>13</sup> revealed the intimate structural details of the propargyl triad with the cationic center being ideally  $sp^2$ -hybridized and through-space coordination causing a structural asymmetry and noticeable shift toward one of the cobalt atoms. In intermolecular coupling reactions, an optimized experimental protocol<sup>14</sup> involves the treatment of propargyl alcohol 15 with a 6-fold excess of tetrafluoroboric acid at 0 °C (Scheme 2).

Scheme 2. Dimerization of Cobalt-Complexed Propargyl Radicals



The protonation of a hydroxyl group releases propargyl cation 16, which readily precipitates in ether due to the significant stabilization by a  $\pi$ -bonded  $\text{Co}_2(\text{CO})_6$  core (Nicholas cation).<sup>2</sup> The reduction step with Zn, as an electron donor, requires a 10-fold excess in order to minimize side reactions and complete the process within a reasonable time frame (4 h, 20 °C). The

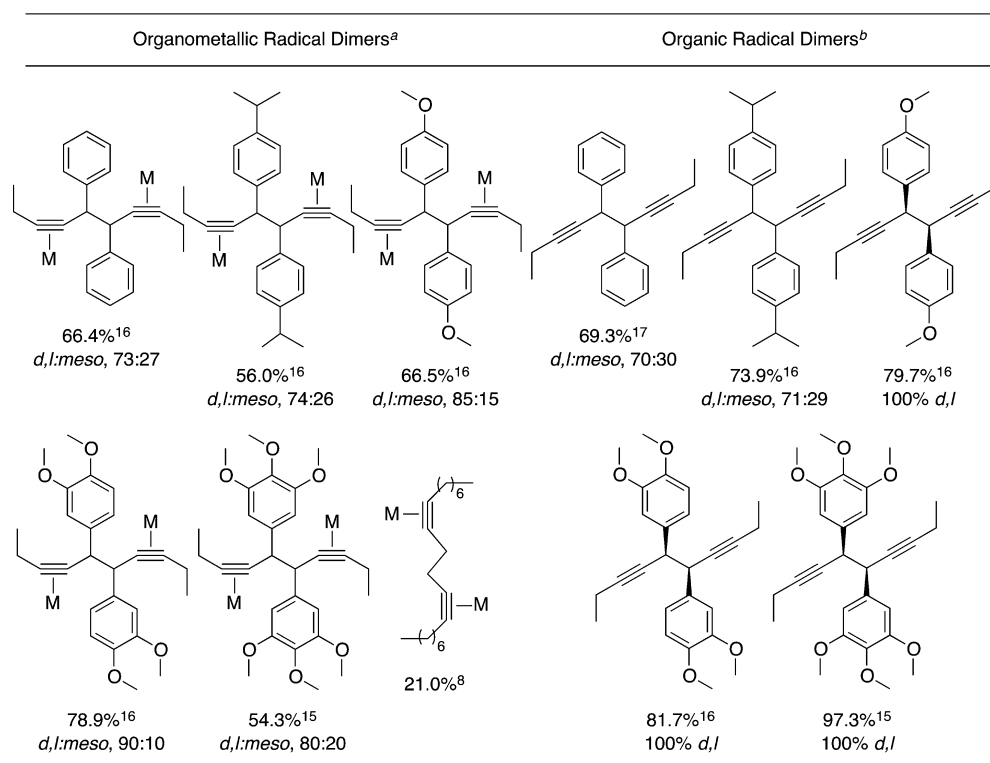
carbon–carbon bond formation in cobalt-complexed propargyl radical 17 occurred in a regioselective fashion due to the structural “lock” being placed on the triple bond by a metal core; it precludes an acetylene–allene rearrangement and formation of inseparable head-to-head, head-to-tail, and tail-to-tail dimers.<sup>1</sup> Diastereomers, *d,l*-18/*meso*-18, 84:16, are distinguishable by NMR and readily separable by chromatographic means (*d,l*-18 62.8%; *meso*-18, 12.5%). Decomplexation with ceric ammonium nitrate was carried out at low temperatures (−78 °C) to release organic dimers 19 in high yields. The scope of the reaction was expanded in a two-dimensional fashion with a variety of substituents being introduced into  $\alpha$ - and  $\gamma$ -positions of the propargyl triad (Table 1).<sup>8,9,11,14–17</sup> The conditions and yields for the cation generation step are dependent upon  $\pi$ -donating power of  $\alpha$  substituents, with  $\alpha$ -aryl groups being clearly preferential to  $\alpha$ -alkyl (2°) and  $\alpha$ -H (1°) counterparts. In contrast, the rate of reduction is lower with the propargyl cations in which the positive charge is reduced due to the efficient delocalization over aromatic nuclei. Thus,  $\alpha$ -aryl propargyl cations are noticeably reduced at +10 °C (1 h, conversion 37.2%),<sup>14</sup> while  $\alpha$ -alkyl cations can be reduced at temperatures as low as −30 °C. The diastereoselectivity is mostly dependent upon the bulkiness of  $\alpha$ -substituents with large  $\alpha$ -phenyl and  $\alpha$ -naphthyl groups providing a higher level of diastereoselection. For the substrates studied, *d,l*-configuration is identified as energetically preferential for converging propargyl radicals (*d,l*-, 63–98%). *meso*-Diastereomers, while isolated and characterized for most substrates, feature a lower stability, less crystallinity, and higher susceptibility to monodecomplexation. Due to the preponderant formation of *d,l*-diastereomers, the latter were mostly used in decomplexation reactions as substrates (Table 1).

Studies on *cross coupling of  $\pi$ -bonded organometallic radicals*<sup>18</sup> were designed to determine to what extent the product distribution, *ratio of homo- and cross-coupling dimers*, can be altered by varying the kinetic and thermodynamic parameters of the requisite cations and radicals. And also, what the substrate structure and experimental conditions might be that would accelerate cross-coupling and maximize the yields of unsymmetrical 1,5-alkadiynes, otherwise hardly accessible. Three types of substrates studied, 20, 21, and 22, formed topologically different types of cross-coupling dimers, 23 and 24, along with symmetrical counterparts 25 and 26 (Figure 3). In cobalt complexes with terminal triple bonds (20, 21), the product distribution was nearly statistical and dependent upon the nature of a reducing agent, Zn,  $\text{Cp}_2\text{Co}$ , one-step mediation with THF, or  $\text{Tf}_2\text{O}$ .<sup>18</sup> In both homo- and cross-coupling

Table 1. Intermolecular Radical Dimerization Reactions with Zinc as a Reducing Agent: Scope and Diastereoselectivity

Organometallic Radical Dimers <sup>a</sup>			Organic Radical Dimers <sup>b</sup>		
75.3% <sup>14</sup> <i>d,l:meso</i> , 84:16	70.4% <sup>14</sup> <i>d,l:meso</i> , 93:7	63.8% <sup>14</sup> <i>d,l:meso</i> , 88:12	88.8% <sup>17</sup> 100% <i>d,l</i>	89.7% <sup>17</sup> 100% <i>d,l</i>	97.9% <sup>14</sup> 100% <i>d,l</i>
61.2% <sup>14,c</sup> <i>d,l:meso</i> , 91:9	45.3% <sup>14</sup> <i>d,l:meso</i> , 89:11	49.5% <sup>14</sup> <i>d,l:meso</i> , 98:2	61.2% <sup>14,d</sup> 100% <i>d,l</i>	98.4% <sup>11</sup> 100% <i>d,l</i>	89.0% <sup>11</sup> 100% <i>d,l</i>
80.8% <i>d,l:meso</i> , 98:2	69.1% <sup>9</sup> <i>d,l:meso</i> , 87:13	32.1% <sup>14,e</sup> <i>d,l:meso</i> , 63:37	54.3% <sup>17</sup> 100% <i>d,l</i>	65.9% <sup>17</sup> 100% <i>d,l</i>	97.2% <sup>14</sup> 100% <i>d,l</i>
48.8% <sup>11</sup> <i>d,l:meso</i> , 87:13	57.5% <sup>11</sup> <i>d,l:meso</i> , 74:26	21.0% <sup>8</sup> <i>d,l:meso</i> , 72:28	47.0% <sup>11</sup> 100% <i>d,l</i>	68.9% <sup>11</sup> 100% <i>d,l</i>	

Table 1. continued



<sup>a</sup>M = Co<sub>2</sub>(CO)<sub>6</sub>. <sup>b</sup>For separable stereoisomeric mixtures, upon chromatographic separation, major *d,l*-diastereomers were decomplexed with Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub>. <sup>c</sup>Yield is given for decomplexed *d,l*-diastereomer, over two steps. <sup>d</sup>The yield over two steps. <sup>e</sup>Data are given for Cp<sub>2</sub>Co as a reductant since reaction with Zn did not form any dimeric products.

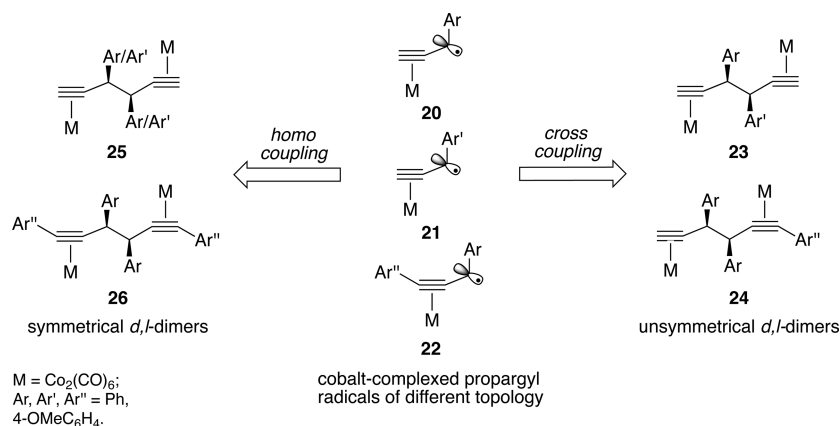
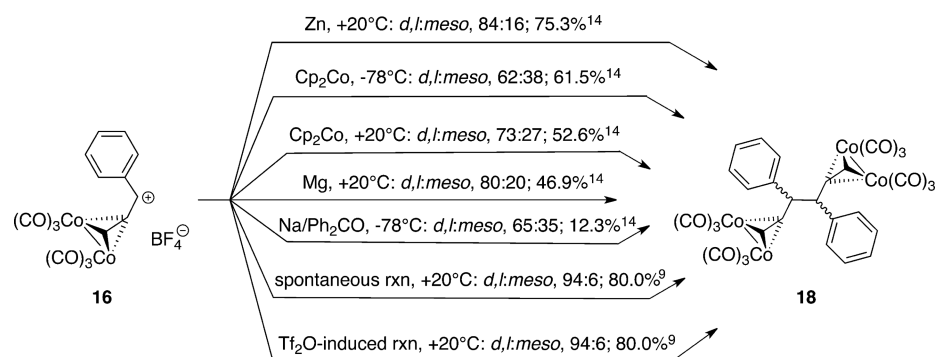

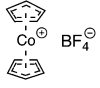
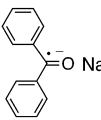
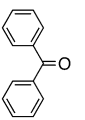
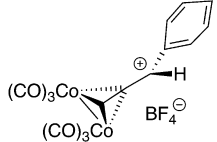
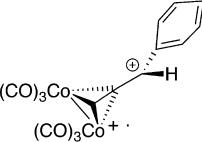
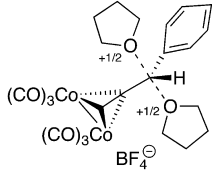
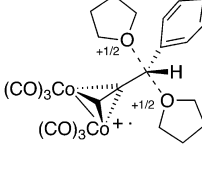


Figure 3. Topology of cross-coupling reactions.

## Scheme 3. Diastereoselectivity of Radical Coupling Reactions: Impact of Reducing Agent



**Table 2.** Dependence of Diastereoselectivity upon Reductant-Derived Oxidized Species: “Free” and “Sequestered” Organometallic Radicals

Entry	Reducing agent	Homogeneity	Reductant-derived oxidized species	Volume <sup>a</sup> (Å <sup>3</sup> )	<i>d,l</i> - <b>18</b> : <i>meso</i> - <b>18</b>
1	Zn	heterogeneous	Zn(BF <sub>4</sub> ) <sub>2</sub>	N/A	84 : 16 <sup>14</sup>
2	Mg	heterogeneous	Mg(BF <sub>4</sub> ) <sub>2</sub>	N/A	80 : 20 <sup>14</sup>
3		homogeneous		199.6	62 : 38 <sup>14</sup>
4		homogeneous		203.6	65 : 35 <sup>14</sup>
5		homogeneous		315.4	94 : 6 <sup>9</sup>
6		homogeneous		501.4	95 : 5 <sup>10</sup>

<sup>a</sup>Volume of oxidized species derived from respective reducing agents.

reactions, the stereoselectivity varied within a wide range (de 40–92%) with the preponderant formation of *d,l*-diastereoisomers. The highest degree of stereocontrol was reported for THF- and Tf<sub>2</sub>O-mediated reactions (de up to 92%), while the reductions with Cp<sub>2</sub>Co were found inferior in both homo- and cross-coupling reactions (de 40–56%). An introduction of a  $\gamma$ -aromatic nucleus allowed for achieving a *kinetic differentiation at the radical generation step* that, in turn, resulted in a nonstatistical distribution of homo- and cross-coupling dimers.<sup>18</sup>

## 5. “SEQUESTERED” VERSUS “FREE” PROPARGYL RADICALS

In the course of the systematic studies on the chemistry of metal-bonded propargyl radicals,<sup>9–11,14,16–18</sup> we found that the diastereoselectivity of radical dimerization reactions is dependent upon the nature of the reducing agent as well as the reaction temperature (Scheme 3). The said notion seems to be counterintuitive since the very term “free radical” implies that the generation method should not affect the stereochemical outcome of the dimerization reactions. Our goal was to determine to what extent the concept of a “free radical”, borrowed from organic chemistry, is applicable to organometallic radicals that are generated from the cationic species by the donation of a single electron from a reducing agent onto a cationic center.

Based on the totality of the experimental data, which involves a number of topologically diverse substrates and reducing agents, we concluded<sup>14</sup> that Co<sub>2</sub>(CO)<sub>6</sub>-complexed propargyl radicals, in general, are not kinetically independent species and cannot be categorized as “free”. Their nature depends upon the

reducing agents, which in turn can be separated into three distinct categories (Table 2): (1) In the case of heterogeneous reductants (Zn, Mg), the precipitation of inorganic salts derived from the reducing agents limits their ability to remain associated with radical species (entries 1, 2). Thus, propargyl radicals generated with either Zn or Mg are the closest to a truly “free radical”. Remarkably, the diastereoselectivities observed for both heterogeneous reductants are close to each other (Zn 84% *d,l*; Mg 80% *d,l*),<sup>14</sup> further emphasizing the commonality of the species involved. (2) In the case of soluble reductants (Cp<sub>2</sub>Co, Na/Ph<sub>2</sub>CO), the respective oxidized species supposedly remain associated with radicals as a radical-ion pair (entries 3, 4). Their volumes are amazingly close to each other [Cp<sub>2</sub>Co<sup>+</sup> BF<sub>4</sub><sup>−</sup> 199.6 Å<sup>3</sup>; Ph<sub>2</sub>CO 203.6 Å<sup>3</sup>], as are the observed levels of diastereoselection (Cp<sub>2</sub>Co<sup>+</sup> BF<sub>4</sub><sup>−</sup> 62% *d,l*; Ph<sub>2</sub>CO 65% *d,l*). Metal-complexed propargyl radicals associated with the reductant-derived species can be called “non-free” or “sequestered” organometallic radicals. (3) This category is analogous to the previous one but reducing species are generated *in situ* (entries 5, 6). The molecular volumes of the respective oxidized species are significantly higher, reaching and even exceeding that of the cobalt-complexed substrates. It is plausible that the excellent *d,l*-diastereoselectivity observed in spontaneous and THF-mediated reactions (94–95% *d,l*)<sup>9,10</sup> can be attributed to the involvement of “non-free” or “sequestered” organometallic radicals associated with bulky reductant-derived, oxidized species. Overall, the concept of “sequestered” organometallic radicals represents a new vehicle for controlling the stereochemistry of radical reactions (Figure 4). In particular, by careful choice of the structure of the homogeneous reducing agents, the coordination between organometallic radicals and reductant-derived oxidized species

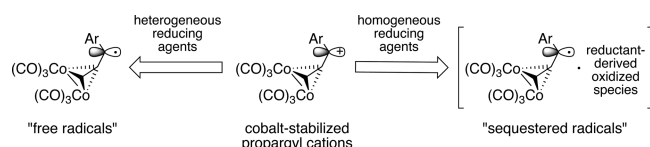


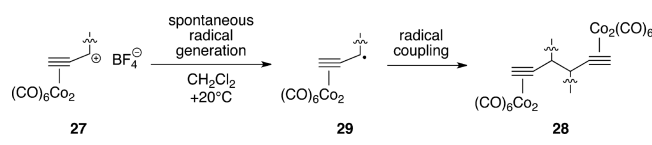
Figure 4. "Sequestered" vs "free" organometallic radicals.

can be fine-tuned in order to achieve the highest level of diastereoselection.

## 6. DISCOVERY OF THE SPONTANEOUS PROPARGYL RADICAL GENERATION REACTION

In 2003, we discovered that  $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations **27** can undergo spontaneous conversion to 1,5-hexadiynes **28** seemingly via respective radicals **29** (Scheme 4).<sup>9</sup> The said reaction occurring in methylene chloride at

### Scheme 4. Spontaneous Conversion of Cobalt-Complexed Propargyl Cations to Propargyl Radicals



ambient temperatures did not have any precedent in metal-alkyne chemistry.<sup>2</sup> Cobalt-complexed propargyl cations themselves have been subject to extensive studies over three decades,<sup>2</sup> but the formation of propargyl radicals was never reported. Further studies<sup>9,19</sup> suggested that the formation of requisite radicals is preceded by a cluster-to-cluster electron transfer wherein two identical cobalt-alkyne complexes **30** form a redox pair (Scheme 5). The reduced,  $37e^-$ -species **31** undergo a cluster-to-ligand reduction and subsequent stereoselective dimerization (**18**,  $R = \text{H}$ , *d,l/meso* 94:6; 80%), while the fate of the oxidized,  $35e^-$ -species **32** remains unknown. Most remarkably, despite an alleged thermal instability of cobalt-complexed propargyl cations,<sup>2</sup> the temperature of the spontaneous reaction can be elevated to  $147^\circ\text{C}$  without any significant decline in either the yields of dimeric products or the level of diastereoselection (*d,l* 90–97%).<sup>19</sup> In particular, increasing the reaction temperature from  $20$  to  $147^\circ\text{C}$  (Figure 5) makes the reaction remarkably fast, that is, 1 min instead of 11 h. In general terms, the spontaneous conversion of diamagnetic species (*propargyl cation*) to paramagnetic counterparts (*propargyl radical*) indicates that the organometallic

### Scheme 5. Tentative Mechanism of Spontaneous Cation-to-Radical Conversion

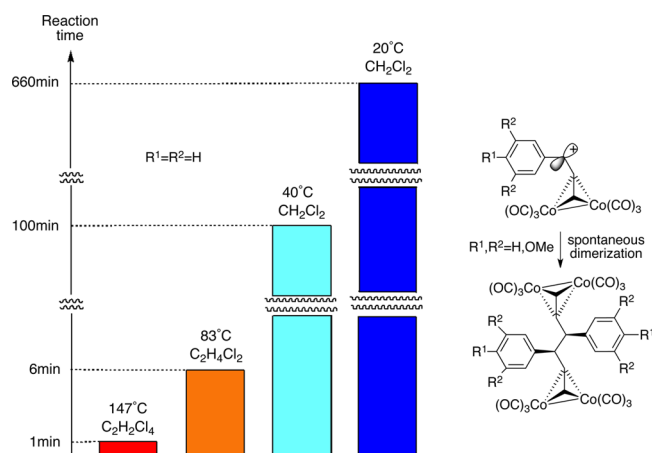
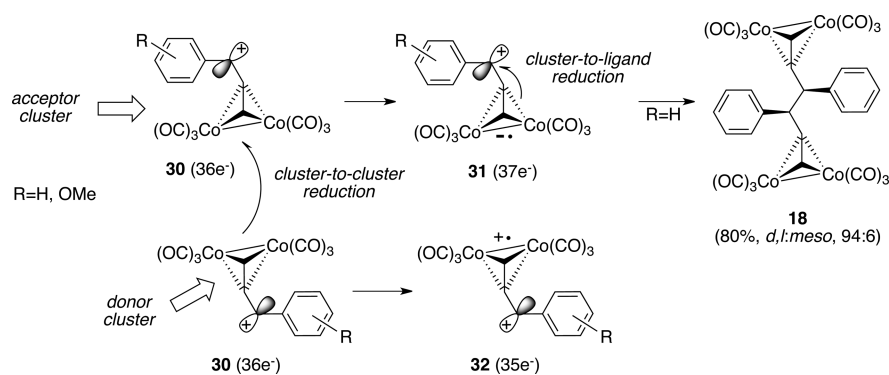


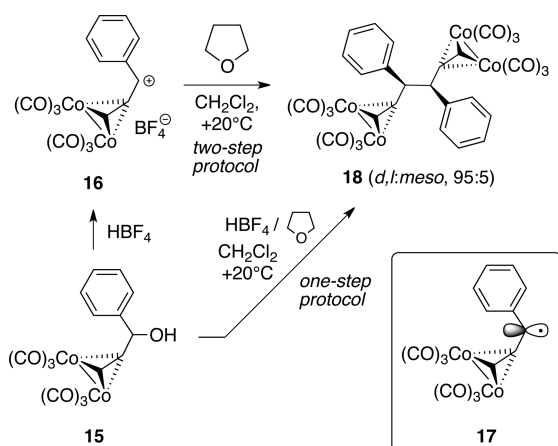
Figure 5. Spontaneous dimerization of cobalt-complexed propargyl cations: Reaction time vs temperature.

cations can act as prototypes for metal-based thermal sensors and electronic devices, as well as find various applications in materials science and biomedical fields. It is worth emphasizing that the spontaneous cation-to-radical conversion represents the *first high-temperature reaction of cationic cobalt-alkyne complexes*.<sup>2</sup>

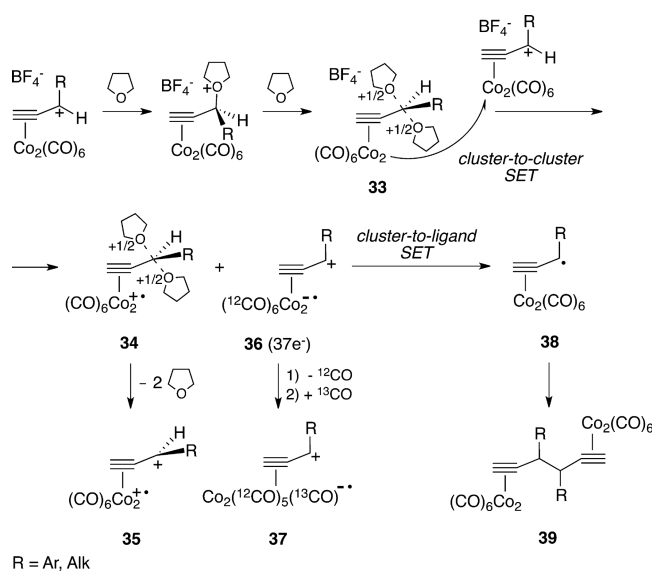
## 7. DISCOVERY OF THE THF-INDUCED PROPARGYL RADICAL GENERATION REACTION

In 1997, we discovered that addition of THF to the solution of cobalt-complexed propargyl cation **16** in methylene chloride triggers a dimerization reaction, yielding 1,5-hexadiyne **18** with excellent *d,l*-diastereoselectivity (*de* 90%; Scheme 6).<sup>20</sup> A more efficient, one-step experimental protocol involved concurrent use of  $\text{HBF}_4$  and THF, which precluded a laborious isolation of cation **16**. While the formation of dimeric products was experimental proof that the propargyl radical **17** is formed along the reaction coordinate, the mechanism for THF mediation remained a puzzle for nearly a decade.<sup>10</sup> Overall, an alleged initiation of the radical reaction was not consistent with THF's synthetic profile: as a mild Lewis donor, it was widely used as an organic solvent with a strong solvating power, and as a reagent, it was known to act as a H atom or hydride ion donor. The follow-up studies allowed us to expand the scope of THF-mediated radical reactions in both inter- and intramolecular settings,<sup>18,20–24</sup> as well as to elucidate the mechanism of the process (Scheme 7).<sup>10</sup> The initial stage includes the coordination of two molecules of THF with the

## Scheme 6. THF-Induced Generation and Dimerization of Propargyl Radicals



## Scheme 7. Mechanism of THF-Induced Radical Dimerization Reaction



propargyl cation thus increasing electron density on the metal core in complex 33 and enabling it to reduce a second molecule of the propargyl cation. An oxidized complex 34 undergoes decomposition, releasing bis-cationic species 35 and THF molecules, while anion-radical 36, subject to a ligand replacement reaction (37) in the presence of “heavy” carbon monoxide, converts to propargyl radical 38 due to a cluster-to-ligand SET. Thus, in coupling reactions affording radical dimer 39, THF acts as a catalyst that accelerates the process by forming electronically enriched transient species 33 and then, upon reaction completion, separates from the organometallic scaffold.<sup>10</sup>

A THF-mediated radical reaction,<sup>10</sup> as well as the spontaneous radical generation from cobalt-complexed propargyl cations<sup>9</sup> (section 6) belong to the field of chemistry coined *unorthodox organometallic radical chemistry*.<sup>3</sup> It includes novel paradigms for radical generation that are conceptually different from traditional, purely “organic” methodologies (thermal decomposition of peroxides or azo compounds, H atom abstraction, photochemical cleavage, bond homolysis, single electron oxidation, or reduction of select bonds).

## 8. CONTROLLING STEREOSELECTIVITY OF INTERMOLECULAR RADICAL COUPLING REACTIONS: 1,3-STERIC INDUCTION

A bent geometry<sup>2,13</sup> of cobalt-complexed propargyl cations such as 40 (Figure 6) provides a new avenue for controlling the

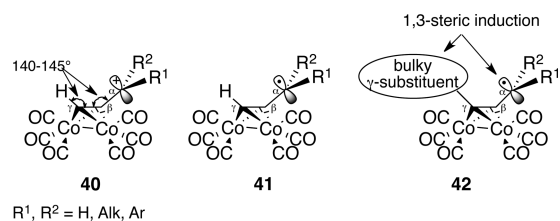


Figure 6. Concept of 1,3-steric induction.

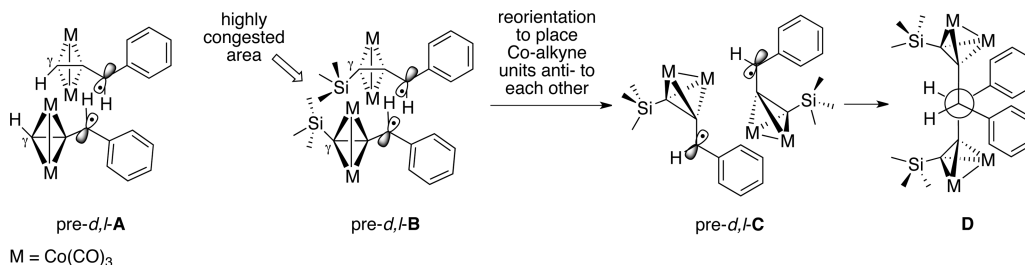
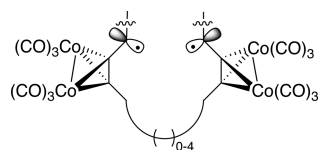
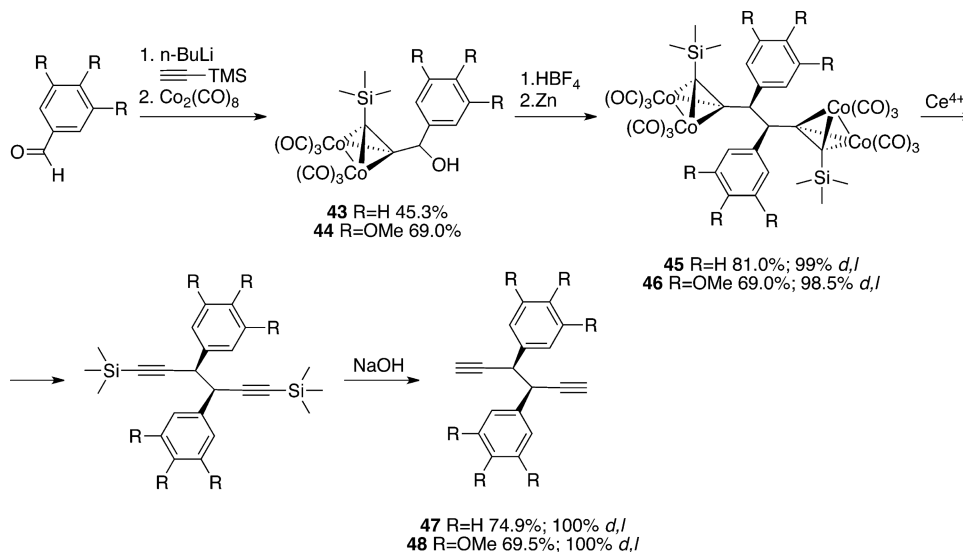
stereochemistry of radical C–C bond formation,  $\alpha$  to a metal core.<sup>25</sup> If the said configuration is maintained upon reduction of cationic species, then introducing a bulky substituent at the  $\gamma$ -carbon atom in radical 41 could induce a 1,3-steric induction over the metal-complexed triple bond. Conformational analysis of radicals 41 and 42 revealed that while  $\gamma$ -H atoms are well tolerated in cobalt complexes with terminal triple bonds (pre-*d,l*-A), introducing  $\gamma$ -TMS groups could create a highly congested area (pre-*d,l*-B) that in turn will impede the convergence of propargyl radicals (Scheme 8). A more favorable orientation can be achieved due to the spatial reorganization that would place bulky  $\gamma$ -TMS bearing cobalt-alkyne moieties anti to each other (pre-*d,l*-C), thus exclusively forming *d,l* diastereomers D.  $\gamma$ -Trimethylsilyl propargyl alcohols (43, 44) were synthesized by a condensation–complexation sequence, followed by treatment with HBF<sub>4</sub> and reduction of cationic salts with zinc (Scheme 9). Radical dimers (45, 46) were isolated in high yields and with an excellent diastereoselectivity (98.5–99% *d,l*). Decomplexation allowed for the release of organic dimers, which were then desilylated to yield isomerically pure *d,l*-47 and *d,l*-48. Overall, the synthetic strategy employing a Me<sub>3</sub>Si-auxiliary group involves five steps and produces (with 28–33% overall yields) individual *d,l*-diastereomers, which are otherwise hardly accessible.<sup>25</sup>

## 9. INTRAMOLECULAR RADICAL CYCLIZATIONS

A transition from intermolecular reactions to their intramolecular variants represents a “natural” progression for any new type of chemistry. Topologically, triple bonds can be positioned both inside and outside the carbon ring, dependent upon the disposition of requisite bis-cobalt–alkyne units. Thus, connecting the terminal carbon atoms in propargyl triads would allow for assembling 1,5-cycloalkadiynes with the ring sizes (C<sub>8</sub>–C<sub>12</sub>) being determined by the length of a carbon tether (Figure 7).

The methodology developed by us<sup>15</sup> for the synthesis of 1,5-cyclodecadiynes involved preparation of requisite bis-propargyl alcohols with a four-carbon tether, HBF<sub>4</sub>-induced conversion to isolable bis-cationic salts, and subsequent reduction with zinc (Scheme 10). 1,5-Cyclodecadiynes 49 are formed in moderate yields with the highest level of diastereoselectivity (*d,l/meso*, 80:20) being observed with a 4-*i*-Pr group as an aromatic substituent. The stereoselectivity drops sharply with overly populated aromatic rings (3,4,5-trimethoxy *d,l/meso*, 54:46) with CH/ $\pi$  coordination and steric repulsion being the main



Scheme 8. Alternative Pre-*d,l*-Dispositions of Converging Propargyl RadicalsScheme 9. Propargyl Alcohols with a Removable  $\gamma$ -Me<sub>3</sub>Si Substituent: Highly Stereoselective Dimerization Reaction

**Figure 7.** Intramolecular cyclizations of cobalt-complexed bis-propargyl radicals: Assembling of 8–12 membered 1,5-cycloalkadiynes.

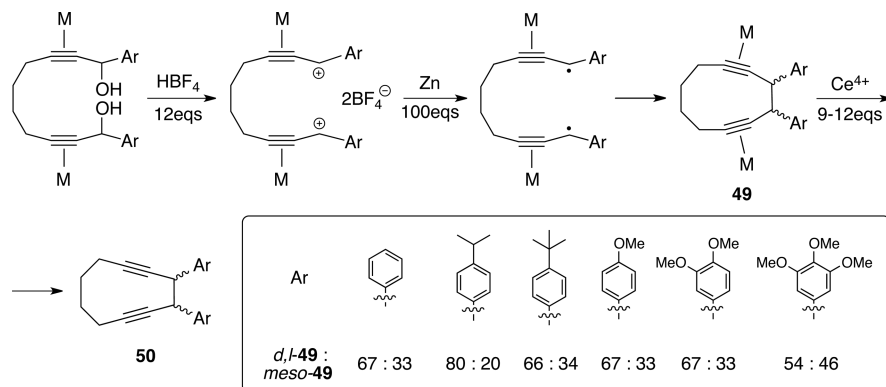
determinants. Decomplexation allows for isolation of organic products **50** in good yields, either as diastereomeric mixtures or as individual isomers. Overall, the four-step protocol provides easy access to *d,l*- and *meso*-3,4-diaryl-1,5-cyclodecadiynes

otherwise hardly accessible. The very design of the synthetic scheme allows for introducing functionalities into the carbon tether or for altering its length and accessing alternative ring sizes such as C<sub>8</sub><sup>21,26</sup> and C<sub>9</sub>.<sup>21</sup> In comparative studies on the stereoselectivity of inter- and intramolecular C–C coupling reactions,<sup>15,16</sup> we found that despite the literature precedent, intermolecular dimerizations can feature a higher *d,l*-stereoselectivity than intramolecular cyclizations of isocarbon analogues ( $d_{\text{inter}} - d_{\text{intra}} \leq 52\%$ ).<sup>16</sup>

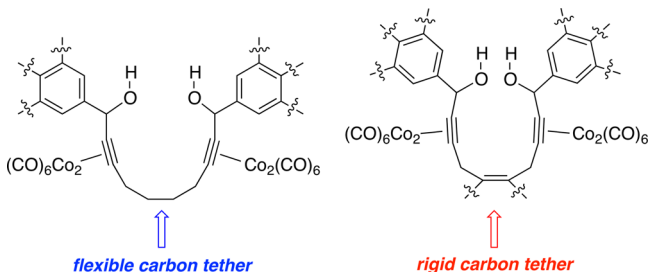
### 9.1. Carbon Tether Rigidity as a Mechanistic Tool for Controlling Stereoselectivity of Intramolecular Cyclizations

The concept of preorganization of reactive termini has been widely used in organic and bioorganic chemistry to enhance

## Scheme 10. Synthesis of 1,5-Cyclodecadiynes



reaction characteristics and achieve more efficient, accelerated reactions. In the context of organometallic radical chemistry, we tried to establish whether introducing a rigidity element into the carbon tether would impose conformational restraints upon converging propargyl radicals, which in turn could result in higher yields and enhanced stereoselectivity (Figure 8). With a



**Figure 8.** Carbon tether rigidity as a new mechanistic tool.

phenyl group incorporated into a carbon link, diol **51** ( $R^1 = R^2 = H$ ) was converted to *d,l*-**52** in 85.3% yield as a single diastereomer (Scheme 11).<sup>27</sup> For comparison, with a flexible carbon tether, the respective 1,5-cyclodecadiyne was obtained in 41.2% yield as an inseparable diastereomeric mixture (*d,l/meso*, 67:33; Table 3, entry 1).<sup>15</sup> A rigid tether was proven efficient even with the most “problematic” 3,4,5-trimethoxy derivative: cyclization occurs nearly stereorandomly with a flexible tether (*d,l/meso*, 54:46)<sup>15</sup> while reaching an excellent level of *d,l*-diastereoselectivity with a rigid carbon chain (*d,l/meso*, 95:5).<sup>27</sup> This mechanistic tool for controlling the stereoselectivity of the radical cyclizations, *de* 90–100%<sup>27</sup> vs 8–34%,<sup>15</sup> can be further expanded to include other configurationally rigid moieties, such as a double bond or cyclic acetal group.

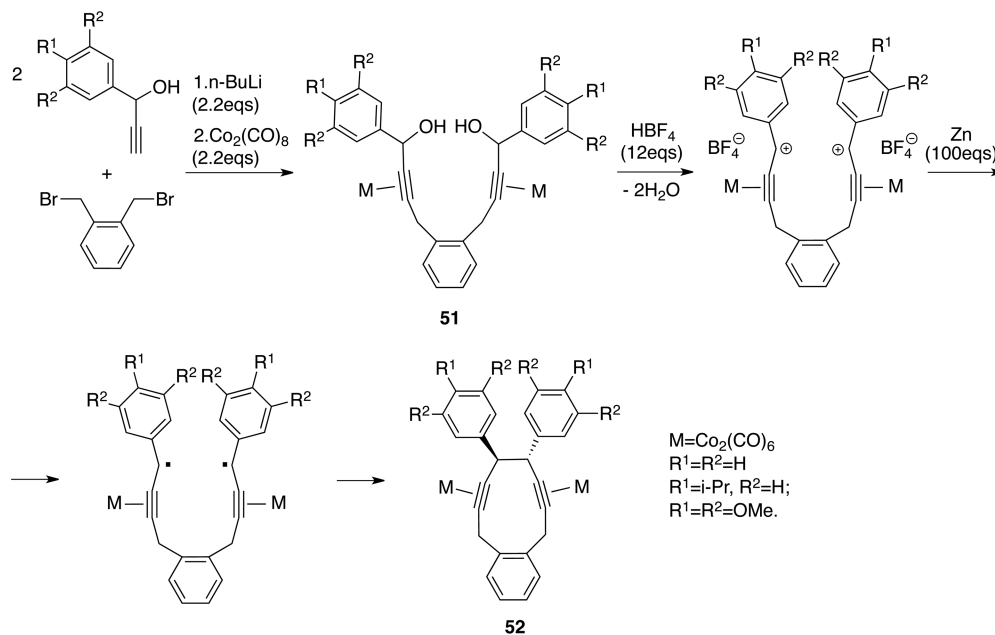
**Table 3.** Tether Rigidity Impact upon Stereoselectivity of Cyclization

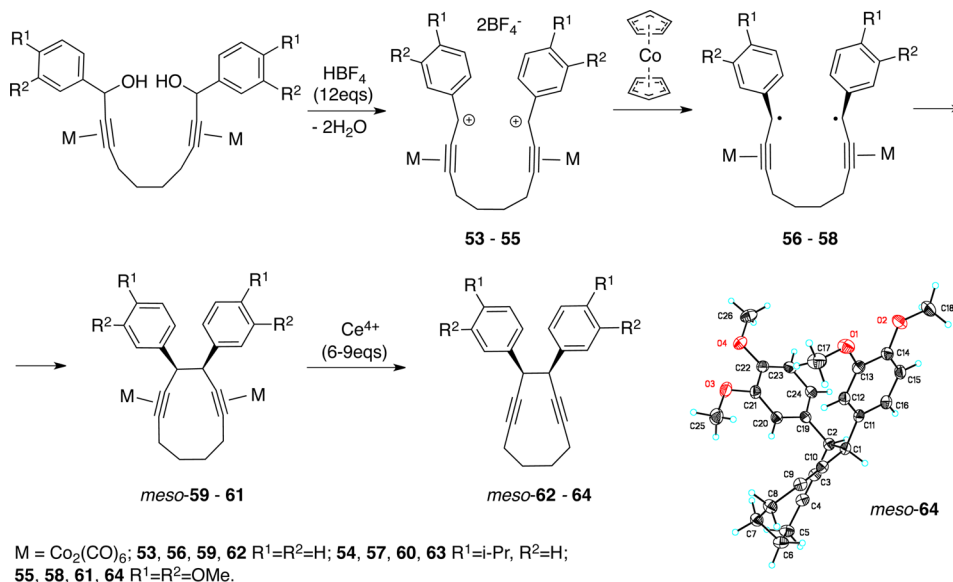
Substrates	Diastereoselectivity			
	with rigid tether <sup>27</sup> <i>d,l/meso</i>	<i>de</i>	with flexible tether <sup>15</sup> <i>d,l/meso</i>	<i>de</i>
$R^1=R^2=H$	100:0	100	67:33	34
$R^1=i\text{-Pr}; R^2=H$	100:0	100	80:20	60
$R^1=R^2=OMe$	95:5	90	54:46	8

## 9.2. Reversal of Stereoselectivity in Intramolecular Cyclization Reactions: Impact of Reducing Agent and Reaction Temperature

In intramolecular cyclization reactions of  $\text{Co}_2(\text{CO})_6$ -complexed propargyl radicals, with zinc as a reducing agent, the ratio of *meso*- and *d,l*-1,5-cyclodecadiynes varies from 33:67 to 20:80 with the *d,l*-configuration being most favored.<sup>15</sup> *Meso*-counterparts, more crowded and less stable, have always been elusive synthetic targets. In 2009, we discovered that replacing zinc with cobaltocene allows for a reversal of stereochemistry and formation of *meso*-1,5-cyclodecadiynes with an excellent stereoselectivity (90–97%).<sup>28</sup> Thus, bis-propargyl cations **53**–**55**, when exposed to the reductant at  $-78^\circ\text{C}$ , rapidly form bis-radicals **56**–**58**, which cyclize to *meso* **59**–**61** with the relative configuration being confirmed by X-ray crystallography (Scheme 12). Under oxidative conditions, organic products

**Scheme 11.** Intramolecular Cyclization of Bis-propargyl Diols with a Rigid Tether



Scheme 12. Stereoselective Synthesis of *meso*-1,5-Cyclodecadiynes

**62–64** can be released from metal bondage with complete preservation of their structural integrities (*meso* 94–95%).<sup>28</sup> Diastereoselectivity data summarizing an unexpected reversal of stereoselectivity are given in Table 4. In 1,5-cyclodecadiyne **59**

**Table 4. Reversal of Stereoselectivity Caused by a Reducing Agent**

bis-cluster	diastereoselectivity		organic product	diastereoselectivity	
	$\text{Cp}_2\text{Co}$ <i>meso:d,l</i>			$\text{Cp}_2\text{Co}$ <i>meso:d,l</i>	$\text{Zn}^{15}$ <i>meso:d,l</i>
<b>59</b>	95:5		<b>62</b>	95:5	33:67
<b>60</b>	90:10		<b>63</b>	95:5	20:80
<b>61</b>	97:3		<b>64</b>	94:6	33:67

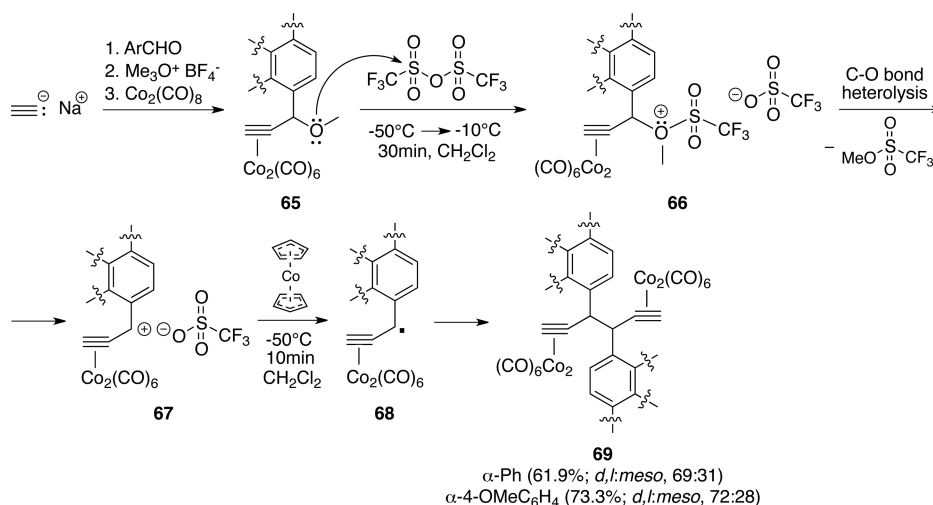
bearing unsubstituted aromatic rings, the diastereomeric ratio of *meso/d,l*, 33:67, converts to 95:5. The impact of the reducing agent is even more striking for 4-isopropylphenyl derivative **60** with the highest observed level of *d,l*-diastereoselectivity (*meso/*

*d,l*, Zn 20:80;<sup>15</sup>  $\text{Cp}_2\text{Co}$ , 90:10<sup>28</sup>). For comparison, in *intermolecular* coupling reactions, the analogous reversal of stereoselectivity was not observed with the concentration of the respective *meso*-diastereomers increasing only incrementally.<sup>14,18</sup>

## 10. PROPARGYL CATION GENERATION UNDER NEUTRAL CONDITIONS

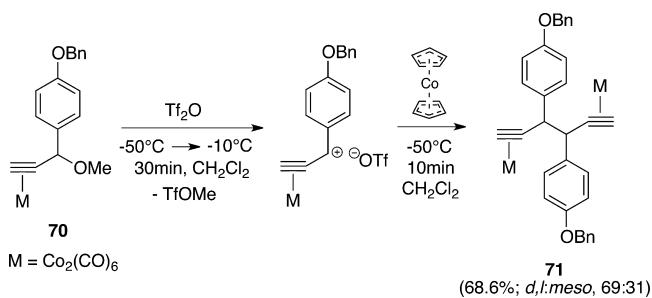
The synthesis of  $\pi$ -bonded, metal-stabilized carbocations under *neutral conditions* has long been the Holy Grail of organometallic chemists.<sup>2</sup> We found<sup>11</sup> that when cobalt-complexed propargyl alcohols are replaced with methyl propargyl ethers, such as **65**, their treatment with triflic anhydride forms ionic pairs **66**, which then transform to propargyl triflates **67** (Scheme 13). With cation-stabilizing groups, such as  $\alpha$ -Ph, a C–OTf bond acquires an ionic nature that enables the reducing agent to deliver electrons toward the cationic center. Propargyl radicals **68** undergo a coupling reaction forming dimers **69** in good to moderate yields ( $\alpha$ -Ar, 46.8–73.3%), albeit with modest diastereoselectivity ( $\alpha$ -Ar, *de* 38–70%).<sup>11</sup> An enhanced

### Scheme 13. Generation of Propargyl Cations under Neutral Conditions and a Low-Temperature Reduction with Cobaltocene



functional tolerance was showcased by introducing the peripheral acid-sensitive functionalities, such as benzyloxy and methylenedioxy groups, and carrying out a five-step conversion under nonacidic conditions.<sup>11</sup> Thus, 4-OBn substituted Me ether **70** was converted to dimer **71** in a good yield (68.6%) by a tandem action of  $\text{TiF}_2\text{O}-\text{Cp}_2\text{Co}$  (Scheme 14). An intramolecular variant was also developed providing higher yields than those observed in zinc-induced cyclizations (56.7%<sup>11</sup> vs 28.7–43.3%<sup>15</sup>).

#### Scheme 14. “Survival” of a Benzyl Protecting Group



### 11. PROPARGYL ACETALS AS SUBSTRATES

In radical chemistry, propargyl acetals belong to one of the least studied classes of organic compounds. An acid-free generation of  $\alpha$ -phenyl- and  $\alpha$ -naphthyl propargyl cations<sup>11</sup> could have been applied if an  $\alpha$ -alkoxy group demonstrates  $\pi$ -donating abilities on par with that of aromatic nuclei (Figure 9). Propargyl triflates **72–74** are ionic in nature and thus reducible with cobaltocene, while an  $\alpha$ -alkyl group provides an insufficient stabilization with triflate **75** remaining structurally covalent. With an alkoxy group as a substituent, ionic form **76** would have been favorable to the reduction process, while its competitor, covalent form **77**, would impede the process. The treatment of cobalt-complexed propargyl acetals **78–80** with triflic anhydride allowed for removal of an alkoxy group and an *in situ* generation of propargyl cations **81–83** (Scheme 15).<sup>29</sup> The latter are doubly stabilized intermediates, which are reducible with cobaltocene, albeit at a lower rate ( $\alpha$ -OEt 2.5 h;<sup>29</sup>  $\alpha$ -Ph 10 min<sup>11</sup>). Propargyl radicals **84–86** readily dimerized to yield *d,l*- and *meso*-3,4-diethoxy-1,5-alkadiynes **87–89**. Diastereoselectivity was determined by the bulkiness of the  $\gamma$  substituent: parent acetal **78** (R = H) exhibited the lowest level of stereoselectivity (*d,l*-**87**/*meso*-**87**, 73:27), while a bulky

TMS group provided for an exclusive formation of *d,l*-diastereomer **89** (1,3-steric induction<sup>25</sup>). Decomplexation of individual *d,l*-diastereomers **88** and **89** removed a metal bondage, releasing isomerically pure *d,l*-**90** and *d,l*-**91**.<sup>29</sup> An intramolecular variant of the parent reaction (Scheme 16) involved a four-step synthesis of bis-propargyl acetal **92**, its consecutive treatment with  $\text{TiF}_2\text{O}$  (4 equiv) and  $\text{Cp}_2\text{Co}$  (6 equiv) affording 1,5-cyclodecadiyne **93** (*d,l*/*meso*, 88:12), and, upon decomplexation, an isomerically pure *d,l*-**94**. Along with a 1,3-steric induction (*d,l*, **73**–100%), the stereoselectivity of the coupling reactions can be controlled by two alternative mechanistic tools, that is, bulkiness of an  $\alpha$  substituent (1,1-steric induction, *d,l*, **83**–92%) and axial ligand introduced to the metal core (axial ligand induction, *d,l*, **91**–97%; Figure 10).<sup>29</sup>

### 12. ASSEMBLING CONTIGUOUS QUATERNARY CARBON CENTERS: $\alpha$ -ALKENYL PROPARGYL RADICALS

Introducing an alkenyl group  $\alpha$  to the metal core creates a new *regioselectivity* dimension in cobalt-assisted radical reactions<sup>14,16,18</sup> wherein the radical C–C bond formation could occur either at the site of the initial cation generation (**95**) or, upon an allylic rearrangement,  $\gamma$  to the metal core (**96**, Figure 11). Three alternative methods for the generation of requisite cations were developed, employing  $\alpha$ -alcohol **97**,  $\gamma$ -alcohol **98**, and  $\gamma$ -Me ether **99** (Figure 12).<sup>30</sup> The former represents the standard protocol<sup>14</sup> wherein the cobalt complex is treated with  $\text{HBF}_4$ , and the respective cation is isolated at low temperatures as a tetrafluoroborate salt. Relocating a hydroxyl group,  $\alpha$ -to- $\gamma$ , creates a new type of alcohol, **98**, in which a hydroxyl group and a metal–alkyne core are separated by a vinyl moiety. Methyl ether **99** was chosen as a new substrate for the  $\text{TiF}_2\text{O}-\text{Cp}_2\text{Co}$  reaction wherein propargyl triflates act as reactive intermediates.<sup>11</sup>  $\alpha$ -Alcohol **100** was converted to allylic cation **101**, which in turn was readily reduced with zinc to yield allylic radical **102** (Scheme 17). Despite a multitude of regio- and stereoisomers that could potentially be formed (seven), the coupling reaction occurred with excellent chemo-, regio-, and stereoselectivities affording tail-to-tail dimer **103** in a nearly quantitative yield. Decomplexation formed organic dimer **104**, which can be desilylated to afford bis-enyne **105** with acetylenic termini recovered. Under analogous conditions, isomeric  $\gamma$ -alcohol yielded dimer **103** in a high yield (98.5%), indicating, first, that the locale of cation generation,  $\alpha$  vs  $\gamma$ , does not

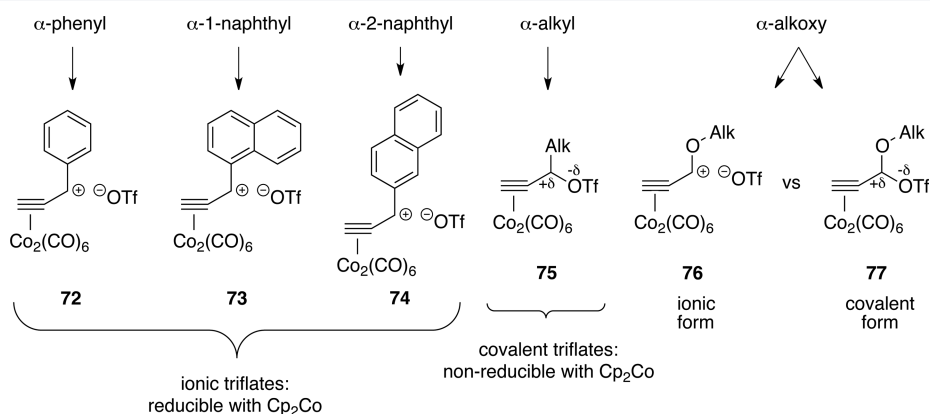
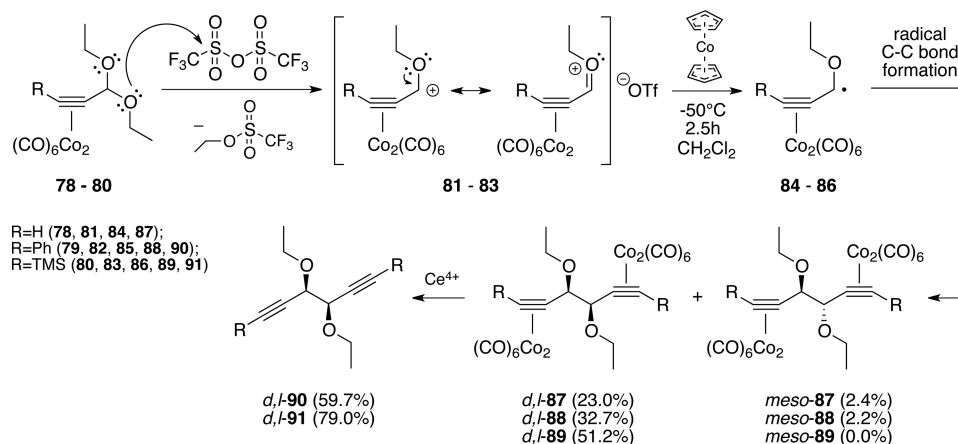


Figure 9. Cobalt-complexed propargyl triflates: Ionic vs covalent forms.

## Scheme 15. Propargyl Acetals as Substrates in Intermolecular Radical Coupling Reactions



## Scheme 16. Intramolecular Cyclizations of Bis-propargyl Acetals

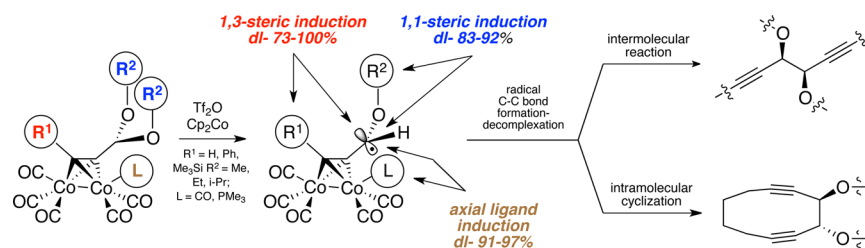
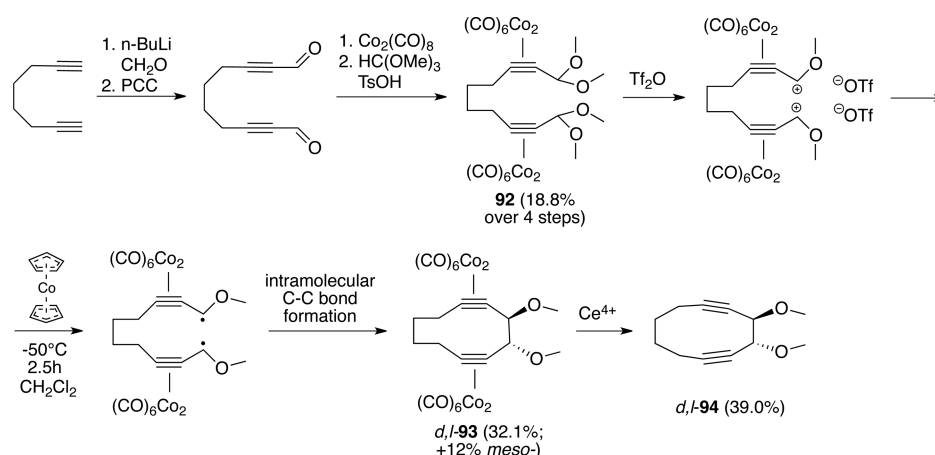
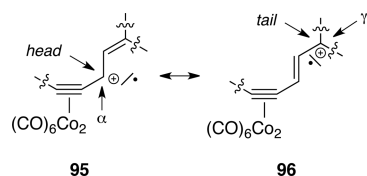


Figure 10. Alternative induction mechanisms in dimerization of propargyl acetals.

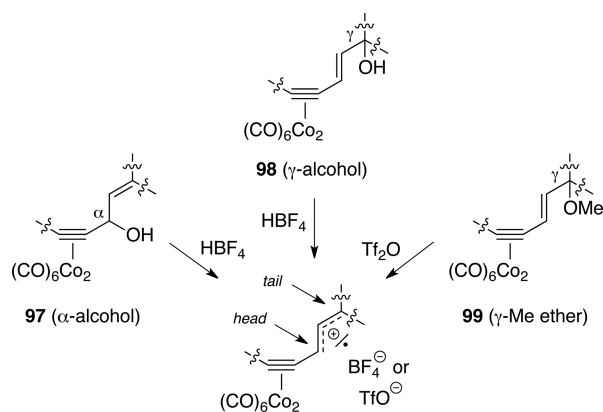
Figure 11.  $\alpha$ -Alkenyl, cobalt-complexed propargyl cations and radicals.

adversely impact the selectivity of the radical reaction and, second, that an  $\alpha,\beta$ -double bond acts as an efficient conduit between a  $\pi$ -bonded electron reservoir and the cationic center. Overall, radical reactions of 1,3- and 1,4- enynes, reacting with the retention and projection of the reaction active sites, respectively, allow for efficient assembly of contiguous quaternary carbon atoms, a highly sought after molecular unit in organic chemistry. The novel method is quite versatile

allowing for the structural variations at  $\alpha$ - and  $\gamma$ -positions, as well as at the acetylenic termini in topologically diverse Co<sub>2</sub>(CO)<sub>6</sub>-complexed propargyl alcohols (Figure 13).

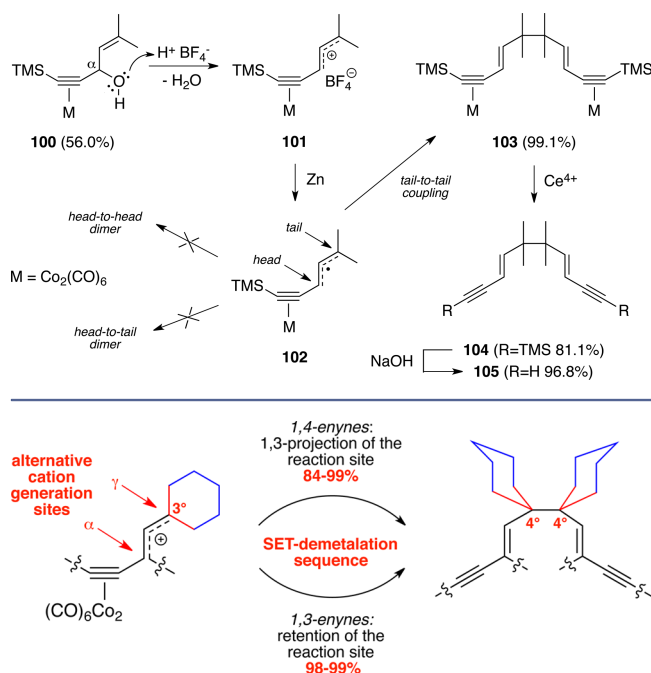
## 13. SUMMARY AND OUTLOOK

We have demonstrated that the  $\pi$ -coordination of propargyl radicals fundamentally transforms their nature, sterically, electronically, conformationally, and energetically, which allows for efficient control of C–C bond formation  $\alpha$  to a metal core. The highest levels of chemo-, regio-, and diastereoselectivities were achieved in inter- and intramolecular settings due to the development of complementary mechanistic tools. The term *unorthodox organometallic radical chemistry* was suggested for newly discovered spontaneous conversion of propargyl cations to radicals and a conceptually related THF-mediated process. The synthetic potential uncovered so far provides facile,



**Figure 12.** Alternative strategies for generation of the cobalt-stabilized propargyl cations and radicals.

### Scheme 17. Regioselective Tail-to-Tail Dimerization of $\alpha$ -Alkenyl Propargyl Radicals



**Figure 13.** Synthetic potential of dimerization reactions of  $\alpha$ -alkenyl propargyl radicals.

stereoselective access to a variety of classes of organic compounds otherwise hardly accessible. The methods and methodologies thus developed are ripe for being used, as a key step, in assembling polyfunctional, carbo- and heterocyclic compounds of immediate relevance to natural product chemistry, materials science, and drug development. Future goals include applying mechanistic tools developed for a propargyl radical to alternative unsaturated groups (dienes, arenes, diynes, and enynes) capable of  $\pi$ -bonding to transition metals (Fe, Cr, Mo, W, and Mn).

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### Notes

The author declares no competing financial interest.

## Biography

**Gagik G. Melikyan** was born in Yerevan, Armenia. He earned a Ph.D. degree (1977) from the Institute of Organoelement Compounds (Moscow) and D.Sc. degree (1990) from Institute of Organic Chemistry, National Academy of Sciences (Yerevan). In 1995, he joined the faculty at California State University Northridge (CSUN) where he currently holds the position of Professor of Chemistry in the Department of Chemistry and Biochemistry. In the field of organic chemistry, Professor Melikyan's major research interests include radical and ionic reactions of transition metal-complexed unsaturated systems and novel, selective methods of carbon-carbon bond formation in organic and organometallic chemistry.

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