

# MELIKYAN GROUP

## NSF Supported Research 2007-2011

### *Research papers (from a total of 77)*

1. Melikyan, G. G.; Floruti, A.; Devletyan, L.; Toure, P.; Dean, N.; Carlson, L. Cross-Coupling of Cobalt-Complexed Propargyl Radicals: Metal Core and  $\alpha$ - and  $\gamma$ -Aryl-Induced Chemo- and Diastereoselectivity. *Organometallics* **2007**, *26*, 3173-3182.

2. Melikyan, G. G.; Wild, C.; Toure, P. Intramolecular Radical Cyclizations of  $\text{Co}_2(\text{CO})_6$ -Complexed Propargyl Radicals: Synthesis of *d,l*- and *meso*-1,5-Cyclodecadiynes. *Organometallics* **2008**, *27*, 1569-1581.

3. Melikyan, G. G.; Mikailian, B.; Sepanian, R.; Toure, P. High-Temperature Reaction of a  $\text{Co}_2(\text{CO})_6$ -Complexed Propargyl Cation. *J. Organomet. Chem.* **2009**, *694*, 785-794.

4. Melikyan, G. G.; Sepanian, R.; Spencer, R.; Rowe, A.; Toure, P. Cobalt-Complexed Propargyl Cations: Generation under Neutral Conditions and Spontaneous, High-Temperature Conversion to Propargyl Radicals. *Organometallics* **2009**, *28*, 5541-5549.

5. Melikyan, G. G.; Spencer, R.; Abedi, E. Stereoselective Synthesis of *meso*-1,5-Cyclodecadiynes. *J. Org. Chem.* **2009**, *74*, 8541-8546.

6. Melikyan, G. G.; Voorhees, E.; Wild, C.; Spencer, R.; Molnar, J. Carbon Tether Rigidity as a Stereochemical Tool Directing Intramolecular Radical Cyclizations. *Tetrahedron Letters* **2010**, *51*, 2287-2290.

7. Melikyan, G. G.; Spencer, R. Inter- and Intramolecular Isocarbon Couplings of Cobalt-Complexed Propargyl Radicals: Challenging the Consensus. *Tetrahedron* **2010**, *66*, 5321-5328.

8. Melikyan, G. G.; Spencer, R.; Rowe, A. 1,3-Steric Induction in Intermolecular Radical Reactions Mediated by a  $\text{Co}_2(\text{CO})_6$ -Metal Core. *Organometallics* **2010**, *29*, 3556-3562.

### ***Book published***

Gagik Melikyan. *Guilty Until Proven Innocent. Antioxidants, Foods, Supplements, and Cosmetics*. Delta 2010, 376pp.

***Presentations by the PI*** (from a total 80: conferences – 54; academic institutions - 13; public appearances - 13)

1. *Invited presentation*: Gagik G. Melikyan. New Radical Reactions in Cobalt-Alkyne Series. International Organometallics Conference 2008, ZING Conferences, Cancun, Mexico, **2008**.

2. *Invited presentation*: Gagik G. Melikyan. Transition Metal-Mediated Radical Reactions and Development of Novel Therapeutic Means for Breast Cancer Treatment. General Assembly of the National of Academy of Sciences, Yerevan, Armenia, **2009**.

3. *Invited presentation*: Gagik G. Melikyan. Inter- and Intramolecular, Homo- and Cross-Coupling Radical Reactions Stereodirected by a Transition Metal Cluster, California State University Long Beach, Long Beach, CA, **2009**.

4. Gagik G. Melikyan, Ruth Sepanian, Louis Carlson, Pogban Toure. Unorthodox Methods for Generation of Transition Metal-Enhanced Propargyl Radicals: Scope, Substrate Base, Function Tolerance, Synthetic Potential, and Diastereoselectivity of C-C Bond Formation. 238<sup>th</sup> ACS National Meeting, Washington, D.C., **2009**.

5. Gagik G. Melikyan, Ruth Sepanian, Louis Carlson, Pogban Toure. Unorthodox Methods for Generation of Transition Metal-Enhanced Propargyl Radicals: Scope, Substrate Base, Function Tolerance, Synthetic Potential, and Diastereoselectivity of C-C Bond Formation. 238<sup>th</sup> ACS National Meeting, Washington, D.C., **2009**.

6. Gagik G. Melikyan, Ryan Spencer, Erin Voorhees, Pogban Toure. Intramolecular Radical Reactions Enabled by Transition Metals. 238<sup>th</sup> ACS National Meeting, Washington, D.C., **2009**.

7. Gagik G. Melikyan, Stepan Harutyunyan, Bianca Rivas, Ruth Sepanian, Louis Carlson, Erin Voorhees. Generation of Cobalt-Complexed Propargyl Cations Under Neutral Conditions: Radical C-C Bond Formation in the Presence of Acid-Sensitive Functionalities. 241<sup>th</sup> ACS National Meeting, Anaheim, CA, **2011**.

8. *Invited Speaker Series*, Phi Delta Epsilon Honor Society. Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics. California State University Northridge, Northridge, CA, **2011**.

9. Speaker, Provost Colloquium, Jeromy Richfield Scholar Award presentation: Controlling Radicals: from Reaction Flask to Food and Body Preservation. California State University Northridge, Northridge, CA, **2011**.

### ***Chairing sessions at conferences***

2011      “*New Reactions and Methodology*,” 241<sup>st</sup> ACS National Meeting, Anaheim, CA.

### ***Awards and Honors***

- 2008     *2008 Outstanding Faculty Award*, California State University Northridge (CSUN), Northridge, CA, 2008.
- 2008     Elected a Foreign Member of the National Academy of Sciences, Armenia.
- 2010     *Jerome Richfield Research Scholar Award*, California State University Northridge, Northridge, CA.

### ***Popularization of Science for High School Students & Community Service***

1. Gagik Melikyan. *Science in the US: the Societal Value, Current State of Affairs and Developmental Problems*. Ferrahian School, Encino, CA, January 23, 2009.
2. Gagik Melikyan. *Why Is It Cool to be a Chemist?* CSUN Honors Day for Juniors, CSUN, Northridge, CA, March 4, 2009.
3. Gagik Melikyan. Consulted junior & high school students preparing presentations for Los Angeles Science Olympiad. AGBU High School, Canoga Park, CA, December 01, 2009.

### ***Public outreach of an educational nature***

Several lectures have been organized for the general public to explain the impact of science on people's everyday lives, the role of radicals in medicine and biology, the importance of radical research for fundamental science and applied medicine, the nature of "oxidative stress," and also the mechanism of action of antioxidants inside the human body.

1. ARPA Institute, Thousands Oaks, CA - Dec 2010.

2. California Writers' Club, San Fernando Valley Chapter, Canoga Park, CA – Feb 2011.
3. Mission Community Hospital, Panorama City, CA – April 2011.

### ***Student presentations***

1. Christopher Wild. Exploiting a Phenomenon of CH/ $\pi$  Coordination: Interpretation of the Diastereoselectivity of Cobalt-Mediated Intramolecular Radical Cyclizations. 12th CSUN Student Research Symposium, Northridge, CA, **2007**.
2. Boghos Mikailian. Novel High-Temperature and Spontaneous Radical Coupling Reaction: Kinetic Studies. 12th CSUN Student Research Symposium, Northridge, CA, **2007**.
3. Christopher Wild. Unexpected Trends in Metal Cluster-Directed, Intramolecular Radical Cyclizations. 235<sup>th</sup> ACS National Meeting, New Orleans, **2008**.
4. Boghos Mikailian. A High-Temperature, Spontaneous, and Cobalt Cluster-Mediated Radical Coupling Reaction. 235<sup>th</sup> ACS National Meeting, New Orleans, **2008**.
5. Boghos Mikailian. Cobalt-Mediated High-Temperature Radical Coupling Reactions. 10th Annual Sigma Xi Scientific Research Society — CSUN Chapter Student Symposium, Northridge, CA, **2008**.
6. Louis Carlson. Toward Non-toxic Therapeutics for a Breast Cancer Treatment: Cobalt-Mediated Stereoselective Synthesis of Substituted *d,l*-3,4-Diphenyl-1,5-hexadiynes. 10th Annual Sigma Xi Scientific Research Society — CSUN Chapter Student Symposium, Northridge, CA, **2008**.

7. Christopher Wild. A Novel Approach Toward the Synthesis of Ene-diyne: Metal-Directed Formation of Medium-Sized Cyclic Diacetylenes. CSU-wide Student Research Competition, CSU Hayward, CA, **2008**.

8. Louis Carlson. Cobalt-Mediated Synthesis of *d,l*-3,4-Diphenyl-1,5-hexadiynes Containing Acid-Labile Aromatic Substituents. Association of Retired Faculty Luncheon, Northridge, CA, **2008**.

9. Gagik G. Melikyan, Boghos Mikailian, Ruth Sepanian. The Effect of Counter-Ion, Temperature, and Substitution upon the Spontaneous, Cobalt-Cluster Mediated Dimerization Reaction. 42<sup>nd</sup> Western Regional ACS Meeting, Las Vegas, **2008**.

10. Gagik G. Melikyan, Louis Carlson, Ryan Spencer. Impact of Aromatic Substitution and Reducing Agent on Diastereoselectivity of Intra- and Intermolecular Cobalt-Mediated Radical Reactions. 42<sup>nd</sup> Western Regional ACS Meeting, Las Vegas, **2008**.

11. Ryan Spencer. Radical Carbon-Carbon Bond Formation Stereodirected by an alpha-Metal Core. 13th CSUN Student Research Symposium, Northridge, CA, **2009**.

12. Ruth Sepanian. Overcoming a Longstanding Challenge: Synthesis of Cobalt-Complexed Propargyl Cations under Neutral Conditions. 11th Annual Sigma Xi Scientific Research Society—CSUN Chapter Student Symposium, Northridge, CA, **2009**.

13. Ryan Spencer. Controlling Stereoselectivity of Cobalt-Mediated Inter- and Intramolecular Coupling Reactions. 11th Annual Sigma Xi Scientific Research Society — CSUN Chapter Student Symposium, Northridge, CA, **2009**.

14. Ruth Sepanian. Generation of Cobalt-Complexed Propargyl Cations under Neutral Conditions. 2009 Southern California Undergraduate Research Conference (SCURC) in Chemistry and Biochemistry, USC, CA, **2009**.

15. Sarine Shahmirian. Propargyl Methyl Ethers: Novel Precursors to Cobalt-Complexed Propargyl Cations. Southern California Junior Academy of Sciences (SCJAS), Claremont, CA, **2009**.

16. Ryan Spencer. Radical Carbon-Carbon Bond Formation Stereodirected by an Alpha Metal Core. Salva Regina University, Newport, RI, **2009**.

17. Sarine Shahmirian. Propargyl Methyl Ethers: Novel Precursors to Cobalt-Complexed Propargyl Cations. AAAS Pacific Division Annual Meeting, San Francisco, CA, **2009**.

18. Ryan Spencer. First Stereoselective Synthesis of *meso*-1,5-Cyclodecadiyne. 14th CSUN Student Research Symposium, Northridge, CA, **2010**.

19. Ruth Sepanian. Novel Methods for the Synthesis of Breast Cancer Aromatase Inhibitors. 14th CSUN Student Research Symposium, Northridge, CA, **2010**.

20. Erin Voorhees. The Use of a Rigid Carbon Tether as a Stereochemical Tool in Intramolecular Radical Cyclizations. 14th CSUN Student Research Symposium, Northridge, CA, **2010**.

21. Ryan Spencer. Novel Methods for Controlling Stereoselectivity of Radical C-C Bond Forming Reactions. Graduate Fellows with Outstanding Research Promise in Science and Mathematics Symposium, College of Science & Math, CSUN, Northridge, CA, **2010**.

22. Ryan Spencer. Inter- and Intramolecular Radical C-C Bond Formation Mediated

by a Transition Metal Core. Thesis defense, Department of Chemistry & Biochemistry, CSUN, Northridge, CA, **2010**.

23. Erin Voorhees. The Use of a Rigid Carbon Tether as a Stereochemical Tool in Intramolecular Radical Cyclizations. CSU-wide Student Research Symposium, San Jose, CA, **2010**.

24. Ruth Sepanian. Generation of Cobalt-Complexed Propargyl Cation Under Neutral Conditions and Their Biological Relevance. Thesis defense, Department of Biology, CSUN, Northridge, CA, **2010**.

25. Ruth Sepanian. Generation of Cobalt-Complexed Propargyl Cation Under Neutral Conditions and Their Biological Relevance. Thesis defense, Department of Biology, CSUN, Northridge, CA, **2010**.

26. Harutyunyan, S.; Rivas, B. Naphthalene-Stabilized Propargyl Cations and Radicals in Carbon-Carbon Bond Forming Reactions. 15th CSUN Student Research Symposium, Northridge, CA, **2011**.

27. Melikyan, G. G.; Harutyunyan, S.; Rivas, B. Generation of Cobalt-Complexed Propargyl Cations Under Neutral Conditions: Expansion of the Substrate Base. 241<sup>th</sup> ACS National Meeting, Anaheim, **2011**.

28. Rivas, B.; Harutyunyan, S. Diastereoselectivity of Radical Carbon-Carbon Bond Formation in Naphthalene-Stabilized Propargyl Cations. Southern California Undergraduate Research Conference, Santa Barbara, CA, **2011**.

### ***Student awards***

1. Christopher Wild. 12th CSUN Student Research Symposium, **2007** - *First Place Award*, Office of Research & Sponsored Projects, CSUN, Northridge, CA.



2. Louis Carlson. **2008 Memorial Award**, Association of Retired Faculty, CSUN, Northridge, CA.

3. Christopher Wild. CSU-wide Student Research Competition, CSU East Bay, Hayward, CA, **2008** – *Second Place Award*.

4. Ryan Spencer. *Sandra L. Jewett Scholarship in Biochemistry*, CSUN, Northridge, CA, **2009**.

5. Ryan Spencer. *Outstanding Graduate Student Teaching Assistant Award*, CSUN, Northridge, CA, **2009**.

6. Ruth Sepanian. Sigma Xi CSUN Chapter Student Symposium, Northridge, CA, 2009 – *Third Place Award*, CSUN, Northridge, CA, **2009**.

7. Ryan Spencer, 2009-2010 College of Science&Math *Graduate Fellow for Outstanding Research Promise in Science and Mathematics*, CSUN, Northridge, CA, **2009**.

8 & 9. Sarine Shahmirian. AAAS Pacific Division Annual Meeting, San Francisco, CA, **2009** – *First Place Award and Award of Excellence*.

10. Ruth Sepanian. 14th CSUN Student Research Symposium, Northridge, CA, **2010** – *Second Place Award*.

11. Erin Voorhees. 14th CSUN Student Research Symposium, Northridge, CA, **2010** – *First Place Award*.

12. Ryan Spencer. *The 2010 Nathan O. Freedman Memorial Award for Outstanding Graduate Student*, CSUN, Northridge, CA, **2010**.

13. McKinzie Garrison, 2011 Outstanding Freshman Chemistry Award, CSUN, Northridge, CA, **2011**.

14. Marina Dykhne, 2011 Analytical Chemistry Award, CSUN, Northridge, CA, **2011**.

### ***M.S. Theses***

1. Arthur Floruti. Cross-Coupling of Cobalt-Complexed Propargyl Radicals: Chemo-, Regio-, and Diastereoselective Access to 3,4-Diaryl-1,5-hexadiynes. Department of Chemistry and Biochemistry, CSUN, Northridge, CA, **2008**.

2. Christopher Wild. Cobalt-Assisted Intramolecular Radical Cyclization Reactions. Department of Chemistry and Biochemistry, CSUN, Northridge, CA, **2008**.

3. Ryan Spencer. Inter- and Intramolecular Radical C-C Bond Formation Mediated by a Transition Metal Core. Department of Chemistry and Biochemistry, CSUN, Northridge, CA, **2010**.

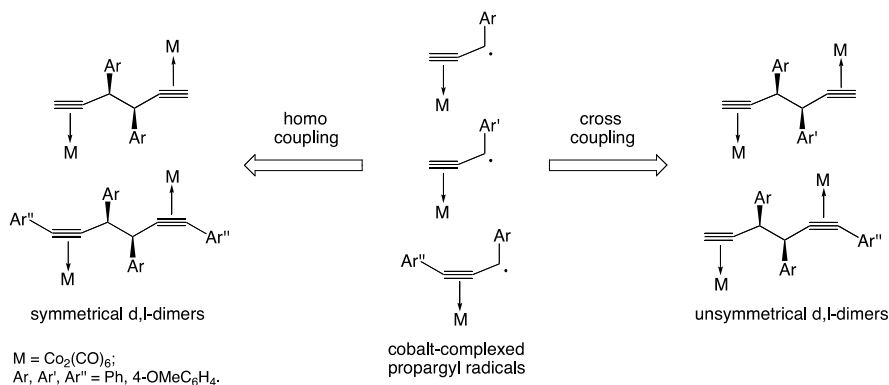
4. Ruth Sepanian. Low-Temperature Generation of Cobalt-Complexed Propargyl Cations Under Neutral Conditions. Department of Chemistry and Biochemistry, CSUN, Northridge, CA, **2010**.

## **Project Findings.**

***Project findings I: The synthesis of unsymmetrical, topologically diverse 1,5-alkadiynes via metal-mediated, cross-coupling radical reactions.***

It was found that the topologically diverse  $\text{Co}_2(\text{CO})_6$ -complexed propargyl radicals can be simultaneously generated and then undergo cross- and homo-coupling reactions

leading to unsymmetrical 1,5-alkadiynes (Gagik G. Melikyan, Arthur Floruti, Lucin Devletyan, Pogban Toure, Norman Dean, Louis Carlson. Cross-Coupling of Cobalt-Complexed Propargyl Radicals: Metal Core and  $\alpha$ - and  $\gamma$ -Aryl-Induced Chemo- and Diastereoselectivity. *Organometallics* **2007**, 26, 3173-3182). The current study was undertaken to determine to what extent the product distribution can be altered by varying the kinetic and thermodynamic parameters of the requisite cations and radicals. In the course of the study it was established that: (1) in the case of cobalt complexes with terminal triple bonds, the product distribution is nearly statistical and dependent upon the reducing agent with the concentration of the cross-coupling products falling in the range of 38-49%; (2) diastereoselectivity varied widely (de 40-92%) with the preponderant formation of *d,l*-diastereoisomers in both homo- and cross-coupling reactions; (3) the highest level of stereocontrol was achieved in THF- and Tf<sub>2</sub>O-mediated reactions (de up to 92%), while the reductions with Cp<sub>2</sub>Co were inferior in both homo- and cross-coupling processes (de 40-56%); and (4) an introduction of a  $\gamma$ -aromatic ring revealed a kinetic differentiation at the radical generation step that, in turn, resulted in a nonstatistical distribution of homo- and cross-dimers; (5) *d,l*-diastereoselec-

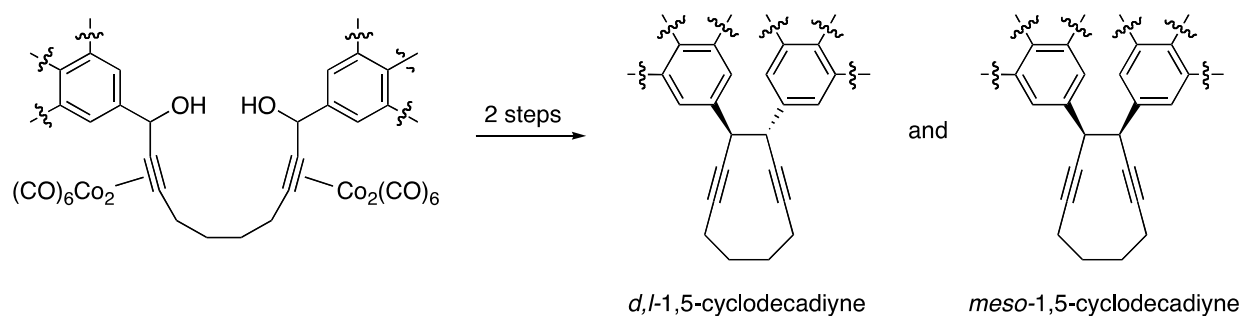


tivity is found to be systematically lower for homo-dimers containing a  $\gamma$ -phenyl substituent at the triple bond (de 14-64% vs 52-84%).

***Project findings II: Intramolecular cyclizations of cobalt-complexed propargyl radicals: a novel route to 1,5-cyclodecadiynes.***

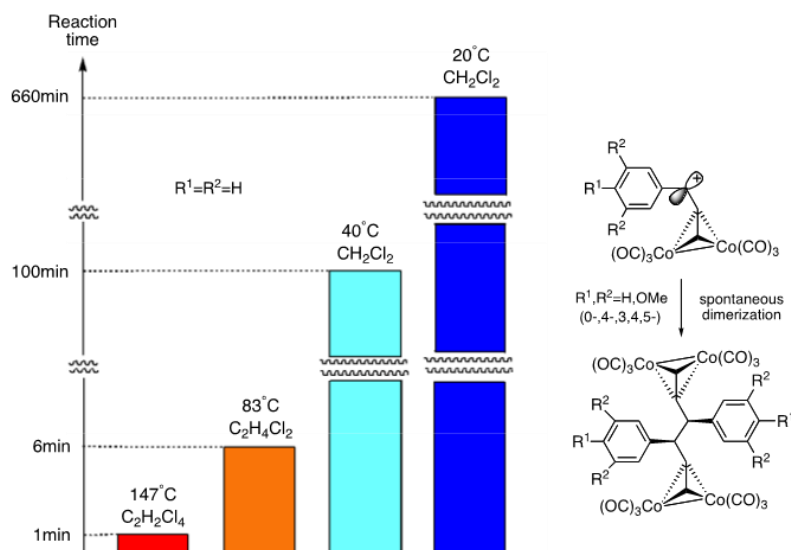
It was found that intramolecular radical cyclizations of bis-propargyl alcohols can be mediated by a Co<sub>2</sub>(CO)<sub>6</sub>-core and yield highly sought after 1,5-cyclodecadiynes,

potential precursors of anticarcinogenic endiynes [Gagik G. Melikyan, Christopher Wild, Pogban Toure. Intramolecular Radical Cyclizations of  $\text{Co}_2(\text{CO})_6$ -Complexed Propargyl Radicals: Synthesis of *d,l*- and *meso*-1,5-Cyclodecadiynes. *Organometallics* **2008**, 27, 1569-1581]. In the course of this study it was established that: (1) diastereoselectivity – *d,l* : *meso* ratio – varies in the range of 54:46 to 80:20, with the separability of individual stereoisomers being dependent upon the nature of substituents (H, OMe, IPr) and their substitution pattern (0-, 4-, 3,4-, 3,4,5-); (2) an accumulation of methoxy groups on the periphery of the aromatic rings facilitates the separation both in intra- and intermolecular reactions; and (3)  $\text{CH}/\pi$  coordination is the main determinant of the stereochemical outcome of the cyclization reactions favoring a *meso*-stereoisomer in *intramolecular* cyclizations, and, to the contrary, its *dl*-counterpart in *intermolecular* coupling reactions. The knowledge thus acquired has a predicting power allowing future substrates to be designed, both topologically and stereoelectronically, in a manner favoring either *d,l*- or *meso*-diastereomers.



***Project findings III: A high-temperature reaction of  $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations.***

It was discovered that at temperatures as high as  $147^\circ\text{C}$ , the  $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations can be generated in situ and then spontaneously converted to respective radicals (Melikyan, G. G.; Mikailian, B.; Sepanian, R.; Toure, P. High-Temperature Reaction of a  $\text{Co}_2(\text{CO})_6$ -Complexed Propargyl Cation. *J. Organomet. Chem.* **2009**, 694, 785-794). The new reaction occurs in a highly stereoselective manner (90-97% *d,l*-) and yields the respective radical dimers, *d,l*-3,4-diaryl-1,5-hexadiynes. In the course of the study, it was established that: (1) despite an alleged



course of the reaction, incorporating up to eight  $^{13}\text{CO}$  ligands into the metal core; (3) reaction kinetics is sensitive toward the electronic nature of the substituents (H, OMe) and to the substitution pattern (0-, 4-, 3,4,5-) on the periphery of the aromatic ring; and (4) spontaneous transfer of a single electron from the metal cluster, onto a pi-bonded propargyl moiety, is dependent upon the negative charge on aromatic  $\text{C}_{1'}$  carbon atom, located alpha to the cationic center.

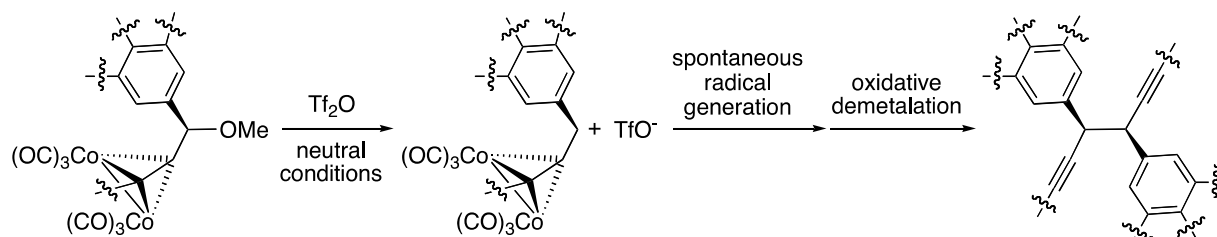
The spontaneous conversion of diamagnetic species (propargyl cation) to paramagnetic counterparts (propargyl radical) indicates that the pi-bonded organometallic cations can act as the prototypes for transition metal-based thermal sensors. Their application in photochemical research, electronic devices, molecular electronics, and biomedical fields can also be envisioned.

***Project findings IV: A novel method for the synthesis of cobalt-complexed propargyl cations under neutral conditions.***

It has long been a Holy Grail of organometallic cation chemistry to synthesize metal-stabilized cationic species under neutral conditions and to use them in a synthetically meaningful manner. It was found that  $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations can be synthesized under neutral conditions by using methyl propargyl ethers as substrates, and triflic anhydride, or trimethylsilyl triflate, or trifluoroacetic anhydride, as a reagent (Melikyan, G. G.; Sepanian, R.; Spencer, R.; Rowe, A.; Toure, P. Cobalt-Complexed Propargyl Cations: Generation under Neutral Conditions and Spontaneous, High

thermal lability and delicate nature of the requisite  $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations, the reaction temperature can be elevated from  $20^\circ\text{C}$  to  $147^\circ\text{C}$ , shortening the reaction time from 660min to less than 1min; (2) an isotopic enrichment takes place in the

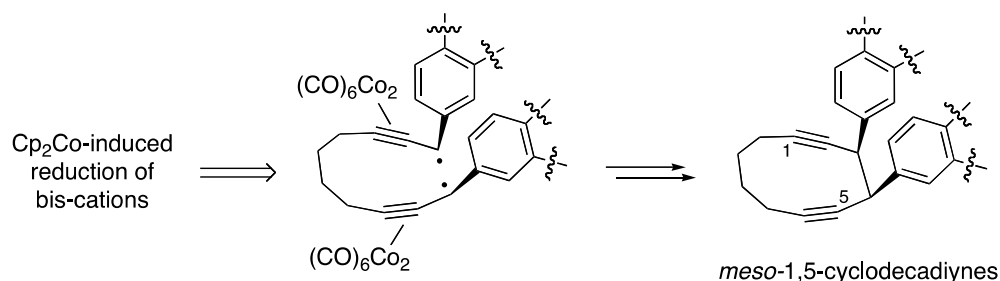
Temperature Conversion to Propargyl Radicals. *Organometallics* **2009**, 29, 5541-5549). The optimized experimental protocol involves the treatment of the respective  $\text{Co}_2(\text{CO})_6$ -complexed propargyl methyl ethers with equimolar quantities of triflic anhydride, at  $83^\circ\text{C}$  for 3min. In the course of the study, it was established that: (1) radical dimeric products, polysubstituted 3,4-diaryl-1,5-alkadiynes, can be isolated in high yields (73-82%) and excellent *d,l*-diastereoselectivity (89-99%); (2) decomplexation with ceric ammonium nitrate affords topologically diverse *d,l*-3,4-diaryl-1,5-alkadiynes (54-90%), otherwise hardly accessible; and (3) substrate and reagent bases can be expanded by using a combination of cobalt-complexed propargyl alcohols and trimethylsilyl triflate, as well as methyl propargyl ether and trifluoroacetic anhydride.



A newly developed method for generation of  $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations under neutral conditions substantially expands the scope of both ionic and radical reactions, allowing for involvement of substrates with acid-sensitive peripheral functionalities (benzylic, acetal, 1,3-dioxolane, enol ether) and functional groups susceptible to protonation (carbonyl, cyano, amino, imino).

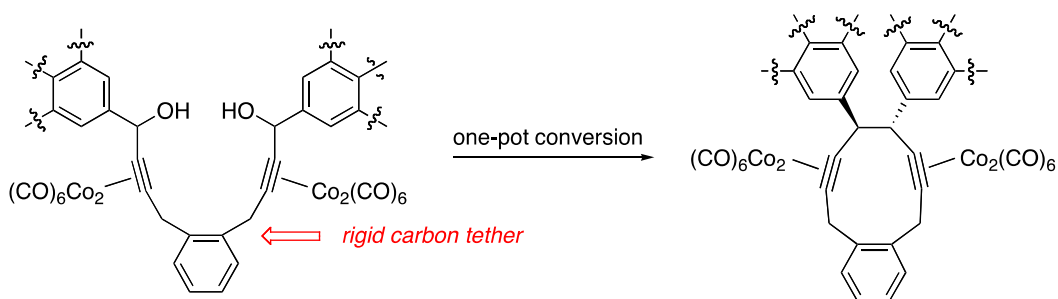
***Project findings V: A novel method for the synthesis of meso-1,5-cycloalkadiynes.***

It was discovered that the reduction of  $\text{Co}_2(\text{CO})_6$ -stabilized bis-propargyl cations with cobaltocene occurs with high *meso*-diastereoselectivity (up to 97%), affording, upon decomplexation, *meso*-1,5-cyclodecadiynes, otherwise hardly accessible (Melikyan, G. G.; Spencer, R.; Abedi, E. Stereoselective Synthesis of *meso*-1,5-Cyclodecadiynes. *J. Org. Chem.* **2009**, 74, 8541-8546). This method represents the first synthetically viable procedure for the synthesis of this class of organic compounds with *meso*-configuration.



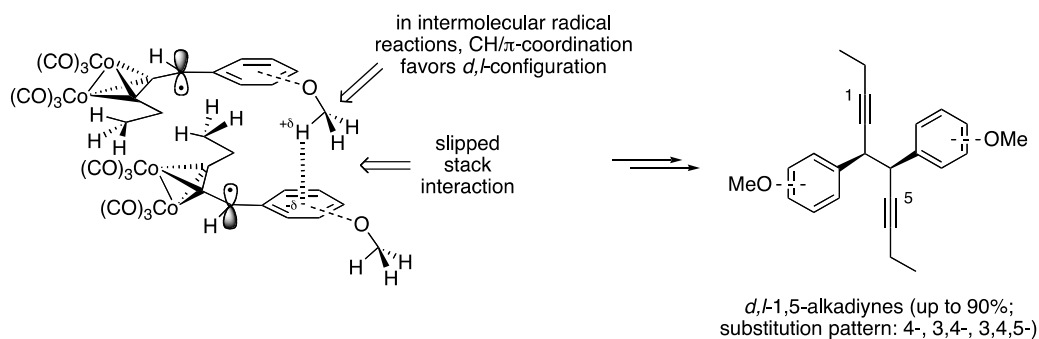
**Project findings VI: Controlling the stereochemistry in intramolecular radical cyclization reactions with carbon tether rigidity.**

It was found that the rigidity of carbon tether can be used as a mechanistic tool to control the stereoselectivity of the intramolecular radical cyclization reactions. In particular, 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<sub>2</sub>(CO)<sub>6</sub>-complexed propargyl intermediates (Melikyan, G. G.; Voorhees, E.; Wild, C.; Spencer, R.; Molnar, J. Carbon Tether Rigidity as a Stereochemical Tool Directing Intramolecular Radical Cyclizations. *Tetrahedron Letters* **2010**, 51, 2287-2290). The 1,5-cyclodecadiyne carbon framework remains one of the fascinating targets in organic chemistry given its immediate structural relevance to enediyne-based cancer therapeutics, 1,5-cyclodecadienes, and bicyclic compounds of different topology, such as [4.4.0], [5.3.0], and [6.2.0].



**Project findings VII: A CH/π coordination as a mechanistic tool for controlling the stereochemistry of intermolecular radical reactions.**

It was found that despite the general consensus, intermolecular radical coupling reactions can be more diastereoselective than isocarbon intramolecular cyclizations. In particular, intermolecular coupling reactions of  $\text{Co}_2(\text{CO})_6$ -complexed,  $\gamma$ -ethyl propargyl radicals occurred with higher  $d,l$ -diastereoselectivity than intramolecular cyclizations of isocarbon analogues ( $d_{\text{inter}}-d_{\text{intra}} \leq 52\%$ ) [Melikyan, G. G.; Spencer, R. Inter- and Intramolecular Isocarbon Couplings of Cobalt-Complexed Propargyl Radicals: Challenging the Consensus. *Tetrahedron* **2010**, 66, 5321-5328]. The observed pheno-



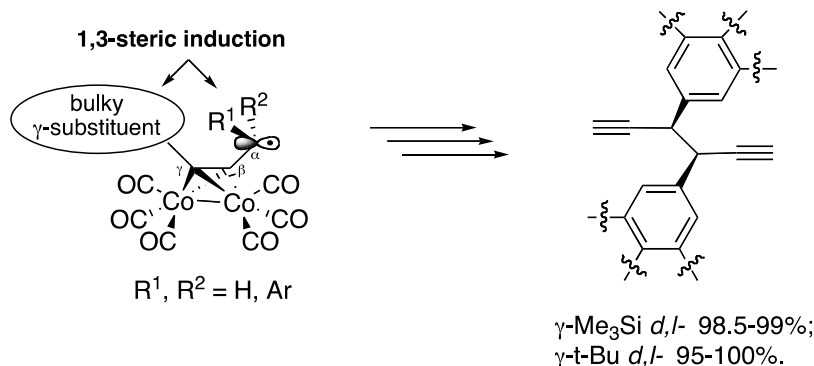
menon was interpreted in terms of a tandem action of two main determinants – steric factor and CH/ $\pi$  coordination – with the latter being enabled by the methoxy groups located on the periphery of the aromatic nuclei (4-, 3,4-, 3,4,5-). The aromatic substituents act as soft acids and coordinate with the aromatic hexagons, in a slipped stack mode.

***Project findings VIII: A 1,3-steric induction as a mechanistic tool for controlling the stereochemistry of intermolecular radical reactions.***

It was found that diastereoselectivity of propargyl coupling reactions can be controlled by using the bulkiness of a  $\gamma$ -substituent as a stereochemical tool. This 1,3-steric induction was observed with  $\gamma$ -*t*-Bu- and  $\gamma$ - $\text{Me}_3\text{Si}$ -groups, both favoring a  $d,l$ -configuration of the head-to-head coupling products, 3,4-disubstituted 1,5-alkadiynes ( $d,l$ - 95-100%). Overall, the synthetic strategy of employing a  $\text{Me}_3\text{Si}$ -auxiliary group involves five steps and affords - with 28 - 33% overall yields - pure  $d,l$ -3,4-diaryl-1,5-hexadiynes, otherwise hardly accessible [Melikyan, G. G.; Spencer, R.; Rowe, A. 1,3-



Steric Induction in Intermolecular Radical Reactions Mediated by a  $\text{Co}_2(\text{CO})_6$ -Metal Core. *Organometallics* **2010**, 29, 3556-3562].



## Contributions within Discipline

Radical reactions have long been the most problematic type of chemical transformations. Among many reasons are a low chemoselectivity at the radical generation step, an incompatibility of radicals with a variety of functional groups, an unavailability of efficient tools, either steric or electronic, to control the reaction stereoselectivity, and also their inherent transiency that precludes a direct observation by analytical methods, or structural characterization by the crystallographic means. This is the reason why the knowledge base in radical chemistry field has always been much more limited than that in ionic reactions. Whenever a given transformation needs to be carried out, then the chemist will first choose an ionic reaction, and only then, out of “desperation”, will try a radical process.

During the NSF grant period, our research was aimed at changing the *status quo* with respect to radical chemistry, its significance, and synthetic potential. The coordination with transition metals, in a pi-bonded fashion, was used to make the generation step highly selective, to access radicals which otherwise cannot be synthesized, and to use a metal core, as a stereoelectronic tool, for achieving a high selectivity in the carbon-carbon bond-forming reactions. The summary of the latest

developments is given below. More detailed description of each finding, along with the pertinent references, can be found in the *Project Findings* section.

### ***Cross-coupling radical reactions.***

It was demonstrated that the concurrent generation of cobalt-complexed propargyl cations, and radicals, is synthetically feasible, and the reaction can be used for the synthesis of the topologically diverse, unsymmetrical *d,l*-/*meso*-1,5-alkadiynes, otherwise hardly accessible. These studies allowed for identifying the stereoelectronic parameters governing the C-C bond formation and lay groundwork for assembling more complex, unsymmetrical organic and organometallic molecules.

### ***Intramolecular cyclization reactions leading to 1,5-cyclodecadiynes.***

The first systematic study on intramolecular radical cyclizations forming 1,5-cyclodecadiynes, a highly sought after class of organic compounds, was carried out. The new knowledge base thus acquired allowed to shed light upon the nature of the steric, electronic, functional, and topological parameters governing the cyclization reactions.

### ***Generation of propargyl cations: an expansion of the temperature range.***

Since their discovery in 1977, the cobalt-complexed propargyl cations were considered to be thermally labile species with their reactions being conducted at the lowest temperature possible. The standard temperature range has long fallen within the range of  $-78^{\circ}\text{C}$  to  $+20^{\circ}\text{C}$ . It was shown by us that the *upper temperature limit could be pushed all the way up to  $+147^{\circ}\text{C}$*  with no significant decline either in reaction yields, or diastereoselectivity of radical dimeric products.

### ***Generation of cobalt-complexed propargyl cations under neutral conditions.***

It has long been a Holy Grail of organometallic cation chemistry to synthesize metal-stabilized cationic species *under neutral conditions*. Two alternative experimental protocols are now available with one of them being carried out at the temperatures as high as  $83^{\circ}\text{C}$ , and an alternative low-temperature procedure which can be

accomplished at  $-50^{\circ}\text{C}$ . The newly developed methods for generation of  $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations under neutral conditions substantially expands the scope of both ionic and radical reactions, allowing for involvement of substrates with acid-sensitive peripheral functionalities (benzylic, acetal, 1,3-dioxolane, enol ether) and functional groups susceptible to protonation (carbonyl, cyano, amino, imino). Enhancing the functional tolerance of radical and ionic reactions will allow for using these reactions, as key steps, in the total synthesis of natural products.

### ***Stereoselective synthesis of meso-1,5-cyclodecadiynes.***

The first method for the synthesis of *meso*-1,5-cyclodecadiynes adds to the synthetic repertoire of radical chemistry mediated by transition metals. Its use, as a key step, in total synthesis of complex molecular assemblies, or as a novel carbon framework in drug development can be envisioned. The method can be expanded toward other carbocycles, in particular 8- and 9-membered cyclic compounds, long known – in intramolecular reactions – to form *d,l*-stereoisomer, either predominantly, or exclusively. The method can also be applied toward the synthesis of *meso*-stereoisomers of heterocyclic compounds by structurally modifying the carbon tether that connects two acetylenic moieties.

### ***Carbon tether rigidity as a stereochemical tool for controlling the stereochemistry of intramolecular radical cyclizations.***

The strategy thus developed – introducing a “phenyl” rigidity into the carbon chain to control the stereoselectivity of intramolecular cyclization – can now be used for stereoselective assembling of 8-, 9-, 11- and 12-membered carbocycles, otherwise hardly accessible. The latter can be used as substrates for a variety of trans-annular cyclizations of 1,5-cycloalkadiynes, a scarcely studied field of synthetic chemistry. The *substrate base expansion* can be achieved by replacing a phenyl tether with alternative configurationally rigid moieties: (a) polyaromatics such as naphthalene or anthracene rings; (b) double bond; (c) cyclic acetal group, such as acetonide; (d) saturated carbocycles, such as cyclohexane; and (e) oxygen-containing heteroaromatics.

***1,3-Steric induction as a stereochemical tool for controlling the stereochemistry of intermolecular radical cyclizations.***

It was demonstrated that due to 1,3-steric induction, the bulky substituents introduced into a gamma-position of the  $\text{Co}_2(\text{CO})_6$ -complexed propargyl radicals act as a stereodirecting tool, affording dimeric products with excellent *d,l*-diastereoselectivity (up to 100%). This methodology can now be used in organometallic radical reactions, other than dimerizations, and also in ionic reactions in order to control the stereoselectivity on the newly formed stereocenters, alpha to the metal core.

**Contributions to Other Disciplines**

***Materials science.*** A newly discovered high-temperature process for conversion of diamagnetic complexes (cations) into their paramagnetic counterparts (radicals) allowed us to establish that the rate of a single electron transfer – from the metal cluster onto a pi-bonded organic ligand - is dependent upon temperature. The higher the temperature (up to 147°C), the faster the reaction comes to completion (up to 1min). These types of reactions could potentially be used in future *temperature sensors*. Their application in photochemical research, electronic devices, molecular electronics, and biomedical and bioengineering fields can also be envisioned.

***Medicinal chemistry.*** The newly developed methods for controlling the stereoselectivity of inter- and intramolecular radical reactions are of immediate interest to medicinal chemistry. In particular, *meso*-1,5-decadiynes can be used in drug development as novel templates capable of holding functional groups in predetermined positions and acting as binary and multiple contact points. A newly acquired ability to carry out the conversion of commercial alkynes and aldehydes to *d,l*- and *meso*-1,5-alkadiynes and 1,5-cycloalkadiynes *under neutral conditions* is critical for the development of *prodrugs*. The latter will have a functional group that can be carried over through the synthetic scheme and then be enzymatically removed inside the human body – in the right place, at the right time – thus providing for a lower toxicity and less side effects. The large-scale syntheses, such as toxicological studies, could also benefit

from the new technology, since the key steps could be carried out under milder conditions, by avoiding corrosive and hazardous acidic reagents.

***Natural products chemistry*** will also benefit from the newly developed strategies toward controlling the stereoselectivity of radical reactions otherwise unruly. For example, the compatibility of the reagents and reaction conditions with the acid-sensitive peripheral functionalities, such as benzyl or acetal, will allow us, and others, to use this methodology in the total synthesis of complex natural products.