

MELIKYAN GROUP

NSF Supported Research 2011-2015

Papers and reviews (total of 85 including 8 reviews)

1. Melikyan, G. G.; Rivas, B.; Harutyunyan, S.; Carlson, L.; Sepanian, R. Cobaltocene-Induced Low-Temperature Radical Coupling Reactions in a Cobalt-Alkyne Series. *Organometallics* **2012**, *31*, 1653-1663.

2. Melikyan, G. G.; Carlson, L.; Sahakyan, N.; Floruti, A.; Garrison, M. Impact of Reducing Agent, Temperature, and Substrate Topology on Diastereoselectivity of the Intermolecular Coupling Reactions, or How “Free” Are Cobalt-Complexed Propargyl Radicals? *Dalton Transactions* **2013**, *42*, 14801–14812.

3. Melikyan, G. G.; Voorhees, E.; Sepanian, R. Radical Reactions of the Cobalt-Complexed Propargyl Acetals: Inter- and Intramolecular Variants. *Organometallics* **2014**, *33*, 69-83.

4. Melikyan G. G.; Hughes, R.; Rivas, B.; Duncan, K.; Sahakyan, N. Assembling Contiguous Quaternary Carbon Atoms: Regio- and Stereoselective Rearrangements in Cobalt-Directed Radical Reactions of 1,4-Enynes. *Organometallics* **2015**, *34*, 242-253.

5. **Invited review:** Melikyan G. G. Propargyl Radical Chemistry: Renaissance Instigated by Metal Coordination. *Acc. Chem. Res.* **2015**, *48*, 1065-1079.

6. Melikyan G. G.; Anker, B. Radical Reactions of 1,4-Alkadiynes: Metal Coordination as an Effective Tool for Controlling the Regio- and Stereoselectivity of the C-C Bond Formation. *Organometallics* **2015**, *34*, 4194-4197.

7. Melikyan, G. G.; Davis, R.; Cappuccino, S. Acquiring and Exploiting Persistency of Propargyl Radicals: Novel Paradigms. *Organometallics* **2016**, *35*, 2854-2867.

8. Melikyan, G. G.; Davis, R.; Anker, B.; Meron, D.; Duncan, K. Acquiring a Prognostic Power in $\text{Co}_2(\text{CO})_6$ -Mediated, Cobaltocene-Induced Radical Dimerizations of Propargyl Triflates. *Organometallics* **2016**, *35*, 4060–4070.

Presentations by the PI (total of 124)

1. Melikyan, G. G.; Carlson, L.; Rivas, B.; Voorhees, E. Debunking Myths about Cobalt-Complexed Propargyl Cations and Radicals. 243rd ACS National Meeting, San Diego, CA, **2012**.

2. Melikyan, G. G.; Voorhees, E.; Rivas, B.; Darabidian, V.; Meron, D.; Garrison, M. Recent Advances in Transition Metal-Assisted Radical Reactions. 243rd ACS National Meeting, San Diego, CA, **2012**.

3. Melikyan, G. G.; Hughes, R.; Sahakyan, N. Allylic Rearrangements in Cobalt-Mediated Radical Coupling Reactions. 245th ACS National Meeting, New Orleans, CA, **2013**.

4. Melikyan, G. G.; Voorhees, E.; Darabidian, V.; Duncan, K. 1,3-Steric Induction in Metal-Mediated Inter- and Intramolecular Radical Reactions. 245th ACS National Meeting, New Orleans, CA, **2013**.

5. Melikyan, G. G.; Anker, B.; Davis, R. Radical Reactions of 1,4-Alkadiynes: Regio-, Chemo-, and Stereoselective C-C Bond Formation Mediated by a Metal Core. 248th ACS National Meeting, San Francisco, CA, **2014**.

6. Melikyan, G. G.; Anker, B.; Hughes, R.; Duncan, K. From Transient to Persistent Propargyl Radicals: Exploiting a Steric Factor. 248th ACS National Meeting, San Francisco, CA, **2014**.

7. Melikyan, G. G.; Davis, R.; Cappuccino, S.; Mousselli, M. Propargyl Radical Chemistry: Unlocking the Potential. 250th ACS National Meeting, Boston, MA, **2015**.

Presentations by the PI at academic institutions (total of 17)

1. University of Oklahoma, Norman, OK. Recent Advances in Cobalt-Mediated Radical Reactions (**2014**).

2. California State University Northridge, Northridge, CA. Propargyl Radical Chemistry: Rebirth (**2014**).

3. California State University Northridge, Northridge, CA. Organic Chemistry Highlights in CSUN Department of Chemistry (**2015**).

Chairing sessions at conferences (total of 6)

2012 "Metal-Mediated Reactions and Syntheses," 243st ACS National Meeting, San Diego, CA.

2013 "Metal-Mediated Reactions and Syntheses," 245st ACS National Meeting, New Orleans, GA.

2014 "Asymmetric Reactions and Syntheses," 248st ACS National Meeting, San Francisco, CA.

2015 "New Reactions and Methodology," 250st ACS National Meeting, Boston, MA.

Awards and Distinctions

2015 The Kennedy Center Stephen Sondheim Inspirational Teacher Award, Washington, D.C.

Literary awards for book titled "*Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*," (2010; 368pp).

2011 Finalist in the "Science" category, The USA "Best Books 2011" Awards competition sponsored by the USA Book News.

2012 Second Place Award in the "Science" category, 2012 International Book Awards competition sponsored by JPX Media.

Public outreach: PI's presentations for the general public (total of 30)

2011 Invited speaker, *Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*. Ararat-Eskijian Museum, book presentation, Mission Hills, CA.

2011 Invited speaker, *Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*. PhiDE Fraternity, book presentation, CSUN, Northridge, CA.

2011 Invited speaker, *Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*. Organization of Istanbul Armenians (OIA), book presentation, Tarzana, CA.

- 2011 Invited speaker, *Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*. California Writer's Club, SFV, book presentation, Canoga Park, CA.
- 2011 Invited speaker, *Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*. Mission Community Hospital, book presentation, Panorama City, CA.
- 2011 Invited speaker, *From Food Preservation to Body Preservation*. Provost Colloquium, Jeromy Richfield Award presentation, CSUN, Northridge, CA.
- 2011 Invited speaker, *Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*. Filipino American Chamber of Commerce of Orange County, book presentation, Garden Grove, CA.
- 2011 Invited speaker, *Staying Healthy and Insights into "Natural" in Health Foods, Remedies, and Cancer Prevention*. Inland Empire Asian Business Association (IEABA), Riverside, CA.
- 2011 Invited Speaker, *Health is Wealth*. USANA Inc. Regional Center, Signal Hills, CA.
- 2012 Speaker, *Book Bazaar, Guilty Until Proven Innocent: Antioxidants, Foods, Supplements, and Cosmetics*. California Writer's Club, SFV, Woodland Hills, CA.

- 2012 Invited speaker, *Dangers of Antioxidants and All-Natural Supplements: a Lonely Voice of Dissent*. Armenian Engineers and Scientists of America (AESA), Glendale, CA.
- 2013 Panelist, California Writers' Club, San Fernando Valley, Woodland Hills, CA.
- 2013 Invited Speaker, *Antioxidants, Supplements, and Cosmetics: Perils of Ignoring Science*. Student Organization for a Holistic-approach to Health and Leadership (SOHHL), Phi Delta Epsilon Fraternity, Chicano's Community Medicine (CCM) Student Organization, CSUN, Northridge, CA.
- 2013 Guest Speaker, *Women's History Month* event, *Antioxidants, Supplements, and Cosmetics: Perils of Ignoring Science*. United States Citizenship and Immigration Services (USCIS) San Fernando Valley Field Office (SFV).
- 2013 Speaker, 30th Anniversary of the Armenian Studies Program, CSUN, Northridge, CA.
- 2013 Guest Speaker, *Food Supplements and Your Health*. Kiwanis International, Northridge Chapter, Northridge, CA.
- 2014 Speaker, *Toxicity of Heavy Metals and a Long-Term Impact of Irresponsible Mining on Public Health*, CSUN, Northridge, CA.
- 2014 Invited Speaker, *Antioxidants and Natural Supplements: Unraveling the Truth*, Pierce College, Woodland Hills, CA.

- 2014 Invited Speaker, *American Public's Perpetual Struggle Against Harmful Business Practices*, Public Advocacy Group Renaissance Armenia (via satellite), Yerevan.
- 2014 Speaker, *Why "Natural" Is Not Synonymous to "Good" and Harmless,* Vroman's Bookstore, Pasadena, CA.
- 2014 Invited Speaker, *Antioxidants, Supplements, and Cosmetics: Perils of Ignoring Science*, Regional High School Science Teachers' Conference, Ferrahian High School, Encino, CA.
- 2014 Invited Speaker, *Teaching Science in the 21st Century: Challenges and Solutions*, Regional High School Science Teachers' Conference, Ferrahian High School, Encino, CA.
- 2015 Invited Speaker, *The Centennial of Armenian Genocide: Did the World Learn the Lesson, or How to Prevent Genocides in the 21st Century?* CSUN, Northridge, CA.

TV appearances (total of 5)

- 2011 CBS KCAL9, Studio City, CA;
- 2012 USArmenia channel, Burbank, CA;
- 2013 *The Book Beat*, LATalkLive channel, Los Angeles, CA.

Radio interviews (total of 9)

- 2012 DresserAfterDark, BBS Radio;

2012	KYNT KSWR radio;
2012	KCWR radio;
2012	KERN Bakersfield Good Morning News radio;
2012	WOCM radio;
2012	KCSN-FM radio;
2012	KFNX radio;
2012	Issues Today radio;
2012	Dr. Joe Radio Show.

Student presentations (total of 108; undergraduate students – 59; names of undergraduate students are underlined)

1. Melikyan, G. G.; Darabidian, V.; Meron, D. Novel Syntheses of Polysubstituted, Alkynylated Cycloalkanes via Transition Metal-Mediated Radical Cyclizations. 243th ACS National Meeting, San Diego, **2012**.

2. Melikyan, G. G.; Voorhees, E.; Garrison, M. Propargyl Acetals as New Substrates in Transition Metal-Mediated Radical C-C Bond Formation Reactions. 243th ACS National Meeting, San Diego, **2012**.

3. Darabidian, V. Assembling Six-Membered Carbocycles via Radical Cyclization Reactions. 15th CSUN Student Research Symposium, Northridge, CA, **2012**.

4. Melikyan, G. G.; Hughes, R.; Sahakyan, N. Alpha-Alkenyl Propargyl Radicals: Regio- and Stereoselectivities of Cobalt-Directed Dimerization Reactions. 245th ACS National Meeting, New Orleans, **2013**.

5. Melikyan, G. G.; Darabidian, V. Stereoselectivity of Intramolecular Radical Cyclizations Mediated by a Transition Metal Core. 245th ACS National Meeting, New Orleans, **2013**.

6. Sahakian, N. Cobalt Cluster-Stabilized, Highly Conjugated Propargyl Radicals: Stereoselectivity of Intermolecular Coupling Reactions. 16th CSUN Student Research Symposium, Northridge, CA, **2013**.

7. Hughes, R. Highly Regioselective Dimerization Reactions of α -Alkenyl Propargyl Radicals. 16th CSUN Student Research Symposium, Northridge, CA, **2013**.

8. Darabidian, V. Toward stereoselective assembling of linearly and angularly fused carbocycles. 16th CSUN Student Research Symposium, Northridge, CA, **2013**.

9. Anker, B. *alpha*-Alkynyl Propargyl Radicals, a New Class of Reactive Intermediates in Transition Metal-Mediated Carbon-Carbon Bond Forming Reactions. 15th Annual Sigma Xi Student Research Symposium, CSUN Chapter of Sigma Xi, CSUN, Northridge, CA, **2013**.

10. Sahakian, N. Cobalt Cluster-Stabilized, Highly Conjugated Propargyl Radicals: Stereoselectivity of Intermolecular Coupling Reactions. CSU-wide Student Research Competition, Pomona, CA, **2013**.

11. Voorhees, Erin. Transition Metal-Mediated Radical Reactions of Propargyl Acetals. Thesis defense, Department of Chemistry & Biochemistry, CSUN, Northridge, CA, **2013**.

12. Anker, Bryan. From the Metal-Stabilized, Highly Conjugated Propargyl Intermediates to a New Generation of Tunable DNA-Cleaving Agents for Cancer Treatment. CSUN Alumni Faculty Recognition Luncheon, CSUN, Northridge, CA, **2013**.

13. Melikyan, G. G.; Duncan, K. An Efficient and Stereoselective Method for Constructing Seven-membered Carbo- and Heterocycles. 44th ACS Western Regional Meeting, Santa Clara, CA, **2013**.

14. Hughes, R. Vitamin E: Stereoselective Syntheses, Biological Role, and Health Implications. Literature seminar, Department of Chemistry and Biochemistry, CSUN, Northridge, CA, **2013**.

15. Hughes, R. Regio- and Stereoselective Rearrangements in Metal-Assisted Radical Reactions: a Novel Access to Topologically Diverse Molecular Assemblies with Contiguous Quaternary Carbons. 17th CSUN Student Research Symposium, Northridge, CA, **2014**.

16. Anker, B. Radical Reactions of 1,4-Alkadiynes: Metal Coordination as an Effective Tool for Controlling a C-C Bond Formation in Highly Delocalized Molecular Structures. 17th CSUN Student Research Symposium, Northridge, CA, **2014**.

17. Hughes, R. Allylic Rearrangements in Cobalt-Mediated Radical Coupling Reactions. Thesis defense, Department of Chemistry & Biochemistry, CSUN, Northridge, CA, **2015**.

18. Melikyan, G. G.; Davis, R.; Anker, B.; Duncan, K. Acquiring a Predictive Power: Metal-Mediated Radical Dimerizations of Propargyl Triflates. 248th ACS National Meeting, San Francisco, CA, **2014**.

19. Melikyan, G. G.; Cappuccino, S. Interaction of Resveratrol with Human Enzymes: Oxidative Conversion to Procarcinogenic *ortho*-Hydroquinones. 248th ACS National Meeting, San Francisco, CA, **2014**.

20. Melikyan, G. G.; Davis, R. Cobalt-Complexed Propargyl Radicals: Transiency vs Persistency. 2015 ACS Southern California Undergraduate Research Conference (SCURC), La Jolla, CA, **2015**.

21. Melikyan, G. G.; Davis, R. Propargyl radicals: From transiency to persistency to reaction site projection. 250th ACS National Meeting, Boston, MA, **2015**.

22. Melikyan, G. G.; Cappuccino, S.; Mousselli, M. Metal cluster-enhanced propargyl radicals: Expanding a substrate base. 250th ACS National Meeting, Boston, MA, **2015**.

23. Ryan, D. Animating periphery in highly conjugated molecular systems: Radical carbon-carbon bond formation epsilon to a cobalt core. 17th Annual Sigma Xi Student Research Symposium, CSUN Chapter of Sigma Xi, CSUN, Northridge, CA, **2015**.

Student awards (total of 48; 31 - by undergraduates; names of undergraduate students are underlined)

1. McKinzie Garrison, **2012 Organic Chemistry Award**, CSUN, Northridge, CA, 2012.

2. Michael Enos, **Henry Klostergaard Award for Outstanding Graduating Chemistry Major**, CSUN, Northridge, CA, 2012.

3. Vahe Darabidian. 16th CSUN Student Research Symposium, 2013 - **First Place Award** (ORSP, CSUN).

4. Nare Sahakyan. 16th CSUN Student Research Symposium, 2013 - **Second Place Award** (ORSP, CSUN).

5. Bryan Anker. Sigma Xi CSUN Chapter Student Symposium, Northridge, CA, 2013 – **First Place Award**.

6. Bryan Anker. 17th CSUN Student Research Symposium, 2014 - **Second Place Award** (ORSP, CSUN).

7. McKinzie Garrison, **2014 Outstanding Graduating Senior Award**, CSUN, Northridge, CA, 2014.

8. McKinzie Garrison, **2014 Wolfson Scholar Award**, CSUN, Northridge, CA, 2014.

9. Ryan Davis, **Outstanding Oral Presentation Award**, 2015 ACS Southern California Undergraduate Research Conference (SCURC), San Diego, CA, 2015.

10. Ryan Davis, Sigma Xi CSUN Student Research Symposium, Northridge, CA 2015 – **Second Place Award**.

11. Ryan Davis, Leslie and Terry Cutler Scholarship Award, CSUN, Northridge, CA, 2015.

Student proposals (total of 28; undergraduates – 24; names of undergraduate students are underlined)

1. Voorhees, E. Propargyl Acetals as New Substrates in Transition Metal-Mediated Radical C-C Bond Formation Reactions. Graduate Thesis Support Grant, Office of Research and Sponsored Projects, CSUN, **2011**, funded (\$1,000).

2. Darabidian, V. Intramolecular Radical Cyclization Mediated by a Transition Metal Core. Graduate Thesis Support Grant, Office of Research and Sponsored Projects, CSUN, **2011**, funded (\$1,000).

3. Hughes, Rhoda. α -Alkenyl Propargyl Radicals: Regio- and Stereoselectivities of Dimerization Reactions. Graduate Thesis Support Grant, Office of Research and Sponsored Projects, CSUN, **2012**, funded (\$1,000).

4. *Davis, Ryan*. A New Design Schlenk Line Acquisition for Advanced Organometallic Syntheses. Associated Students Research Competition, CSUN, **2014**, funded (\$2,000).

Graduate theses (total of 11)

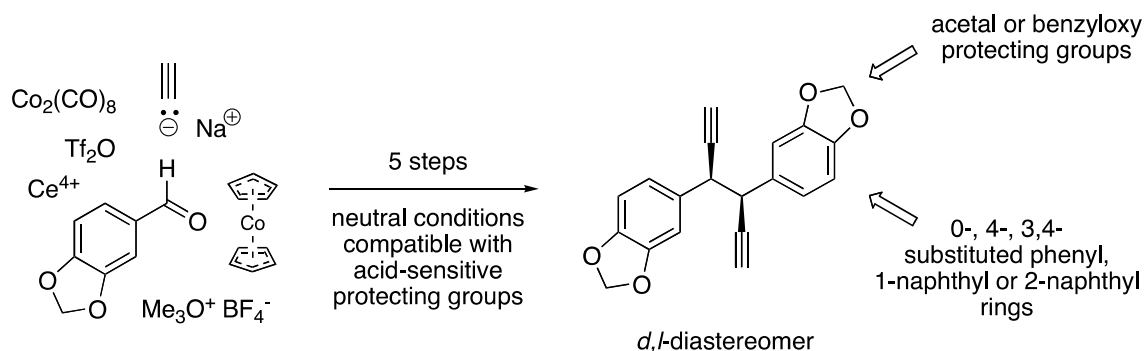
1. Voorhees, E. Transition Metal-Mediated Radical Reactions of Propargyl Acetals. Department of Chemistry and Biochemistry, CSUN, Northridge, CA, **2013**.

2. Hughes, R. Allylic Rearrangements in Cobalt-Mediated Radical Coupling Reactions. Thesis defense, Department of Chemistry & Biochemistry, CSUN, Northridge, CA, **2015**.

Project Findings.

Project findings I. Gagik G. Melikyan, Bianca Rivas, Stepan Harutyunyan, Louis Carlson, Ruth Sepanian. Cobaltocene-Induced Low-Temperature Radical Coupling Reactions in a Cobalt-Alkyne Series. *Organometallics* **2012**, *31*, 1653 - 1663.

A novel method for the low-temperature generation of $\text{Co}_2(\text{CO})_6$ -propargyl cations (-50°C to -10°C) under neutral conditions and their reduction with cobaltocene (-50°C) was developed, affording topologically diverse α -aryl and α -1-/2-naphthyl substituted *d,l*- and *meso*-1,5-(cyclo)alkadiynes. Over the course of this study it was established that: (1) cobalt-complexed propargyl cations can be generated *under neutral conditions* by the interaction of methyl propargyl ethers and triflic anhydride; (2) cobalt-complexed propargyl cations carrying a cation-stabilizing α -phenyl group, are ionic compounds which can be reduced with cobaltocene at low temperatures (-50°C); (3) *d,l*-configuration is the most preferable steric arrangement in intermolecular radical C-C bond-forming reactions (*d,l*- 69-92%), while a reversal of stereoselectivity is observed in intramolecular cyclizations (*meso*- 79%); (4) *d,l*-3,4-diaryl- and *d,l*-3,4-(1-/2-naphthyl)-1,5-hexadiynes – otherwise hardly accessible – can be synthesized in good to excellent yields (47-98%); (5) An enhanced functional tolerance is showcased by introducing the peripheral acid-sensitive functionalities, such as benzyloxy and methylenedioxy groups, and carrying out a five-step conversion – from commercial aromatic aldehydes to radical dimers – in an acid-free environment.

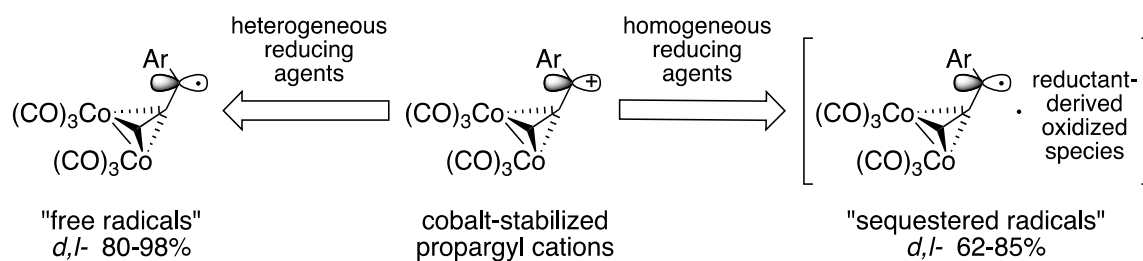


The generation of the propargyl cations under neutral conditions and their reduction with cobaltocene at low temperatures (-50°C) allowed us to achieve five synthetic objectives, while maintaining the neutrality of the medium. First, to avoid the high temperatures (83°C – 147°C) that are typical for the spontaneous generation of radicals carried out in the absence of the external reducing agent. Second, to prove that cobalt-complexed propargyl triflates are propargyl cation mimics due to the high polarizability

of the carbon-triflate bond located alpha to the metal core. Third, to enhance an atom economy with respect to the spontaneous radical reactions for which two equivalents of cobalt-complexed propargyl cations are required for the generation of one equivalent of the requisite propargyl radicals. Fourth, to minimize a partial decomplexation of the triple bonds, a known deficiency in high-temperature processes that, in turn, requires a recomplexation of the respective mono-complexes. Fifth, to achieve a long sought after compatibility between the cation generation conditions and a reducing agent that allowed us to eliminate the laborious cation isolation step.

Project findings II. Melikyan, G. G.; Carlson, L.; Sahakyan, N.; Floruti, A.; Garrison, M. Impact of Reducing Agent, Temperature, and Substrate Topology on Diastereoselectivity of the Intermolecular Coupling Reactions, or How “Free” Are Cobalt-Complexed Propargyl Radicals? *Dalton Transactions* **2013**, 42, 14801 – 14812.

An applicability of the term “free radical” to organometallic radicals was studied by using the diastereoselectivity of the radical C-C bond formation as a diagnostic mechanistic tool. It is concluded that organometallic radicals can be placed into two categories - “free” or “sequestered” - dependent upon the nature of a reducing agent. In case of heterogeneous reducing agents, such as Zn or Mg, for the same substrate, the stereoselectivity is nearly identical (80%; 84%); respective $\text{Co}_2(\text{CO})_6$ propargyl radicals are considered “free” due to the separation from a reducing surface, following a transfer of the single electron toward a metal-stabilized cationic center. To the contrary, in case of homogeneous reducing agents, such as Cp_2Co or $\text{Na/Ph}_2\text{CO}$, propargyl radicals remain supposedly associated with the reductant-derived, soluble oxidized species. Such an assembly manifests itself in different stereochemical outcome due to the conformational restrictions and the term “sequestered” is suggested to reflect the true nature of these associated, non-free radicals.

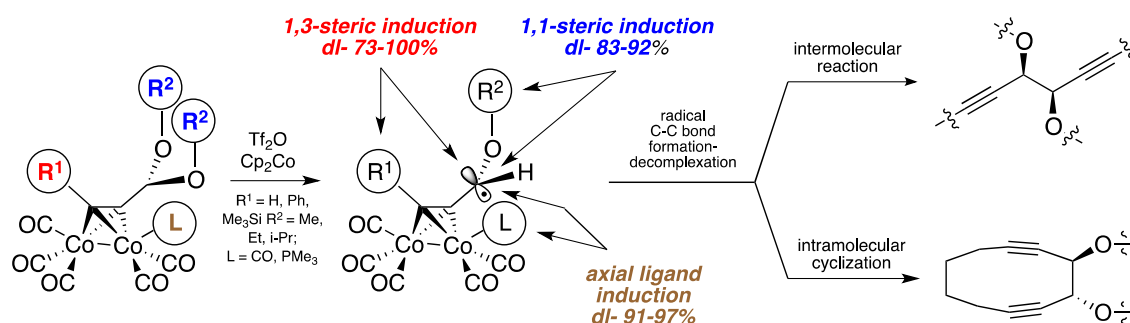


An newly established fact of the dependence of the diastereoselectivity of radical C-C bond formation, alpha to a metal core, upon the nature of the reducing agent provides an important tool for *controlling the stereoselectivity of radical reactions*. In the purely organic setting, dimerizations occur with no, or low, diastereoselectivity. Complexation of the triple bond with a $\text{Co}_2(\text{CO})_6$ -cluster, and targeted, computation-based choice of the reducing agent, allows for controlling the dimerization process and achieving the levels of *d,l*-diastereoselection as high as 95%. An oxidative decomplexation of radical dimers releases topologically and functionally diverse, alpha-aryl *d,l*-1,5-alkadiynes otherwise hardly accessible. The latter can readily be converted, via conventional methods, to a variety of classes of organic compounds (1,5-alkadienes, 1,4-/1,6-diketones, cyclopentenes, cyclopentenones, cycloalkane-1,2-diols, enediynes, fused carbocycles), further highlighting its value and significance to synthetic organic chemistry.

Project findings III. Gagik G. Melikyan, Erin Voorhees, Ruth Sepanian. Radical Reactions of the Cobalt-Complexed Propargyl Acetals: Inter- and Intramolecular Variants. *Organometallics* **2014**, *33*, 69 - 83.

Propargyl acetals are used as a new type of substrate in cobaltocene-induced radical reactions stereodirected by a π -bonded $\text{Co}_2(\text{CO})_6$ metal core. The experimental protocol involves treatment of the cobalt-complexed acetals with triflic anhydride, an in situ generation of ionic propargyl triflates, and a single electron, low-temperature reduction of α -alkoxy stabilized, $\text{Co}_2(\text{CO})_6$ -complexed propargyl cations. Inter- and intramolecular reactions provide a facile access to polyfunctional, topologically diverse 3,4-dialkoxy-1,5-alkadiynes and 3,4-dialkoxy-1,5-cyclodecadiynes with a predominant formation of the

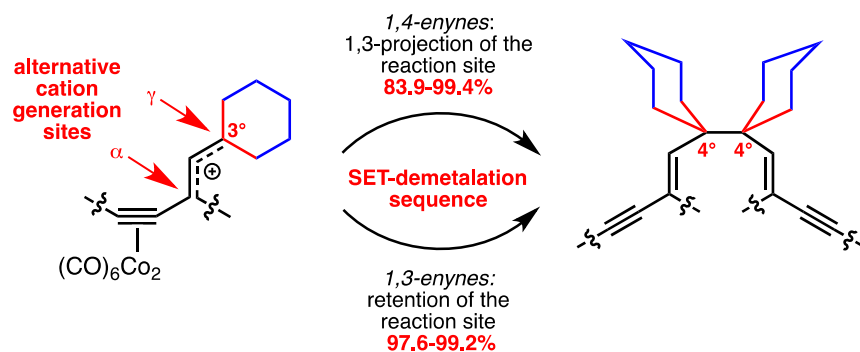
respective *d,l*-diastereomers (73-100% *d,l*). The stereo- and chemoselectivities are found to be dependent upon the (1) bulkiness of the gamma substituent (*1,3-steric induction*; *d,l*- 73 – 100%), (2) presence of a phosphorous ligand altering the π -bonded metal core (*axial ligand induction*; *d,l*- 91 – 97%), and (3) steric hindrance created by an alpha alkoxy group (*1,1-steric induction*; *d,l*- 83 – 92%). The said leverages can be used – alone, or in any combination – to further enhance the stereoselectivity of the radical dimerizations, and also to fine-tune the radical C-C bond-forming reactions in order to access much larger, topologically and functionally diverse molecular assemblies. The presence of vicinal alkoxy groups is essential for the secondary functionalizations – α,α' – by using radical and ionic reactions, either in a purely organic setting, or in the transition metal-mediated reactions.



Project findings IV. Gagik G. Melikyan, Rhoda Hughes, Bianca Rivas, Kellyanne Duncan, Nare Sahakyan. Assembling Contiguous Quaternary Carbon Atoms: Regio- and Stereoselective Rearrangements in Cobalt-Directed Radical Reactions of 1,4-Enynes. *Organometallics* **2015**, *34*, 242 - 253.

Radical coupling reactions of Co₂(CO)₆-complexed 1,4-enynes occur in a regio- and stereoselective fashion providing access to 3E,7E-decadien-1,9-diyne in excellent yields (84 - 99%). The formation of contiguous quaternary carbon atoms follows a tandem allylic rearrangement that projects an original reaction site gamma to the metal core. Propargyl alcohols with an α -alkenyl group as a substituent, are treated with HBF₄, followed by the reduction of the highly conjugated propargyl cations with zinc. The

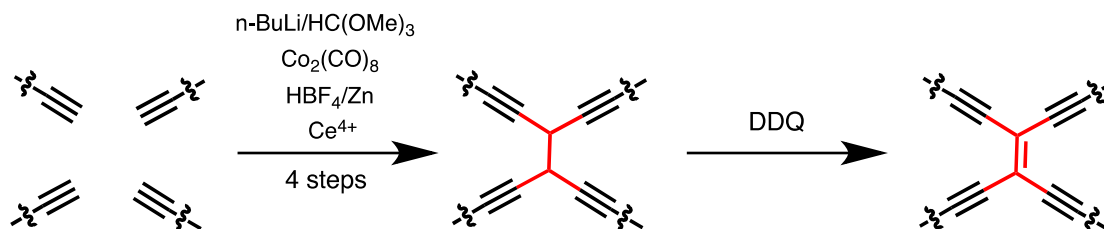
scope of the reaction is expanded to include 1,4-enyne complexes with cyclic and acyclic substituents gamma to the metal core, as well as aliphatic and aromatic substituents attached to the acetylenic termini. The alternative design includes relocation of the cation generation site – α -to- γ – prior to the reduction step, employing either the cation isolation technique with HBF_4 , or an in situ generation of ionic propargyl triflates with Tf_2O . Retention of the reaction site in 1,3-enynes is observed in both γ -alcohols and γ -Me ethers, affording respective γ,γ -radical dimers in excellent yields (98 - 99%). The “reaction-site-projection” strategy can be applied for the synthesis of organic molecules containing contiguous quaternary carbon atoms, and also for probing an upper limit of projection span in ionic and radical reactions.”



Project findings V. Gagik G. Melikyan, Bryan Anker. Radical Reactions of 1,4-Alkadiynes: Metal Coordination as an Effective Tool for Controlling the Regio- and Stereoselectivity of the C-C Bond Formation. *Organometallics* **2015**, 34, 4194 - 4197.

A novel method for selective generation of radicals in 1,4-alkadiynes is developed by employing π -bonded $\text{Co}_2(\text{CO})_6$ -core as a triple-bond immobilizing, cation-stabilizing, and radical-guiding auxiliary group. The isolation of α -alkynyl cobalt-complexed propargyl cations and their reduction with zinc occurred in a regio- and stereoselective manner, giving rise to tetraethynylethanes with predominant formation of *d,l*-diastereomers (82 - 93%). The methodology provides an easy access to tetraethynylethanes and, upon oxidation, to practically important tetraethynylethenes (TEE). We also report on the novel phenomenon of “chiralization by metal complexation” with achiral tetraynes

being converted to chiral bis-clusters due to highly regio- and stereoselective complexation of the acetylenic groups.

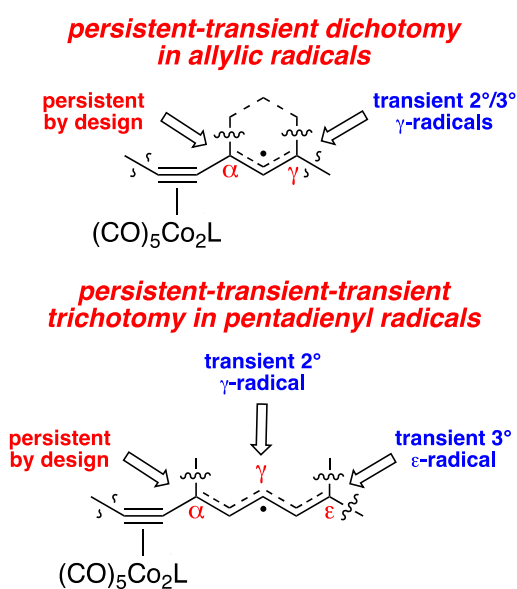


A highly regio- and stereoselective bis-complexation of acyclic tetraynes has two synthetically important ramifications. First, the concept of “*chiralization by metal complexation*” would allow for chirality to be introduced into an achiral molecule without compromising the carbon framework of the substrate, or forming any new σ -bonds, then for targeted modifications in select parts of the molecule - those that would potentially benefit from a newly acquired chirality -, and, at the final step, for an easy removal of π -bonded metal cores, and retrieval of the original carbon framework. Second, introducing a triple bond, by design, into a constrained area of the molecule that would make it unreactive toward metal coordination, or possibly other reagents, represents a new method for protecting acetylenic moieties wherein the structural integrity of the functional group is fully preserved, while an access of reagents to the said functionality is restricted for steric reasons (“*caged*” triple bond).

Project findings VI. Gagik G. Melikyan, Ryan Davis, Samantha Cappuccino. Acquiring and Exploiting Persistency of Propargyl Radicals: Novel Paradigms. *Organometallics* **2016**, *35*, 2854 - 2867.

Three complementary methods for altering an intrinsic nature of propargyl radicals, from transient to persistent, were developed by fine-tuning the bulkiness and degree of substitution around the secondary and tertiary propargylic carbons, as well as by sterically enhancing a π -bonded $\text{Co}_2(\text{CO})_6$ metal core. The latter was employed, as a

mechanistic tool, for precluding an acetylene-allene rearrangement, stabilizing propargyl cations, and creating a steric hindrance that could provide for said transition from transient to persistent propargyl radicals. A window of opportunities was identified wherein the steric bulkiness in propargyl radicals remains below the “persistence threshold,” providing good to excellent stereoselectivities in radical dimerization reactions (*d,l*- 62 – 100%). Along with the persistence threshold for tertiary propargyl radicals (278.2\AA^3), two different thresholds for persistence in secondary propargyl radicals were established – 306.5\AA^3 and 576.0\AA^3 – dependent upon the molecular architecture and the nature of the substituents populating the radical centers. Three alternative molecular platforms were designed to exploit a newly acquired dichotomy in allylic radicals (α -persistent- γ -transient) and trichotomy in pentadienyl radicals (α -persistent- γ -transient- ϵ -transient), providing access to molecular assemblies with contiguous 4° - 4° , 4° - 3° , and 3° - 3° carbon atoms.

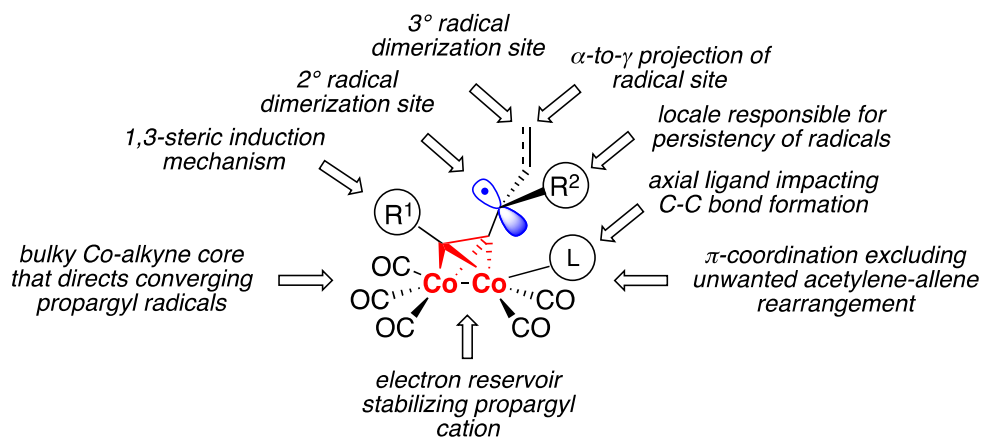


Project findings VII. Invited review: Gagik G. Melikyan. Propargyl Radical Chemistry: Renaissance Instigated by Metal Coordination. *Acc. Chem. Res.* **2015**, *48*, 1065 - 1079.

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 π -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, allowed for α -to- γ 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 didn’t adversely impact the yields and levels of *d,l*-diastereoselectivity. Third, π -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 π -bonded unsaturated units (dienes, arenes, diynes, enynes) and transition metals other than cobalt (Fe, Cr, Mo, W, Mn).



Contributions within Discipline

The conventional protocol for generating transition metal-stabilized carbocations involves treatment of the respective alcohols, ethers, esters, epoxides, aldehydes, acetals, or halides with Lewis or Bronsted acids, such as HBF_4 , BF_3 , CF_3COOH , H_2SO_4 , HBr ,

TiCl₄, TfOH, TsOH, and FSO₃H. While efficient with chemically robust substrates, the use of strong acids, usually in excess, imposes severe limits on the substrate base. The existing protocols hardly apply to the compounds bearing the acid-sensitive – benzyloxy, acetal, 1,3-dioxolane, enol ether – moieties, as well as the functional elements susceptible to protonation, such as carbonyl, cyano, amino or imino groups. Thus, ***development of the novel method for cation generation under neutral conditions has long been the Holy Grail of organometallic chemistry.***

Over the course of the NSF-sponsored project, we developed a novel method for the low-temperature generation of Co₂(CO)₆-propargyl cations (-50 °C to -10 °C) *under neutral conditions* and their reduction with cobaltocene (-50 °C), affording topologically diverse, α -aryl and α -1-/2-naphthyl, *d,l*- and *meso*-1,5-hexadiynes and 1,5-cyclodecadiynes (Gagik G. Melikyan, Bianca Rivas, Stepan Harutyunyan, Louis Carlson, Ruth Sepanian. Cobaltocene-Induced Low-Temperature Radical Coupling Reactions in a Cobalt-Alkyne Series. *Organometallics* **2012**, *31*, 1653 - 1663). An enhanced *functional tolerance* is showcased by introducing the peripheral acid-sensitive functionalities, such as benzyloxy and methylenedioxy groups, and carrying out a full, five-step conversion cycle – from commercial aromatic aldehydes to radical dimers – under *non-acidic conditions*. The novel method for radical C-C bond formation, alpha to the metal core, represents a viable approach to the synthesis of acyclic and cyclic alkadiynes with 1,5-disposition of the triple bonds. The latter can readily be converted, via conventional methods, to a variety of classes of organic compounds, such as 1,5-alkadienes, 1,4-/1,6-diketones, cyclopentenes, cyclopentenones, cycloalkane-1,2-diols, enediynes, fused and bridged carbocycles. It should be emphasized that *d,l*-3,4-disubstituted-1,5-alkadiynes are not easily accessible by alternative means. In a purely “organic” setting, propargyl-propargyl coupling exhibits a poor regioselectivity due to an unwanted acetylene-allene rearrangement, and attendant with it, the formation of inseparable mixtures of isomeric dimers (*head-to-head*, *head-to-tail*, *tail-to-tail*).

A new concept of the “sequestered” organometallic radical is introduced: The very concept of “free-ness” of organometallic radicals was probed in radical dimerization reactions mediated by a dicobalthexacarbonyl core (Gagik G. Melikyan, Louis Carlson, Nare Sahakyan, Arthur Floruti, McKinzie Garrison. Impact of Reducing Agent, Temperature, and Substrate Topology on Diastereoselectivity of the Intermolecular Coupling Reactions, or How “Free” Are Cobalt-Complexed Propargyl Radicals? *Dalton Transactions* **2013**, 42, 14801 – 14812). It is established that $\text{Co}_2(\text{CO})_6$ -complexed propargyl radicals, in general, are not kinetically free species and cannot be called “free radicals,” given the established dependency of the diastereoselectivity of radical C-C bond formation upon the reduction mode. Three distinct categories of reducing agents were identified providing either for “free” or “sequestered” organometallic radicals. The level of diastereoselection was found to be dependent upon the volume of the counterions derived from reducing agents thus creating a remarkable opportunity for controlling the stereoselectivity by fine-tuning the volume of the reducing agents. A new vehicle for controlling the stereochemistry of radical reactions can be used in alternative types of π -bonded unsaturated units (dienes, arenes, diynes, enynes) and transition metals other than cobalt (Fe, Cr, Mo, W, Mn).

New class of organic compounds – propargyl acetals – is used as a precursor to previously unknown α -alkoxypropargyl radicals: In organic chemistry, not a single reaction has ever been reported for propargyl acetals as pro-radical substrates. We have demonstrated that the protection of the triple bond with a dicobalthexacarbonyl group and application of the novel $\text{Tf}_2\text{O-Cp}_2\text{Co}$ protocol allows for selective generation of radical species alpha to the metal cluster (Gagik G. Melikyan, Erin Voorhees, Ruth Sepanian. Radical Reactions of the Cobalt-Complexed Propargyl Acetals: Inter- and Intramolecular Variants. *Organometallics* **2014**, 33, 69 – 83). Dimerization of alpha alkoxy propargyl radicals provides access to 3,4-dialkoxy-1,5-alkadiynes in a highly stereoselective manner. We have also demonstrated that the very topology of the cobalt clusters provides the effective tools for controlling the mode of coupling for

converging propargyl radicals. In particular, by fine-tuning substituents at the acetylenic termini (*1,3-steric induction*), alpha to the cationic center (*1,1-steric induction*), or directly at the metal core (*axial ligand induction*), the levels of diastereoselectivity as high as 100% *d,l*- can be achieved. Dealkylation of vicinally arranged alkoxy groups would provide access to respective 1,2-diols, a class of compounds of significant value to synthetic organic and medicinal chemistry. The methodology developed for the synthesis *d,l*-3,4-dialkoxy-1,5-cyclodecadiynes can also be expanded toward other carbocycles (C9-C12) by simply modifying the length of the carbon tether in starting 1,*n*-alkadiynes (*n* = 6, 8, 9).

New method for assembling contiguous quaternary carbon atoms. The contiguous quaternary carbon atoms – a molecular unit present in many natural compounds – are difficult to assemble. In organic chemistry, there are only a handful of cases when radical reactions were used for assembling of the contiguous quaternary atoms by the dimerization of the tertiary radicals; these reactions are limited in scope and suffer from low chemo- and stereoselectivities. The novel method that employs 1,4-enynes as substrates allows for projecting the reaction center from an alpha to a gamma position in cobalt-alkyne complexes, the generation of tertiary carbon-centered radicals, and a subsequent C-C coupling reaction arranging the quaternary carbon atoms vicinal to each other (Gagik G. Melikyan, Rhoda Hughes, Bianca Rivas, Kellyanne Duncan, Nare Sahakyan. Assembling Contiguous Quaternary Carbon Atoms: Regio- and Stereoselective Rearrangements in Cobalt-Directed Radical Reactions of 1,4-Enynes. *Organometallics* **2015**, *34*, 242 – 253). Overall, the new method represents an expansion of the substrate base as well as an expansion of the product base providing access to otherwise hardly accessible 1,5-diene-1,9-diynes of unique topology. In a single framework, several important classes of conjugated systems, i.e., 1,3-enynes, 1,5-dienes, 1,7-enynes, and 1,9-diynes, as well as 1,5-diynes are present and ripe for a multitude of the transition metal-mediated intramolecular cyclization reactions.

A new concept of “chiralization by metal complexation” and the first radical reaction of 1,4-alkadiynes in the last four decades: A novel method for selective radical generation in 1,4-diynes was developed with alkynyl propargyl radicals dimerizing regioselectively alpha to the metal core (Gagik G. Melikyan, Bryan Anker. Radical Reactions of 1,4-Alkadiynes: Metal Coordination as an Effective Tool for Controlling the Regio- and Stereoselectivity of the C-C Bond Formation. *Organometallics* **2015**, *34*, 4194 – 4197). A bulky, electron-donating dicobalthexacarbonyl group provides protection to the triple bonds, stabilizes the requisite carbocations, prevents an acetylene-allene rearrangement, and stereodirects converging propargyl radicals. The reduction of α -alkynyl propargyl cations with zinc occurs stereo- and regioselectively giving rise to symmetrical *d,l*-tetraalkynylethanes (82–93%) and upon oxidation, to 1,1,2,2-tetraalkynylethenes (TEE). A new phenomenon coined “***chiralization by metal complexation***” is described with *achiral* tetraynes converting to *chiral* bis-clusters via a highly regio- and stereoselective complexation of the acetylenic groups. The methodology allows for introducing chirality into the molecule without actually creating new stereocenters, or altering the carbon framework, or introducing the chiral auxiliaries. A new method for generating bis- α,α -acetylenic radicals can now be used in radical addition reactions across the activated multiple bonds (C=C, C \equiv C, C=N).

Introducing dichotomy in allylic radicals (α -persistent- γ -transient) and trichotomy in pentadienyl radicals (α -persistent- γ -transient- ϵ -transient): We explored a scarcely studied concept of the “projection of the reaction site” in organometallic radicals, first, by making propargyl radicals persistent, and then by exploiting persistency in order to achieve selective radical dimerization reactions on the periphery of the carbon framework (Gagik G. Melikyan, Ryan Davis, Samantha Cappuccino. Acquiring and Exploiting Persistency of Propargyl Radicals: Novel Paradigms. *Organometallics* **2016**, *35*, 2854 - 2867). Novel approaches for making both secondary and tertiary propargyl radicals persistent is critically important since they allowed for dimerization to occur as an activated, not diffusion-controlled process, and to achieve levels of stereocontrol

that are unprecedented in an all-carbon environment in a purely organic setting. An introduction of the conjugated double bonds allowed for projecting a radical center away from the metal coordination site and studying dimerization reactions at the remote locations, such as γ - or ε -carbon atoms. These methods allowed for assembling contiguous 4°-4°, 4°-3°, and 3°-3° carbon atoms with three alternative molecular platforms designed to exploit a dichotomy in allylic radicals (*α -persistent- γ -transient*) and trichotomy in pentadienyl radicals (*α -persistent- γ -transient- ε -transient*).

Contributions to Other Disciplines

Medicinal chemistry

A novel method for the low-temperature generation of $\text{Co}_2(\text{CO})_6$ -propargyl cations under neutral conditions and their reduction with cobaltocene (-50°C) affords topologically diverse, polysubstituted 1,5-alkadiynes and 1,5-cycloalkadiynes (Gagik G. Melikyan, Bianca Rivas, Stepan Harutyunyan, Louis Carlson, Ruth Sepanian. Cobaltocene-Induced Low-Temperature Radical Coupling Reactions in a Cobalt-Alkyne Series. *Organometallics* **2012**, *31*, 1653-1663). The method that features an enhanced functional tolerance toward peripheral acid-sensitive functionalities, can now be used, as a key step, in the total synthesis of potential *anticancer (pro)drugs*, *aromatase inhibitors (AIs)*, and *selective estrogen receptor modulators (SERMs)*. The topology and geometric parameters of some products are such that these compounds could successfully compete with natural compounds for select enzymatic sites thus functioning as effective enzyme inhibitors. A new method for selective dimerization of propargyl acetals yields vicinal dialkoxy 1,5-alkadiynes (Melikyan, G. G.; Voorhees, E.; Sepanian, R. Radical Reactions of the Cobalt-Complexed Propargyl Acetals: Inter- and Intramolecular Variants. *Organometallics* **2014**, *33*, 69 - 83), a class of chemical compounds which is otherwise hardly accessible and which can be used as a key step in drug development, lead optimization, and enzyme inhibitor syntheses as well as in creating libraries of potential drug metabolites. Also relevant is a novel method for the

synthesis of compounds with vicinal quaternary carbon atoms (Melikyan G. G.; Hughes, R.; Rivas, B.; Duncan, K.; Sahakyan, N. Assembling Contiguous Quaternary Carbon Atoms: Regio- and Stereoselective Rearrangements in Cobalt-Directed Radical Reactions of 1,4-Enynes. *Organometallics* **2015**, *34*, 242 - 253), a common structural motif in biologically active compounds isolated from plant and animal kingdoms.

Natural product chemistry

Introducing alkenyl groups alpha to the cobalt-alkyne core allowed for a regio- and stereoselective projection of the reaction site and assembling of quaternary carbon atoms in a highly efficient manner (Melikyan G. G.; Hughes, R.; Rivas, B.; Duncan, K.; Sahakyan, N. Assembling Contiguous Quaternary Carbon Atoms: Regio- and Stereoselective Rearrangements in Cobalt-Directed Radical Reactions of 1,4-Enynes. *Organometallics* **2015**, *34*, 242 - 253). The method can be an asset not only for medicinal chemistry as it is mentioned above, but also for natural product chemistry because the highly congested molecular units (4°-4°, 4°-3°, 3°-3°) are quite abundant in natural products.

Materials science, dendrimer chemistry

The incorporation of alkynyl groups alpha to the metal-alkyne core allowed us to gain an easy access to symmetrically substituted tetraynes and their dehydrogenated analogs, i.e., tetraethynylethenes (TEE) (Melikyan G. G.; Anker, B. Radical Reactions of 1,4-Alkadiynes: Metal Coordination as an Effective Tool for Controlling the Regio- and Stereoselectivity of the C-C Bond Formation. *Organometallics* **2015**, *34*, 4194 – 4197). Both classes of compounds can be used in materials science for assembling of larger, highly conjugated molecular systems by using said molecular units as a central theme and structurally expanding in select directions by exploiting the terminal acetylenic functionalities. Tetraalkynylethenes (TEEs) can be used in molecular electronics and dendrimer chemistry for creating molecular assemblies with valuable electrooptical and mechanical properties.