Published in final edited form as:

Chem Soc Rev. 2018 October 29; 47(21): 7845–7850. doi:10.1039/c8cs00298c.

Questions in Natural Products Synthesis Research that Can (and Cannot) be Answered Using Computational Chemistry

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Abstract

Questions of relevance to those working in the field of natural products synthesis that can be answered, at least in part, using computational chemistry approaches are described. Illustrative examples are provided, as are descriptions of limitations.

Table of Contents

Questions of relevance to synthetic chemists that can be answered, at least in part, using quantum chemical computations are highlighted.

1 Introduction

Those working in the field of applied theoretical organic chemistry should be, in the author's opinion, willing to make experimentally testable predictions — and should be eager to have these predictions tested. There are many testable predictions of relevance to natural products synthesis and it is the purpose of this tutorial review to shine light on them. Often, these predictions result from a question posed by a synthetic chemist to a theoretically oriented chemist and that is how this tutorial review is structured: typical questions are posed and strategies for answering them using computational chemistry are described. Strengths and limitations of theoretical approaches are stated explicitly, i.e., with which questions can theory help and with which can it not? Several recent reviews provide additional examples.¹

2 Questions

Was the natural product target structure correctly assigned?

No one wants to invest years of effort into synthesizing a natural product found in the literature only to discover that the reported structure, having yielded to total synthesis, is not actually the structure of the isolated natural product.² One approach to avoiding this sort of disaster is to compute the ^1H and ^{13}C chemical shifts (and coupling constants, if desired) for the reported structure using computational quantum chemistry and compare the computed values to those reported.³ This aspect of applied computational chemistry has advanced to the point where the accuracy of (in many cases, routine) predictions can be comparable to the accuracy of experiments (given variations due to aggregation, equipment, etc.).³ Representative examples of natural product structures reassigned in this way are shown in Figure 1.^{4,5} Clearly very different synthetic approaches to the originally proposed and revised structures would be needed.

It would seem wise to carry out such calculations (or convince a friend with a theoretical bent to do so) before embarking on a multi-step synthesis – the effort will surely be less than completing a total synthesis. When would such an approach not be necessary? (a) If an X-ray crystal structure of the natural product is reported. (b) If the reported spectroscopic characterization of the natural product is beyond reproach (*caveat emptor*).

When might accurate NMR calculations not be feasible or require more effort than would be justified? (a) If the molecule in question is exceedingly flexible – accurately capturing the mix of conformations contributing to a spectrum under the conditions used for its acquisition (solvent, temperature, concentration) lead to accurate predictions and the converse is often true. (b) If the molecule has ionisable groups – here, one must again capture all contributing structures, including different protonation states and complexes; this issue makes computing NMR chemical shifts for basic amines and acidic carboxylic acids difficult (and also complicates comparisons between synthetic and natural compounds).⁶ These issues are not insurmountable, but outlaying time and resources to overcome them is often impractical.

How does one carry out such calculations? There are several approaches, and these have been reviewed elsewhere.³ In short, there is the manual approach, one version of which has been summarized nicely by Hoyer and co-workers,^{3x} and there are automated approaches.⁷ The former obviously requires more specialized expertise than the latter to implement but can be essential for tackling problematic cases such as those described above.

Other questions that can be answered with the same approaches—Which regioisomer/diastereomer/enantiomer did I synthesize? What is the structure of my byproduct?

Which of these conformers is more stable?

Whenever one asks about stability, I ask, “what do you mean by stability?” i.e., kinetic or thermodynamic? relative to what?^{1g} The question of which conformer is more stable is generally asked from a thermodynamic perspective. Since two conformers are comprised from the same numbers and types of atoms, their relative energies can be compared directly.

Then, what must be done is to choose a reliable level of theory, decide whether or not to (and how to) treat solvent and plunge ahead. Choosing an appropriate level of theory always involves balancing speed and expected accuracy. Sometimes one just cares which conformer is lower in energy for a “typical” organic molecule, in which case very rapid force field (classical molecular mechanics) calculations may be sufficient (sometimes a plastic model – a physical manifestation of a force field with steep potentials – is sufficient; constructing a physical model should generally be a first step even if computations are to be pursued).⁸ In other cases, unusual substructures are present or intramolecular dispersion interactions play important roles, requiring appropriate (and comparatively expensive) quantum chemical methods.⁹

Other questions that can be answered with the same approaches—Which product is the thermodynamic product? Which intermediate is lower in energy?

Some questions of stability are more difficult to answer than those discussed above. For example, it is often desirable to know which of two molecules *that are not isomers* is “more stable,” but simply comparing energies of the two structures in question is not a viable approach – in quantum chemical computations, molecules with more atoms have lower total energies. As a result, one must set up an isodesmic equation (a “fake equilibrium”) with the same numbers and types of atoms on each side. For example, the energy change (H , G , pick your poison) for the hypothetical equilibrium shown in Figure 2 could be used to compare (in effect, define) the thermodynamic stability of the two dienes shown or, in other words, to quantify the strain (a common form of stability of interest to organic chemists) for the diene at the far left associated with embedding it within an 11-membered ring.¹⁰ There is a whole hierarchy of types of isodesmic equation that differ in their expected accuracy and ease of interpretation.¹¹

How acidic is this proton?

The simplest approach to computing acidity is to compute deprotonation energies (relative energies of acid and conjugate base; these values will be on the order of hundreds of kcal/mol, since an acid and conjugate base have different numbers of atoms) for a series of molecules for which experimental acidities (pK_a 's in particular solvents, gas phase acidities) are known and then hope for a strong correlation between computed and experimental values.^{1g,12a} If such a correlation is found, acidity for a proton not included in the experimental data set can be predicted by calculating the associated deprotonation energy and plugging into the derived correlation equation.

Other questions that can be answered with the same approaches—How basic is this lone pair, π -bond, etc.? What is the pK_a of my molecule? This question is complicated by the fact that one is asking for a number to be compared with an absolute scale derived from experimental data. Which proton in my complex molecule is easiest to remove? For this question, a correlation with experimental acidities is not necessary, because one is comparing multiple protons in the same molecule, i.e., relative energies of conjugate bases arising from deprotonation at different sites can be compared directly. This approach was recently applied to predict the relative energies of various tautomers of the molecule shown in

Figure 3, as well as its conjugate base.^{12b} This information was used to refine a mechanistic model that allowed for the rationalization and prediction of preferred products formed when this molecule was exposed to base.

Unfortunately, the approaches described above do not always work well.^{1g,12a} A major source of complications is the importance of specific interactions between the acid in question and both the base that removes the proton and solvent in a specific experiment. Nonetheless, problems associated with treating these issues are often the same for related molecules (or different protons within the same molecule), allowing the issue to be avoided as a result of fortuitous cancellation of errors. One must be careful, however, and judge, for each specific case, whether errors are indeed likely to cancel; they may not, for example, if the accessibility of protons being compared differs greatly.

What is the origin of the observed kinetic selectivity?

In most cases, answering this question boils down to computing the relative energies of competing transition states, the predicted product ratio corresponding to K in the following well-known equation:

$$\Delta\Delta G = -RT \ln k \quad (1)$$

Structures of the competing transition states are optimized and their free energies (G) compared. In many cases, however, the process is more complicated.

First, one really should be using Boltzmann weighted averages of all relevant conformations/configurations of transition states. In some cases, complete conformation/configuration searches on transition states are not carried out – this is very dangerous. Even if one's chemical intuition is of high enough quality to pinpoint the lowest energy conformation of each transition state, there is no guarantee that using just those conformations will lead to a meaningful selectivity prediction. For example, imagine a scenario where product A can be formed only via a single transition state structure while product B can be formed by five transition state structures close in energy to each other – this would provide an enhancement to product B formation (this can be considered an entropy effect) that would be missed if only the lowest energy B-forming transition state is considered. Not only do conformations need to be considered in such an analysis, but also configurations for systems where multiple configurations are energetically accessible. For example, Wheeler and co-workers demonstrated that many different Si-ligand coordination modes are viable, and contribute to different extents, for the reaction shown in Figure 4 (relative positions of bipyridine *N*-oxide, two chlorides, aldehyde electrophile and allenylsilane nucleophile), precluding the development of a universal model for selectivity.¹³ This issue looms larger today than in the past when small models of systems of interest were used – using actual large systems generally means having to deal with more degrees of freedom.

Second, the Curtin-Hammett principle does not necessarily apply to all reactions of interest.¹⁴ This is the principle used to justify comparing only transition state energies, but it is predicated on the assumption that the conformations/configurations of reactants that are

productive for product formation interconvert at a much higher rate than they are converted to products. In some cases, predicted barriers and expected accuracy of calculations lead to difficulties in deciding whether or not the Curtin-Hammett principle should apply. The Pd(0)-promoted difunctionalization of dienes studied by Sigman, Wu, Wiest and co-workers provides an interesting example of this scenario.^{14b}

Third, selectivity for some reactions may result from non-statistical dynamic effects, i.e., may result from vibrational properties of molecules not captured by potential energy surfaces (PES) and classic transition state theory. Two representative examples are discussed here, but reviews on this topic exist.¹⁵ The hydroboration reaction shown in Figure 5, a classic “textbook reaction” was studied by Singleton and co-workers.¹⁶ These researchers convincingly argued that experimentally observed selectivities cannot be reproduced using traditional transition state theory arguments, but can be when non-statistical dynamic effects are modelled in a reasonable manner.

The reaction shown in Figure 6 involves what is termed a post-transition state bifurcation (PTSB) – a scenario in which a reaction pathway bifurcates after a transition state (termed an ambimodal¹⁷ transition state) leading to two products without the intermediacy of a discreet PES minimum.¹⁸ Calculations showed that this dirhodium tetracarboxylate-promoted CH-insertion reaction (rhodium catalyst not shown) leads, via a PTSB, to a β -lactone and a ketene-ketone pair.¹⁹ The former was the desired product, while the latter was actually observed as the major product,²⁰ demonstrating that seemingly esoteric mechanistic peculiarities can play key roles in controlling (by)product distributions. This mechanistic model was derived using both quantum chemical computations on the PES and direct dynamics calculations²¹ on reaction trajectories that take into account molecular vibrations occurring during reaction.

Other questions that can be answered with the same approaches—Can the selectivity of my reaction be predicted before I invest in synthesis? Can the selectivity of my reaction be improved through computation-aided design?[‡]

How did this unexpected product form?

This question can be rephrased as, “what is an energetically viable mechanism for formation of this product?” Traditionally, this question would be answered by computing minima (reactant(s), product(s), intermediate(s) if any) and transition state structures (first order saddle points), i.e., PES “stationary points”), along a path from reactant(s) to product(s). In some cases, more than one such path can be found. Ideally, these stationary points will also be connected by intrinsic reaction coordinates (IRC).²² As described above, this picture can be complicated by conformational issues and non-statistical dynamic effects. In addition, accurately modelling proton transfer reactions, which are arguably the simplest reactions encountered in organic chemistry, is notoriously difficult due to the involvement of specific solvent molecules.²³ An example highlighting the potential pitfalls in modelling mechanisms was provided by Plata and Singleton, who compared a variety of theoretical

[‡]In principle, quantum mechanical tunnelling could also influence selectivity and rates for key synthetic reactions en route to natural products (see P. R. Schreiner, *J. Am. Chem. Soc.*, 2017, 139, 15276).

approaches for modelling the Morita-Baylis-Hillman reaction (Figure 7). For some reactions, most reasonable theoretical approaches agree on energetic viability, but when they do not, as in this case, extensive mechanistic experiments are key to ruling out mechanistic pathways. It is also important to remember that finding an energetically viable pathway does not prove that that pathway is the one that leads to most of the observed product, i.e., one cannot prove a mechanism.²⁴

Other questions that can be answered with the same approaches—What is the mechanism by which my major product formed? Does my reaction involve an intermediate that might lead to scrambling/loss of stereochemical information?

How do I make this reaction faster?

This question comes down to controlling rates of particular reaction steps, i.e., modulating their activation barriers. As described above, one can compute a reaction barrier by optimizing the electronic structures of reactants and transition state structures and comparing their energies, subject, of course, to the issues of conformational searching, solvation, etc. described above. Assuming that non-statistical dynamic effects do not play a major role, these barriers will reflect rate constants for formation of products (i.e., via the Eyring equation). With barriers in hand, one can attempt to alter them by changing, for example, solvent, substituents and catalysts. This process can boil down to computation-aided screening, or it can be done rationally (or a combination of both approaches can be used). For the latter approach, one is dependent on chemical intuition, but this is best applied when one has detailed structural information and a model for the origin of a barrier height – the sort of information that can be derived from the results of computational experiments. For example, one can compare favourable intramolecular interactions (e.g., hydrogen bonds, both strong and weak,²⁵ dispersion interactions,⁹ cation- π interactions)²⁶ or steric clashes and strain (e.g., via the distortion-interaction/activation strain model),^{1g,27} in reactants and transition state structures and then set about modulating these by making changes to the structure of reactants, solvents or catalysts.¹ The results of these changes can be predicted ahead of laboratory experiments, allowing laboratory testing of the most promising changes to be prioritized.

This process is nicely illustrated by Overman's approach to the total synthesis of (–)-chromodorolide B, in which a key radical cascade (Figure 8) was optimized via a combination of theory and experiment:²⁸ “Examination of the transition structures of the two diastereomeric transition states of the radical pathway... was instructive. ...analysis suggested a potential destabilizing steric interaction between the chloride of the hydrindane fragment and a substituent larger than hydrogen at the α -carbon of the butenolide fragment... The computationally predicted lowest energy transition structures for the 3-chloride analogue are shown... As envisioned, the **TS-B-trans** is affected significantly, with the forming C–C bond distance decreased from 2.38 to 2.18 Å. As a consequence, the kinetic barrier for forming the *trans* product is increased from 7.9 to 11.3 kcal/mol... The transition state that would lead to the... product having the C-8 configuration of (–)-chromodorolide B... is now predicted to be more stable by 1.9 kcal/mol... We opted to explore this computational prediction by utilizing a 3-chlorobutenolide... The pentacyclic

C-8 epimer... was not detectable by NMR analysis [and] the computationally guided structural modification of the butenolide coupling partner resulted in doubling the yield of the pivotal pentacyclic intermediate... and decreasing the amount of butenolide acceptor required in this step by 4-fold.”

Other questions that can be answered with the same approaches—How do I make this reaction slower? How do I control selectivity, i.e., relative rates of competing processes? How can I increase my yield? How can I shorten my reaction time? Can I improve nucleophilicity or electrophilicity?

3 Prospects

Improvements in software and hardware not only will make answering questions of the types described above faster but will also lead to more accurate answers. Areas in which improvements can have immediate major impact include: (a) Faster and more reliable conformational searching, especially for transition state structures. Programs like Wheeler’s *AARON* are making strides in this direction.²⁹ (b) Broader appreciation and implementation of dynamics trajectory calculations. The percentage of organic reactions for which non-statistical dynamic effects have been recognized to play significant roles has risen dramatically in recent years.^{15,18} (c) Rapid, automated prediction of NMR spectra and mass spectra. Grimme’s software is a huge step towards achieving this goal.^{7,30} (d) Improved treatment of explicit solvent, including its role in modulating non-statistical dynamic effects.^{18b} Improvements in all of these areas will allow creative chemists, of both the theoretical and synthetic varieties, to increase the rate at which ideas are turned into useful experimental results, thereby facilitating the *design* of *new* reactions and reaction conditions that make natural products synthesis safer, greener and more efficient.

Acknowledgments

Research in the Tantillo group on natural products and synthetically relevant reactions has been generously supported by the US National Science Foundation (NSF), the US National Institutes of Health (NIH), the US Defense Threat Reduction Agency (DTRA), the US Department of Defence Advanced Research Projects Agency (DARPA), the American Chemical Society Petroleum Research Fund (ACS-PRF) and the France-Berkeley Fund.

References

1. Cheng G-J, Zhang Z, Chung LW, Wu Y-D. J. Am. Chem. Soc. 2015; 137:1706. [PubMed: 25568962] Nguyen QNN, Tantillo DJ. Chem. Asian J. 2014; 9:674. [PubMed: 24376231] Peng Q, Duarte F, Paton RS. Chem. Soc. Rev. 2016; 45:6093. [PubMed: 27722685] Vogel P, Lam Y, Soimon A, Houk KN. Catalysis. 2016; 6:128. M. Fianchini. Phys. Sci. Rev. 2017:20170134. Tantillo DJ. Acc. Chem. Res. 2016; 49:741. [PubMed: 27050387] (introduction to a special issue on “Computational Catalysis for Organic Synthesis”); Tantillo DJ. Applied Theoretical Organic Chemistry. World Scientific 2018. Issues of stability: Chapter 1, distortion-interaction model: Chapter 13, acidity predictions: Chapter 16.
2. Nicolaou KC, Snyder SA. Angew. Chem. Int. Ed. 2005; 44:1012.
3. a) Lodewyk MW, Siebert MR, Tantillo DJ. Chem. Rev. 2012; 112:1839. [PubMed: 22091891] b) Grimblat N, Sarotti AM. Chem. Eur. J. 2016; 22:12246. [PubMed: 27405775] c) Willoughby PH, Jansma MJ, Hoyer TR. Nature Protocols. 2014; 9:643. [PubMed: 24556787]
4. a) Rychnovsky SD. Org. Lett. 2006; 8:2895. [PubMed: 16774284] b) Porco JA Jr, Su S, Lei X, Bardham S, Rychnovsky SD. Angew. Chem. Int. Ed. 2006; 45:5790. c) Williams AJ, Elyashberg

- ME, Blinov KA, Lankin DC, Martin GE, Reynolds WF, Porco JA Jr, Singleton CA, Su S. J. Nat. Prod. 2008; 71:581. [PubMed: 18257535] d) Saelli G, Bagno A. Org. Lett. 2009; 11:1409. [PubMed: 19215104]
5. a) Lodewyk MW, Soldi C, Jones PB, Olmstead MM, Rita J, Shaw JT, Tantillo DJ. J. Am. Chem. Soc. 2012; 134:18550. [PubMed: 23101682] b) Saya JM, Vos K, Kleinnijenhuis RJ, van Maarseveen JH, Ingemann S, Hiemstra H. Org. Lett. 2015; 17:3892. [PubMed: 26186274] c) Wang B, Xie Y, Yang Q, Zhang G, Gu Z. Org. Lett. 2016; 18:5388.d) Pauli GF, Niemitz M, Bisson J, Lodewyk MW, Soldi C, Shaw JT, Tantillo DJ, Saya JM, Vos K, Kleinnijenhuis RJ, Hiemstra H, Chen S-N, McAlpine JB, Lankin DC, Friesen JB. J. Org. Chem. 2016; 81:878. [PubMed: 26812443]
6. Saunders CM, Tantillo DJ. Marine Drugs. 2017; 15:171.
7. Grimme S, Bannwarth C, Dohm S, Hansen A, Pisarek J, Pracht P, Seibert J, Neese F. Angew. Chem. Int. Ed. 2017; 56:14763.
8. a) Ainsworth SL. Chem. Eng. News. 2014; 92:34.b) Fieser LF. J. Chem. Educ. 1963; 40:457.c) Mayp SL, Olafson BD, Goddard WA III. J. Phys. Chem. 1990; 94:8897.
9. a) Wagner JP, Schreiner PR. Angew. Chem. Int. Ed. 2015; 54:12274.b) Liptrot DJ, Power PP. Nat. Rev. Chem. 2017; 1:0004.c) Pollice R, Bot M, Kobylanskii IJ, Shenderovich I, Chen P. J. Am. Chem. Soc. 2017; 139:13126. [PubMed: 28823152]
10. Boon BA, Green AG, Liu P, Houk KN, Merlic CA. J. Org. Chem. 2017; 82:4613. [PubMed: 28407711]
11. Wheeler SE, Houk KN, Schleyer PvR, Allen WD. J. Am. Chem. Soc. 2009; 131:2547. [PubMed: 19182999]
12. a) Ho J, Coote ML. WIREs Comput. Mol. Sci. 2011; 1:649.b) Zhu JS, Son J-H, Teuthorn AP, Haddadin MJ, Kurth MJ, Tantillo DJ. J. Org. Chem. 2017; 82:10875. [PubMed: 28922917]
13. Lu T, Zhu R, An Y, Wheeler SE. J. Am. Chem. Soc. 2012; 134:3095. [PubMed: 22229866]
14. a) Seeman JI. Chem. Rev. 1983; 83:83.b) Xu L, Zhang X, McCammant MS, Sigman MS, Wu Y-D, Wiest O. J. Org. Chem. 2016; 81:7604.
15. a) Carpenter BK. Angew. Chem. Int. Ed. 1998; 37:3340.b) Rehbein J, Carpenter BK. Phys. Chem. Chem. Phys. 2011; 13:20906. [PubMed: 22033619] c) Black K, Liu P, Doubleday C, Houk KN. Proc. Natl. Acad. Sci. USA. 2012; 109:12860. [PubMed: 22753502]
16. a) Oyola Y, Singleton DA. J. Am. Chem. Soc. 2009; 131:3130. [PubMed: 19215077] b) Bailey JO, Singleton DA. J. Am. Chem. Soc. 2017; 139:15710. [PubMed: 29029560]
17. Pham HV, Houk KN. J. Org. Chem. 2014; 79:8968. [PubMed: 25216056]
18. a) Ess DH, Wheeler SE, Iafe RG, Xu L, Çelebi-Ölçüm N, Houk KN. Angew. Chem. Int. Ed. 2008; 47:7592.b) Hare SR, Tantillo DJ. Pure Appl. Chem. 2017; 89:679.
19. Hare SR, Tantillo DJ. Chem. Sci. 2017; 8:1442. [PubMed: 28451284]
20. Lee EJ, Woon K, Seong KY. Tetrahedron Lett. 1990; 31:1023.
21. a) Lourderaj U, Park K, Hase WL. Int. Rev. Phys. Chem. 2008; 27:361.b) Ma X, Hase WL. Phil. Trans. R. Soc. A. 2017; 375:20160204. [PubMed: 28320906] c) Nyman G. Int. J. Quant. Chem. 2014; 114:1183.d) Salem L. Acc. Chem. Soc. 1971; 4:322.e) Wang ISY, Karplus M. J. Am. Chem. Soc. 1973; 95:8160.
22. a) Maeda S, Harabuchi Y, Ono Y, Taketsugu T, Morokuma K. Int. J. Quantum Chem. 2015; 115:258.b) Fukui K. Acc. Chem. Res. 1981; 14:363.c) Gonzalez C, Schlegel HB. J. Phys. Chem. 1990; 94:5523.
23. Plata E, Singleton DA. J. Am. Chem. Soc. 2015; 137:3811. [PubMed: 25714789]
24. Buskirk A, Baradaran H. J. Chem. Educ. 2009; 86:551.
25. Johnston RC, Cheong PH-Y. Org. Biomol. Chem. 2013; 11:5057. [PubMed: 23824256]
26. a) Ma C, Dougherty DA. Chem. Rev. 1997; 97:1303. [PubMed: 11851453] b) Kennedy CR, Lin S, Jacobsen EN. Angew. Chem., Int. Ed. 2016; 55:12596.
27. Bickelhaupt FM, Houk KN. Angew. Chem. Int. Ed. 2017; 56:10070.
28. Tao DJ, Slutskyy Y, Muuronen M, Le A, Kohler P, Overman LE. J. Am. Chem. Soc. 2018; 140:3091. [PubMed: 29412658]
29. Guan Y, Wheeler SE. Angew. Chem. Int. Ed. 2017; 56:9101.

30. Bauer CA, Grimme S. J. Phys. Chem. A. 2016; 120:3755. [PubMed: 27139033]

Biography

Dean Tantillo was born and raised in Quincy, Massachusetts, USA. He received an A.B. degree in Chemistry in 1995 from Harvard and a Ph.D. in 2000 from UCLA (with Ken Houk) and then moved to Cornell where he did postdoctoral research with Roald Hoffmann. Dean joined the faculty at UC Davis in 2003. Research in Dean's group is driven by puzzling mechanistic questions in the areas of biosynthesis, organometallic chemistry, and stereoselective synthetic reactions, with a focus on cyclization/rearrangement reactions used by Nature and by chemists to synthesize complex natural products.

Key learning points

1. Typical questions of interest to synthetic chemists with which computational chemistry can help are highlighted.
2. Strengths and limitations of computational approaches are described.

hexacyclinol

*originally proposed
structure*

*revised
structure*

aquatolide

*originally proposed
structure*

*revised
structure*

Figure 1.

Representative misassigned natural products whose structures were corrected using NMR chemical shift calculations and subsequently further verified via total synthesis.^{4,5}

Figure 2.
Sample isodesmic equation.

Figure 3.
A synthetic intermediate whose tautomers were examined using quantum chemistry.^{12b}

Figure 4. Propargylation reaction studied by Wheeler and co-workers.¹³

Figure 5.
Hydroboration reaction studied by Singleton and co-workers.¹⁶

Figure 6.
Rh-promoted CH-insertion reaction studied by Hare and Tantillo (Rh catalyst not shown).¹⁹

Figure 7.

Energetics from multiple levels of theory for the Morita-Baylis-Hillman reaction studied by Plata and Singleton.²³ Reproduced from ref. 23 with permission from the American Chemical Society, copyright 2015.

Figure 8. Radical cascade reaction used by Overman and co-workers in the synthesis of (-)-chromodorolide B.²⁸