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14. Thickness of GRZ estimated from map and cross sections of C. H. Smith, T. N. Irvine, D. C. Findlay, *Geol. Surv. Can. Maps 1213-A* and *1214-A* (1966).
15. Sample M-156, collected from a xenolith-rich region just below the roof, was provided by T. N. Irvine; all other samples were collected by D.J.D. in a 1983 expedition. Stratigraphic positions of samples within C.U. 25 (Table 1) are estimated from their field relations and map locations and are given relative to the base of C.U. 25, which is assumed to have an average thickness of 170 m. Whole-rock samples of 100 to 500 g were crushed and split, and 100- to 500-mg aliquots were dissolved with HF + $HClO_4$. After spiking with tracer solutions of Rb, Sr, Sm, and Nd, the cations of interest were separated by standard ion-exchange techniques. Concentrations and isotopic ratios were determined by thermal ionization mass spectrometry, and all elements were run as metal species except Nd, which was run as NdO^+. Most measurements were carried out on VG single collector machines at the University of California, Los Angeles (UCLA) and the Berkeley Center for Isotope Geochemistry (BCIG), with some Sr isotopic analyses run on the BCIG VG multicollector. Both single-collector machines give the same values for $^{143}Nd/^{144}Nd$ within measurement uncertainties, and all $^{87}Sr/^{86}Sr$ ratios are corrected to the pre-1989 UCLA value for NBS987 of 0.71031.
16. All values of $^{87}Sr/^{86}Sr$ and ϵ_{Nd} quoted in the text are initial ratios (corrected for decay of ^{87}Rb and ^{147}Sm since the time of crystallization). In this study we assume a crystallization age of 1257 Ma (million years ago), based on an internal Sm-Nd isochron from a two-pyroxene gabbro collected from C.U. 22 (sample 83DM-3, Table 1); this age of 1257 ± 40 Ma (2σ) is within error of the U-Pb age of 1270 ± 4 Ma of A. N. LeCheminant and L. M. Heaman [*Earth Planet. Sci. Lett.* **96**, 38 (1989)]. Age-corrected Nd isotopic ratios are reported as ϵ_{Nd}, with

$$\epsilon_{Nd}(T) = 10^4\left(\frac{^{143}Nd/^{144}Nd_{SAMP}(T)}{^{143}Nd/^{144}Nd_{CHUR}(T)} - 1\right)$$

where T is the crystallization age of the Muskox intrusion and CHUR is the chondritic reservoir. The chondritic isotopic composition at time T is given by: $^{143}Nd/^{144}Nd_{CHUR}(T) = 0.511836 - 0.1967[\exp(\lambda_{Sm}T) - 1]$. Decay constants used are 0.0142 per 10^9 years for λ_{Rb} and 0.00654 per 10^9 years for λ_{Sm}.
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22. In our model, we assume that the coexisting magmas achieve a steady-state condition of two-layer convection on a time scale that is short relative to the time scale of crystallization. This is a particularly good assumption for the Muskox intrusion, because the GRZ was already in a convective state when the final pulse of mafic magma was emplaced. For further discussion of the relevant magma chamber dynamics, see C. M. Oldenburg, F. J. Spera, D. A. Yuen, and G. Sewell [*J. Geophys. Res.* **94**, 9215 (1989)] and B. D. Marsh [*J. Petrol.* **30**, 479 (1989)]; see also discussion of Marsh's paper by H. E. Huppert and J. S. Turner [*ibid.* **32**, 851 (1991)].
23. To maintain constant Sr concentration in the silicic liquid, there must be a net flow of the other Sr isotopes (^{88}Sr, ^{86}Sr, and ^{84}Sr) into the silicic liquid to balance the loss of ^{87}Sr. This can be ignored for our purposes because the total change in $[^{86}Sr]_a$ is only about 0.1% (see Eq. 2).
24. The boundary layer would in fact consist of both mafic and silicic components; however, diffusivities of Sr and Nd in basalt are faster by up to an order of magnitude than diffusivities in rhyolite (*5*, *6*), making diffusion in the silicic portion of the boundary layer the rate-limiting process.
25. In Eqs. 3 and 4, we use the approximation that the concentration of Sr is independent of the $^{87}Sr/^{86}Sr$ ratio ($[^{86}Sr]/[Sr]$ = constant), which is generally accurate to better than 0.5%.
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31. In order to supply enough Sr to produce the increase in $^{87}Sr/^{86}Sr$ observed in C.U. 25, the roof zone of molten wall rock overlying the Muskox cumulates must have been more extensive during crystallization than the current exposure would suggest. Two possible explanations are that (i) the GRZ thickens to the north of the current Muskox exposure where the intrusion dips beneath sedimentary cover, or (ii) much of the GRZ was vented during and after crystallization of the mafic magma. The lack of a downward-crystallizing roof sequence in the Muskox intrusion, even in regions where wall rock breccia is not present, suggests that such a liquid layer was present throughout the entire roof zone during crystallization of the cumulates.
32. For contrasting views, see H. E. Huppert and R. S. J. Sparks [*J. Petrol.* **29**, 599 (1988)] and A. N. Halliday *et al.* [*Earth Planet. Sci. Lett.* **94**, 274 (1989)], as well as discussion by R. S. J. Sparks, H. E. Huppert, and C. J. N. Wilson [*ibid.* **99**, 387 (1990)].
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Reaction Planning: Computer-Aided Discovery of a Novel Elimination Reaction

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Algorithms based on graph theory and implemented in a computer program have been used to search for unprecedented reactions. This approach is illustrated by a systematic and exhaustive screening of pericyclic reactions in order to find new reactions useful in the synthesis of conjugated dienes. Two reactions were found. They were optimized by structural variation with the aid of quantum-chemical calculations and were then experimentally verified.

MOST DISCOVERIES OF THE IMportant synthetic organic reactions have been serendipitous (*1*). For example, the Wittig reaction, H. C. Brown's hydroboration, and low-pressure polymerization of ethylene were not designed with the aim of synthesizing or functionalizing olefins or polymerizing ethylene but were discovered during experiments based on completely different ideas (*2*). In contrast to the case of synthesis planning (*3*), there are few general problem-solving strategies available to "invent" chemical reactions. Recently, a general methodology for the systematic search and design of organic reactions was reported. The task of finding the complete set of basic reaction schemes that comply with a given mechanism can be reduced to a graph-theoretical problem (*4*). A similar algorithm has been implemented in the program IGOR (*5*). The methods are used to thoroughly screen areas of organic chemistry for unprecedented reactions (*6*–*8*). The search, design, and experimental verification of two reactions aimed at the synthesis of conjugated dienes serve as an example.

Conjugated dienes are important in general organic synthesis and polymer chemistry. Because pericyclic reactions are usually stereoselective, this class of reactions was selected as the search area for new synthetic methods. Generation of the complete set of conceivable pericyclic reactions with three to six atoms, four to six electrons, and a maximum of one lone pair involved in the transition state yielded 44 basic reaction schemes (*8*), of which 5 are suitable for the synthesis of dienes: electrocyclic ring-

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opening of cyclobutenes, the chelotropic reaction, the retro Diels-Alder reaction, the 1,5-sigmatropic shift, and the concerted 1,4-elimination. Because these reactions are known and well investigated, the search was extended to the seven-center, eight-electron pericyclic reactions. In Fig. 1 the 72 basic reaction schemes of this category are listed. Of these reactions, 26 contain a 1,3-diene substructure and are preliminary candidates for a synthetic method. However, general access to dienes can only be expected from those reactions yielding an exact butadiene structure. Suitably substituted reactants would thus give correspondingly substituted dienes. Because octet structures of elements in the first period are more stable than sextet structures, only reactions in the given direction (sextet on reactant side and octet on product side, Fig. 1) were considered. This reduced the number of candidates to the three basic reaction schemes 8, 38, and 60 in Fig. 1. Reaction 60 is known with several examples (*9*), but reactions 8 and 38 are unprecedented, even as heteroanalogs. Because the reactions are generated exclusively on the basis of combinatorial fundamentals, chemical reasoning has to be introduced to "design" the proposed reactions before verification in the laboratory.

Reaction 8 was considered first for experimental verification. Carbenes are known to undergo 1,2-hydrogen shifts. To prevent this side reaction, we introduced heteroatoms at the two positions neighboring the carbene center. According to semiempirical quantum-chemical calculations (*10*) performed on the reaction coordinate of the dioxygen, dinitrogen, and disulfur heteroanalogs of reaction 8 (Fig. 2), the disulfur compound exhibited by far the lowest activation enthalpy for the anticipated fragmentation reaction and was therefore the most promising candidate for experimental verification. To obtain more reliable estimates of the reaction parameters of the disulfur system, we performed ab initio calculations (*11*). These calculations predicted the disulfur carbene **1** to have a boat conformation with a barrier for ring flipping of 12.3 kcal/mol. The transition state for the fragmentation process to form butadiene and carbon disulfide was predicted to lie only 3.3 kcal/mol above the transition state of the ring flipping process, and the heat of reaction was computed to be as large as 35 kcal/mol (*12*). Thus, side reactions were not expected, and because of the large exothermicity it was predicted that it would be possible to synthesize even strained or unstable dienes through this mechanism.

To prove the theoretical predictions, we prepared three different carbene precursors (Fig. 3). The tosylhydrazone **2** was synthesized by cyclization of 1,4-dichlorobut-2-ene with the *S,S'*-sodium-potassium salt of dithiocarbonic acid–tosylhydrazone, the diazo compound **3** was synthesized by careful pyrolyzation of the dry Na salt of compound **2**, and the trithiocarbonate **4** was synthesized from 1,4-dichloro-but-2-ene and potassium trithiocarbonate in dimethyl sulfoxide. Compound **2** was pyrolyzed under Bamford-Stevens conditions, compound **3** was photolyzed at room temperature, and compound **4** was desulfurized with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (PR_3) according to the Corey-Winter procedure (*13*). In each case, butadiene and carbon disulfide were formed in yields greater than 95% (Fig. 3) (*14–16*).

The predicted large heat of reaction and low barrier of activation and the high yields in the parent system suggested a more general applicability of our fragmentation reaction. Indeed, the reaction is not restricted to the parent system but can be applied to the synthesis of synthetically useful dienes, for example, *o*-quinodimethanes (which are important intermediates, for example, in steroid synthesis). Starting from the commercially available

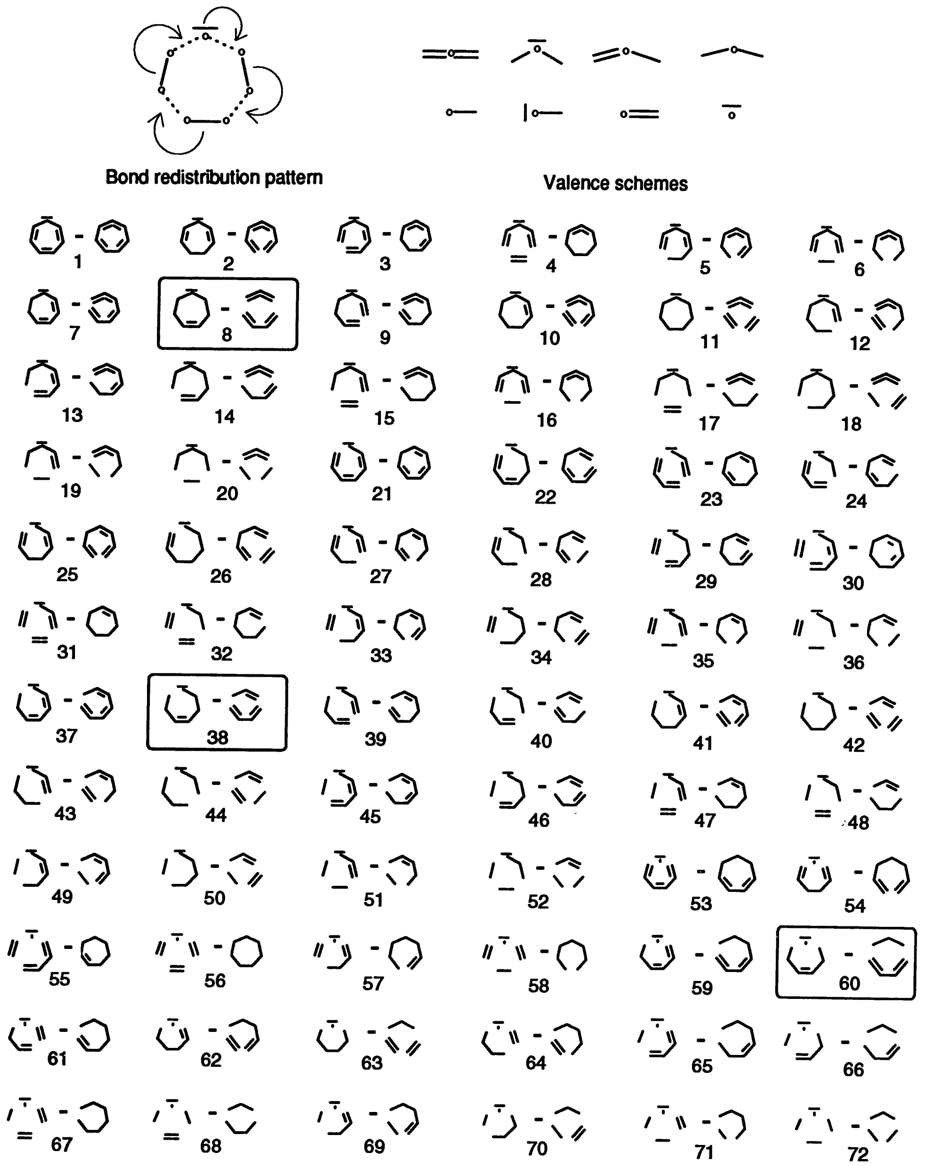


Fig. 1. Computer-generated basic reaction schemes of the seven-center, eight-electron pericyclic reactions. The set of 72 reactions is defined by the cyclic bond redistribution pattern and the valence schemes of the atoms involved in the reaction. The set of "allowed" valence schemes is indicated at top. Substituents and lone pairs that are not involved in the reaction are not shown. Hence, hetero variants of each reaction with any element combination, except variants with triple bonds, can be derived (if triple bonds are included, 470 basic reaction schemes are conceivable). Only a few of these reactions are known (such as reaction 21 as a nitrene reaction). Reactions 8, 38, and 60 are suitable for the synthesis of butadienes and were selected for further consideration.

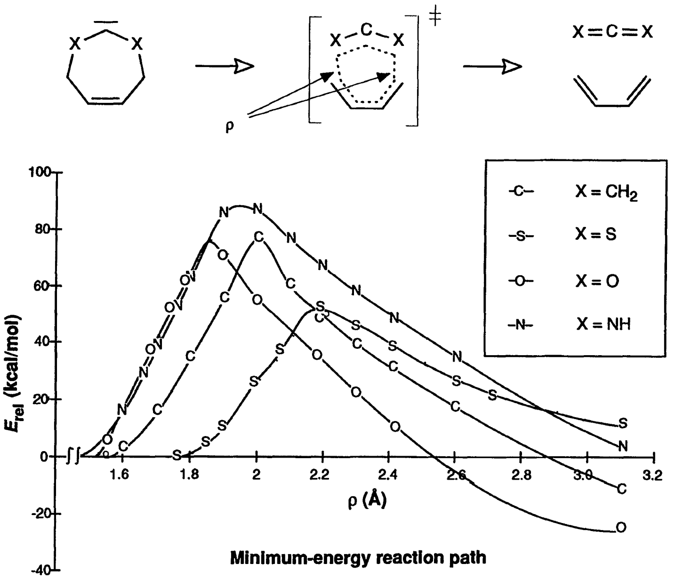
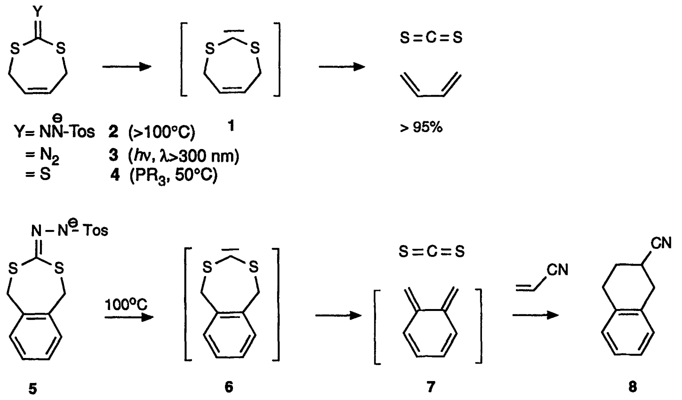
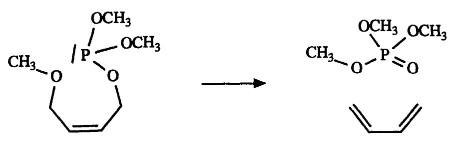


Fig. 2. Semiempirical quantum-chemical calculations on the reaction coordinate of hetero variants of reaction 8 (Fig. 1). The relative energy E_{rel} of four 1,3-hetero-substituted systems was calculated as a function of the C–X bond length ρ. The S compound exhibited by far the lowest barrier of activation.

Fig. 3. Experimental verification of reaction 8 (Figs. 1 and 2). Three different carbene precursors, 2, 3, and 4, were synthesized (Tos = tosylate). With suitable reaction conditions, they give butadiene and carbon disulfide in almost quantitative yields. Application of the reaction to the benzoanellated system shows that the method can be used to generate synthetically important dienes that are not readily accessible.



chemicals α,α′-dichloro-*o*-xylene, carbon disulfide, potassium hydroxide, and tosylhydrazide, we prepared the benzoannelated dithiepine **5** (Fig. 3) in a one-pot synthesis with 60% isolated yield. Pyrolysis of the Na salt of compound **5** gave *o*-quinodimethane **7**, which can be trapped by dienophiles such as acrylonitrile in yields of 85% (*17*). With reaction temperatures of 100°C, the simple preparation of the starting material, and the high yields, our fragmentation reaction is probably superior to alternative methods (*18*). Reaction 38 was "designed" in a way similar to reaction 8 and experimentally verified with a heteroanalog that contained P (*19*).



A large collection of powerful organic reactions are already known. However, there must still be numerous potentially useful reactions waiting to be discovered. Reaction planning has now provided a systematic approach to tracing those reactions that in the past escaped the chemist's notice. Because the algorithms generate the complete solution to the given problem, no reaction complying with the user-defined boundary conditions can be overlooked. Transition-metal chemistry, however, is more difficult to describe with these methods. Compared to other rational approaches in chemistry, such as molecular modeling or synthesis planning, reaction planning is still at an early stage, but the results described above hint at the potential of this new method for the discovery and optimization of useful reactions.

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9. For example, reduction of 1,4-dichloro-but-2-ene with Zn.
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11. Geometries were optimized on the self-consistent field (SCF) level with a split valence basis set augmented by polarization functions on S ($3\text{-}21G^{(*)}$ basis set). Stationary points on the energy hypersurface were characterized by harmonic frequency analysis as minima or transition states, and energies were calculated with the SCF geometries, including correlation corrections of the second-order perturbation theory (MP2) on a split valence basis set with polarization functions on C and S (3-21G* basis set). The calculations were performed on a CRAY Y-MP4/432 with the CADPAC program package: R. D. Amos and J. E. Rice, CADPAC: The Cambridge Analytic Derivatives Package, Issue 4.0, CRAY Version; Cambridge, 1987.
12. The ab initio calculations predict the disulfur carbene **1** to have a singlet ground state. The lowest triplet state (C_2 symmetry) lies 19.2 kcal/mol above the singlet ground state (C_s symmetry).
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14. On desulfurization of compound **4** the carbon disulfide is trapped by the excess of the base.
15. The 1,3-oxygen analog of compound **4** treated with various P bases did not give carbon dioxide and butadiene but polymers. This result is in agreement with the calculations (Fig. 2), which predict a much higher barrier of activation for the dioxygen system.
16. Trapping experiments, carried out to prove the intermediacy of a carbene, were unsuccessful. This result can be explained by the predicted low barrier of fragmentation and thus the short half-life of the carbene.
17. There is evidence for the intermediacy of carbene **6**. The carbene was trapped with acrylic *tert*-butyl ester, forming the corresponding cyclopropane. In the absence of trapping reagents and under conditions in which large stationary concentrations of the carbene are generated (large concentration of the carbene precursor and pyrolysis temperatures >120°C), the carbene dimerization product was formed with 15% yield.
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19. The reaction proceeds in the gas phase (flash thermolysis) at 0.4 torr and 350°C with 0.3-s contact time, gives a 40% yield of butadiene, and thus is probably less useful in synthesis than other methods.
20. This article is dedicated to G. A. Olah on the occasion of his 65th birthday. R.H. is grateful for his support. The work has been supported by the Deutsche Forschungsgemeinschaft.

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