

# Automatic discovery of chemical reactions using imposed activation

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## Abstract

Computational power and quantum chemical methods have improved immensely since computers were first applied to the study of reactivity, but the *de novo* prediction of chemical reactions has remained challenging. We show that complex reactions can be efficiently and autonomously predicted using chemical activation imposed by simple geometrical constraints. Our approach is demonstrated on realistic and challenging chemistry, such as a triple cyclization cascade involved in the total synthesis of a natural product and several oxidative addition reactions of complex drug-like molecules. Notably and in contrast with traditional hand-guided computational chemistry calculations, our method requires minimal human involvement and no prior knowledge of products or mechanisms. Imposed activation can be a transformational tool to screen for chemical reactivity and mechanisms as well as to study byproduct formation and decomposition.

## Main

Under typical conditions, chemical kinetics, with timescales of seconds to days, is at least fifteen orders of magnitude slower than the femtosecond timescales of quantum dynamics. Even the most facile reactions are vanishingly unlikely to occur spontaneously in large-scale, state-of-the-art computer simulations.<sup>1</sup> Consequently, the *de novo* prediction of chemical reactivity remains one of the most important challenges in computational chemistry.

Despite the unfavourable timescales, multiple methods have been developed to predict chemical reactions using dynamical simulations, potential energy surface exploration, and machine learning (ML). In dynamical approaches, time-dependent simulations are biased to increase the probability of rare events by artificial attractive interatomic forces<sup>2–5</sup> or by performing simulations under high-energy conditions.<sup>6,7</sup> Alternatively, reaction paths can be generated by “walking” the potential energy surface between products and reactants, probing only necessary dimensions of the full surface.<sup>8–10</sup> Machine learning

models can predict chemical reactions based on learned information from the literature and databases (e.g., patent filings).<sup>11–15</sup> Finally, heuristics approaches encode and formalize human-derived chemical transformation rules.<sup>16–18</sup>

Nevertheless, current techniques have significant drawbacks that curtail their general use. Standard computational chemistry techniques require fairly accurate initial guess structures to converge to reasonable transition states. Importantly, this necessitates knowledge of the reaction mechanism itself. Systematic and exhaustive reaction pathway searches are computationally costly,<sup>19</sup> and difficult to scale to larger molecules.<sup>20–22</sup> Heuristics approaches can map extensive reaction networks<sup>23</sup> but face issues when confronted with non-conventional bonding and organometallic complexes.<sup>16</sup>

Although these issues could, in principle, be solved using ML and data mining, the available data (e.g., from patent filings and publications) is heavily clustered around molecular families thought to be of economic or academic importance<sup>24</sup> and is skewed towards reactions commonly performed.<sup>13</sup> Data biases produce, for example, unnecessary sequences of protection and deprotection steps.<sup>14</sup> ML approaches trained on currently available data can be thought of as predicting the actions of chemists rather than the actions of molecules.

Herein, we describe a simple computational approach that automatically and robustly explores chemical reaction pathways from knowledge only of the reactants and their reactive bonds. Specifically, we show that these pathways can be obtained by conformational exploration with a chemically activating constraint. Reactions of sizable molecules are found rapidly with only modest computational resources using state-of-the-art semi-empirical methods.<sup>25</sup> We demonstrate this approach using three case studies: (1) an epoxide-initiated stereoselective polyene tricyclization cascade with many side products, (2) a solvent-mediated Michael addition with a proton shuttle involving multiple water molecules, and (3) the late-stage oxidative addition of ten drug-like molecules with electronically unsaturated palladium phosphine complexes.

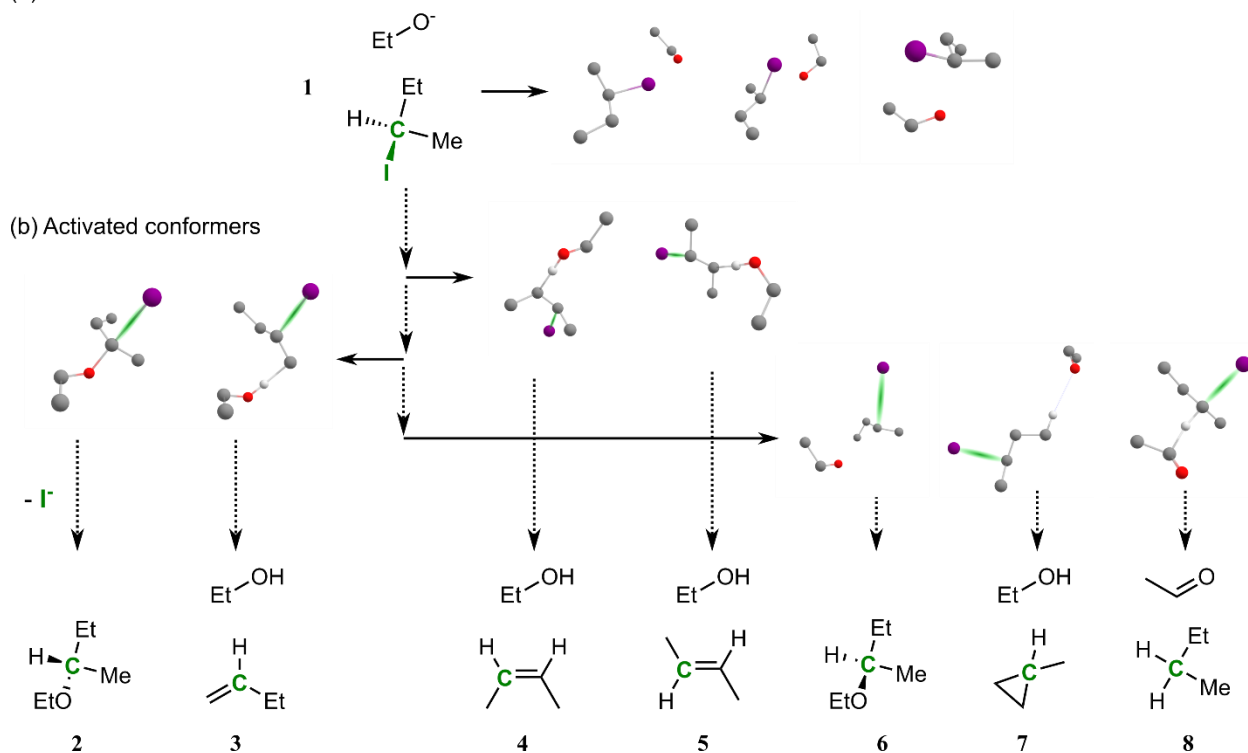
Transition state theory describes chemical reactions as primarily occurring through the transition state, the highest energy saddle point (a critical point of order 1) that lies on the reaction coordinate connecting reactants and products.<sup>26</sup> If the barrier to products is a mountain range, the transition state is the highest point on the most accessible pass through this range.<sup>27</sup> Transition states are not readily found without a suitable initial geometry. The high dimensionality of the coordinate space of even moderately sized molecules precludes any brute force search,<sup>28</sup> and characterizing transition states requires costly second-derivative calculations.<sup>29</sup>

Conformer generation,<sup>30</sup> the identification of local minima on the potential energy surface, suffers from the same dimensionality issues but is otherwise significantly simpler. Indeed, energy minimization always yields a local minimum, irrespective of starting structure, as a consequence of the variational principle.<sup>26</sup> Modern conformer generation methods can

rapidly and reliably find and identify many low-lying conformers starting from only a single reasonable chemical structure as input.<sup>31–35</sup>

Here, we find reaction pathways and products in a fully automated fashion. Conformer generation is performed while constraining a particular molecular coordinate to a value between the initial reactant structure and possible product structures. To continue with the mountain range analogy, this corresponds to a search for valleys, local energy minima in the constrained space amidst the range separating products from reactants. These valleys, found by conformational exploration, are possible reaction pathways. A subsequent relaxed scan of this constraint pushes the molecular coordinates along discovered pathways, walking the valleys to the products. Importantly, we note that neither approximate transition structures, nor the identity of reaction products, nor any training data are required in the search.

(a) Relaxed conformers



**Figure 1: Diagram of reaction search by conformer exploration with imposed activation.** (a) Conformer search methods generate stable three-dimensional molecular structures, such as those shown for complex **1**, composed of a molecule of *(R)*-2-iodobutane and an ethoxide anion. (b) Our reaction prediction methodology consists of constraining a specific activation coordinate to out-of-equilibrium values (vertical dotted arrows) and performing constrained searches for activated conformers (solid horizontal arrows). This is demonstrated here on **1**, using the carbon-iodine bond as activation coordinate (green). Further increasing the carbon-iodine distance of the activated conformers yield reaction pathways to multiple products (compounds **2–8**). Non-reacting hydrogen atoms are omitted.

For example, consider the various elimination and substitution reactions of *(R)*-2-iodobutane and ethoxide anion. Generating ground-state conformers for this system

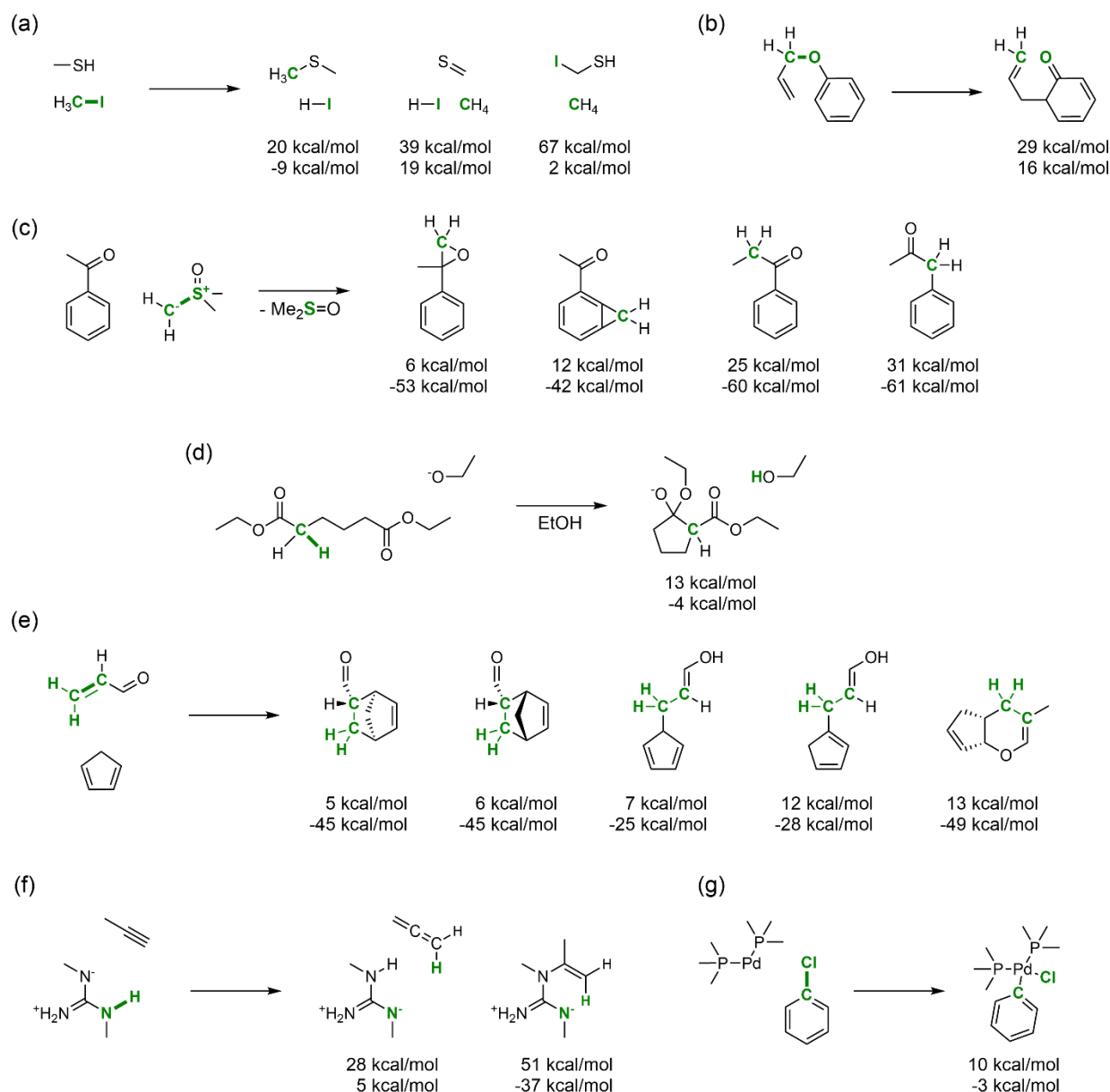
yields many loosely bound complexes (Figure 1a). Reaction prediction from these structures is challenging, as they are quite far from any transition states, such as those shown in Figure 1b.

The traditional approach to obtaining a transition state for a given reaction requires setting up the reacting molecules in a configuration close to the transition state, but this necessitates a fairly good assessment of the reaction mechanism and transition state geometry.<sup>36</sup> Coordinate driving and related approaches circumvent this issue by pulling together (in relaxed scans) pairs of atoms to induce new bonds to form.<sup>20,21,37</sup> For example, bringing together the ethoxide anion oxygen and the  $\alpha$ -carbon of 2-iodobutane produces the  $S_N2$  reaction. However, a fully systematic search of all possible bond-forming pairs scales quadratically with the number of atoms<sup>21</sup> and generally can only be performed for small systems.<sup>5</sup>

The cornerstone of our approach is to activate the reactants using a single coordinate that can produce many interesting reactions, thereby circumventing the scaling issues of searching for possible bond formation pairs systematically. In the case of the (*R*)-2-iodobutane molecule shown in Figure 1, bond dissociation energies dictate that the carbon-iodine bond is readily broken.<sup>38</sup> Stretching the carbon-iodine bond produces an activated electrophilic molecule. In this case, a conformer search yields geometries close to the  $S_N2$  transition state, as the ethoxide oxygen stabilizes the complex when it lies close to the halogenated carbon. A relaxed scan along the carbon-iodine distance starting from one of these transition structures results in the  $S_N2$  products (**2** in Figure 1).

Notably, other activated conformers corresponding to different reactions are found. Indeed, solely stretching the carbon-iodine bond of other activated structures also yields E2 and E1 elimination reactions (with Hofmann<sup>39</sup> product **3** and Zaitsev<sup>40</sup> products **4** and **5**),  $S_N1$  substitution reactions (with products **2** and **6**),  $\gamma$ -elimination to methylcyclopropane **7** as well as a curious alkoxide hydride transfer<sup>41</sup> forming **8**. The latter two reactions, which have significantly higher estimated activation energies, are unlikely to occur in this system but demonstrate the complex chemistry that can be obtained automatically from imposed activation by a single constrained coordinate.

Reactions from coordinate scans are highly dependent on starting geometries, especially when the scanned coordinate is not bond-forming. Indeed, for an iodine-carbon bond scan to alone generate a pathway to compound **7** by  $\gamma$ -elimination requires the ethoxide to be placed in very close proximity to the eliminated hydrogen. The diversity of products and paths discovered by the imposed activation approach comes at a cost: initial guess structures need to be relatively close to reactive pathways. Crucially, constrained conformer generation can produce these higher-energy, activated structures,<sup>31,42</sup> and is critical to making our approach practical.



**Figure 2: Selected set of diverse chemical reactions obtained by imposed activation.** Representative products are shown in each case, annotated with estimated activation energy (top) and reaction energy (bottom) calculated at the semi-empirical GFN2-xTB level.<sup>25</sup> All results are obtained directly from the automated search without additional refinement. Activated bonds and constituent atoms are shown in green. In (e), an improper dihedral angle is activated instead of a bond length. Details of each reaction are in the text.

## Results and Discussion

Initial tests were performed using the small but chemically diverse set of simple reactions depicted in Figure 2. All these reactions are adequately captured without any reaction-

specific tuning. The relatively small size of the molecules involved allows this entire set of reactions to be run on a single compute node in less than 5 hours.

The S<sub>N</sub>2 reaction of methanethiol and iodomethane (Figure 2a) is readily obtained by stretching the carbon-iodine bond. Some high-energy side products include thioformaldehyde formation (by transfer hydrogenolysis) and iodomethanethiol (by a stepwise  $\sigma$ -bond metathesis). The aromatic Claisen<sup>43</sup> rearrangement (Figure 2b) is found as the sole product of stretching the allyl ether bond. Energies of the two expected transition structures, six-membered rings with chair and boat conformations, respectively, are well reproduced.<sup>44</sup>

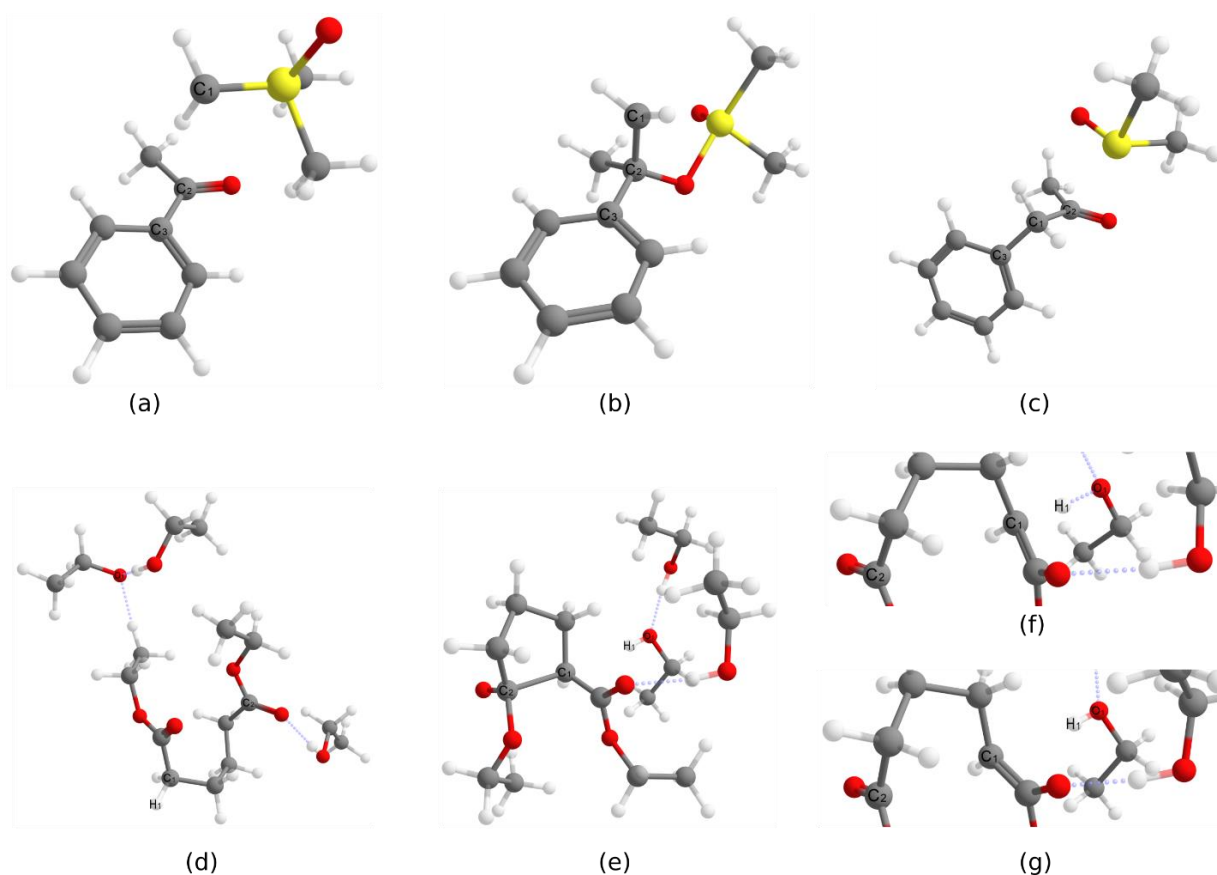
In Figure 2c, the Johnson-Corey-Chaikovsky reaction<sup>45</sup> is obtained from stretching the methylene-sulfur bond on the ylide. The expected epoxide has by far the lowest estimated activation energy. Interesting side products include addition to the aromatic ring as well as homologations by methylene insertion into a C–H bond and by insertion into the aryl-carbon bond. This last reaction has been reported previously for benzophenones<sup>46</sup>, with a hypothesized mechanism matching the one found here. The stretching of the sulfur-methylide (C<sub>1</sub> in Figure 3a) bond yields the reactive intermediate shown in Figure 3b. Insertion of C<sub>1</sub> between carbons marked C<sub>2</sub> and C<sub>3</sub> occurs through a four-membered cyclic transition state, displacing the sulfoxide and forming the homologation product (Figure 3c).

The Dieckmann condensation<sup>47</sup> in Figure 2d is found readily upon dissociation of a carbon-hydrogen bond in the presence of an ethoxide molecule. The reactants (an ester, an ethoxide molecule and two molecules of ethanol) are initially arranged without regard to the expected transition structure. The assembly is optimized to obtain the initial conformer in Figure 3d. The explicit solvent is required here to stabilize the ethoxide. The reaction search finds the Dieckmann condensation product in Figure 3e, with the standard<sup>48</sup> two-step mechanism of formation of an enolate ion followed by a nucleophilic attack. Approximate transition structures are shown in Figure 3f-g. It should be noted that the initial input structure is highly dissimilar to both the structures of the transition states and the products, illustrating that our method allows handling explicit solvent molecules without prior spatial placement by the user.

For the Diels-Alder reaction, activation can be imposed in two ways: by stretching the dienophile double bond to the length of a single bond or by pyramidalizing one of the dienophile carbons through an improper dihedral constraint applied to the two ene carbons and terminal hydrogen atoms. Both approaches yield the same products, with the pyramidalization resulting in significantly better transition structures and energies due to the asymmetric dienophile and resulting asynchronous transition state<sup>49</sup>. The results for this reaction are shown in Figure 2e with the atoms of the dihedral constraint marked in green. Notably, both the endo- and the exo-products are obtained, though the activation energy is approximated too poorly to reproduce experimental selectivities. Observed side reactions include Michael additions as well as an inverse electron-demand Diels-Alder

reaction, with the acrolein acting as the diene and the cyclopentadiene acting as the dienophile.

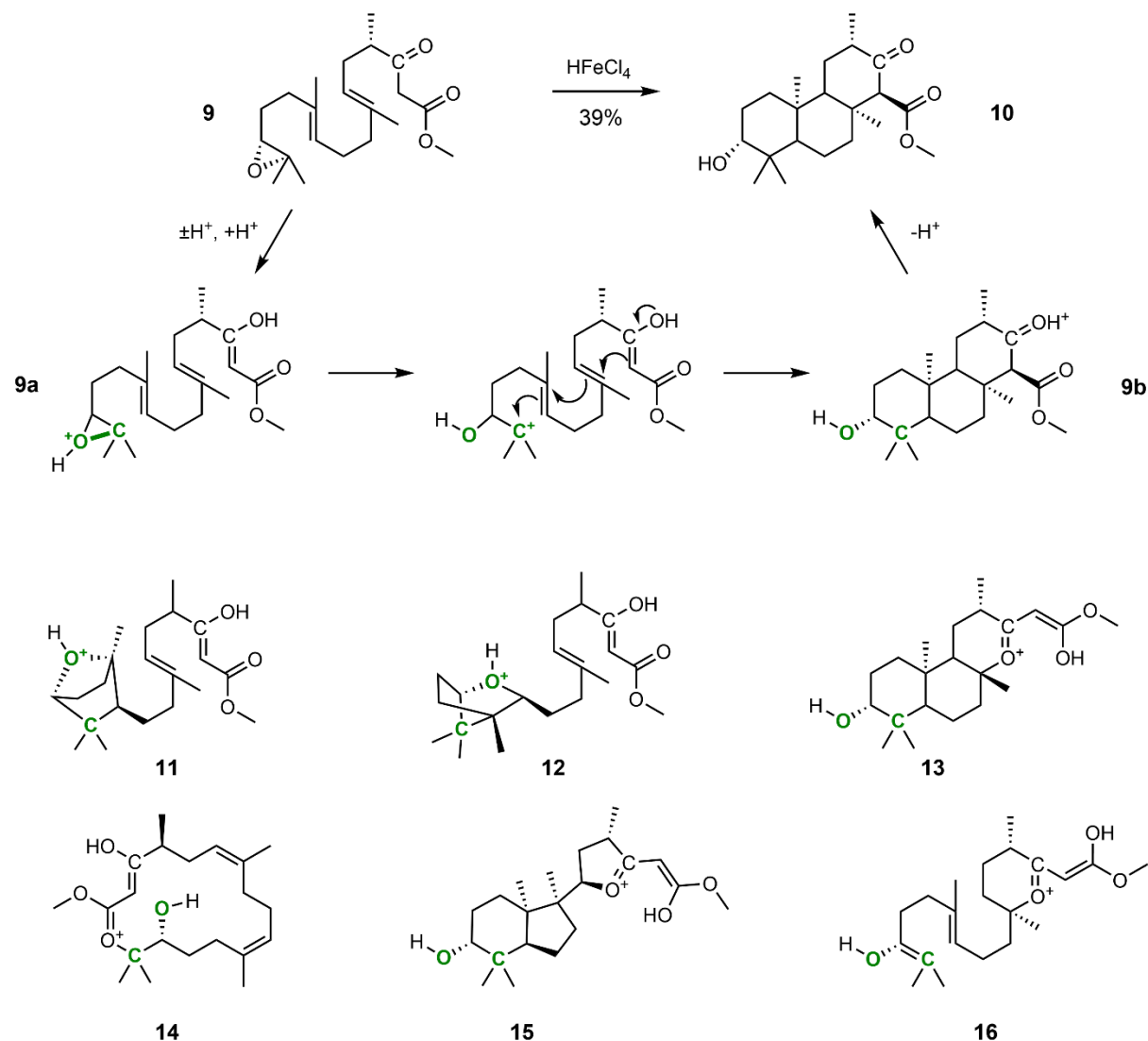
The final two examples are taken from catalysis and organometallic chemistry, respectively: a base-catalysed alkyne-allene isomerization and an oxidative addition of palladium bisphosphine into a carbon-chlorine bond (Figure 2f and g). In the first case, the N-H bond on the catalyst is stretched to obtain the isomerization, and the reaction pathway and transition structure are near identical to those obtained by traditional means.<sup>50</sup> The oxidative addition of Pd in Figure 2g is readily found by increasing the Ph-Cl bond distance, showing that imposed activation can be applied to organometallic reactions using extended density-functional tight-binding theory.<sup>51</sup>



**Figure 3: Detailed structures for Johnson-Corey-Chaikovsky methylene insertion and Dieckmann condensation reactions.** (a-c) Reactants (a), reactive intermediate (b), and product structures (c) obtained for the homologation reaction by methylene insertion in Figure 2c. (d-g) Input structure (d) and products (e) for the Dieckmann condensation in Figure 2d and transition structures of the two steps, formation of an enolate (f) and nucleophilic attack (g), as obtained from a single relaxed scan.

## Cyclization Cascade in the Synthesis of a Natural Product

A robust and automated reaction prediction approach can help to understand and rationalize complicated reactions with multiple outcomes. This is demonstrated here using the epoxide-initiated polycyclization of **9** to form **10** (Figure 4), an essential step in a short total synthesis of the fungal meroterpenoid berkeleyone A.<sup>52</sup>



**Figure 4 : Reaction mechanism and obtained side-products for an epoxide-initiated  $\beta$ -keto ester-terminated triple cyclization reaction.** The polycyclization yielding **10** from **9** is an essential step in the total synthesis of berkeleyone A presented in ref. 52. Here, a reaction search is performed starting from **9a** (details in the text), the protonated enol form of **9**, using the epoxide C-O bond of the tertiary carbon (green) as the reactive coordinate. Compounds **11** to **16** are side-products obtained in computations.

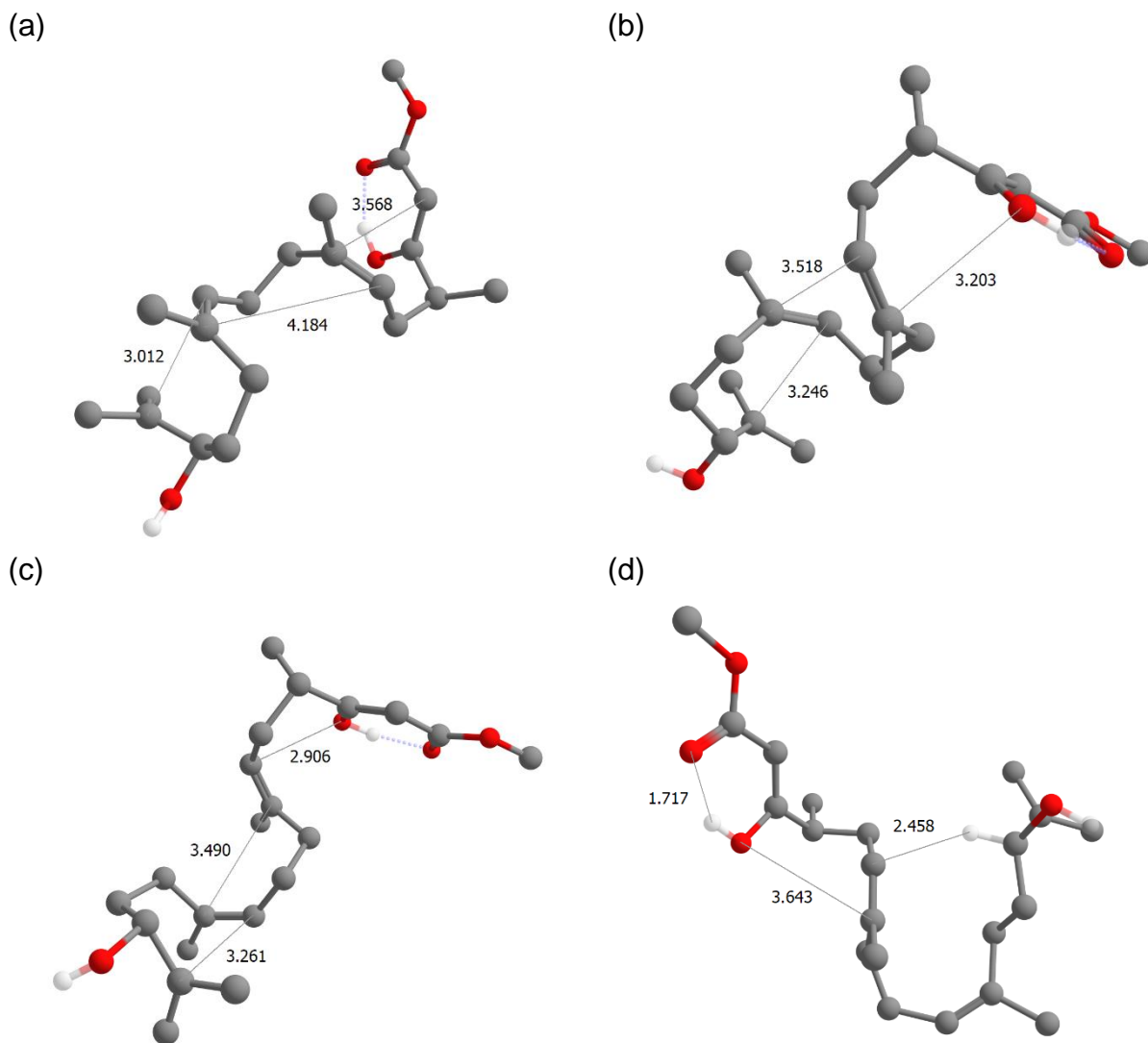
This triple cyclization was chosen as it is a complex reaction, with the potential to form many byproducts.<sup>53–56</sup> Indeed, the 39% yield reported in ref. 52 was only achieved after extensive optimization of reaction conditions. Previous attempts at similar reactions



yielded a range of mono- and polycyclic, fused and bridged products from ether formation by the epoxide and cyclization at the  $\beta$ -keto ester oxygen instead of the desired carbon cyclization.<sup>57</sup> Here, we initiate the computation from **9a**, the reactive enol form of **9** protonated at the epoxide. Compound **9a** is activated by opening the epoxide on the tertiary carbon side using the carbon-oxygen distance as the constraint (highlighted in green in Figure 4). More than 200 distinct reaction pathways are discovered, including many tautomerizations and high energy processes as well as all experimentally reported modes of action.

A subset of thermodynamically favourable products with estimated activation energies below 35 kcal/mol is shown in Figure 4. Notably, **9b** is discovered by the reaction search from an epoxide-initiated triple cyclization cascade terminating at the  $\beta$ -keto ester and forming the desired product **10** by deprotonation. The approximate transition state for this reaction is shown in Figure 5a, with the three bond-forming atoms highlighted. The cyclization cascade is barrier-free after this transition structure. **11** and **12** result from 1,2-addition of the epoxide to the nearest alkene, forming bridged bicyclic ethers.<sup>53</sup> Triple cyclization terminating at the  $\beta$ -keto ester oxygen forms **13**, a major experimental byproduct,<sup>57</sup> by a mechanism that differs from that forming **9b** only in the terminating atom (Figure 5b). The nucleophilic opening of the epoxide by the same oxygen yields **14**, a 16-membered ring. Product **15** is obtained when the second step of the triple cyclization cascade is a five-membered, not six-membered, ring closure, as shown in Figure 5c. Finally, the surprising product **16** is formed from the transfer of a proton from the epoxide (which forms an enol<sup>54</sup>) to the far alkene followed by an oxygen cyclization, as shown in Figure 5d.

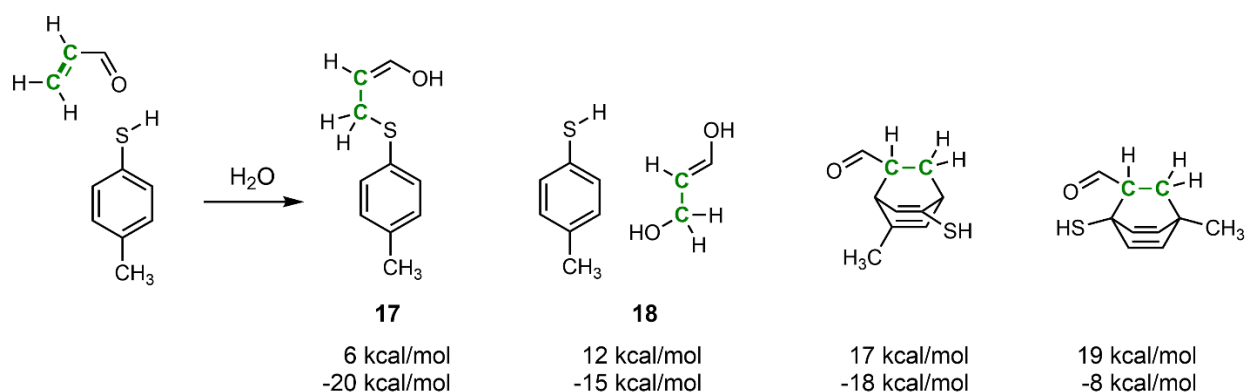
The short duration and easy initialization of our computational experiments compensate for their unsystematic nature. All the above reactions were obtained from a single calculation targeting compound **9a**, which took only 6.3 hours on a single compute node. In this case, we note that success followed a failed search initiated from the less reactive keto form of **9a**. Similarly, computations starting from a tautomer of **9a** with protonation of the ester carbonyl instead of the ketone uncovers significantly fewer reactions and, specifically, fails to yield **9b**. In practice, the problem of sensitivity to the initial molecular identity is solved by iteratively trying new tautomeric structures, an approach enabled by the fast turnaround times of these calculations, and the ease of generating tautomers of a given structure using basic chemical rules.



**Figure 5: Selected transition structures forming triple cyclization products.** (a-d) Transition state guesses for the formation of **9b** (a), **13** (b), **15** (c) and **16** (d). Bond-forming atoms are connected by thin lines annotated with their interatomic distances. Non-reacting hydrogen atoms are omitted.

### Water-Mediated Michael Addition

Automated reaction search is specifically useful when the reacting system consists of multiple loosely bound fragments with many possible arrangements. This is the case, for example, in solvent-mediated reactions, where specific solvation geometries play a major role in transition structures.<sup>58</sup> Setting up traditional transition state calculations for such systems is very time-consuming and error-prone, as it requires carefully arranging fragments in different reactive geometries.<sup>59</sup>



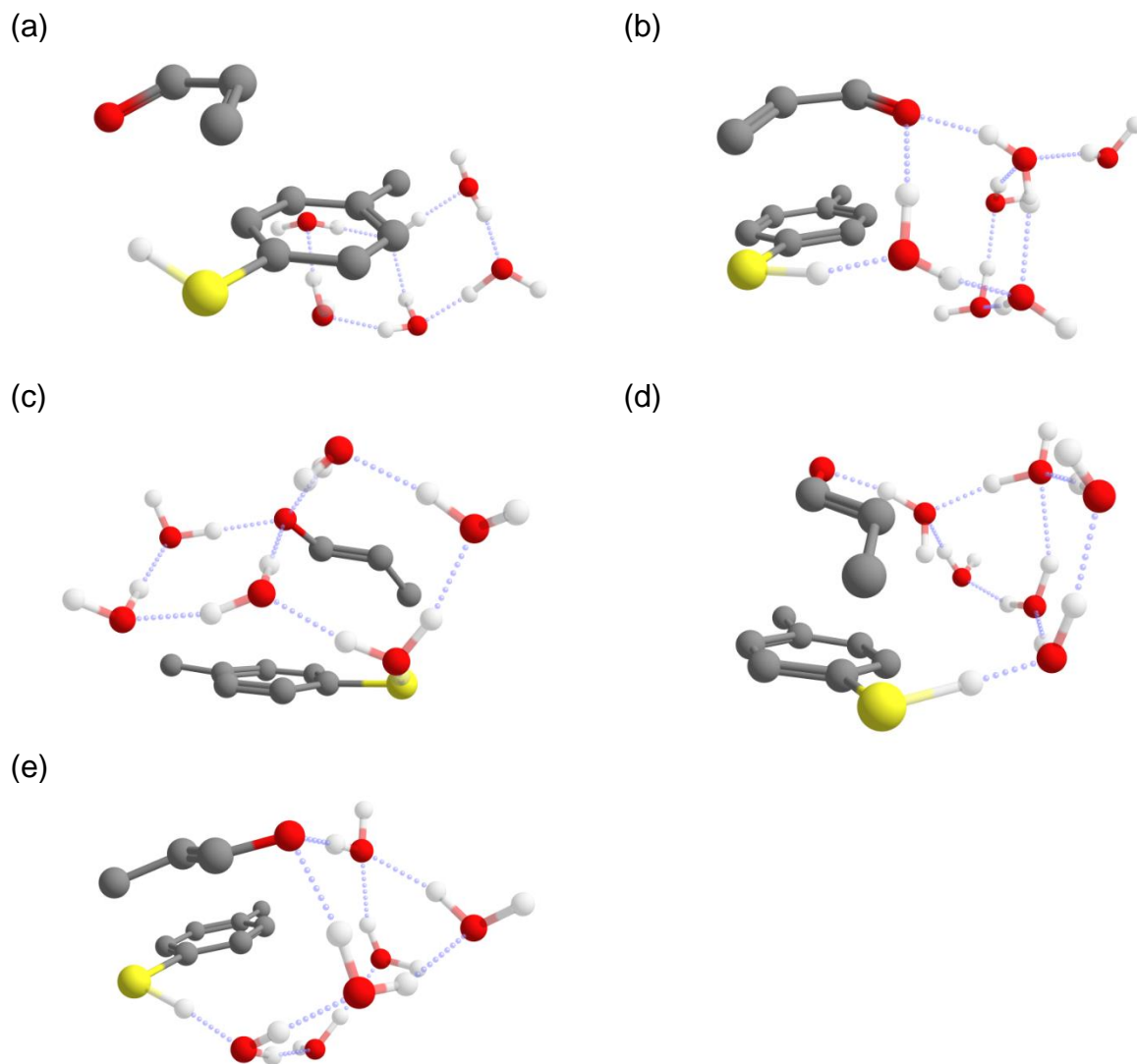
**Figure 6: Water-catalyzed 1,4-addition reaction and some important side-products obtained by imposed activation.** Reactions were obtained by stretching the carbon-carbon double bond of an acrolein molecule (shown in green) in the presence of *p*-toluenethiol and six explicit water molecules. Products are annotated with semi-empirically estimated activation energy (top) and reaction energy (bottom).

**Table 1.** The 176 reaction trajectories yielding **17**, decomposed based on transition structure characteristics. For each entry, the estimated activation energies in kcal/mol (bold, <12 kcal/mol) and the number of occurrences are provided.

Acrolein isomer	TS conformation	Number of H <sub>2</sub> O molecules in H <sup>+</sup> transfer chain				
		0	1	2	3	4
<i>s-cis</i>	compact	21.2   6	<b>8.7   20</b>	<b>11.2   8</b>	—	—
	expanded	—	15.6   17	13.6   5	17.1   1	—
<i>s-trans</i>	compact	—	27.4   1	<b>5.8   49</b>	<b>8.5   14</b>	20.6   1
	expanded	—	23.3   4	<b>9.8   41</b>	17.1   11	16.6   1

Estimated  $\Delta E^\ddagger$  (kcal/mol) | no. of occurrences

Here, results are presented from an automated reaction search performed on the water-mediated Michael addition of acrolein to *p*-methylthiophenol, shown in Figure 6, an example inspired by a recent popular science article.<sup>60</sup> Six explicit water molecules are added to the reacting system. The addition reaction forming **17** is obtained as both the thermodynamic product and the kinetic product upon stretching the carbon-carbon double bond of the acrolein. Byproducts include hydration of acrolein to 3-hydroxypropanal (**18**), a biologically important process,<sup>61</sup> and various Diels-Alder reactions between acrolein and *p*-methylthiophenol.



**Figure 7: Some representative transition structures of the addition reaction forming **17**.** (a-d) Transition geometries include (a) a direct proton transfer and proton transfer shuttled by (b) one, (c) two, and (d) four water molecules. (a-b) are *s-cis* and (c-d) are *s-trans*, compact conformations. (e) An expanded, *s-trans* conformation with two-water-molecule shuttling.

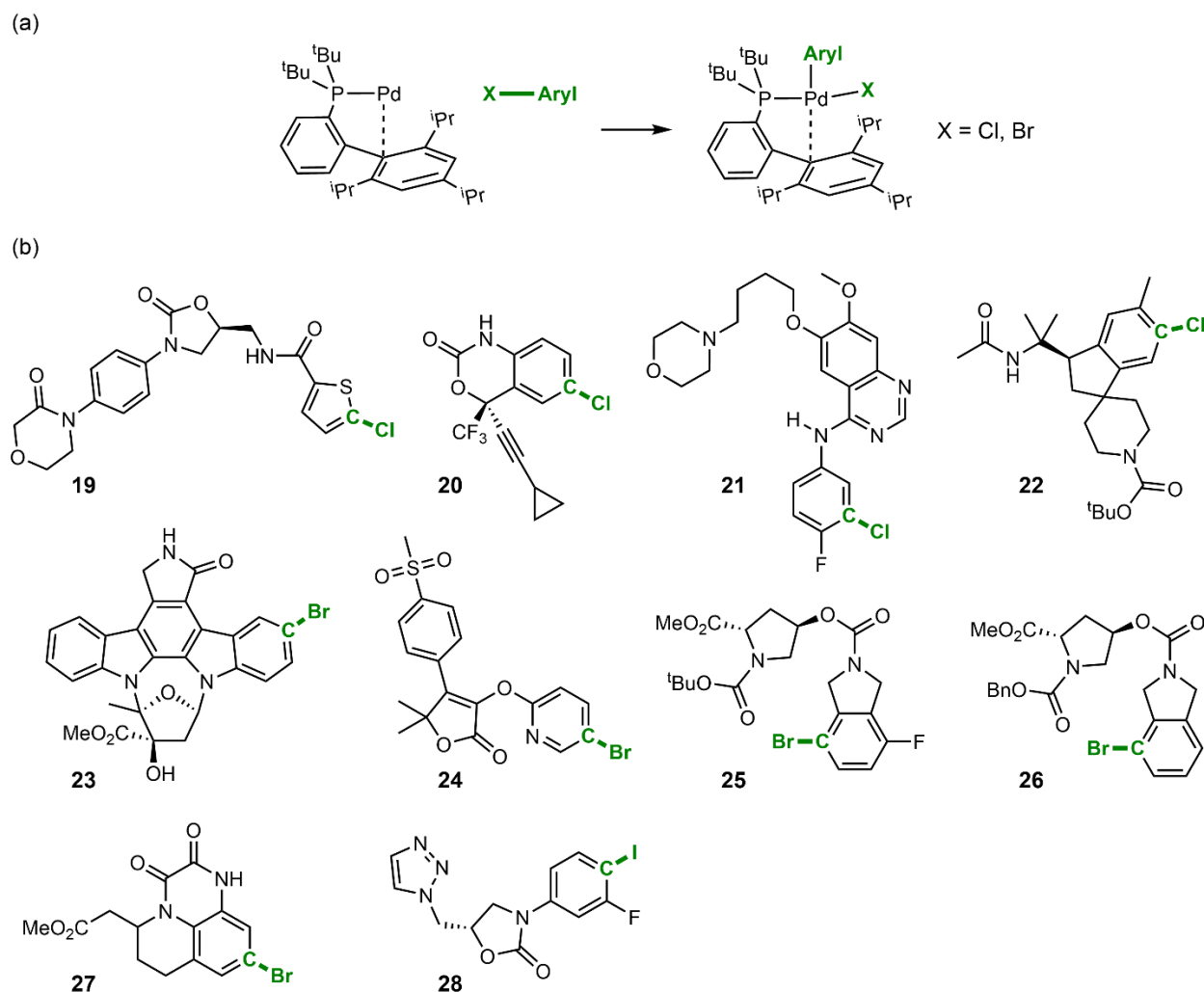
The Michael addition involves the transfer of a proton from the thiol to the carbonyl group of acrolein, which is facilitated by a chain of hydrogen-bonded water molecules. Acrolein has *s-cis* and *s-trans* isomers, and the transition state for this reaction has the acrolein double bond either lying along the aromatic ring (the compact conformation) or away from it (the expanded conformation). Amongst the possible combinations of isomers, conformers, and number of chained water molecules, our reaction search method identifies, in a single run, fourteen different pathways and distinct transition structures (**Table 1**), five of which are kinetically favoured over the formation of **18**.

The uncatalyzed reaction only occurs for the *s-cis* isomer, as it requires the carbonyl and thiol to be in proximity (Figure 7a). The larger distance required for the proton transfer in the *trans* isomer favours proton shuttling by two or three water molecules. In contrast, addition of the *cis* isomer is efficiently mediated by one water molecule (Figure 7b). The lowest activation energy is obtained for the *trans* isomer facilitated by two water molecules in the compact conformation (Figure 7c). The longest identified water chain comprises four water molecules (Figure 7d) with a total of five distinct proton transfers. In the expanded conformation, only *trans*-acrolein with a two-water molecule bridge is favourable (Figure 7e).

A significant saving in human labour is achieved using the automated search, at the cost of moderate computational resources. Indeed, obtaining sufficient sampling of all these transition structures took only 20 hours of wall-clock time on a mid-range workstation. This calculation required minimal human involvement as the search is entirely automatic, even starting from a structure far from the identified reactive pathways. By contrast, the human labour needed to set up any one of those 14 transition state searches using traditional means is on the order of hours.

### **Oxidative Addition Complexes of Drug-Like Compounds**

In addition to the exploration of chemical pathways, our reaction search methodology can also minimize the effort of setting up transition state calculations. We demonstrate this application here using calculations on the oxidative addition of a palladium catalyst to a set of drug-like molecules.<sup>62</sup> Forming oxidative addition complexes in this way provides a potentially powerful means of late-stage diversification in screening studies and avoids the still-inconsistent performance of catalytic Buchwald-Hartwig couplings of highly functionalized substrates.

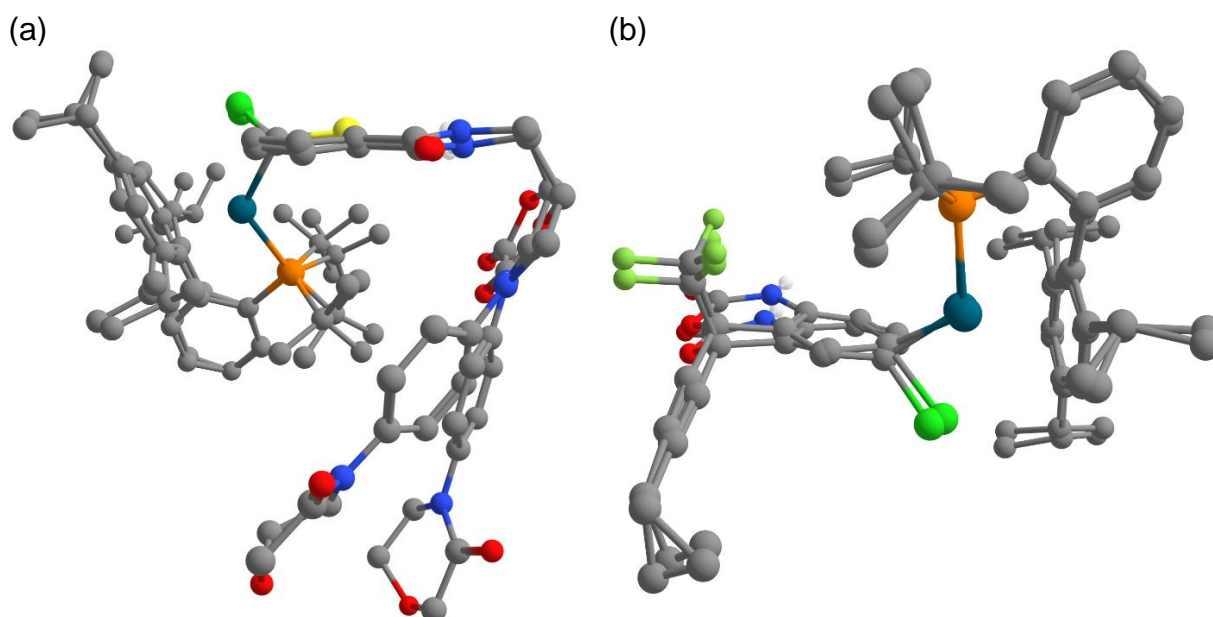


**Figure 8: Formation of oxidative addition complexes of drug-like substrates.** (a) The reaction studied here is the formation of complexes with  $t\text{BuXPhosPd}$  by oxidative addition. The aryl-halide distance is the activation coordinate (green). (b) Imposed activation reaction search is performed for the ten drug-like, functionalized molecules **19–28**.

Computational studies of organometallic catalysis generally include either complex ligands or complex substrates, but very rarely both, due to the required computational resources. Such studies are specifically challenging when including designer catalysts such as  $t\text{BuXPhosPd}$  (studied here and shown in Figure 8a) and functionalized ligands, due to the many possible coordination modes around the metal catalyst.<sup>63</sup>

Here, we present transition state calculations enabled by our methodology for ten reactions exhibiting both catalyst and substrate complexity. Because the aims of this section differ from those of the previous two (*i.e.*, finding transition states for a predetermined reaction as opposed to searching for new reactions), the calculations were set up slightly differently. In these computations, the activated catalyst was initially placed (programmatically) such that the Pd atom is ~5 angstroms away from the target halide;

the halide-aryl bond is the reactive coordinate. Imposed activation reaction search was performed on this structure and the most accessible reaction pathway was selected. Finally, the lowest-energy reactant and product structures were re-optimized at a higher level of theory. Transition states were obtained by relaxing the automatically obtained approximate transition structures using DFT with the aryl-halide bond constrained, followed by a subsequent systematic transition state optimization. Qualitative features of the transition state are well-reproduced by imposed activation using extended density-functional tight-binding as shown in Figure 9.



**Figure 9: Superimposed approximate transition structures from imposed activation and DFT-optimized transition state.** (a-b) Structures are shown for compound (a) **19** and (b) **20**. The semi-empirical transition structures are obtained directly from an activation scan, without additional computational refinements.

The corresponding results are shown in Table 2. The data show two general trends. First, as expected, activation energies tend to decrease when changing the halogen from chlorine to bromine to iodine.<sup>64,65</sup> Secondly, electron-rich (hetero)aromatic rings seem to lead to more facile oxidative addition. This is in contrast to the expected trends for bisligated palladium(0) catalysts but in line with the results obtained for monoligated palladium(0), as the pre-reactive complexes of monoligated palladium(0) and aryl halide tend to be more tightly bound for electron-poor (hetero)aromatic rings.<sup>65,66</sup> Furthermore, oxidative addition products with electron-poor (hetero)aromatic rings tend to be more thermodynamically favourable, as previously demonstrated.<sup>66,67</sup> Moreover, all the estimated oxidative addition barriers are consistent with facile room temperature reactions, as observed in the original study.<sup>62</sup> Looking at the contributions of London dispersion to the reaction energies, we find that larger Gibbs free energies of activation

correlate with more repulsive dispersion contributions. This indicates that attractive interactions are lost during the oxidative addition, causing an overall higher barrier, and suggests that proper alignment of noncovalent interactions in the transition states is important in accelerating these reactions.<sup>68,69</sup>

**Table 2.** Summary of reaction searches and DFT calculations for the oxidative additions shown in Figure 8. The first four columns provide the substrate, the total number of atoms in the system, the reacting halide and the reacting aromatic system on the substrate. Gibbs free energies of activation  $\Delta G^\ddagger$  and Gibbs free energies of reaction  $\Delta G$  are obtained from PBE-D3/def2-SVP calculations. The last two columns compare the times required (in hours) for the reaction search and DFT optimizations of product, reactant, and transition state geometries.

Substrate	$N_{\text{atoms}}$	Halogen	Core aryl group	Reaction energies (kcal/mol)		Compute time (node hours)	
				$\Delta G^\ddagger$	$\Delta G$	Reaction search	DFT Optimizations
<b>19</b>	123	Cl	Thiophene	13.5	-12.2	10.6	4.5
<b>20</b>	106	Cl	Benzoxazinone	8.9	-16.7	4.8	5.1
<b>21</b>	131	Cl	Benzene	16.0	-6.7	10.3	3.7
<b>22</b>	141	Cl	Indane	4.4	-15.8	10.5	4.5
<b>23</b>	132	Br	Indole	1.1	-18.1	8.7	4.1
<b>24</b>	118	Br	Pyridine	12.2	-12.1	7.6	3.9
<b>25</b>	130	Br	Isoindoline	7.6	-9.6	9.6	4.1
<b>26</b>	131	Br	Isoindoline	8.0	-5.6	10.7	4.6
<b>27</b>	110	Br	Quinoxalinedione	4.7	-16.2	5.2	6.1
<b>28</b>	106	I	Benzene	6.0	-2.1	4.9	4.3

## Conclusions

Automatic simulations of chemical reactions could significantly accelerate the search for novel catalysts, automatically flag detrimental reaction pathways (e.g., solvolysis or formation of side products), and help discover new reaction mechanisms. However, chemical reactions are extremely rare events not spontaneously captured by *in silico* dynamics. The complexity of all but the smallest molecules limits full, systematic searches of all possible bonding patterns and bonding transformations.

We showed that conformer searches with constraints can identify chemical pathways and provide approximate transition state structures using modest computational resources. Leveraging some human-derived heuristics, that is, the selection of one chemical bond to undergo reaction, allows us to bypass the quadratic scaling of possible bond-forming processes encountered by more systematic approaches<sup>4,20,21</sup> while still maintaining sufficient chemical freedom to discover new reaction products and mechanisms. In essence, imposed activation is analogous to starting a curly arrow mechanism by breaking one bond, then computationally completing the mechanism by systematically finding the most energetically feasible responses. Importantly, imposed activation search is sufficiently low-cost to be deployed in an exploratory fashion for medium- to high-throughput virtual screening, predicting and studying the mechanisms behind byproduct



formation or catalyst decomposition, and exploring the role of explicit solvation in chemical reactions.

Although the semi-empirical calculations used here are appropriate for qualitative discovery, they are not accurate enough for quantitative analysis.<sup>42</sup> However, most of the time required by a computation is currently spent performing uncorrelated relaxed scans of activated conformers, an embarrassingly parallel task. Hence, these scans can be performed on distributed systems, which would compensate for the computational power required by higher levels of theory.<sup>70</sup> Efforts are ongoing in this direction. Additionally, we are currently investigating the use of machine learning methods (such as Gaussian process regression<sup>29,71,72</sup>) to systematically and robustly refine the transition state guesses obtained using semi-empirical calculations at higher levels of theory.

Investigations are also underway to improve systematicity by, for example, automating the selection of activation coordinates using chemical and computational means. This kind of automation could enable the study of complex chemical reaction networks<sup>16,73</sup> by applying imposed activation computations recursively over obtained products.<sup>23</sup> Finally, the inclusion of automated (de)protonation and tautomerization capabilities<sup>74,75</sup> could increase the range of chemistry that can be studied systematically.

## Methods

The results presented in this paper were obtained using the xTB package<sup>76,77</sup> and a custom interfacing and data analysis code. Additional results for the Buchwald-Hartwig coupling reactions were computed using ORCA,<sup>78</sup> as described below. Timing data is reported for a single dual-socket compute node with two 20-core, 2.4 GHz Intel Skylake processors.

## Algorithm

The reaction search consists of the four steps below, followed by post-processing of obtained reaction trajectories.

1. The initial structure of the reactants is optimized, and the user selects a reactive coordinate  $q$  (*i.e.*, an interatomic distance, a bending angle, or a torsional angle). With the reactive coordinate fixed at its equilibrium value  $q_0$ , an initial conformer search is performed to obtain a diverse set of structures. A relaxed scan of the reactive coordinate follows, starting with one of the initially generated conformers, to an intermediate value between that of reactants and products  $q_i$ .
2. A second, shorter and less exhaustive conformer search is undertaken with the reactive coordinate constrained at  $q_i$  to explore the local energy landscape.
3. All the structures thereby generated are scanned from  $q = q_i$  to  $q_N$  to obtain new reaction products. A backward scan from  $q_i$  to  $q_0$  yields a complete trajectory back to a reactant conformation.

4. Finally, structures corresponding to energy minima of the trajectory (potential reactants and products conformations) are optimized without constraints to ensure stability.

Steps 2 to 4 above are then repeated for different values of  $q_i$  to obtain an ensemble of reactive trajectories sampled from multiple transition structures.

For generating conformers, the metadynamics module integrated in xTB is used with parameters based on those of the highly reliable algorithm of Grimme et al.<sup>31</sup> In effect, molecular dynamics are performed with regular snapshots, and these simulations are augmented with a biasing potential  $V_{\text{bias}} = \sum_i k \exp(-\alpha \Delta_i^2)$  where  $\Delta_i$  is the root-mean-square displacement (RMSD) between the current structure and the  $i$ -th previous snapshot, and  $k$  and  $\alpha$  are numerical parameters. The biasing potential strongly drives the discovery of new structures. The obtained structures are then optimized, with similar structures being removed based on RMSD, rotational constant and energy thresholds.<sup>31</sup> Finally, structures exceeding a maximum energy threshold are discarded.

In the examples presented, the overall number of sampled trajectories varies between 100 (Figure 2b) and 10,000 (e.g., to obtain the results of **Table 1**), depending on the number of atoms and the chosen sampling parameters. The duration of metadynamics simulations, and thus the number of trajectories, is generally proportional to the size of the system. A more thorough sampling is chosen for the 1,4-addition to obtain a wide range of reactive geometries.

The trajectories are collected and parsed into reactions by transforming geometries of trajectory minima to canonical SMILES using Open Babel<sup>79</sup> and identifying changes in the SMILES strings. For structures containing a metal complex, the metal atom is removed before conversion to eliminate spurious bond changes. The transition structure of a trajectory is taken to be the highest energy structure between reactants and products. The guess transition state for a given reaction is the lowest energy transition structure amongst all trajectories for this reaction, and the estimated activation energy (as reported in, for example, Figure 2) is computed by subtracting the energy of the most stable identified reactant conformer from the energy of the approximate transition state.

### Refinement of Trajectories for Oxidative Addition Complexes

Additional refinement of reaction trajectories was performed for the results shown in Table 2. The specific protocol described here broadly follows that of the computational study by Barder et al. involving a similar catalyst.<sup>80</sup> We note that our study involves more substrates and that those substrates are more complex. DFT calculations were performed at the PBE-D3/def2-SVP level of theory.

Approximate transition structures obtained from the reaction search were used to find transition states with Berny optimization at the semi-empirical level of theory employed in the search (GFN2-xTB). Here, performance is excellent, with every guess transition structure converging to a transition state. At this point, further transition state refinements

were attempted using DFT, but GFN2-xTB was found to significantly overestimate the length of the aryl-halide bond in the transition state, hindering convergence and making the transition state poorly transferable to higher-level theory. Hence, a more sophisticated procedure was followed for transition state refinements. Specifically, a first transition state guess was obtained by geometry optimization of the xTB-obtained transition state, constraining the carbon-halogen bond. Unconstrained geometry optimization of the resulting structures resulted in the respective oxidative addition products in all cases. Subsequently, a relaxed scan of the carbon-halogen bond to 0.8 times the initial bond length starting from the geometry obtained after constrained optimization was carried out. In addition, a partially relaxed scan of the palladium-halogen bond to 1.5 times the initial bond length was performed by constraining the carbon-halogen bond length. Relaxed geometry optimization of either the last point of the first scan or the minimum energy structure of the second scan, whichever was lower in energy, yielded the reactant structure. Next, nudged elastic band (NEB) calculations together with a subsequent transition state optimization (keywords NEB-TS or ZOOM-NEB-TS in Orca) was performed using the reactant as starting structure and the transition state guess from the constrained geometry optimization as product structure. Final optimizations of reactants, products and transition states were performed using exact initial Hessians to remove any residual imaginary frequencies. The transition states were verified by calculating both the forward and backward intrinsic reaction coordinates and comparing the resulting endpoint structures with the respective reactant and product structures.

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## **Author Contributions**

C.L., G.P.G. and R.P. conceived the project based on an idea by C.L. C.L. designed and wrote the custom codes used in reaction discovery and data analysis, with scientific input from G.P.G. and R.P. DFT computations on oxidative addition complexes were performed by R.P. and C.L. C.L., G.P.G., R.P., and A.A.-G.. contributed to the analysis of generated data. All authors contributed to the writing of the manuscript.

## Supporting Information and Code

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