Domino Reactions

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Bio-inspired Domino oxa-Michael/Diels–Alder/oxa-Michael Dimerization of *para*-Quinols

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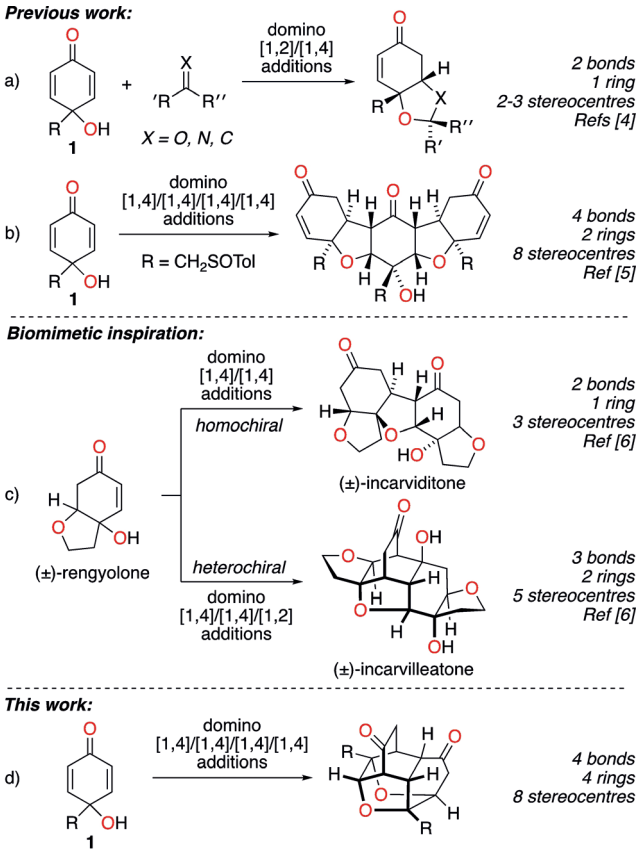
Abstract: *A bio-inspired, pyrrolidine-mediated, dimerization of para-quinols has been developed. It represents one of the most complex, yet general, dimerization reactions ever disclosed, selectively forming four new bonds, four new rings, and eight new contiguous stereogenic centres. The para-quinol starting materials are easily handled, bench-stable compounds, accessed in just one step from aromatic feedstocks. The reaction can be scaled up to give grams of polycyclic material, primed for further elaboration.*

The structural complexity of natural products is a longstanding inspiration for the development of new reactions and strategies in organic synthesis. Multiple-bond-forming domino reactions, which often draw design elements from biosynthetic processes, are the subject of intense research because they impart brevity to synthetic sequences that target natural-product-like complexity.[1] A key consideration in the design of any multiple-bond-forming process is the starting material, which must be suitably reactive to undergo multiple-bond-forming events, yet not so difficult to synthesize or handle as to render its use impractical. *para*-Quinols (**1**; Scheme 1) are ideal in this regard, since they are readily available through oxidation of commonplace phenols and they feature an abundance of electrophilic and nucleophilic sites.[2] Indeed, they have been showcased as useful reactants in several domino multiple-bond-forming reactions.[3] Many domino reaction sequences have been reported that involve initial addition of the *p*-quinol alcohol onto an electrophile with subsequent 5-*exo*-*trig* cyclization to generate a new fused five-membered ring (Scheme 1 a).[4] One of the most complex examples of a multiple-bond-forming reaction involving *p*-quinols comes from the Carreño laboratory, where they demonstrated that [(*p*-tolylsulfinyl)methyl]-*p*-quinol can participate in a spectacular, albeit unique, quadruple domino reaction sequence to form a pentacyclic trimer (Scheme 1 b).[5]

In our own laboratory, we have achieved a short biomimetic synthesis of the natural products (±)-incarviditone and (±)-incarvilleatone through dimerization of (±)-rengyolone, a *p*-quinol-derived natural product (Scheme 1 c).[6] Herein, we describe our exploration of this biomimetic strategy with simple and more readily available *p*-quinols, to access unnatural structures of even greater molecular complexity than the originally targeted natural products (Scheme 1 d).



Scheme 1. Domino multiple-bond-forming reactions of *p*-quinols. Tol = $CH_3C_6H_4$.

Initial attempts to dimerize methyl-substituted *p*-quinol **1a** revealed that slow addition of one equivalent of pyrrolidine to a solution of **1a** in $(CH_2Cl)_2$ at 70 °C furnished a single diastereomer of tetracycle **2a** as the major product (Table 1; Entry 1). Repeating a similar reaction in $CDCl_3$ again led to tetracycle **2a** as the major product,[7] but a quantity of a hexacyclic-caged structure **3a**, which was only observed in trace quantities when using $(CH_2Cl)_2$, was also isolated (Table 1; Entry 2). It was found that extended reaction times led to higher conversion to hexacycle **3a**, although we found it more practical to simply add 1,8-diazabicyclo-(5.4.0)undec-7-ene (DBU) to accelerate the final oxa-Michael

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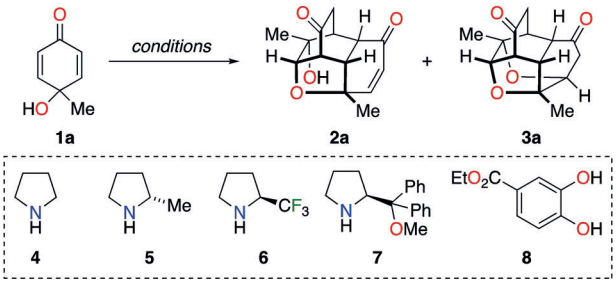
Table 1: Screening of dimerization conditions.



Entry	Conditions	% Conversion[a] (e.r.)[b] 2a	3a
1	**4** (100 mol%, slow addition), DCE, 70°C, 5 d	85	trace
2	**4** (30 mol%), $CDCl_3$, 60°C, 48 h	65	10
3	**4** (30 mol%), $CDCl_3$, 60°C, 48 h *then* DBU, RT, 16 h	trace	80
4	**5** (30 mol%), $CDCl_3$, 60°C, 48 h	50 (41:59)	10 (nd)
5	**6** (30 mol%), $CDCl_3$, 60°C, 5 d	25 (67:33)	–
6	**7** (30 mol%), **8** (60 mol%), $CDCl_3$, 60°C, 48 h	trace (89:11)	–

[a] Conversions were determined using ^{1}H NMR spectroscopy. [b] Enantiomeric ratios were determined using chiral-HPLC (Chiracel OD-H column). DCE = 1,2-dichloroethane, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.

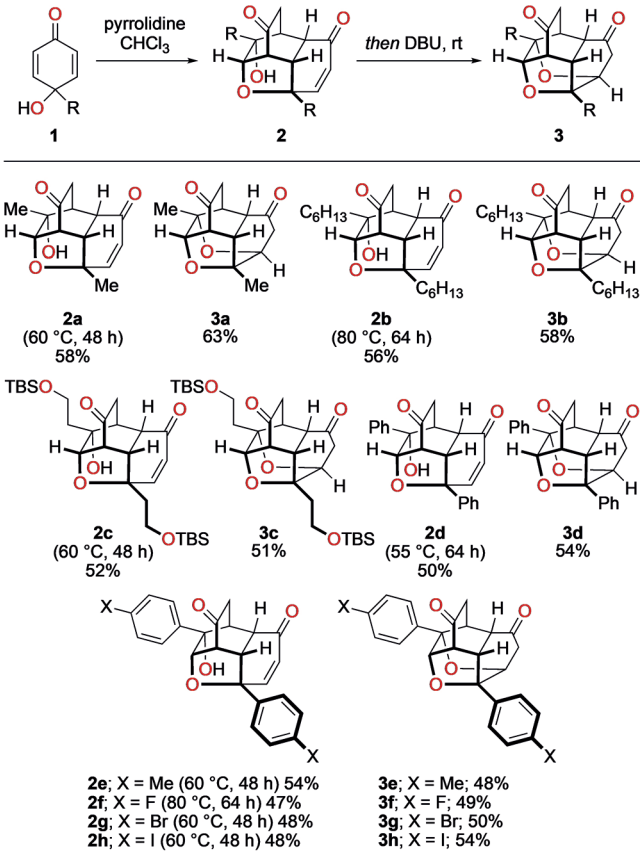
reaction (Table 1; Entry 3). Given the complexity of the transformation, we reasoned several mechanisms were possible, and therefore screened a number of catalysts and promoters, spanning primary, secondary, and tertiary amines, phosphines, bases, phosphoric acids, thioureas, and combinations thereof (see the Supporting Information for complete list of conditions). Of these, only secondary amines produced dimers (**2a** or **3a**), the yields of which dropped off significantly when more sterically hindered amines were used (Table 1; Entries 4–6). Indeed, whilst good enantioselectivity could be obtained with highly hindered secondary amine **7** and co-catalyst **8** (Table 1; Entry 6),[8] the reaction afforded a complex mixture with only trace quantities of dimer obtained.

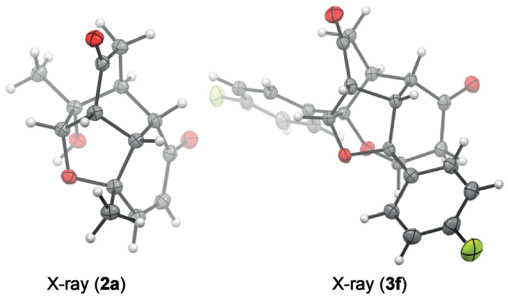
We synthesized a range of *p*-quinols **1a–h** through oxidative dearomatization of the corresponding 4-substituted phenols, and subjected them to the dimerization conditions (Scheme 2). In each case, by using chloroform as the solvent, we were able to isolate tetracycles **2a–h** in yields ranging from 47–58%, featuring a variety of alkyl and aryl substituents. Performing the reaction again but adding DBU at the end, we were able to isolate hexacycles **3a–h** as the major products instead, in yields ranging from 48–63%, thus providing easy access to two polycyclic manifolds, with DBU differentiating the outcome. The dimerizations were all performed in standard glassware under an atmosphere of air.

Attempted cross-dimerizations gave intractable mixtures of all the expected products. *p*-Quinols with *ortho* and/or *meta* substituents failed to produce dimers when subjected to our conditions. The structure of each dimer was assigned using extensive NMR spectroscopy, and crystal structures for both a tetracycle and hexacycle (**2a** and **3f**, respectively) were obtained (Scheme 2).[9] The complexity this collection of polycyclic compounds exhibits, with seven or eight newly formed contiguous stereogenic centres and numerous fused and bridged (hetero)cycles, is truly remarkable given that they are made from aromatic feedstocks in two simple and general steps.

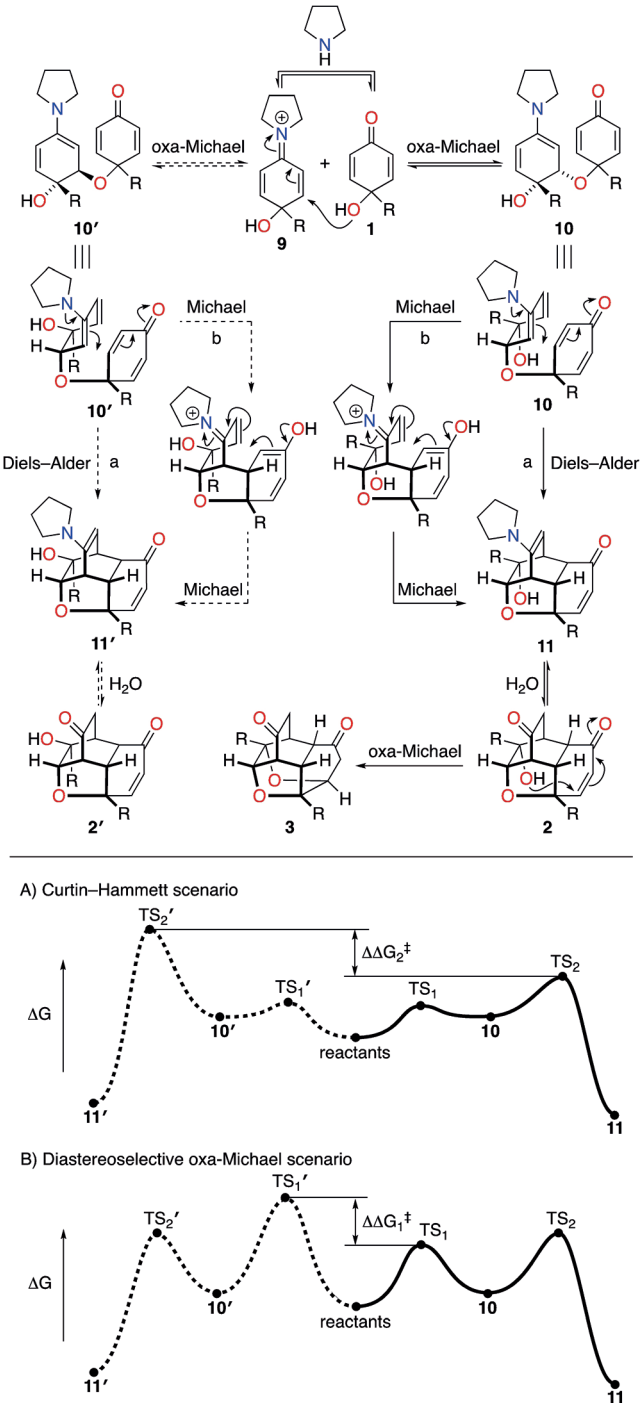
Based on our observation that secondary amines were singularly effective in promoting these reactions, and that chiral induction was observed when using chiral amines (Table 1; Entries 4–6), we propose an iminium-mediated mechanism for this transformation (Scheme 3). Thus, condensation of *p*-quinol **1** with pyrrolidine would lead to iminium ion **9**. Oxa-Michael addition of a second molecule of *p*-quinol **1** to intermediate **9** gives adduct **10**, which has an electron-rich diene and an electron-deficient alkene in close proximity. An intramolecular [4+2] cycloaddition, through either a concerted or stepwise mechanism (Scheme 3; Pathway a or b), then forms two new C–C bonds to give **11**, which upon hydrolytic removal of pyrrolidine furnishes tetracycle **2**. The final oxa-Michael addition to give hexacycle **3** then occurs slowly in the presence of pyrrolidine, or can be accelerated by the addition of the strong base DBU. We considered two stereocontrol scenarios that could account for the remarkable selectivity observed for this domino reaction sequence (Scheme 3, kinetic models A and B). Firstly, given that intermolecular oxa-Michael reactions are known to be reversible,[10] the observed selectivity could be explained by invoking the Curtin–Hammett principle,[11] wherein intermediates **10** and **10′** are in rapid equilibrium and the [4+2] cycloaddition is faster for intermediate **10** (Scheme 3, kinetic model A). Alternatively, the initial oxa-Michael reaction may exhibit high selectivity for the formation of ether **10** over **10′** (Scheme 3, kinetic model B).[12]

Density functional theory (DFT) calculations, at the SMD[$(CH_2Cl)_2$]-M06-2X/Def2QZVP//M06-2X/6-31G* level of theory, were undertaken to probe the reactivity and selectivity of this process for methyl-substituted *p*-quinol **1a** (Scheme 4). This revealed that the reaction is likely not under Curtin–Hammett control; the initial oxa-Michael reaction is calculated to exhibit high selectivity for intermediate **10a** over **10a′** ($\Delta\Delta G_1^{\ddagger} = 12.9$ kcal mol^{-1}) (Scheme 4). This is principally due to steric factors and a favourable H-bonding interaction between the incoming nucleophile and the hydroxy group of the Michael acceptor, which can only be achieved when the nucleophile approaches *syn* to the hydroxy group (TS_1; Scheme 4). The subsequent cycloaddition of ether **10a** to afford tetracycle **11a** is calculated to proceed via a concerted, asynchronous ($\Delta r = 34$ pm), transition state ($\Delta G_2^{\ddagger} = 28.8$ kcal mol^{-1}; Scheme 4). The initial Michael reaction for the alternative stepwise mechanism (Scheme 3; Pathway b) was found to have a higher barrier ($\Delta G_3^{\ddagger} = 30.6$ kcal mol^{-1}; Scheme 4). Thus, we propose that the pyrrolidine-mediated dimerization of *p*-quinols involves an initial kinetically selective, though reversible, intermolecular oxa-Michael addition followed by an irreversible intramolecular Diels–Alder cycloaddition (Scheme 4; see the Supporting Information for full computational details). If our mechanistic proposal is correct, this work represents the first activation of the *p*-quinol moiety by iminium catalysis for intermolecular reactivity.[13] Given our clear demonstration of both the





Scheme 2. Dimerization of a variety of *p*-quinols. Typical experimental procedures: For **2**, *p*-quinol (0.18 mmol), and pyrrolidine (0.054 mmol) were dissolved in $CHCl_3$ and heated at the given temperature and time until the reaction was complete, as determined by no-D ^{1}H NMR spectroscopy. Reactions were then concentrated and purified by flash column chromatography. For **3**, at the completion of the reaction, DBU (0.18 mmol) was added and the reaction left at RT for 16 h. After aqueous workup with 2 M HCl the products were purified by flash chromatography. TBS = *tert*-butyldimethylsilyl.

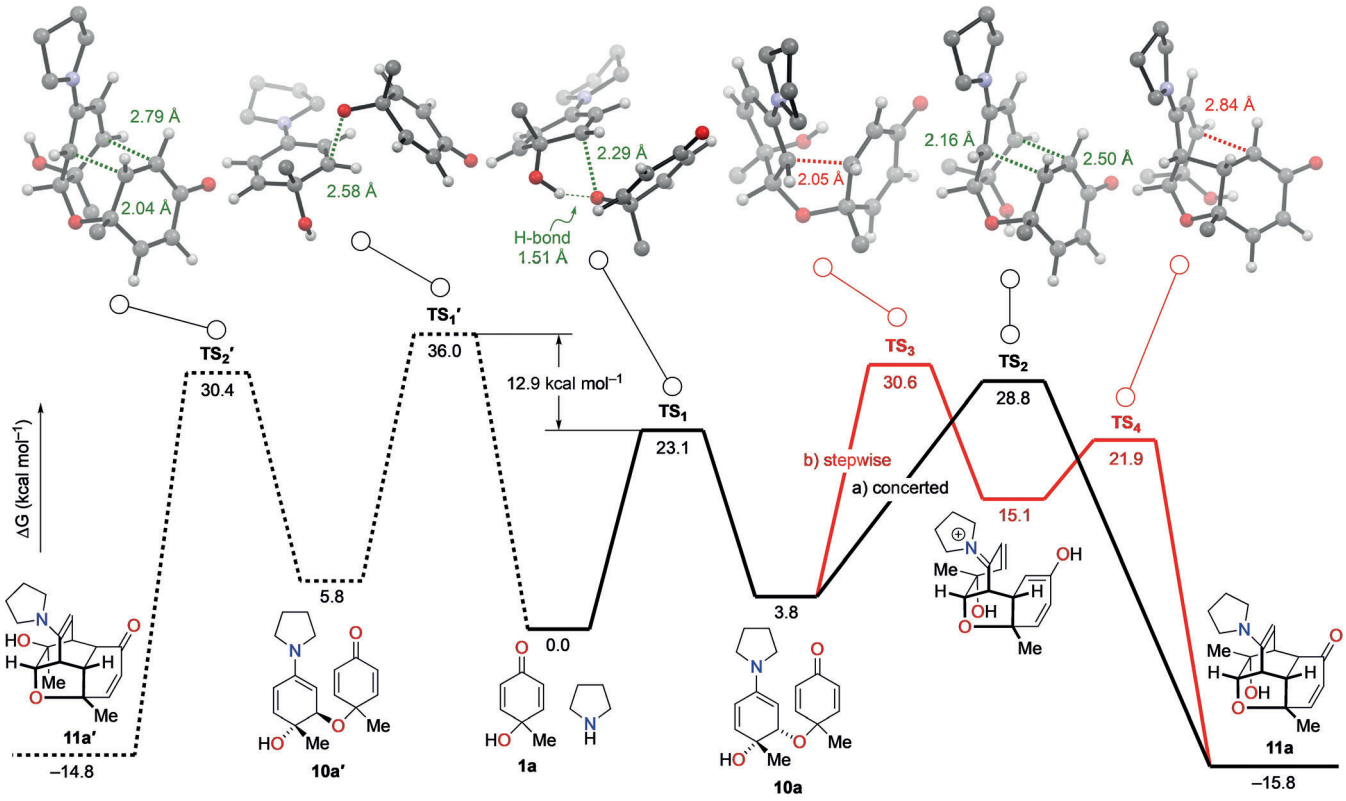


Scheme 3. Proposed mechanism for the pyrrolidine-mediated dimerization of *p*-quinols, with two qualitative free-energy diagram scenarios (assuming [4+2] cycloaddition is concerted).

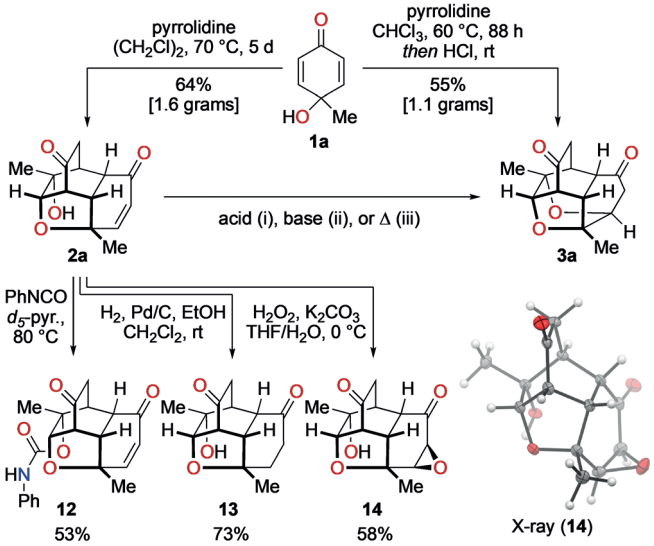
potential of the substrates in this setting and the shortcomings of currently available catalysts (in terms of reactivity and enantioselectivity), additional catalyst development is clearly warranted.

With a collection of dimers in hand, we set out to expand our targetable chemical space through further derivatization. We employed scaled-up reactions (subject to slight modification, see the Supporting Information for details) to provide gram-scale quantities of both tetracycle **2a** and hexacycle **3a** (Scheme 5). The diversity of functional groups available presented a number of options. Conversion of tetracycle **2a** into hexacycle **3a** is easily achieved thermally, or through treatment with acid or base. The tertiary alcohol in tetracycle **2a** can, if required, be protected with phenyl isocyanate to afford carbamate **12**. Hydrogenation of tetracycle **2a** gives saturated polycycle **13**, and reaction of **2a** with hydrogen peroxide selectively delivers epoxide **14** (Scheme 5).[9]

In summary, a bio-inspired strategy has resulted in one of the most complex, yet general, dimerizations ever disclosed.



Scheme 4. Free-energy profile and optimized transition-state (TS) structures for reaction pathways shown in Scheme 3 for *p*-quinol **1a** (energies calculated at the SMD[$(CH_2Cl)_2$]-M06-2X/Def2QZVP//M06-2X/6-31G* level of theory). Hydrogen atoms on the pyrrolidine and methyl groups are omitted for clarity.



Scheme 5. Gram-scale dimerizations and derivatizations. i) *p*TSA (0.1 equiv), CH_2Cl_2, 30 °C, 7 h, 78%. ii) NaOMe (0.2 equiv), MeOH, RT, 16 h, 76%. iii) [D_6]DMSO, 100 °C, quant. conversion.

This 4-bond, 4-ring, 8-stereocenter dimerization surpasses all previous reactions of *p*-quinols in terms of complexity generation, yet proceeds under straightforward conditions, delivers a collection of products with a range of substituents, and can be scaled to yield grams of polycyclic material primed for further elaboration. Remarkably, this domino multiple-bond-forming process proceeds from bench-stable, achiral substrates that are synthesized through simple oxidation of aromatic feedstocks. Such a dimerization demonstrates the power of biomimetic principles when combined with reactive substrates in the design of new domino reactions for complex molecule synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biomimetic synthesis · dimerization · domino reactions · polycycles · synthetic methods

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Communications

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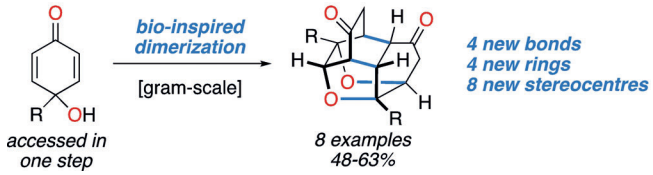

One *four* all: A bio-inspired dimerization of *para*-quinols was developed. This highly complex yet general dimerization reaction selectively forms four new bonds, four new rings, and eight new contiguous stereogenic centres. The *para*-quinol starting materials are easily handled, bench-stable compounds, accessed in just one step from aromatic feedstocks. The reaction can be scaled up to give grams of polycyclic material, primed for further elaboration.

