

# Selectivity in Transition Metal-Catalyzed Cyclizations: Insights from Experiment and Theory

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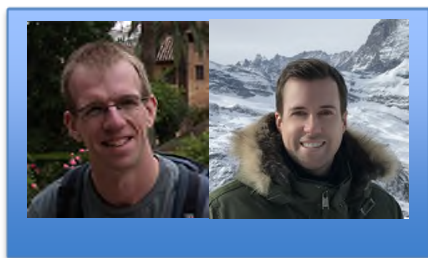
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*Abstract:* Transition metal-catalyzed cycloisomerization reactions offer a powerful tool for the synthesis of complex cyclic organic molecules from acyclic precursors. In addition to ring formation, these processes can result in the generation of new stereocentres at the site of ring formation; understanding the origins of stereoselectivity enables the use of cycloisomerization chemistry in synthesis, and promotes the design of new reactions. In this article, some recent developments from our groups in regio- and stereoselective cycloisomerization reactions are discussed. Alongside experimental observations, crucial to developing a robust understanding of selectivity has been the use of computation to explore theoretical reaction pathways, which provides an exceptional level of insight into selectivity. In its most valuable form, this correlation between experiment and theory enables the design of improved catalyst systems exhibiting both enhanced reactivity, and selectivity.

**Keywords:** Transition metal catalysis • Cycloisomerization • Mechanistic Study • Theoretical Analysis • Selectivity



Edward Anderson completed his PhD with Andrew Holmes in Cambridge. Following postdoctoral work with Erik Sorensen at the Scripps Research Institute in La Jolla, Ed returned to Cambridge as a Junior Research Fellow at Homerton College, working with Ian

**Portrait photo(s)** Paterson. In 2007, he took up an EPSRC Advanced Research Fellowship at Oxford, and in 2009 was appointed to a University Lectureship at Jesus College. In 2014 He was appointed as an Associate Professor, and as Professor in 2016. His interests cover the full range of organic chemistry, including asymmetric catalysis, new synthetic methods, natural products, ynamide and organosilicon chemistry, bioisosteres, biosynthesis, and nucleic acids.

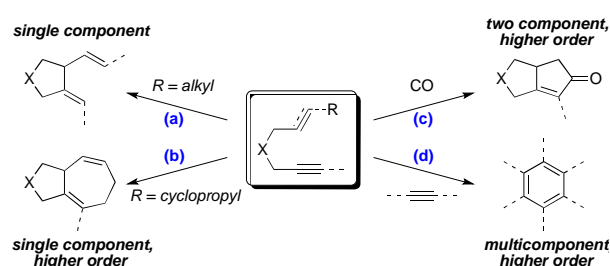
Robert Paton obtained his PhD with Jonathan Goodman in Cambridge. Following a Junior Research Fellowship at St Catharine's College, Cambridge, and a period in the group of Feliu Maseras at ICIQ, Rob conducted postdoctoral research with K. N. Houk at UCLA from 2009-2010. In 2010 he was appointed as a University Lecturer at Oxford, and as an Associate Professor in 2014. He is the recipient of the MGMS Silver Jubilee Prize, the RSC Harrison-Meldola Memorial Prize, and an ACS OpenEye Outstanding Junior Faculty Award. In 2018, Rob moved to Colorado State University. His interests span all aspects of computational organic chemistry, in particular understanding catalytic processes, and rationalizing synthesis and biosynthesis.

## Introduction

Transition metal-catalyzed cycloisomerizations are among the most efficient means to construct cyclic organic molecules from relatively simple acyclic precursors.<sup>[1]</sup> These processes are highly attractive to synthetic chemists not only due to their high atom economy, but also the range of different ring architectures that can arise from a given precursor through choice of the catalyst system. Some examples of general reaction classes (Scheme 1) include single component cyclizations (such as enyne cycloisomerization, path a), higher order single component processes (for example, [5+2] cycloisomerizations, path b), two component higher order processes (such as the Pauson-Khand reaction, path c), and multicomponent higher order reactions (exemplified by [2+2+2] cyclotrimerization, path d). Along with this catalyst- and substrate-dependent diversity of product connectivity, exquisite control can also be achieved over the stereochemistry at new stereocentres or double bonds formed during the cyclization, rendering these reactions powerful tools in synthesis. Nonetheless, establishing robust

models to explain reaction outcomes – which would enable the confident implementation of cycloisomerization strategies in target-oriented synthesis – is non-trivial due to the potential operation of different reaction pathways. In this article, we discuss three recent examples of transition metal-catalyzed cyclization reactions from our groups, where the combination of theoretical and experimental chemistry provided detailed insight into reaction mechanisms, rationalization of selectivities in product formation, and even facilitated optimization in the design of more reactive and selective catalyst systems. Collectively, these studies illustrate how computational analysis of reaction pathways can not only serve as a tool for post-reaction rationalization, but can also influence reaction design, and offer fresh insight into the fundamental steps of even the most classical of cycloisomerizations.<sup>[2]</sup>

### Scheme 1: General examples of transition metal-catalyzed cycloisomerization

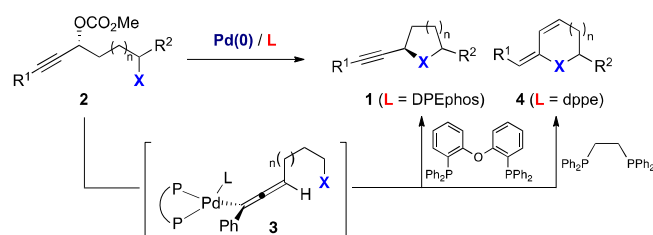


### Palladium-catalyzed cyclization reactions of propargylic carbonates<sup>[3]</sup>

Our forays into the combined use of computation and experiment to rationalize selectivity in transition metal-catalyzed transformations began with the palladium-catalyzed synthesis of alkynyl heterocycles (**1**, Scheme 2) from propargylic carbonates (**2**) equipped with internal nucleophiles. This process involves a formal substitution of the carbonate leaving group with overall retention of configuration, due to the high stereochemical fidelity of the initial  $S_N2'$  oxidative addition of the substrate (to give an allenylpalladium(II) intermediate **3**),<sup>[4]</sup> and the subsequent  $S_N2'$  reductive elimination by attack of the tethered nucleophile. In the course of reaction optimization, particularly for sulfonamide nucleophiles, an additional product was observed – heterocyclic enamide **4**. Particularly intriguing was that the ratio of alkynyl heterocycle / enamide (**1** : **4**) appeared to be related to the nature of the bidentate phosphine ligand employed in the reaction: the large bite angle ligand DPEphos ( $\phi \sim 105^\circ$ ) favoured the formation of **1**, while the small bite angle ligand dppe ( $\phi \sim 86^\circ$ ) favoured **4**. The bite angle of bidentate phosphine ligands is well-recognized to be an important factor in controlling reaction outcomes,<sup>[5]</sup> but the reasons for this switch in regioselectivity were not clear. Nonetheless, the ability to control the site of nucleophilic attack on an allenylpalladium complex simply through selection of an appropriate ligand

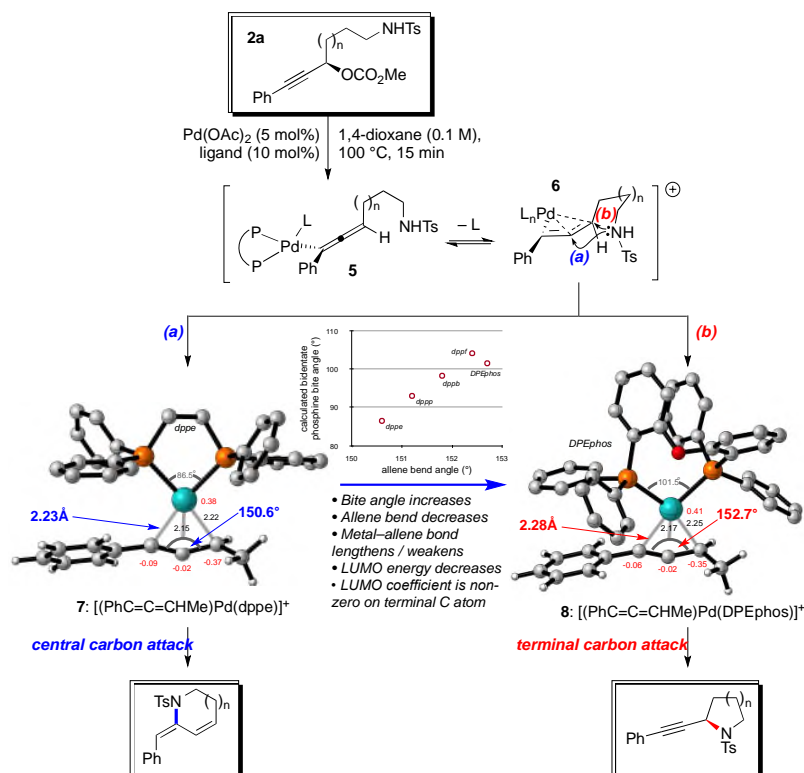
could undoubtedly provide useful synthetic opportunities; it is also notable that this behaviour contrasts with that typically observed in an intermolecular context, in which nucleophiles engage the allenylpalladium intermediate at its central carbon atom.<sup>[6]</sup>

**Scheme 2: Ligand-dependent regioselective palladium-catalyzed cyclization reactions of propargylic carbonates.**



Allenylpalladium complexes<sup>[7]</sup> typically exist in equilibrium between  $\eta^1$ -complexes **5** (Scheme 3), which may be neutral or cationic depending on the nature of the ligand, and cationic  $\eta^3$ -complexes **6**,<sup>[8]</sup> in which the orthogonal 'distal' alkene also coordinates to the metal ion. Theoretical analysis of this more electrophilic  $\eta^3$  complex enabled rationalization of the observed selectivity, based on the finding that the structure of **6** varies subtly with the extent of complexation of the second alkene. This results in differing degrees of 'bending' of the allene unit; using model complexes (e.g. **7** and **8**), we were able to explore the dependence of the calculated angle of allene bend on calculated bidentate ligand bite angle (see inset graph, wB97XD/6-31G(d) level of theory). This revealed a more significant distortion from linearity of the allenylpalladium geometry for smaller bite angle ligands, correlating with stronger binding of the metal to the distal alkene of the allenylpalladium complex. Greater complexation in turn raises the energy of the Pd–C antibonding orbital (calculations at the wB97XD/def2-TZVPP level of theory), disfavours attack at the remote carbon atom, with reaction at the central carbon atom thus being observed. However, as the ligand bite angle increases, the allene geometry becomes more linear, and the Pd–C bond to the distal carbon atom lengthens. This weakens metal-carbon bonding at this site, lowering the energy of the LUMO (which has a non-zero coefficient at this position) and rendering this carbon atom more susceptible to nucleophilic attack – leading to the alkynyl heterocycle product. Interestingly, the charge distribution across these atoms varies little between these structures, ruling out a purely electrostatic explanation. Overall, the experimentally observed change in regioselectivity for these two complexes can thus be explained by stereoelectronic effects arising from the geometric influence of the ligands.

**Scheme 3: Computational rationalization of regioselectivity profiles reveal a stereoelectronic influence of ligand bite angle on allenylpalladium reactivity.**



**Palladium(II) acetate-catalyzed cycloisomerization reactions of enynamides and enynes<sup>[9]</sup>**

Within the field of cycloisomerization chemistry, palladium-catalyzed enyne cycloisomerizations (of general form **9**→**10/11**, Scheme 4a) are among the most well-established, with this chemistry originating in the groundbreaking publications by Trost in the 1980s<sup>[10]</sup> and early 1990s.<sup>[11]</sup> A number of relatively simple catalyst systems are available, including palladium(0) pre-catalysts (e.g.  $\text{Pd}_2\text{dba}_3$  / AcOH, with or without phosphine ligand) and palladium(II) complexes (e.g.  $\text{Pd}(\text{OAc})_2$  /  $\text{PPh}_3$ ). Our own interest in this field stemmed from various applications of enynamides in ring-forming reactions,<sup>[12]</sup> as enynamide cycloisomerization offers an attractive and atom-economical entry to azacycles. We discovered that enynamides **9** ( $\text{X} = \text{CH}_2$ ,  $\text{Y} = \text{NTs}$ ) are indeed excellent substrates for this chemistry; some example products are shown (Scheme 4b), in which efficient formation of various azacycles, including bicyclic products, could be achieved using  $\text{Pd}(\text{OAc})_2$  in combination with the ligand *bis*-benzylidene ethylenediamine (bbda). Of particular appeal to us was the installation of, and control over, new stereocentres in the course of ring formation, where very high levels of substrate stereocontrol