Isotope effects in mechanistic studies of transition metal-catalyzed cycloisomerization

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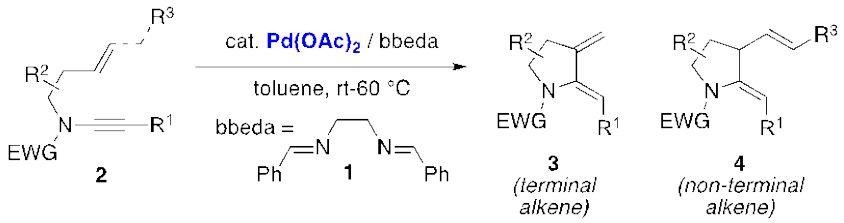
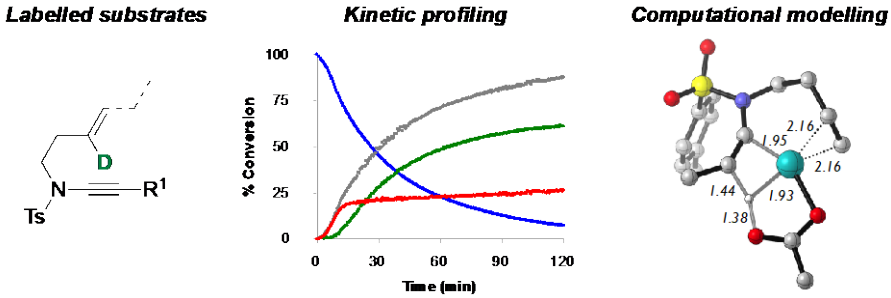
Transition metal-catalyzed cycloisomerization reactions offer an atom-economic route from simple acyclic unsaturated precursors to relatively complex (hetero)cyclic products. The product structure depends intimately on the reaction mechanism, which varies widely between different catalysts.[1]

Among the most well-established cycloisomerization catalyst systems are the palladium(II) and palladium(0) catalyzed transformations of enynes into 1,3- and 1,4-dienes, developed extensively by the Trost group.[2] Our group has found that the combination of $Pd(II)(OAc)_2$ and the ligand *bis*-benzylidene ethylenediamine (bbeda, **1**, Scheme 1)[3] is particularly efficient at promoting the cyclization of enynamides **2** to various azacycles **3** / **4**.[4] However, the mechanism by which this cycloisomerization proceeds has remained a mystery for almost 30 years.



Using a combination of isotopically-labelled substrates and catalysts, deuterium-enriched reaction media, computational modelling, and kinetic profiling, we have gathered a significant body of evidence that offers a solution to this mechanistic puzzle, and in doing so reveals unusual mechanistic features of this classic cyclization process.[5] The details of our investigations will be discussed in this talk.



References

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