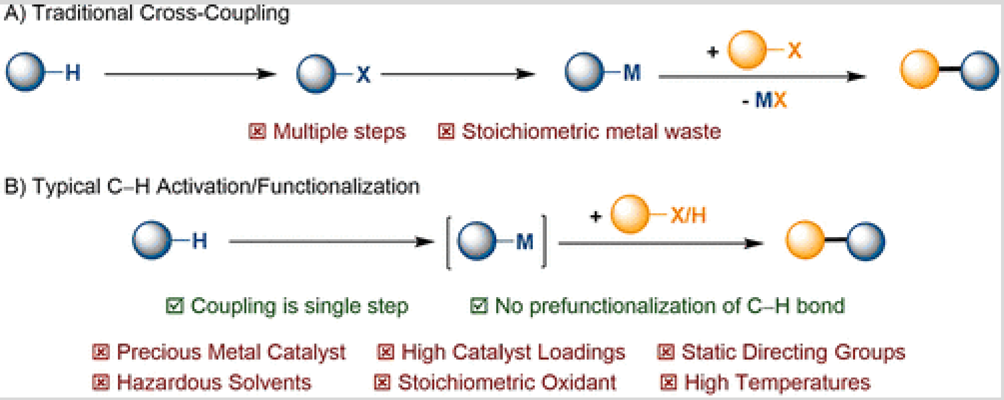
C-H Activation with Transition Metal Complexes

Models/Topics Covered: LFT, CBC, Green-Davies-Mingos Rules, η/κ/μ-notation,

"*The replacement of a hydrogen atom in a carbon-hydrogen (C-H) bond by another element or functional group brings together collaborations from all areas of chemistry. The replacement of the hydrogen atom in methane is so important that it has been highlighted as one of the grand challenges of chemistry. The interest stems from the* ***high atom economy*** *these transformations provide along with the* ***potential environmental benefits of using alkanes as chemical building blocks****. The two main challenges regarding these reactions are* ***(1) poor selectivity****, due to the abundance of C-H bonds with similar bond dissociation energies and reactivity, and* ***(2) the chemical inertness of hydrocarbon C-H bonds****, often due to the inherent low polarity. Furthermore, the potential atom economy of C-H activation/functionalisation reactions remains* ***limited by the need for stoichiometric reagents****, such as oxidants, which are critical in most reactions and hamper uptake by industry.*" **Ref[3]**

"***C-H Activation****: A specific mechanistic step involving the direct cleavage of a C-H bond that occurs due to an interaction with a transition metal, where the result is a new carbon-metal bond.*

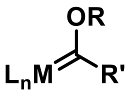
C-H Functionalisation*: A process involving the replacement of a C-H bond by another element or functional group but where the functionalisation is most often preceded by a C-H activation event.*" **Ref[3]**



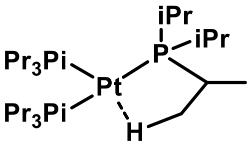
C-H Activation: Intrinsic Opportunities. Reproduced from Ref[9].

Question 1 (Refresher on Organometallics)

Identify which of the following organometallic species contain ligands of the following types: (i) alkyl, (ii) alkane, (iii) agostic.



A



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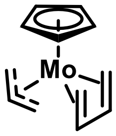

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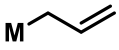

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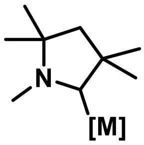

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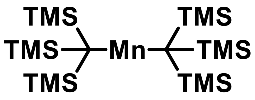

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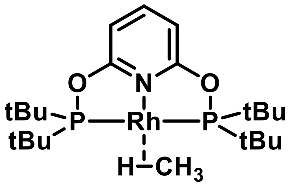


H

I

J

For each of these ligand classes, indicate:

(i). Which molecular orbitals electron density is being donated from and to.

(ii). The hapticity, η, denticity, κ, and degree of bridging, μ shown in the examples.

(iii). The CBC character of the ligand class.

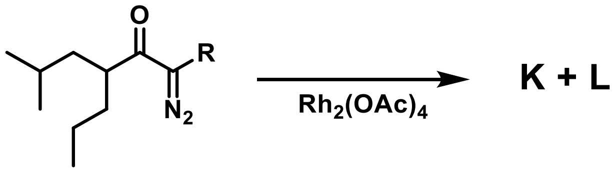
(iv). The effect of binding a ligand of this class on the metal oxidation state.

(v). Which classes are examples of C-H bond activation.

Question 2 (C-C Bond Formation via C-H Activation with Rh 'Carbenoids')

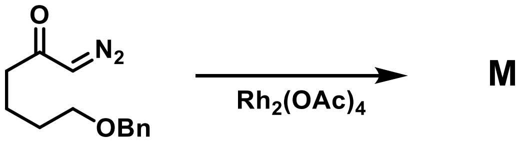
Predict the product(s) of the following reactions featuring C-H activation by a dirhodium carboxylate, and provide a mechanism. Note that the activation step is the same each time, so need only be included once.

(i). **J. Am. Chem. Soc. 1986, 108, 7686**



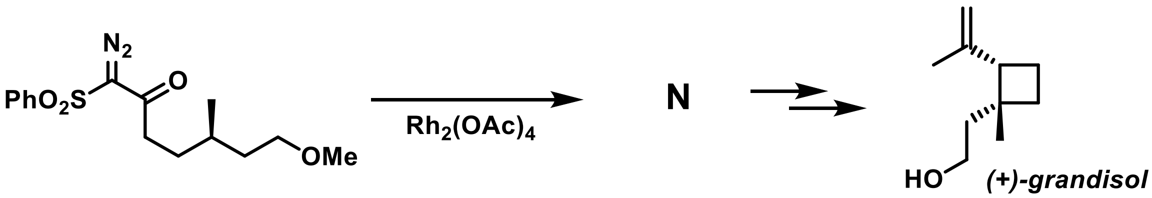
Two products are formed in a 23:1 ratio.

(ii). **Tetrahedron 1991, 47, 1765**



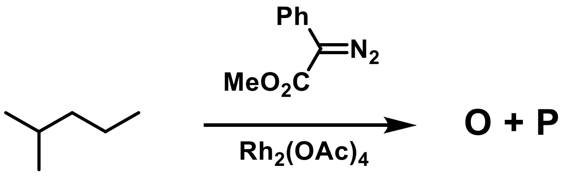
A single product is formed in 30% yield.

(iii). **Tetrahedron 1996, 52, 3879**



A single product is formed in 60% yield. Include stereochemistry of **N** in your answer.

(iv). **J. Am. Chem. Soc. 2000, 122, 3063**

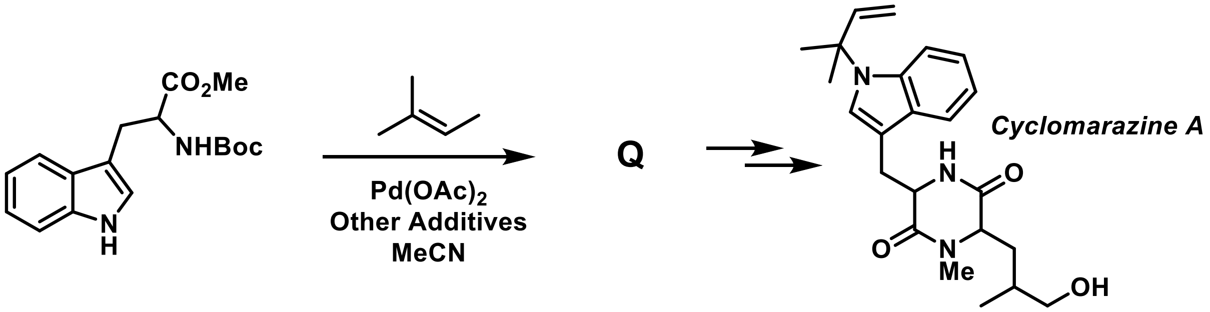


The two products are formed in a 44% and 31% yield respectively. This highlights a lack of selectivity in the intermolecular C-H activation of certain species.

Question 3 (Application of Pd C-H insertion in Total Synthesis)

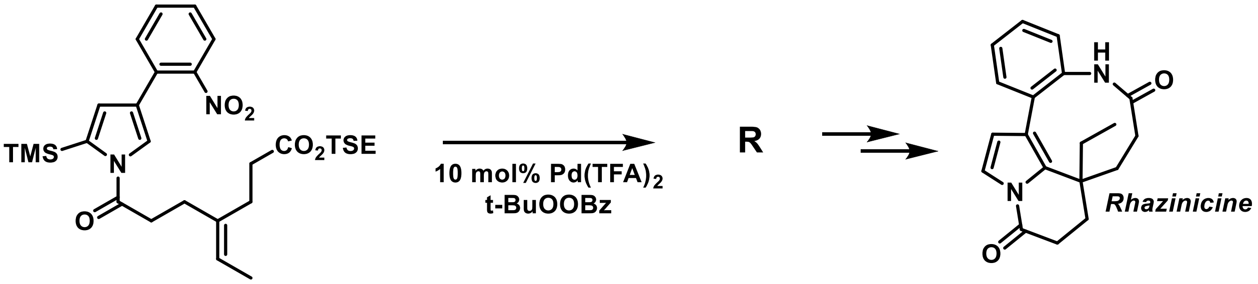
For each of the following, provide (i) the electron count and oxidation number of the catalyst at each stage, (ii) the reaction product(s), and (iii) a mechanism for the reaction (NOTE: this does not need to be a curly arrow mechanism; transition states or catalytic cycles may be more appropriate). Stereochemistry is ignored in all but the last question.

(i). Cyclomarazine A – 2010 – Baran / Moore

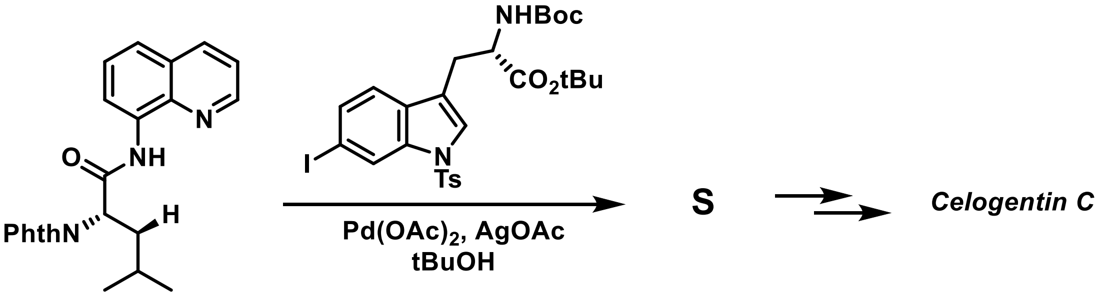


Mechanism is not completely understood, and as such there are two highly divergent answers here. 'Other additives' are $Cu(OAc)_2$ and AgTFA. Ignored here to simplify the problem, in light of their undetermined mechanistic role.

(ii). Rhazinicine – 2008 – Gaunt



(iii). Celogentin C – 2010 – Chen



The reaction proceeds via activation of the H atom shown with 85% yield. This information is relevant to the mechanism.

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[15] Davies, Beckwith ‘Catalytic Enantioselective C-H Activation by Means of Metal-Carbenoid-Induced C-H Insertion’ *Chem. Rev.* 2003, **103**, 2861 (DOI: 10.1021/cr0200217)
[16] Set of three presentations from other groups on the reactivity of Rh-carbenoids:
    a. https://gousei.f.u-tokyo.ac.jp/seminar/pdf/Lit_Takasu_D2.pdf
    b. https://macmillan.princeton.edu/wp-content/uploads/JEC-chact.pdf
    c. https://stoltz2.caltech.edu/seminars/2004_Tambar.pdf
[17] Plus, the various Organic Chemistry Portal pages for the named reactions covered. Giving them explicitly would be too easy. ☺