Regio- and Stereoselectivity in Ru-catalyzed Hydroamidation and Hydrocarboxylation of Terminal Alkynes: A Computational Insight

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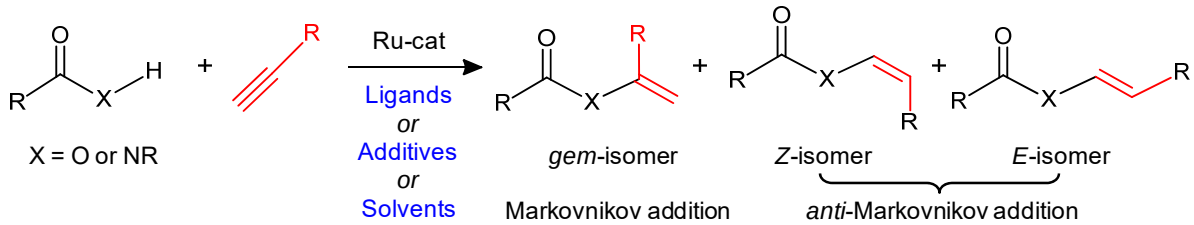
Abstract:
The ruthenium-catalyzed alkyne to carboxylic acid (or amide) coupling reactions is an excellent methodology for the synthesis of enol-esters (or enamides) (refer Scheme 1). The most disadvantage of this method lies in the formation of product mixture, Markovnikov and *anti*-Markovnikov *E*- or *Z*-isomers. To control the regio- and stereoselectivity by the modulation of the electronic and steric environment in catalyst system is a major challenge in catalyst community during last few decades. Recently, Gooßen *et al.* have developed a unique catalyst [(cod)Ru(met)$_2$], which is highly efficient in term of stereoselectivity depending on external ligands and additives in hydroamidation reaction.[1] On the basis of DFT calculations we have proposed that the *E*-/*Z*- selectivity of enamide is governed by the intramolecular nucleophilic transfer step from vinylidene intermediate.[2] In presence of monodentate phosphine, P^{n}Bu$_3$, and N,N-dimethyl-amino pyridine (DMAP) ligand the alkyl group rotates towards *anti*- to the incoming nucleophile and hence, *E*-enamide is found to be major product. On the other hand, selectivity is reversed in bidentate phosphine ligand, dcypm that imposes more steric influences and finally *Z*-enamide is observed.

Similarly, the selectivity in hydrocarboxylation of terminal alkyne is controlled by the size of chelating phosphine ligand present in initial catalyst [(Ph$_2$P(CH$_2$)$_m$PPh$_2$)Ru(met)$_2$] (m = 1, 2, 3 and 4), reported by Dixneuf.[3] Theoretical results reveal that difference coordination modes of alkyne, either η^2-complex or vinylidene, is affected by the steric nature of bidentate phosphine ligand that in turn governs the regio- and stereoselectivity of enol-ester formation.[4] Another interesting development is made by Yi and Gao using different solvent medium to control the selectivity in hydrocarboxylation of terminal alkyne.[5] Our results support the experimental observation that in presence of non-polar CH_2Cl_2 (DCM) solvent, Markovnikov addition occurs to produce *gem*-enol-ester whereas, in presence of polar coordinating solvent, THF, the *anti*-Markovnikov addition is favored and the *Z*-enol-ester is formed *via* Ru-vinylidene intermediate.



Scheme 1. Selectivity in Ru-catalyzed hydroamidation/hydrocarboxylation of terminal alkynes.

References and Notes:

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