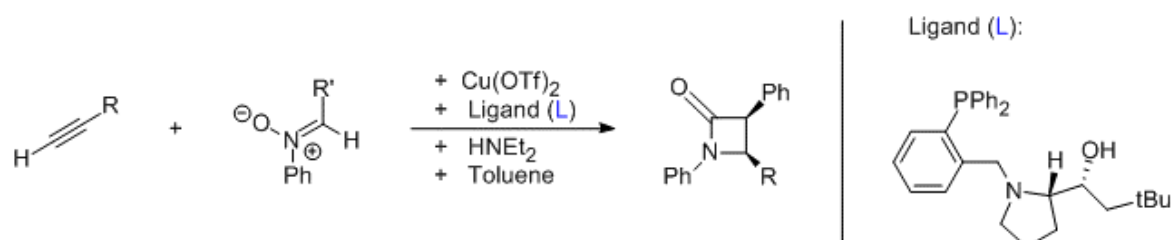


Mechanistic insights into the asymmetric Kinugasa reaction of nitrones with terminal alkynes by copper catalysis

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Directionalized hydrogen bonds often play a key role in stabilizing transition states and therefore are a very important element in developing new catalysts for asymmetric synthesis. This study focuses on the reaction of nitrones with terminal alkynes, which can be controlled by copper catalysis utilising prolinol-based hydroxy amino phosphane ligands to selectively form a 1-(*R*)-2-(*S*)- β -lactam (Scheme 1).



Scheme 1 Reaction of substituted nitrones with terminal alkynes via copper catalysis.

The initial stereoselective carbon-carbon bond formation has been investigated with the density functional BP86 and the basis set def2-SVP. For the purpose of this study, the system has been truncated to generate a more suitable model and speed up the calculations, i.e. the neopentyl moiety of the ligand has been replaced by a hydrogen atom.

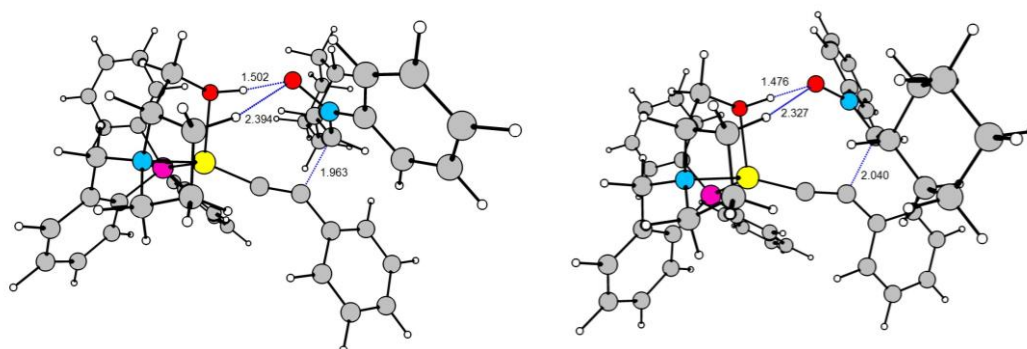
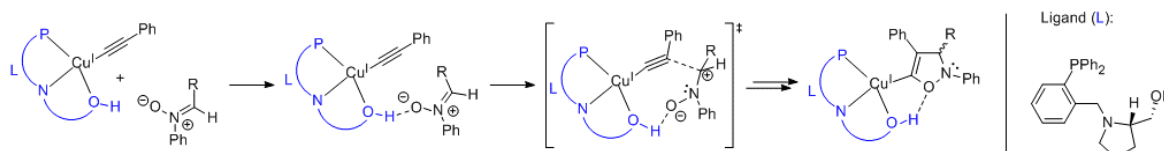


Figure 1 Molecular geometries of the lowest lying *R*- (left) and *S*- transition states (right). Bond lengths are given in Å. Gaussian09 BP86/def2-SVP.



Scheme 2 Schematic representation of the formation of the five membered ring intermediate.

Based on our previous work,^[1] from the initially considered 320 possible conformations of the reaction system, a subset of 80 states has been treated to the full extent. These converged into six pathways for each stereochemistry. From the remaining possible conformations, which have been expected to be much higher in energy, some paths have been treated representatively. The most energy efficient pathway leads to *R* stereochemistry and has an activation barrier of $\Delta G^{298K} = 17.8$ kcal/mol relative to the resting state. The lowest lying transition states *S* stereochemistry has a slightly higher barrier of $\Delta G^{298K} = 19.2$ kcal/mol (Figure 1). Employing transition state theory, this energy difference can be translated to a *R/S* ratio of 9:1 or 83% ee. The results are in good agreement with experimental findings of an *R/S* ratio of 8:2 or 60% ee at -40 °C for this system.^[2]

The optimized geometries provide valuable insights into the mechanism of this reaction and explain the reason for the stereo selectivity of this reaction. Intramolecular O–H···O hydrogen bonding (*R*: 1.502 Å; *S*: 1.476 Å) plays a key role into stabilising the transition state conformations. A notable secondary interaction arises from a non-classical C–H···O hydrogen bond (*R*: 2.394 Å; *S*: 2.327 Å). This is supported by an analysis in terms of the quantum theory of atoms in molecules, which reveals bond paths for these interactions.

For steric reasons the *S* transition state is slightly disfavored, because of the interactions between the cyclohexyl moiety and the phenyl moiety of the acetylene.

The reaction mechanism of this first stereo selective step can be described as a pseudo [3+2] cycloaddition, where the first carbon-carbon bond formation is the rate determining step, while the carbon-oxygen bond formation occurs without a barrier (Scheme 2).

The model system has been verified against a variety of other density functionals and a different basis set has been tested. Grimme's dispersion treatment has also been employed. The influence of the solvent toluene has been treated with the polarizable continuum model. The used methodology for the model system has been confirmed stable to these variations. BP86/def2-SVP performs reasonably well. The study has also been extended to include the original ligand with the neopentyl moiety. In addition to this a CH₂Si(CH₃)₃ substituted ligand has been investigated. Only marginal changes in the predictions have been found. The model system has also been extended to include different substituted acetylene reactants.

References:

- [1] Ishii, T.; Watanabe, R.; Moriya, T.; Ohmiya, H.; Mori, S.; Sawamura, M.; *Chem. Eur. J.* **2013**, *19*, 13547.
 [2] Ishii, T.; Schwarzer, M. C.; Konno, R.; Ohmiya, H.; Mori, S. and Sawamura, M.; *in preparation*.