

Computational study of the copper-catalyzed α -alkylation of aryl acetonitriles with benzyl alcohols

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Considerable efforts have been made towards achieving step and atom economy in organic synthesis focusing on environmentally benign processes, through the use of abundant, low cost transition metals.[1-2] Recently, a highly efficient, in-situ formed CuCl₂/TMEDA catalytic system (TMEDA = N,N,N',N'-tetramethylethylene-diamine) for the cross-coupling reaction of aryl acetonitriles with benzyl alcohols was reported, where the use of a low catalyst loading and a catalytic amount of base leads to the synthesis of α -alkylated nitriles in up to 99% yield. A mechanistic pathway was proposed based on the experimental findings.[3]

In this presentation, the computational study of the copper-catalyzed α -alkylation of aryl acetonitriles with benzyl alcohols is presented. DFT methodology was employed to study the Cu-catalytic reaction mechanism. The computational study investigates possible reaction steps proposed for the formation of the aldehyde from the corresponding alcohol. A variety of different Cu^{II} complexes were used, and the preferred reaction pathway has energy barriers of up to 24 kcal/mol. The homolytic cleavage of the C(sp³)-H bond of the benzyl alcohol is favored energetically, and the release of H₂ is very likely to occur. DFT calculations provide further insight in the experimental data, confirming the proposed, unprecedented reaction mode for this transformation.[3]

References:

- [1] T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* 38 (2009) 3010.
- [2] T. Gaich, P. S. Baran, *J. Org. Chem.* 75 (2010) 4657–4673.
- [3] M. Danopoulou, L. P. Zorba, A. Karantoni, D. Tzeli, G. C. Vougioukalakis, *J. Org. Chem.* 89 (2024) xxx; 10.1021/acs.joc.4c01662.