Abstract

C-C-bond-forming reactions, including the acyloin reaction, are essential methods in organic synthesis. In the present work quantum mechanical calculations for estimating catalyst and substrate reactivities in the acyloin reaction were performed with the aim to gain fundamental insights into the different catalytic steps and the electronic and geometric properties of umpolung catalysts. Of fundamental importance is the investigation of the nucleophilicity and electrophilicity of the catalysts. The nucleophilicity can be calculated from the thermodynamic tendency to add to carbonyl systems. The electrophilicity can be determined from the kinetic inclination for the umpolung. For this, the reaction steps were analyzed by DFT calculations (GAUSSIAN03/GAUSSIAN09).

In comparison of the three catalysts (cyanide, thiazol-2-ylidene, glycol phosphonate) the nucleophilic addition to the umpolung substrate, the umpolung and the electrophilic stabilization of the acyl anion equivalent is strongly favored for thiazol-2-ylidene with all considered substrates (acetaldehyde, benzaldehyde, acylsilane, benzoylsilane). This applies to all the mechanisms of the umpolung considered: The symmetry forbidden 1,2-H-shift has a much higher activation energy as the concerted umpolung via a five-membered transition state with a protic reaction partner (*t*BuOH) and is thus improbable. If acylsilane is employed instead of acetaldehyde and benzoylsilane instead of benzaldehyde as the umpolung substrates, a [1,2]-Brook rearrangement takes place, which reduces the activation energies for all three catalyst types compared to the 1,2-H-Shift by 20 to 40 kcal mol^{-1}.

Electrophilic counterions (M = Li^+, Na^+, K^+) in the glycolphosphonate catalyzed cross benzoin reaction activate as Lewis acids both the carbonyl function of benzoylsilane and that of benzaldehyde. The Lewis acidity of the alkali metal ions has a strong influence on the activation. In agreement with the Coulombs law and the HSAB concept, the activation of the (hard) carbonyl function correlates reciprocally with the ion radius of the counterion. Smaller counterions thus lower the activation energy for the umpolung step, making lithium the counterion of choice in the cross benzoin reaction with benzoylsilane and benzaldehyde.

The assessment of all calculated N-heterocyclic carbenes (NHCs) in the benzoin reaction reveals the abnormal r-NHC pyridyl-3-ylidene as the catalyst with the lowest activation energy. 1N-NHCs and r-NHCs are both more nucleophilic and electrophilic than 2N/NX-NHCs. The nucleophilicity of the carbene carbon atom increases due to the lower electronegativity and therefore the lower electron withdrawing effect of the adjacent carbon

atom. Electrophilicity also increases due to the lack of π-donation. Since pyridyl-3-ylidene is abnormal, the resulting negative charge in the d^1-acyl anion equivalent is significantly less stabilized so that it is not too exergonic for the addition to benzaldehyde. Among the normal classical NHCs studied, oxazol-2-ylidene has the lowest activation energy in the benzoin reaction for the rate-determining step.

This work proves NHCs to be the strongest umpolung catalysts. Based on the results obtained, NHCs with the highlighted electronic properties can be synthesized for use in the enantioselective acyloin reaction.