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Micellar-driven substrate selectivity in Cr(salen)Cl catalytic Diels–Alder reaction in water

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ABSTRACT

A 3.5 increase in catalytic activity was observed in the Cr(III) (salen)Cl **3** catalyzed Diels–Alder reaction between cyclopentadiene **1** with the longer trans-2-decenal **2g** compared to the shorter *trans*-2-butenal **2a** dienophile under aqueous micellar conditions, while in chloroform the two substrates react with comparable activities.

Selectivity is a crucial concept in catalysis and it commonly refers to the ability of a catalyst to preferentially produce one product out of a number of possible ones. Enzymes are outstanding examples of product selective catalysts but they also represent impressive examples of substrate selectivity because of their ability to select the substrate that fits better the geometric and electronic properties of the active site.[1–4] Geometric factors have long been exploited in some classes of heterogeneous catalysts to provide substrate selectivity, because porosity properties can be tuned to ensure size and shape discrimination of the reagents.[5]

In homogeneous catalysis, apart from kinetic resolution where the two enantiomeric substrates react with different rates,[6] only rare examples are known. In most cases substrate selectivity is determined comparing the activity of different reagents in single experiments rather than testing all substrates at the same time in direct competitive experiments. More importantly, the range of substrates compared[7–9] generally not only share the functional group that has to be reacted upon but also bear extra functionalities such as for example hydrogen bonding or ionic moieties[10–14] (Scheme 1A) that enable secondary interactions with the catalyst, acting as a recognition site favoring one substrate over the other. Less common is the comparison between substrates that differ only for small changes in positions remote from the reactive center and lacking recognition sites (Scheme 1B). In the latter case substrate selection is usually based on steric interactions.[15–17] Outstanding examples are supramolecular water soluble capsules as catalysts capable of selecting only hydrophobic substrates with size and shape matching the dimensions of the cavity.[18,19] Much more difficult is to control substrate selectivity with common soluble metal catalysts where the surface interaction between reagent and catalyst is lower and exclusion phenomena are not possible.

Micelles are supramolecular aggregates, spontaneously forming in water when amphiphilic species are added, that can be easily investigated with NMR spectroscopy and other techniques.[20] They can be used as reaction media to dissolve substrates and catalysts making water a viable environmentally friendly medium. Micelles associated with organic soluble catalysts have been demonstrated to enhance product selectivity at all levels,[21] in particular micellar media enabled higher diastereo and enantioselectivities[22] thanks to supramolecular interactions between surfactants, substrate, and catalyst, in this respect resembling enzymes.

Herein we report about the substrate selectivity observed in the catalytic Diels–Alder (DA) reaction between cyclopentadiene **1** and C_4–C_{10} α,β-unsaturated aldehydes **2a–g** mediated by Cr(III) (salen)Cl **3** in water in the presence of micelles (Scheme 2), in comparison with an organic medium.

To determine substrates and catalyst positioning in micellar media, ^{1}H NMR as well as 2D NOESY experiments (see Supplementary data) were acquired on each species in water with and without sodium dodecylsulfate (SDS, 0.24 M) as surfactant, in order to compare the extent of interaction between each substrate and micelles. While the smaller unsaturated aldehyde *trans*-2-butenal **2a** is completely soluble in water and its chemical shift was independent of the addition of SDS, the other dienophiles from C_5 to C_{10} led to a gradual shift of the resonances of the dienophile upon the addition of SDS, proving the increasing affinity of more apolar substrates with the supramolecular micellar aggregate.

For the longer dienophiles **2e–g** several resonances are present in water, some sharp ones attributed to the portion of the substrate soluble in water and broad ones likely due to undissolved liquid substrate. All these resonances become sharp and merge into a single species upon addition of SDS (see Supplementary data). For all dienophiles but **2a and 2b**, NOESY experiments reveal the presence of cross peaks of increasing intensity between the vinyl resonances of the dienophile and the central methylene units of SDS indicating close contact between the substrate and the micellar aggregate.

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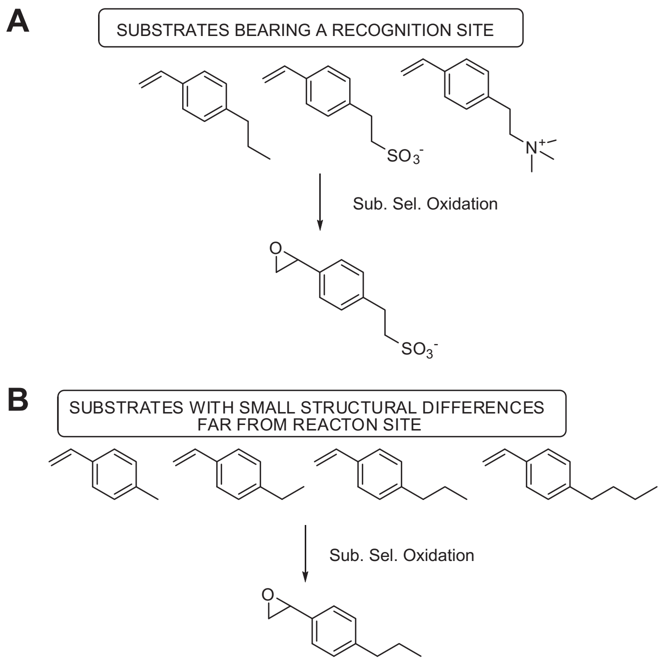
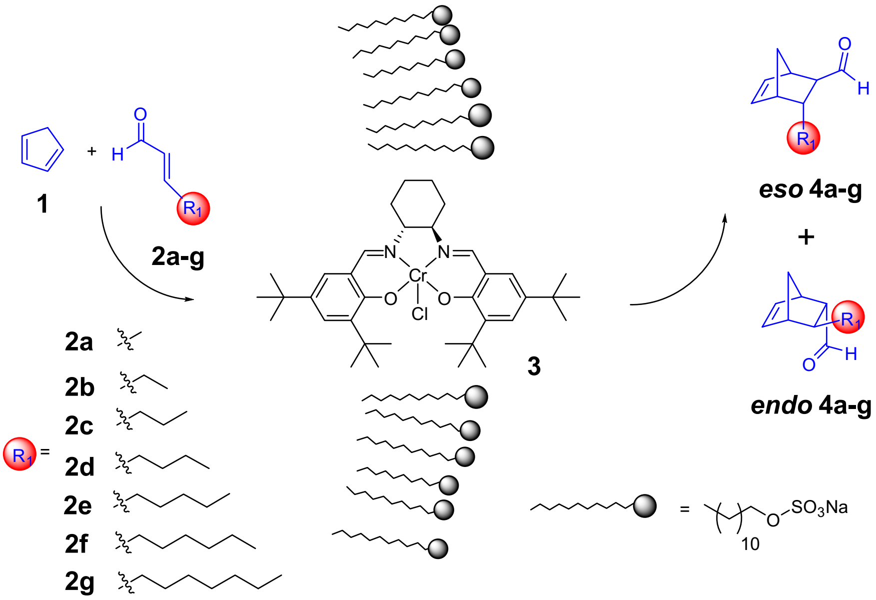


Scheme 1. Examples of substrate selectivity displayed by homogeneous catalysts: (A) substrates differing for the presence of extra functional groups that provide recognition for the catalyst; (B) substrates with small structural differences far from the reactive site.

Analogous NMR experiments were performed on diene **1** which is known to have a maximum solubility of 10 mM in water. The spectrum without surfactant is broad and becomes sharp upon addition of SDS and weak cross peaks are observed between **1** and SDS in the NOESY spectrum due to its intermediate solubility in water. Neutral paramagnetic Cr(III) catalyst **3** is insoluble in pure water but it can be dispersed upon addition of SDS. ^{1}H NMR experiments were performed in D_2O/SDS in which increasing amounts of catalyst **3** were added observing an increasing broadness of the SDS peaks without any preference for specific resonances, indicating that the catalyst is likely to be uniformly present within the micelles. Overall it can be deduced that, under micellar conditions, the following distribution of species is present: (i) Catalyst **3** is dissolved and distributed inside the micelles; (ii) cyclopentadiene **1** is partially hosted in the apolar core of SDS micelles; (iii) unsaturated aldehydes apportion differently between bulk water and micellar aggregates, with shorter **2a** completely water soluble and longer **2g** completely associated to the micelles. The other dienophiles present an intermediate distribution with increasing affinity for the micellar aggregate on going from **2b** to **2e**.

The series of linear *trans*-α,β-unsaturated aldehydes **2a–g** were tested all together at the same molar concentration (0.09 M) in DA competitive experiments in the presence of 2.1 equiv of cyclopentadiene **1** (total concentration 1.35 M) for each aldehyde added, mediated by catalyst **3** (2 mol %). Reactions were carried out both in water/SDS and in chloroform as reaction medium. In the latter, no supramolecular aggregates are formed and all dienophiles are expected to react with comparable activity. In Figure 1 are reported the yields as sum of *endo/exo* diastereoisomers **4a–g** as a function of the number of carbon atoms of the dienophile. Only marginal dimerization of cyclopentadiene **1** was observed after 20 h at 25 °C both in micellar medium as well as in chloroform (20% and 15%, respectively). The reactions in water/SDS and in chloroform in the presence of **3** showed comparable conversions for all dienophiles **2a–g** in the range 70–85%, with only a small decrease with increasing length of substrate.

In chloroform without **3** the reaction is much slower but a more pronounced difference in activity for shorter compared to longer aldehydes is present, with **2a** giving 20% yield and **2b**–**g** between 11% and 7%. This confirms that **2a** is intrinsically more reactive compared to longer analogs **2b–g** probably because of slightly higher electrophilicity, while the other aldehydes react almost evenly, indicating that for the Cr(III) mediated reaction the length of the alkyl chain has almost negligible influence on the reaction outcome. The cycloaddition reaction in water in the absence of **3** was faster compared to chloroform and showed a decreasing trend with increasing length of the dienophile, in agreement with the solubility of the species and the observations of Breslow on the hydrophobic effect.[23] Addition of SDS to the reaction without **3** in water caused an increase of activity for all dienophiles indicating that anionic micelles act as effective catalysts for the reaction. The



Scheme 2. Substrate selective Diels–Alder reaction between cyclopentadiene 1 and α,β-unsaturated aldehydes **2a**–**g** mediated by Cr(III) (salen)Cl **3** in water with SDS as surfactant.