Selenium-based Lewis Acids

Chalcogen Bonding Utilized for Homogenous Catalysis

In the field of homogeneous catalysis, an extensive number of transition metal-based catalysts are known. Though highly potent, they have critical drawbacks, like high costs or toxicity. Thus, the application of metal-free catalysts got in the focus of research during the last years.

Transition metal complexes enable a variety of transformations like carbon-carbon bond formations, functional group interconversions, or the activation of small molecules [1]. Classical examples of such complexes for cross coupling reactions are Pd(PPh₃)₄ or Pd(Cl)₂(PPh₃)₂ [1-2]. Other metal centers like ruthenium are established in well-known catalysts for metathesis reactions [3]. In all these cases, the reaction mechanism involves the formation of covalent bonds between the substrate and the catalyst. Even though these catalysts are quite potent, they are also quite expensive (due to the use of precious metals) and/or toxic (e.g. if chromium or nickel is required).

At this point, the development of metal-free catalysts gains growing attention [4,5]. Such catalysts make use of non-covalent interactions of electrophilic hydrogen- or halogen-substituents with a (partially) negatively charged functional group or molecule [4a,6]. In case of halogens, their function as Lewis acids may seem counterintuitive at first. A closer inspection of the electronic distribution of such substituents reveals, though, that the electron distribution is anisotropic and thus there are also positively polarized areas on the surface of the halogens. One disadvantage of both hydrogen and halogen bond donors is the fact that they are monovalent, which means that a modification of the active center – the hydrogen or halogen substituent – is not directly possible. Rather, every optimization or modification must be performed at the backbone structure of the catalyst, which may be somewhat far from the interaction with the substrate.

Chelating Ligands with Chalcogen Bond Donors

This problem can be avoided when substituents from the sixth main group (chalcogens, Ch) such as sulphur, selenium or tellurium are used as active centers.
These are able to form a very similar interaction to halogen or hydrogen bonding, accordingly called “chalcogen bonding” (ChB). In analogy to the other mentioned interactions, the corresponding Lewis acids are called “chalcogen bond donors”. Due to the divalency of chalcogens, there is now a second substituent on the chalcogen atom, which is perpendicular to the backbone-Ch bond. This constitution allows structural modifications much closer to the center of complex formation. Additionally, this feature bears a high potential for organocatalysts based on the sixth main group: starting from one precursor compound, a larger batch of different ChB donors can be synthesized. Thus, a wide range of catalysts with different electronic and steric properties may be screened in a short period of time.

First applications of chalcogen bonding in solution were reported by Beer, Taylor and Matile et al. using different types of ChB donors for anion recognition [7-9]. Moreover, applications in solid state chemistry, such as the synthesis of nanostructures, make use of inter- and intramolecular chalcogen bonding. However, there is only one example applying chalcogen bonding in homogeneous catalysis, and it is based on sulfur: recently, Matile et al. published the reduction of quinoline derivatives with dithienothiophene-based compounds [10]. Overall, chalcogen bonding has been very sparsely used for applications in solution despite its advantages over halogen bonding.

**Why Selenium?**

The design of new cationic selenium-based chalcogen bond donors offers two advantages in comparison to sulphur and tellurium: first, selenium is more polarisable than sulfur, leading to a stronger interaction; second, organoselenium compounds are more stable than organotellurium compounds under standard conditions and do not require inert gas atmosphere. A cationic core structure of the chalcogen bond donor is important to establish a strong interaction with the substrate, as a suitable polarization of the backbone-Ch bond is required. More precisely, the activator candidates were based on 2-chalcogenated benzimidazolium
moieties. This type of core structure had already successfully been used in halogen bond catalysis [11]. A variety of different mono- and bidentate ChB donors was synthesized; selected compounds are shown in figure 1.

Compounds **syn-1** and **anti-1** carry an additional trifluoromethyl group in 2-position on the central benzene ring which retains a fixed syn- and anti-configuration of the chalcogen bond donor through preventing rotation of the benzimidazolium substituent. Moreover, it enables monitoring the reaction behavior of the catalyst via $^{19}$F NMR spectroscopy. Additionally, the trifluoromethyl group increases the strength of the ChB donor through its electron withdrawing properties and enhances the solubility of the catalyst.

**Carbon-Bromine Bond Cleavage**

As a simple benchmark reaction for potential chalcogen bonding based activators, the cleavage of a carbon bromine bond in a Ritter-type reaction was chosen, which was already successfully applied with halogen bonding (fig. 2) [12]. This reaction features several advantages which make it a valuable benchmark reaction for this purpose: it is unreactive in the presence of acid traces, it can be simply monitored by $^1$H NMR spectroscopy, and it has no substantial background reactivity at room temperature. Therefore, activation by the tested ChB donors can be unambiguously assigned to chalcogen bonding, if possible other interactions, like anion-π and hydrogen bonding, had been ruled out by appropriate comparison experiments.

First kinetic experiments displayed a 30-fold rate acceleration for the reaction with **syn-1** in contrast to the blank reaction. A comparison of chalcogen bond donor **syn-1** and its halogenated analogue **3** displayed a three times higher acceleration by the former. Based on that promising data, experiments with several activating agents were performed for which only the most interesting results are presented here. For **syn-1**, NMR yields of 64% and for **anti-1**, yields of 45% of compound **6** were determined. Against this, the appropriate halogen bond donor **3** yielded only 35% of compound **6**. The corresponding selenium urea **4**, as well as the hydrogen bond analogue **2**, were virtually inactive. Therefore, the activation of compound **5** can be ascribed to chalcogen bonding because both, hydrogen bonding and weak anion-π interactions can be excluded through these reference experiments. Interestingly, the **syn** atropisomer is not markedly more active than its **anti**-analogue, although DFT calculations gave evidence that **syn-1** may bind in a bidentate fashion. In contrast to that, **anti-1** behaves like a twofold monodentate chalcogen bond donor, as confirmed through single crystal X-ray diffraction analysis (fig. 2). It thus seems that **syn-1** does not bind in a clean bidentate fashion to bromide, even though the **syn** variant is more active than the **anti** one.
In summary, the first application of selenium based chalcogen bond donors as intermolecular Lewis acids in organic synthesis was presented using a carbon-bromine bond cleavage benchmark reaction. It was shown that chalcogen bond donors are superior to halogenated compounds from the same period, and that a locked syn configuration enhances the activity of these potentially bidentate compounds.

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