

## Organocatalysis | Hot Paper |

## Catalytic Carbon–Chlorine Bond Activation by Selenium-Based Chalcogen Bond Donors

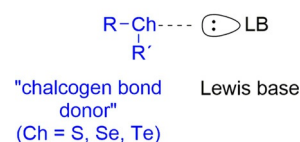
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**Abstract:** Chalcogen bonding is a noncovalent interaction based on electrophilic chalcogen substituents, which shares many similarities with the more well-known hydrogen and halogen bonding. Herein, the first application of selenium-based chalcogen bond donors in organocatalysis is described. Cationic bifunctionalized organoselenium compounds activate the carbon–chlorine bond of 1-chloroisochroman in a benchmark reaction. While imidazolium-based derivatives showed no noticeable activation, benzimidazolium backbones yielded potent catalysts. In all cases, *syn*-isomers were markedly more active, presumably due to bidentate coordination, which was confirmed by DFT calculations. Comparison experiments with the corresponding non-selenated as well as the non-cationic reference compounds clearly indicate that the catalytic activity can be ascribed to chalcogen bonding. The rate acceleration by the catalyst—compared to the non-selenated derivative—was about 10 fold.

In noncovalent organocatalysis, the majority of applications are based on hydrogen bonding (HB).<sup>[1]</sup> However, in the last years, interactions like anion– $\pi$ <sup>[2]</sup> and halogen bonding (XB)<sup>[3]</sup> have begun to emerge as viable alternatives to hydrogen bonding in several fields, including anion recognition and said organocatalysis. Another type of interaction that is closely related to halogen bonding is chalcogen bonding (ChB), that is, the attraction between an electrophilic chalcogen substituent Ch in compounds R–Ch–R' (Ch = S, Se, or Te) and Lewis bases (LB; Figure 1).<sup>[4]</sup> In this context, the organochalcogen compound is called a chalcogen bond donor even though it acts as a Lewis acid (electron acceptor).

Similarly to halogen bonding, chalcogen bonding is highly directional, with an R–Ch...LB angle of approximately 180°.<sup>[5,6]</sup> Its electronic origins are based on electrostatics<sup>[7]</sup> and orbital

chalcogen bonding:



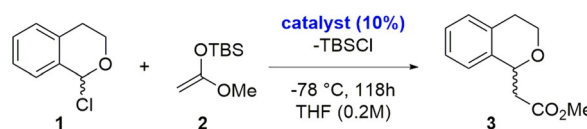
**Figure 1.** Definition of chalcogen bonding (R, R' = substituents, LB = Lewis base).

interactions,<sup>[5]</sup> both of which explain the demand for electro-negative substituents R to obtain stronger binding.<sup>[8]</sup>

Most applications of chalcogen bonding concern solid state structures and supramolecular assemblies like nanotubes,<sup>[9a,b]</sup> nanosheets,<sup>[9c]</sup> and macrocycles.<sup>[9d]</sup> Its use in solution is still very rare and is limited to a few fundamental studies on anion binding<sup>[10a–c]</sup> and related applications; seleno- and telluriumtriazol(ium) motifs, for instance, were used by Beer et al. in anion-binding rotaxanes.<sup>[10d]</sup> In addition, Matile et al. showed that sulfur-based ChB donors with a dithienothiophene (DTT) core unit are suitable for anion transport.<sup>[11]</sup>

The same group also reported the first use of ChB Lewis acids as organocatalysts using DTT derivatives for the catalytic hydrogenation of quinoline to the corresponding dihydroquinolines.<sup>[12]</sup> Even though these findings clearly indicate the potential of organosulfur compounds for organocatalysis, selenium as the more polarizable element should yield even stronger ChB donors. Consequently, in a recent publication, selenium-based ChB donors were shown to activate the carbon–bromine bond of benzhydryl bromide in a solvolysis reaction.<sup>[13]</sup> In this case, however, the organoselenium compounds had to be used in stoichiometric amounts.

Herein, we present, to the best of your knowledge, the first catalytic application of selenium-based ChB donors in organocatalysis. As a benchmark reaction for the activation of a carbon–chlorine bond, the substitution of 1-chloroisochroman **1** with a silyl ketene acetal (**2**) was chosen (Scheme 1), since it had already successfully served as test case for hydrogen bonding and halogen bonding organocatalysis.<sup>[14a,b]</sup> As back-



**Scheme 1.** Benchmark reaction of 1-chloroisochroman (**1**) with silyl ketene acetal **2** in presence of ChB (chalcogen bonding) catalysts. TBS = *tert*-butyldimethylsilyl. A slight excess of **2** (1.5 equiv) was used.

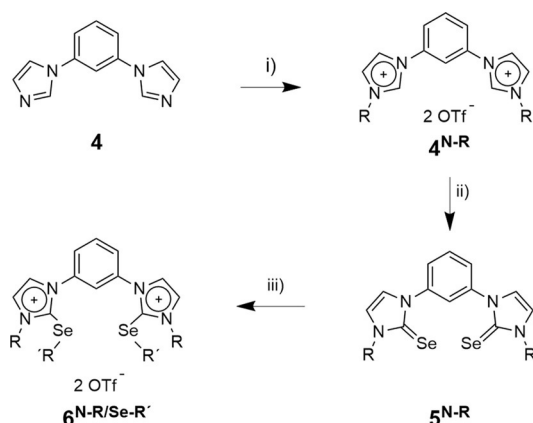
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bones for suitable catalyst candidates, bisimidazolium structures as well as the already successfully employed bisbenzimidazolium moieties were considered. With selenium as the chalcogen, two to three different alkyl groups as second substituent were used to obtain a first idea on the role of this parameter. In the bisbenzimidazolium compounds, an additional trifluoromethyl group was placed on the central benzene core. This served different purposes, namely a) as a marker for  $^{19}\text{F}$  NMR monitoring, b) as further electron-withdrawing group, and c)—most importantly—as a barrier to rotation of the benzimidazolium groups, enabling the separation of *syn*- and *anti*-atropisomers.

The bisimidazolium-based compounds were synthesized according to Scheme 2, starting from compound **4** (for further details see the Supporting Information).

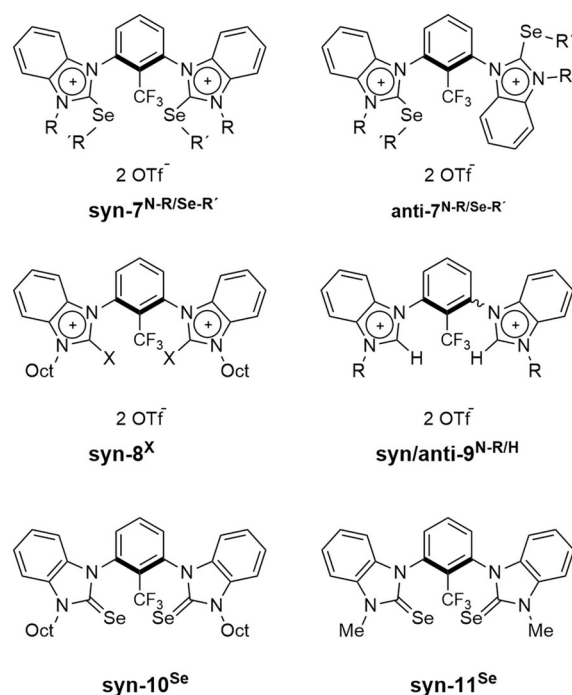


**Scheme 2.** Reagents and conditions: i) R-OTf (3 equiv.; R = methyl (Me), octyl (Oct)) CH<sub>2</sub>Cl<sub>2</sub> (0.3 M), rt, 24 h; ii) Se (2.5 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (2.5 equiv.), MeOH (0.2 M), reflux, 24 h;<sup>[13]</sup> iii) R-OTf (4 equiv.; R = Me, Oct), CH<sub>2</sub>Cl<sub>2</sub> (0.03 M), rt, 24 h. Selected yields: 90% of **4<sup>N-Oct</sup>**, 95% of **4<sup>N-Me</sup>**, 49% of **5<sup>N-Oct</sup>**, 22% of **5<sup>N-Oct</sup>**, 75% of **6<sup>N-Oct/Se-Me</sup>**, 56% of **6<sup>N-Me/Se-Oct</sup>**.

The bisbenzimidazolium compounds that were envisaged as catalyst candidates or reference compounds (see Figure 2 for structures and nomenclature) were synthesized as recently published by our group.<sup>[13]</sup>

Prior to the actual catalysis studies with ChB donors, some initial experiments were performed, most importantly to rule out activation by anion- $\pi$  interactions of the cationic moieties or by other effects not related to chalcogen bonding (Table 1).

It had already been shown that several possible impurities—especially traces of acid—do not act as catalyst in this reaction.<sup>[14a,16]</sup> In the absence of any additive, no background reaction was observed at  $-78^\circ\text{C}$  even after 118 h (Table 1, Entry 1). The non-selenated reference compounds (and HB donors) *syn/anti-9<sup>N-Me/H</sup>* and *syn/anti-9<sup>N-Oct/H</sup>* showed little to no activity, indicating that the cationic moieties in themselves (as well as the counterions) are not capable of catalysis via anion- $\pi$  interactions or other effects. The inactivity of the corresponding imidazolium-derived hydrogen bond donors (**4<sup>N-R</sup>**) had already been demonstrated.<sup>[14a]</sup> Hence, any activity by the selenated derivatives must be caused by the additional alkylselenyl group and, thus, by chalcogen bonding.



**Figure 2.** Overview of all benzimidazolium-based catalyst candidates. R' = methyl (Me), octyl (Oct), or isopropyl (*i*Pr); X = I or Br; OTf = trifluoromethanesulfonate. In case of *syn/anti-9<sup>N-R/H</sup>*, an inseparable mixture of both isomers was used.

**Table 1.** Overview of initial experiments; background activity and reference compounds to rule out activation by other effects than chalcogen bonding.

No.	Catalyst	Mol %	Yield of <b>3</b> [%] <sup>a,b</sup>
1	–	0	≤ 5
2	<i>syn/anti-9<sup>N-Me/H</sup></i>	10	≤ 5
3	<i>syn/anti-9<sup>N-Oct/H</sup></i>	10	9

[a] Reaction time was 118 h. [b] Yield of **3** according to  $^1\text{H}$  NMR analysis (see the Supporting Information).

Based on these results, the reaction was then performed in the presence of various cationic chalcogen bond donors and comparison compounds (Table 2). All reactions were monitored by  $^{19}\text{F}$  NMR to check catalyst stability and all compounds proved to be stable under the reaction conditions.

Bisimidazolium-based chalcogen bond donors **6<sup>N-Oct/Se-Me</sup>** and **6<sup>N-Me/Se-Oct</sup>** were inactive as catalysts (Table 2, Entries 3 and 4). Possibly, the imidazolium groups do not provide sufficient polarization of the selenium centers. In addition, the free rotation of the chalcogen bonding substituents does not allow the formation of strong ChBs due to the loss of entropy upon binding (especially compared to the locked benzimidazolium structures in Figure 2). Unfortunately, all attempts to synthesize locked atropisomers of the bisimidazolium compounds have failed so far.

In contrast, all tested bisbenzimidazolium compounds showed catalytic activity, with the *syn* isomers (Table 2, Entries 10–12) reaching up to 92% yield of product **3**. The corre-

No.	Catalyst	Mol %	Yield of <b>3</b> [%] <sup>[b]</sup>
1	<i>syn-8</i> <sup>I</sup>	10	≥ 95 <sup>[c]</sup>
2	<i>syn-8</i> <sup>Br</sup>	10	40
3	<b>6</b> <sup>N-Oct/Se-Me</sup>	10	≤ 5
4	<b>6</b> <sup>N-Me/Se-Oct</sup>	10	≤ 5
5	<i>syn-10</i> <sup>Se</sup>	10	≤ 5
6	<i>syn-11</i> <sup>Se</sup>	10	26
7	<i>anti-7</i> <sup>N-Oct/Se-<i>i</i>Pr</sup>	10	42
8	<i>anti-7</i> <sup>N-Oct/Se-Me</sup>	10	19
9	<i>anti-7</i> <sup>N-Me/Se-Oct</sup>	10	24
10	<i>syn-7</i> <sup>N-Oct/Se-<i>i</i>Pr</sup>	10	74
11	<i>syn-7</i> <sup>N-Oct/Se-Me</sup>	10	66
12	<i>syn7</i> <sup>N-Oct/Se-Oct</sup>	10	92

[a] Reactions were performed at least two times. [b] Yield of **3** according to <sup>1</sup>H NMR analysis (see the Supporting Information). [c] After 24 h.

sponding *anti* analogues (Table 2, Entries 7–9) were markedly less active for all three derivatives. This indicates that while the *anti* isomers effectively act as twofold monodentate chalcogen bond donors, the *syn* isomers seem to bind in an at least partially bidentate fashion to chloride. Orientating DFT calculations were performed to demonstrate the feasibility of such a bidentate coordination of a bis(benzimidazolium)-based model chalcogen bond donor (with methyl groups on nitrogen and selenium) to chloride (for details, see the Supporting Information). The complex is shown in Figure 3.

Comparably weak activity was observed for the corresponding neutral selenourea compounds *syn-10*<sup>Se</sup> and *syn-11*<sup>Se</sup> (Table 2, Entries 5 and 6). As these nonalkylated species are expected to be much weaker chalcogen bond donors, this further corroborates the mode of activation by chalcogen bonding—and it also stresses the need for cationic core structures for catalytic activity.

The dependency of the activity of chalcogen bond donors *syn-7*<sup>N-R/Se-R'</sup> on the alkyl group R' on selenium is slightly different for the *anti* (*i*Pr > Oct > Me) and the *syn* (Oct > *i*Pr > Me) isomer. In general, bulkier groups seem to induce more activity than methyl ones for currently unknown reasons.

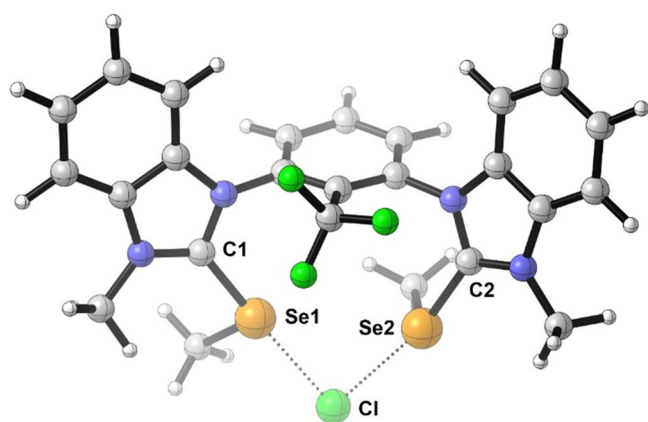


Figure 3. DFT calculation of the complex of a model bidentate chalcogen bond donor with chloride. Plot by CYLview<sup>[17]</sup>.

A direct comparison of ChB with XB (Table 2, Entries 1 and 2) showed that the iodinated Lewis acid *syn-8*<sup>I</sup> is markedly more active than even the best chalcogen bond donor. In contrast, the XB donor with the element of the same period (*syn-8*<sup>Br</sup>) is somewhat less active than ChB donors *syn-7*<sup>N-R/Se-R'</sup>. This is in agreement with the relative performance of these compounds as activators in a solvolysis reaction.<sup>[13]</sup>

To obtain further insights into the relative activity of chalcogen bonding versus halogen bonding, kinetic measurements with the strongest ChB donor *syn-7*<sup>N-Me/Se-Oct</sup>, the corresponding brominated XB donor *syn-8*<sup>Br</sup>, and the neutral selenourea *syn-11*<sup>Se</sup> as reference compound were performed (Figure 4). The background reaction was unsuitable as a reference, since, even after 118 h, less than 5% of product **3** were formed.

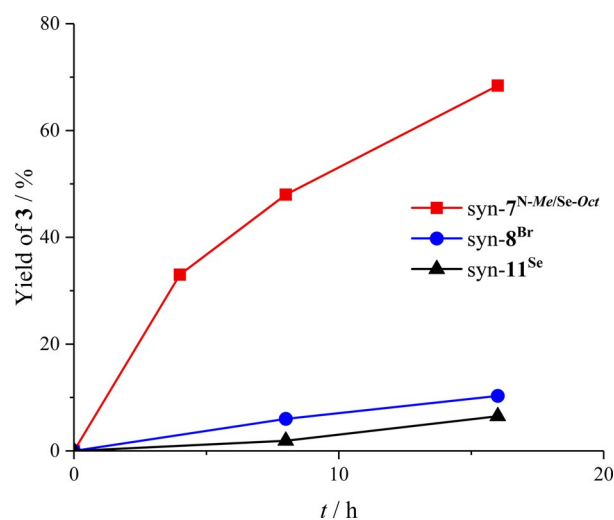


Figure 4. Yield-versus-time profile of selected reactions of Table 2. Yields were determined by <sup>1</sup>H NMR spectroscopy (see the Supporting Information).

Compared to selenourea *syn-11*<sup>Se</sup> ( $k_{\text{rel}} = 1.0$ ), XB donor *syn-8*<sup>Br</sup> ( $k_{\text{rel}} = 1.5$ ) was slightly more active. In contrast, ChB donor *syn-7*<sup>N-Me/Se-Oct</sup> ( $k_{\text{rel}} = 10.8$ ) was still seven times more active than the brominated compound. These results illustrate the fact that the difference between ChB and XB donors with elements of the same period is somewhat underestimated by the yields in Table 2.

Finally, <sup>1</sup>H NMR titration experiments<sup>[18]</sup> were performed with ChB donors **6**<sup>N-Oct/Se-Me</sup>, **6**<sup>N-Me/Se-Oct</sup>, and *syn-7*<sup>N-Oct/Se-*i*Pr</sup> to correlate their binding strength to halides with their catalytic activity. Unfortunately, the obvious choice of chloride as guest with THF as solvent was not feasible due to slight decomposition of the hosts and due to precipitation of the complexes after addition of less than one equivalent of chloride. Thus, only bromide as guest in CD<sub>3</sub>CN as solvent proved to be a suitable titration system at room temperature (Table 3).

The binding constants obtained for all three ChB donors were relatively similar at around 300 M<sup>-1</sup>. While the data of **6**<sup>N-Oct/Se-Me</sup> and **6**<sup>N-Me/Se-Oct</sup> (317 M<sup>-1</sup> and 351 M<sup>-1</sup>) may be in line with their inactivity in the test reaction, the virtually identical binding constant of *syn-7*<sup>N-Oct/Se-*i*Pr</sup> (341 M<sup>-1</sup>) is evidently in

**Table 3.** Titration experiments for selected ChB donors with tetraoctylammonium bromide at room temperature.

No.	Catalyst	Solvent	Anion	$K$ [M <sup>-1</sup> ] <sup>[a]</sup>
1	6 <sup>N-Oct/Se-Me</sup>	CD <sub>3</sub> CN	Br <sup>-</sup>	317
2	6 <sup>N-Me/Se-Oct</sup>	CD <sub>3</sub> CN	Br <sup>-</sup>	351
3	syn-7 <sup>N-Oct/Se-iPr</sup>	CD <sub>3</sub> CN	Br <sup>-</sup>	341

[a]  $K$  = binding constant.

stark contrast to the catalysis study. While this likely indicates that, inter alia, the relative binding strengths to bromide in CD<sub>3</sub>CN are different from the ones to chloride in THF, the data still provides a rough first estimate of the chalcogen bonding strength for these systems.

In conclusion, the first application of selenium-based ChB donors as Lewis acidic organocatalysts was presented. While bisimidazolium-derived ChB donors were inactive, bisbenzimidazolium-based ones provided up to 92% yield in the benchmark reaction of 1-chloroisochroman with a silyl ketene acetal. Comparison experiments with the analogous HB donors ruled out other possible modes of activation next to chalcogen bonding. The *syn*-atropisomers were reproducibly more active than the related *anti*-isomers, pointing towards an at least partially multidentate binding of chloride by the most active ChB donors. Compared to a brominated XB donor, the rate acceleration by the XB donor was about 7 fold stronger. All these findings provide a solid basis for the further development of chalcogen bonding organocatalysis.

Even though the interaction may be generally weaker than HB or XB, it also features some unique advantages. Maybe the most notable one with respect to the catalysis presented herein is the presence of a second substituent on the electrophilic atom that is orientated at a 90° angle to the electrophilic axis. This close proximity to the substrate may offer additional control not possible with HB or XB. Studies towards the utilization of this effect are currently underway.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** chalcogen bonding · Lewis acids · noncovalent interactions · nucleophilic substitution · organocatalysis

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