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Carbon-Halogen Bond Activation by Selenium-Based Chalcogen Bonding

Patrick Wonner,[a] Lukas Vogel,[a] Maximilian Düser,[a] Luís Gomes,[a] Florian Kniep,[a] Bert Mallick,[a] Daniel B. Werz,[b] and Stefan M. Huber[a]*

Abstract: Chalcogen bonding is a little explored non-covalent interaction similar to halogen bonding. This manuscript describes the first application of selenium-based chalcogen bond donors as Lewis acids in organic synthesis. To this end, the solvolysis of benzhydryl bromide served as a halide-abstraction benchmark reaction. Chalcogen bond donors based on a bis(benzimidazolium) core provided rate accelerations versus background reactivity in the order of 20-30. Several comparison experiments provide clear indications that chalcogen bonding is the origin of the observed activation. The performance of the chalcogen bond donors is superior to that of the related brominated halogen bond donor.

In recent years, the application of previously little-explored interactions like anion-π[1] and halogen bonding[2] in solution has received increased interest. Closely related to halogen bonding is chalcogen bonding, i.e. the attractive interaction between an electrophilic chalcogen substituent Ch (S, Se, or Te) and Lewis bases LB (Figure 1).[3] Such Lewis acids R/R'-Ch are typically – albeit somewhat confusingly – called *chalcogen bond donors* (despite their function as electron acceptors).

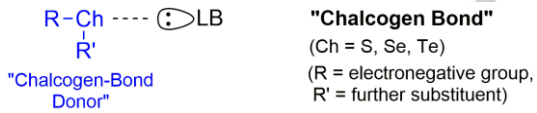

Figure 1. Definition of chalcogen bonding (LB = Lewis base).

Several components likely contribute to the overall interaction energy: similarly to halogen bonding, the electronic distribution of heavier chalcogen atoms is anisotropic, with reduced electron density in the elongation of the R-Ch axes. In suitably polarized compounds, a region of positive electrostatic potential ("σ-hole")[4] is formed, which interacts favorably with the negatively polarized Lewis base. Furthermore, electronegative groups R lower the σ* orbital of the R-Ch bond and increase its coefficient on the Ch substituent. Thus, chalcogen bonding may also be described as an n→σ* charge transfer interaction[5] between the chalcogen bond donor and the nonbonding lone pair of the Lewis base. Finally, dispersion contributions will also be relevant for heavier chalcogens.

Due to its electronic origin, chalcogen bonding is highly directional,[5,6] as reasonably strong chalcogen bonding requires R-Ch···LB angles of approximately 180°. Even though it is typically weaker than halogen bonding,[7] chalcogen bonding features two distinct advantages over the latter: firstly, the second substituent R' on the chalcogen atom - orientated at 90° relative to the Ch···LB interaction - interacts more directly with the substrate than the backbone R of halogen bond donors R-X. Secondly, if both substituents R and R' are sufficiently electronegative, two perpendicular electrophilic axes on the chalcogen substituent are present.

In the solid state, chalcogen bonding has been applied in some few cases to construct supramolecular assemblies like nanotubes,[8a,b] nanosheets,[8c] wires,[8d] and macrocycles.[8e] In solution, fundamental studies and applications are arguably even more rare and focus mostly on anion recognition. Investigated systems include a mixed telluronium/boron Lewis acid,[9a] benzotelluradiazoles as monodentate receptors[9b] and tellurophene derivatives as bidentate ones.[9c] Very recently, Beer et al. also reported the use of seleno- and telluriumtriazol(ium) motifs in anion-binding rotaxanes.[10] Even though sulfur-based chalcogen bond donors are expected to form weaker interactions than selenium- or tellurium-based ones an appropriately designed bidentate dithienothiophene (DTT) derivative has been used by Matile et al. for anion transport.[11]

Since Lewis acids based on "unconventional" weak interactions like anion-π[12] and halogen bonding[13] have by now been introduced in organic synthesis and organocatalysis, a similar approach seems feasible for chalcogen bonding. The few currently known examples related to this concept focus almost exclusively on *intramolecular* binding as a tool to rigidify structural motifs.[14]

In contrast, the first chalcogen bonding based organocatalysis by the *intermolecular* coordination and activation of a substrate has recently been published by Matile.[15] In this case, DTT derivatives catalyzed the reduction of quinolone derivatives.

Herein, we present the first application of selenium-based chalcogen bond donors as noncovalent activators, utilizing a C-X activation ("anion binding") benchmark reaction.[16] These kind of proof-of-principle studies pose two main challenges: i) since chalcogen bonds are rather weak, other interactions will likely also contribute and it is difficult to ascribe the action of an activator to chalcogen bonding as main cause and ii) it is often difficult to rule out the action of impurities, most importantly hidden traces of acid.

As a consequence, a relatively simple test reaction, the solvolysis of benzhydryl bromide **1** in wet acetonitrile, was chosen (Scheme 1). This transformation, which we already

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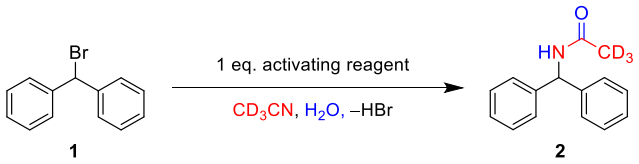
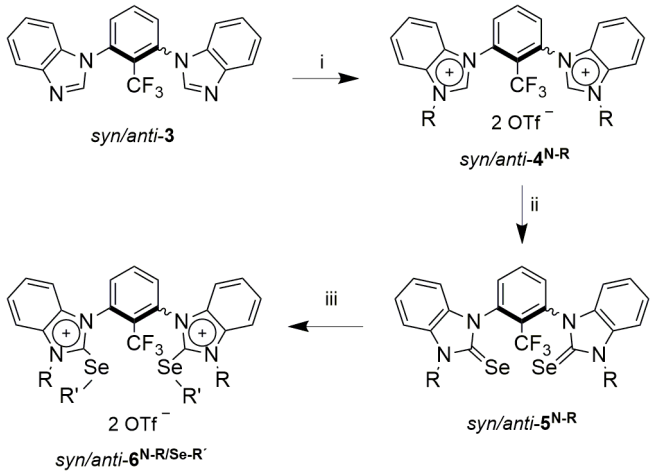
applied in fundamental studies on halogen bonding, was shown to be immune to hidden acid catalysis.[16] In addition, it has virtually no background reaction at room temperature and is easy to follow via ^{1}H NMR spectroscopy.



Scheme 1. Anion-binding benchmark reaction.

For the design of strong chalcogen bonding based activator candidates, we decided to rely on cationic backbones R in order to achieve a strong polarization of (at least one) R-Ch bond.[17] More precisely, the bis(benzimidazolium)-based backbone structure of **4** (Scheme 2) was selected since the corresponding halogen bond donor had shown a relatively strong Lewis acidity.[18] The trifluoromethyl group in these compounds prevents rotation of the benzimidazolium groups and allows monitoring via ^{19}F NMR. As chalcogen, selenium was selected, since it should provide stronger Lewis acidity than sulfur, but be less prone to decomposition than tellurium. Ideally, a bidentate coordination of substrates by chalcogen bond donors **4** is aspired, as is predicted by gas-phase calculations (see SI). Since selenium is smaller than iodine, it remains uncertain whether this binding motif can indeed be realized in solution. Finally, simple alkyl groups were introduced as second substituents on the chalcogen: octyl or isopropyl for good solubility, methyl for crystallization studies.



Scheme 2. Synthesis of chalcogen bond donors; i) R-OTf, CH_2Cl_2 (R = Me, Oct); ii) Se, Cs_2CO_3, MeOH; iii) R-OTf, CH_2Cl_2 (R = Me, Oct, iPr). Selected yields: *syn/anti*-**4**$^{N\text{-}Oct}$ 84%, *syn*-**5**$^{N\text{-}Me}$ 80%, *anti*-**5**$^{N\text{-}Me}$ 87%, *syn*-**5**$^{N\text{-}Oct}$ 33%, *anti*-**5**$^{N\text{-}Oct}$ 63%, *syn*-**6**$^{NOct/Se\text{-}iPr}$ 95%, *anti*-**6**$^{NOct/Se\text{-}iPr}$ 90%, see also SI.

The synthesis of the chalcogen bond donors is depicted in Scheme 2. Starting from an (inseparable) *syn/anti* mixture of **4**$^{N\text{-}Me}$ or **4**$^{N\text{-}Oct}$, selenation was achieved with caesium carbonate and elemental selenium.[19] In both cases, the resulting selenated isomers could be separated via column chromatography (**4**$^{N\text{-}Me}$: 38% *syn*, 62% *anti*; **4**$^{N\text{-}Oct}$: 26% *syn*, 74% *anti*). Subsequent alkylation with methyl, octyl or isopropyl triflate proceeded with good to excellent yields and provided the desired cationic chalcogen bond donors (see SI). All chalcogen bond donors are stable under air and moisture and show no signs of decomposition in acetonitrile solution even after three months (in ^{1}H and ^{19}F NMR).

The X-ray structural analysis of compound *anti*-**6**$^{N\text{-}Me/Se\text{-}Me}$ included two dications and four triflates in the unit cell (Figure 2).

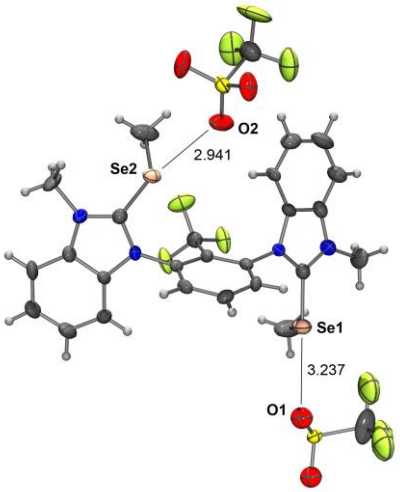


Figure 2. X-ray structural analysis of *anti*-**6**$^{N\text{-}Me/Se\text{-}Me}$. One ion pair of two in the unit cell is shown (ellipsoids at 50% probability). Selected bond lengths [Å] and angles [°]: C-Se2 = 1.891, C-Se1 = 1.900, C-Se2-O2 = 163, C-Se1-O1 = 173.

All four selenium centers feature a chalcogen bond (in elongation of the $C_{benzimidazolium}$-Se bond) to oxygen atoms of triflate. The corresponding Se···O distances range from 2.94 to 3.24 Å, all markedly below the sum of the van-der-Waals radii of both elements (3.42 Å).[20] The C-Se···O angles (163° to 173°) are in general agreement with the expected linearity, with one slight exception (151°), which is likely due to additional packing effects. Overall, the crystal structure clearly confirms the expected σ* acidity of the carbon-selenium bonds.

With these promising findings in hand, several activator candidates were tested in the benchmark reaction mentioned above (Scheme 1). All reactions were reproduced at least twice with only minor variations. In all cases, a clean transformation to amide **2** was observed. Even after 140 h, the background reactivity amounts to only 10% yield of **2** (Table 1, entry 1).

Table 1. Effect of various chalcogen bond donors and reference compounds on the anion-binding benchmark reaction of Scheme 1.

Entry	Activating reagent	Equiv.[a]	Yield [%][b]

1	---	---	10
2	*syn/anti*-**4**$^{N\text{-}Oct}$	1.0	11
3	*syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$	1.0	64
4	*anti*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$	1.0	45
5	*syn*-**5**$^{N\text{-}Oct}$	1.0	< 5[c]
6	iPrBr	1.0	< 5
7	**7**^{H}	2.0	16
8	**8**	2.0	< 5[c]
9	**9**$^{Se\text{-}Oct}$	2.0	34
10	**9**$^{Se\text{-}iPr}$	2.0	45
11	**7**^{I}	2.0	48[d]
12	*syn*-**10**^{I}	1.0	> 95%[e]
13	*syn*-**10**^{Br}	1.0	35%

[a] Equivalents of activating reagent (relative to **1**). [b] Yield of **2** after 140 h at room temperature according to ^{1}H NMR analysis (see the Supporting Information). [c] Low solubility in acetonitrile. [d] Yield after 96 h. [e] Quantitative yield of **2** after 24 h.

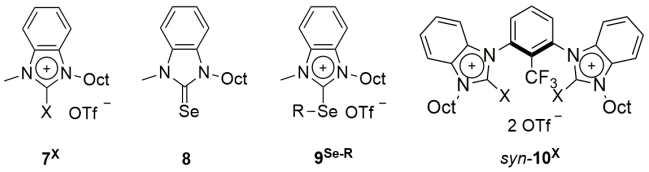
Next, several potentially bidentate activating reagents were employed. The (so far inseparable) *syn*/*anti*-mixture of non-selenated reference compound **4**$^{N\text{-}Oct}$ resulted in only 11% product formation (Table 1, entry 2) and thus provided no noticeable activation of **1**.

In contrast, all selenated (cationic) derivatives induced a marked increase in the yield of **2**. Compound *syn*-**6**$^{N\text{-}Oct/Se\text{-}Me}$, for instance, lead to approx. 60% yield after 96 h. However, NMR spectra of the reaction showed clear signs of activator decomposition by dealkylation of the selenium center, as formation of MeBr was observed. Titration experiments with bromide confirmed that this chalcogen bond donor is not stable under the reaction conditions. The same is true, albeit to a somewhat lesser extent, for the octylated variant *syn*-**6**$^{N\text{-}Me/Se\text{-}Oct}$ and thus both were not considered further. Since dealkylation will likely occur via an S_N2 mechanism, we reasoned that a secondary alkyl substituent on selenium should provide more stability. Indeed, activator candidate *syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$ showed only minor signs of decomposition (4% after 140 h according to ^{19}F NMR) and was thus considered suitable for further activation experiments. Amide **2** was formed with 64% yield (Table 1, entry 3; for a stackplot see SI). The NMR spectra indicate that the slight decomposition of *syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$ over time is again due to dealkylation with formation of isopropyl bromide. To rule out any activity of *syn*-**5**$^{N\text{-}Oct}$ and iPrBr - which would have to be catalytic -, both were also tested and provided less than 5% yield of product (Table 1, entries 5 and 6).

All findings presented so far provide strong indications that the activity of *syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$ is based on chalcogen bonding: acid catalysis can be ruled out in this reaction and the otherwise identical non-selenated compound (which should form at least as strong anion-π interactions) is completely inactive. Thus, the selanylalkyl group must constitute the active site, and the X-ray structural analysis of *anti*-**6**$^{N\text{-}Me/Se\text{-}Me}$ as well as the DFT calculations (see SI) clearly show chalcogen bonding as its binding mode.[21]

The corresponding *anti*-isomer of **6**$^{N\text{-}Oct/Se\text{-}iPr}$ was somewhat less active (45 % yield of **2**, entry 4), but the difference to the *syn*-isomer was not very strong. This seems to indicate that *syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$ does not bind to bromide in a clean bidentate fashion, as a more pronounced effect might be expected in this case.

Subsequently, several simple monodentate benzimidazolium derivates (Figure 3) were used as potential activating reagents, to further elucidate any effect of the backbone structure of *anti*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$ on the activity of the individual seleno-benzimidazolium moieties. Two equivalents of these species were used in the test reactions to provide the same number of active centers as with the bifunctional chalcogen bond donors described before.



7^{X} **8** **9**$^{Se\text{-}R}$ *syn*-**10**^{X}

Figure 3. Further reference compounds (X = H, Br, I; R = Oct, iPr).

Similarly to the previous findings, the selenated derivates **9**$^{Se\text{-}Oct}$ (34% yield, entry 9) and **9**$^{Se\text{-}iPr}$ (45% yield, entry 10) were markedly more active than the non-selenated reference compound **7**^{H} (16%, entry 7) and the non-alkylated precursor **8** (< 5%, entry 8). Thus, since the activity of two equivalents of **9**$^{Se\text{-}iPr}$ is identical to that of one equivalent of *anti*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$, there seems to be no additional effect of the backbone of the latter on its chalcogen bonding subunits.

Finally, a direct comparison of the activation by chalcogen bonding with the already established one by halogen bonding was aspired. To this end, closely related halogenated analogues were also used, and in the case of **7**^{I} (48% yield after 96 h, entry 11), the performance was somewhat superior to the one of **9**$^{Se\text{-}iPr}$ The difference was more pronounced for the bidentate variants, as *syn*-**10**^{I} lead to quantitative product formation after 24 h.[22] Part of this difference might be due to a less strained bidentate binding of bromide by the iodinated Lewis acid. However, an arguably more fair comparison is the one to the halogen of the same period, and *syn*-**10**^{Br} is indeed even slightly less active (35 %, entry 13) than *syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$.

Yield-versus-time profiles for selected reactions are presented in Figure 4. Based on the initial slopes of product formation, it can be estimated that the reaction rate increases by about one order of magnitude by *syn*-**10**^{Br} compared to the background (k_{rel} = 9). The rate acceleration by the chalcogen bond donors, in turn, is about twice (*anti*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$, k_{rel} = 23) or three times (*syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$, k_{rel} = 34) that of *syn*-**10**^{Br}.

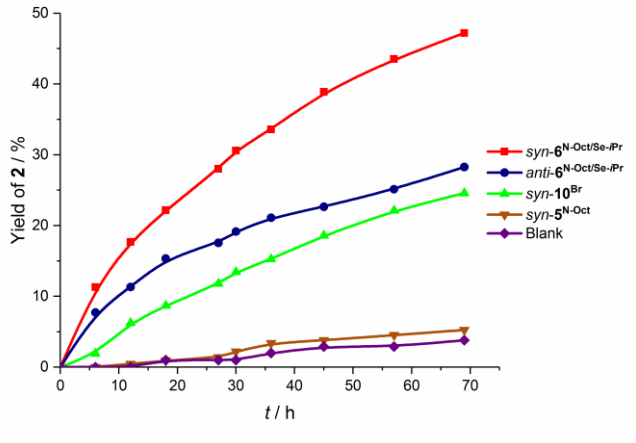


Figure 4. Yield-versus-time profile of selected reactions.

In conclusion, the first intermolecular use of selenium-based chalcogen bond donors as Lewis acids in organic synthesis was presented. Using a suitable benchmark reaction for halide binding reactivity and several comparison experiments, strong indications for chalcogen bonding as the actual mode of action were obtained - most notably the fact that the corresponding non-selenated reference compound was inactive. Even if the observed effect is less strong than the activity of bidentate iodine-based halogen bond donors, further detailed investigations on the use of chalcogen bonding in solution will likely provide the basis for more sophisticated mixed catalyst systems, in which chalcogen bonding could play an important role.

Acknowledgements

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Keywords: chalcogens • noncovalent interactions • Lewis acids • chalcogen bonding • solvolysis

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[21] In further experiments to rule out active impurities, different batches of elemental selenium were used and different materials for column chromatography were employed, with virtually identical results in all cases.

[22] Titration experiments with $NOct_4Br$ in acetonitrile also showed that *syn*-**6**$^{N\text{-}Oct/Se\text{-}iPr}$ binds weaker to bromide ($K = 340\ M^{-1}$) than *syn*-**10**^{I} ($K = 3.5 \cdot 10^6\ M^{-1}$, ref. [18]), see SI.

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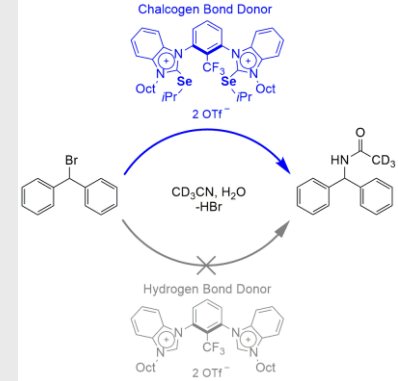

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Carbon-Halogen Bond Activation by Selenium-Based Chalcogen Bonding

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