

Noncovalent Catalysis | Very Important Paper |

VIP

 σ -Hole Interactions in CatalysisMartin Breugst,^{*,[a]} and Dr. Jonas J. Koenig^[a]*Dedicated to Professor Jörg Pietruszka on the occasion of his 55th birthday*

Abstract: Noncovalent interactions like halogen, chalcogen, and pnictogen bonding are known for a very long time. During the last decade, these interactions have found different applications in catalysis. These forces are often called σ -hole interactions which can be explained by the anisotropic distribution of

the electron density around these atoms. In this MiniReview, we will present recent applications of halogen, chalcogen, and pnictogen bonding in catalysis and discuss experimental and computational investigations to gain more insights into the underlying mechanisms.

Introduction

Noncovalent interactions play an important role in many aspects of chemistry including biochemistry, molecular recognition processes and materials.^[1] Consequently, it is not surprising that many researchers have focused on the applicability of these interactions in catalysis. Hydrogen bonding can probably be considered to be the best-researched noncovalent interaction with numerous examples in synthesis and catalysis.^[2] In the last decade, noncovalent interactions like halogen, chalcogen,

and pnictogen bonding have emerged as new catalytic motifs. In these “unconventional” interactions, the Lewis-acidic region of a halogen, chalcogen, or pnictogen atom interacts with the electron pair of a Lewis base to form the corresponding Lewis acid-base complex. At a first glance, it seems rather unusual that a reactive site that still features at least one lone pair should act as a Lewis acid rather than as a Lewis base. Already in 1972 Alcock summarized a survey of crystal structures and employed the term “secondary bond” for what is today known as halogen, chalcogen, or pnictogen bonds.^[3]

The name “ σ -hole interactions” that is frequently used to describe these noncovalent forces was initially proposed by Clark, Murray, and Politzer in 2007.^[4] Electrostatic potentials as shown for selected examples in Figure 1 reveal an anisotropic distribution of the electron density around heavy atoms that result in electropositive regions (blue surface areas in Figure 1), the so-called σ -holes. The name was chosen to reflect the relative position in elongation of σ -bonds. Halogen-bond donors like ICF₃ possess only one σ -hole, while the chalcogen-bond donor Te(CF₃)₂ displays two and the pnictogen-donor Sb(CF₃)₃ three σ -holes. Although this approach provides an illustrative under-

[a] Priv.-Doz. Dr. M. Breugst, Dr. J. J. Koenig
Department für Chemie, Universität zu Köln,
Greinstraße 4, 50939 Köln, Germany
E-mail: mbreugst@uni-koeln.de
<http://physorg.uni-koeln.de>

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Martin Breugst studied chemistry at the Ludwig-Maximilians-Universität in Munich (Germany). He obtained his Ph.D. in physical-organic chemistry there in 2010 under the supervision of Prof. Dr. Herbert Mayr. Afterwards, he moved to the University of California, Los Angeles as a Feodor-Lynen postdoctoral fellow of the Alexander-von-Humboldt foundation where he worked with Prof. Dr. Kendall N. Houk on different aspects of computational organic chemistry. In 2013, he started his independent academic career at the Department of Chemistry at the University of Cologne supported by a Liebig scholarship of the Fonds der Chemischen Industrie and completed his habilitation in 2017. Afterwards, he worked as an interim professor at the University Regensburg and the RWTH Aachen University. His research interests include noncovalent interactions and the elucidation of reaction mechanism by experimental and computational approaches.



Jonas J. Koenig obtained his M. Sc. in Chemistry from the RWTH Aachen University (Germany) in 2016. Afterwards, he joined the group of Martin Breugst at the University of Cologne and completed his Ph.D. in 2020. His research interests are focused on iodine and halogen-bond catalysis.

standing of these interactions, theoretical investigations have clearly shown that besides these electrostatic contributions, charge transfer and dispersion are also important for a proper description of these noncovalent interactions.^[5] In line with these findings, Huber, Weiss, and colleagues recently reported on complexes involving “anti-electrostatic” halogen bonds:^[6] in these structures, the halogen-bond donor, a 1,2-bis(dicyanomethylene)-3-iodo-cyclopropanid ion, is negatively charged and nonetheless directly interacts with the equally negatively charged iodide anion (Figure 2). In these compounds, the electrostatic potential at the iodine atom is negative, but these structures engage in halogen bonding nonetheless. Computational investigations reveal that polarization and $n \rightarrow \sigma^*$ orbital interactions are important for these halogen bonds. Consequently, these examples clearly show that the static σ -hole explanation is highly problematic for the rationalization of these interactions. However, in lieu of a better terminology for these noncovalent interactions, we will still refer to those as σ -hole interactions.

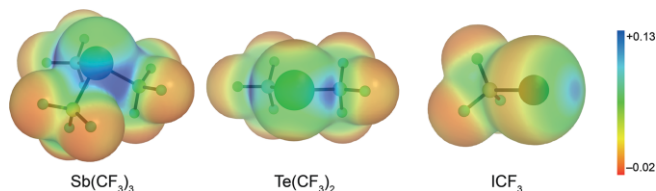


Figure 1. Calculated electrostatic potential for a pnictogen-, chalcogen, and halogen-bond donor on the 0.001 au isodensity surface (ω B97X-D/aug-cc-pVTZ).

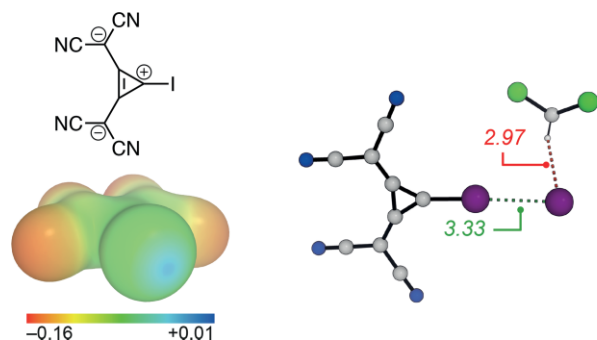


Figure 2. 1,2-Bis(dicyanomethylene)-3-iodo-cyclopropanid as a negatively charged halogen-bond donor, its calculated electrostatic potential on the 0.001 au isodensity surface (ω B97X-D/aug-cc-pVTZ), and the crystal structure (WUJGAM) highlighting the “anti-electrostatic” halogen bond to iodide (selected bond lengths are given in Å).^[6]

Despite these problems, Huber and colleagues recently analyzed which parameter best predicts the strengths of halogen bonds.^[7] While the static σ -hole depth already resulted in acceptable results, predictions could be improved by combining the σ -hole depth with the energy of the σ^* -orbital of the C–I bond. The revised Ω_{σ^*} parameter shows an excellent correlation (r^2 around 0.95) with the binding energies of various halogen-bond donors to both chloride and ammonia and allows practical predictions for subsequent applications.

Conclusions drawn from the more prominent halogen bond might also be transferable to related noncovalent interactions. Based on atomic polarizabilities (Table 1), it can be expected that these interactions should be strongest for heavier elements and increase from right to left. Electron-withdrawing substituents at the Lewis-acidic center will further strengthen the noncovalent interaction. Consequently, strong σ -hole interactions should be accompanied by bonding angles to the Lewis base of close to 180°. Given the increasing number of σ -holes (Figure 1), multiple interactions should also be possible for chalcogen and pnictogen donors.

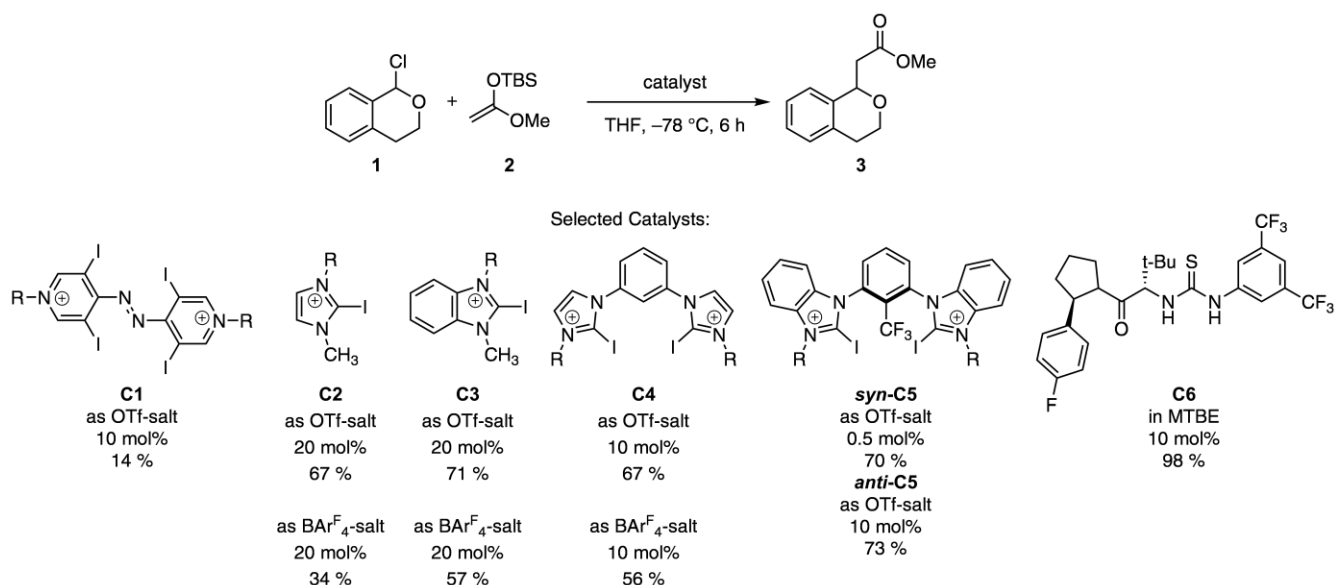
In this MiniReview, we will focus on three σ -hole interactions (halogen, chalcogen, and pnictogen bonding) and describe their recent applications in noncovalent catalysis. In each chapter, we will briefly discuss the strengths of the interaction and present selected experimental and computational investigations that help to better understand the role of these interactions in catalysis. Although this MiniReview will not cover applications in other fields of chemistry such as crystal engineering, supramolecular chemistry, or anion recognition, we will relate conclusions from these areas with the observed catalytic activities.

2. Halogen Bonding

Among the σ -hole interactions, halogen bonding can be considered to be the most established. Although this interaction is known since 1814,^[9] applications in various fields of chemistry have only emerged within the last 30 years.^[10] Applications of halogen bonds in synthesis and catalysis have recently been summarized in different reviews.^[11] Similarly, iodine-catalyzed reactions which can often be described with a halogen-bond activation have lately been discussed in detail.^[12] Halonium ions – important intermediates in various organic reactions – are also very strong halogen-bond donors due to their electron-deficient character and often engage in these noncovalent interactions.^[13] Consequently, we refer the interested reader to

Table 1. Calculated atomic polarizabilities (in a. u.; MP2/aug-cc-pVTZ for C–Br or aug-cc-pVTZ-PP for Sn–I) for elements of groups 14–17.^[8]

Group 14 (tetrel)	Group 15 (pnictogen)	Group 16 (chalcogen)	Group 17 (halogen)
C	N	O	F
11.5	7.1	4.9	3.4
Si	P	S	Cl
38.1	25.0	19.3	14.3
Ge	As	Se	Br
40.3	29.7	25.4	20.5
Sn	Sb	Te	I
55.6	43.3	38.3	32.3



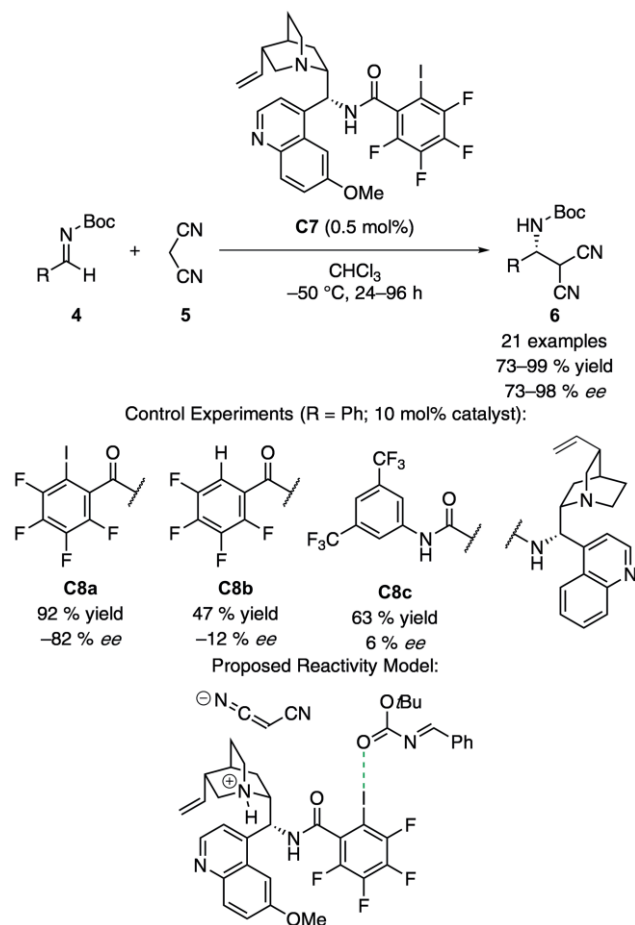
Scheme 1. Comparison of the catalytic activities of different halogen-bond donors in the chloride abstraction reaction of 1-chloroisochroman ($R = C_8H_{17}$).^[16]

these articles for a comprehensive discussion. In this section, we will only give a short summary of important concepts and highlight very recent applications of halogen bonding in catalysis.

Over the last decade, different catalysts have been presented as halogen-bond donors in various transformations. Scheme 1 summarizes the activities of selected catalysts in the chloride abstraction reaction of 1-chloroisochroman (**1**). Although mono-dentate structures like **C2** or **C3** already display useful catalytic effects, bidentate analogs (e.g., **C4**, **C5**) are typically more active. Furthermore, preorganization within the catalyst (e.g., **C5** in Scheme 1) is extremely beneficial and in this case very small catalyst loadings of only 0.5 mol% could be employed for this transformation. A quantitative comparison to hydrogen-bond donors is often difficult, as slightly different conditions have been employed. Previous investigations by Jacobsen and colleagues indicate that several chiral thioureas (like **C6**) provide yields around 60–98 %.^[14] The excellent performance of halogen-bond donor **C5** in this model reaction already indicates that this noncovalent interaction can also compete with more familiar interactions.

A major challenge in halogen-bond catalysis aims to achieve stereoselective transformations. One approach combines the halogen-bond interaction with other catalytic motifs. For example, Arai and colleagues combined a perfluorinated iodo-benzene unit with a chiral quinidine-derived amine in the bifunctional catalyst **C7**.^[15] This catalyst provides excellent yields and enantioselectivities in the addition of malononitrile (**5**) to several N-Boc imines **4** with a very low catalyst loading of only 0.5 mol% (Scheme 2). To support a halogen-bond activation, the authors have performed several control experiments: when the iodine atom is replaced by a hydrogen atom (e.g., **C8a** → **C8b**, Scheme 2), both yield and selectivity decrease significantly. This is further confirmed by characteristic upfield shifts in both ¹H and ¹⁹F-NMR spectra upon mixing the imine with the halogen-bond donor. From this, the authors propose

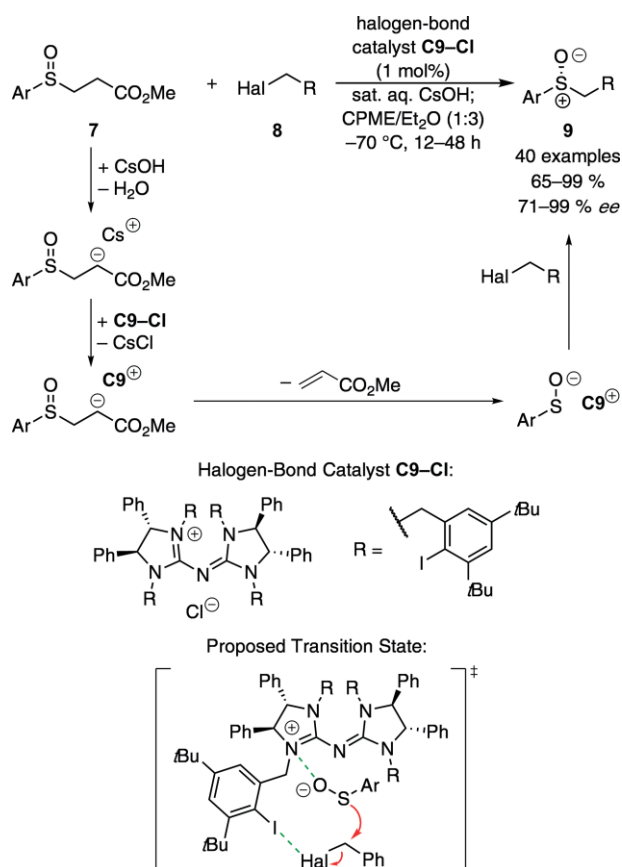
that the iodine atom activates the Boc-protected imine via a halogen bond, while the tertiary amine deprotonates the C–H acid (Scheme 2). Interestingly almost no enantioselectivity was



Scheme 2. Application of a bifunctional halogen-bond catalyst in the addition of malononitrile (**5**) to imines (Boc = *tert*-butyloxycarbonyl).^[15]

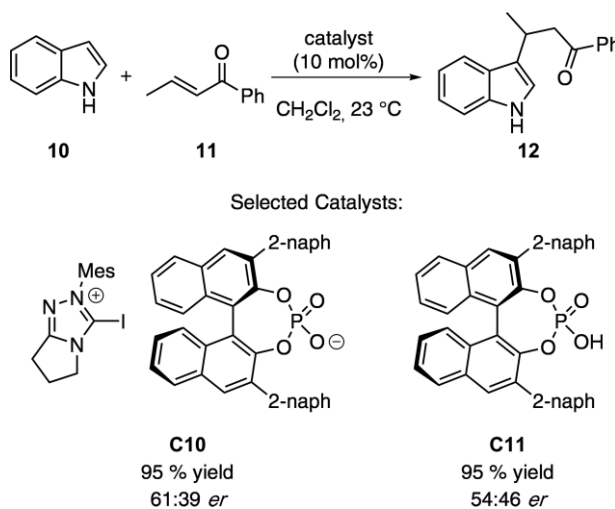
detected, when the halogen-bond motif was replaced by a thio-urea group within catalyst **C8c** (Scheme 2). In 2020, this approach was also extended to the analogous synthesis of non-natural amino acids through the addition of malononitrile to α -ketiminoesters.^[17]

In 2014, Kee, Tan, and colleagues reported on iodinated pentanidium ions (e.g., **C9**) as phase-transfer catalysts in the enantioselective alkylation of sulfonate anions (Scheme 3).^[18] The resulting sulfoxides **9** are typically obtained with high enantioselectivities and yields. Computational investigations propose a halogen-bond interaction between the leaving halide anion and the iodine atom of the catalyst within the transition state (Scheme 3). Furthermore, the calculated *er* (88:12) agreed well with the experimentally observed value (95.5:4.5). However, more detailed mechanistic investigations are difficult, as the non-iodinated catalyst also shows a significant catalytic activity in the reaction between the 2-thiophenyl-substituted sulfoxide **7** and benzyl bromide (61 % *ee* for the non-iodinated catalyst and 91 % *ee* for the iodinated catalyst **C9**). Very recently, the non-halogenated pentanidium system was also employed in enantioconvergent halogenophilic nucleophilic substitution reactions.^[19] In these S_N2X -type reactions, the leaving group (Br^-) forms a transient halogen bond to the thiocarboxylate nucleophile. A subsequent asymmetric counterion-directed catalysis (ACDC)^[20] by the chiral counterion is then responsible for the high enantioselectivity.



Scheme 3. Phase-transfer catalysis with a halogen-bond donor (CPME: cyclopentyl methyl ether).^[18]

Since Huber's first synthesis of a chiral, bidentate halogen-bond donor in 2012,^[21] several groups have successfully designed similar chiral azolium-derived compounds. Kanger and colleagues subsequently relied on similar click chemistry to obtain different mono- and bidentate iodinated triazolium salts.^[22] While halogen bonding was confirmed by crystal structures and NMR titrations, no stereinduction could be observed in different transformations. Similar conclusions were drawn by Scheidt and colleagues in 2019 working on chiral azolium salts that are frequently used as carbene precursors (Scheme 4).^[23] As test reaction, the authors chose the Michael addition between indole (**10**) and *trans*-crotonophenone (**11**) that has been studied in the context of halogen-bond catalysis with achiral catalysts before.^[24] Although a moderate enantioinduction was observed for an azolium ion with a chiral phosphoric acid counter anion, comparison with the free chiral phosphoric acid renders a hidden Brønsted-acid catalysis more likely.

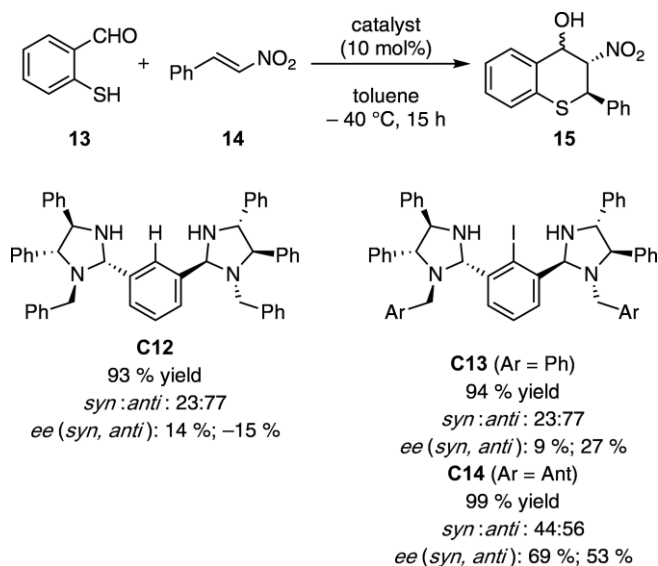


Scheme 4. Iodinated triazolium salts with chiral counter anions as catalysts in the Michael addition of indole and *trans*-crotonophenone.^[23]

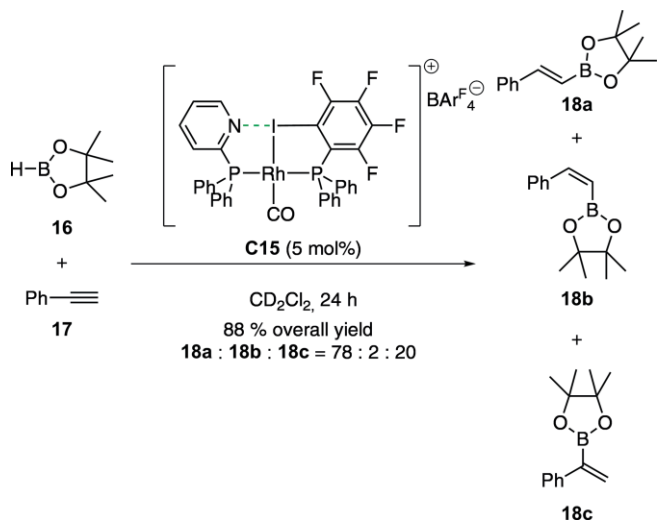
Significantly higher enantioselectivities were reported by Arai and co-workers in 2017. They developed a series of chiral bis(imidazolidine)iodobenzenes and successfully applied them in the asymmetric Michael/Henry reaction between **13** and **14** (Scheme 5).^[25] However, a clear conclusion on the importance of the underlying halogen bond is difficult. For smaller catalytic systems, iodinated and non-iodinated structures (i.e., **C12** vs. **C13**) show only slightly different enantioselectivities indicating that the catalyst could also act as a hydrogen-bond donor. Furthermore, halogen bonds involving nonfluorinated iodo-benzenes in solution should be relatively weak.^[10]

A very promising strategy was proposed by van Leeuwen, Vidal-Ferran, and colleagues:^[26] the authors propose to combine traditional transition-metal catalysis with halogen bonding to design new (and potentially chiral) catalysts (Scheme 6). The Rh-catalyst **C15** features an additional $N \cdots I$ halogen bond and can, as an example, be employed to catalyze the hydroboration of aryl-substituted acetylenes.

A major break-through in asymmetric halogen-bond catalysis was recently reported by Huber and colleagues.^[27] The authors were able to synthesize chiral halogen-bond donors **C16** that



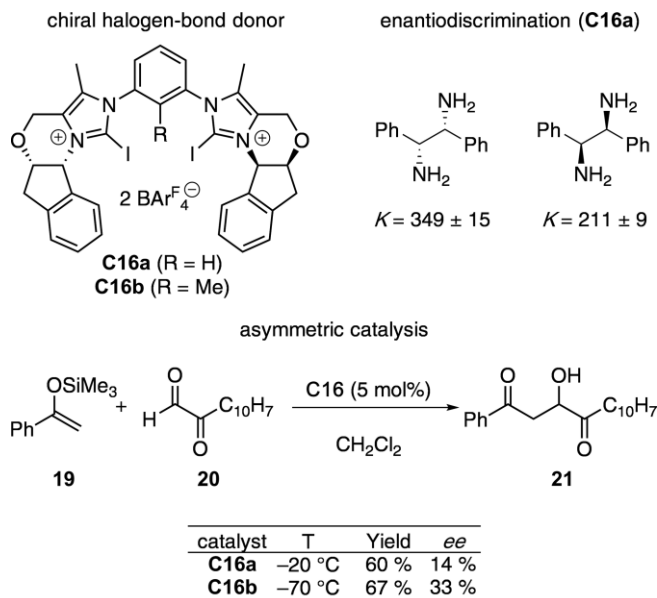
Scheme 5. Application of a chiral monodentate halogen-bond donor in asymmetric Michael/Henry reactions.^[25]



Scheme 6. Halogen bonding within a Rh complex in the hydroboration of aryl acetylenes.^[26a]

are able to differentiate between both enantiomers of different benzylamine derivatives. NMR titrations indicated that the (1*R*,2*R*)-enantiomer of 1,2-diphenyl-1,2-ethylenediamine binds slightly stronger to the halogen-bond donor **C16a** than the (1*S*,2*S*)-diamine (Scheme 6). In a proof-of-principle study, a Mukaiyama aldol reaction was chosen. The reaction does not proceed in the absence of a catalyst, while a significant rate enhancement is observed for the halogen-bond catalysts. The best stereoselectivity could be observed for the preorganized methylated catalyst with a *syn*-orientation of both halogen-bond motifs (Scheme 7). Despite the only moderate enantioselectivity, this is the first application of a “pure” bidentate halogen-bond donor in enantioselective catalysis.

Given the numerous applications of halogen bonding in catalysis and the first examples for stereoselective transformations, these interactions can probably be already considered to



Scheme 7. Application of bidentate chiral halogen-bond donors in the enantiodiscrimination of 1,2-diamines and in asymmetric catalysis (C₁₀H₇ = 2-naphthyl).^[27]

be an established motif in organocatalysis. In selected cases, halogen bonding even outperforms traditional hydrogen-bond donors^[15,28] (see also Scheme 1 and Scheme 2) and the future will most likely provide further seminal applications in enantioselective catalysis.

3. Chalcogen Bonding

The chalcogen bond is the noncovalent interaction between a chalcogen atom (e.g., S, Se, Te, but usually not O) and a Lewis base. The chalcogen bond is closely related to the halogen bond discussed above but is much less investigated. Short O...S contacts have been identified in different crystal structures almost 60 years ago and selected examples are shown in Figure 3.^[29] In these cases, the S...O distances are considerably smaller than the sum of the van-der-Waals radii of 3.39 Å.^[30] Similar interactions have also been observed in the gas phase, e.g., for the 2-nitrobenzenesulfonyl chloride.^[31] Later, du Mont, Pohl, and colleagues reported on the crystal structure of a diphenyldisilane-iodine complex (Figure 3).^[32] Within this complex, both a halogen-bond (2.99 Å) and a chalcogen-bond interaction (3.59 Å) occur between the selenium and iodine atom. Again, both distances are shorter than the sum of the van-der-Waals radii (3.86 Å)^[30] with a dominant halogen-bond interaction. This complex nicely illustrates the bimodal nature of these atoms acting both as a Lewis acid and a Lewis base.

Vargas-Baca and colleagues analyzed the dynamic behavior of different 1,2-chalcogenazole oxides in their aggregation to form tetramers (Figure 4).^[33] In 2010, they concluded that “[m]any tellurium compounds display similar Lewis acid behaviour, even when they are electron precise. The strength of their interactions with electron donors ranges from weak – in which case they fall within Alcock’s definition of secondary bonding – to strong covalent hypervalent bonds.”^[33a]

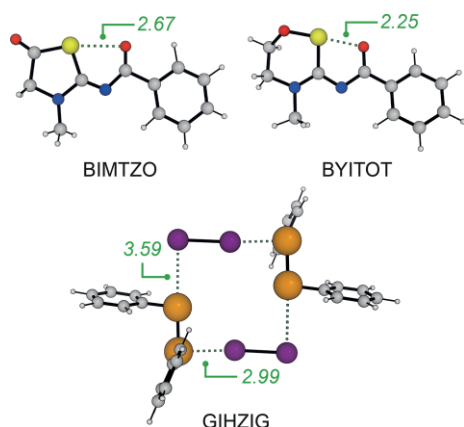


Figure 3. Crystal structures with selected bond lengths (in Å) highlighting the short S...O contacts (top) and the diphenyldiselenane-iodine complex (bottom).^[29a,b,32]

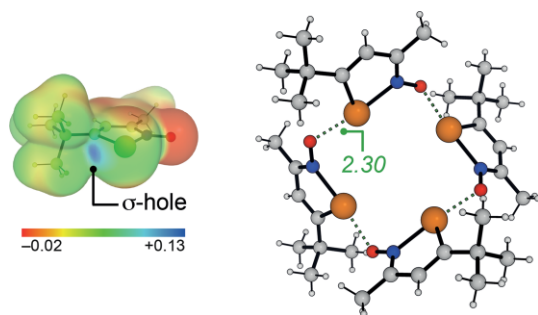


Figure 4. Calculated electrostatic potential (ωB97X-D/aug-cc-pVTZ) for the monomeric 3-methyl-5-tert-butyl-iso-tellurazole N-oxide and the crystal structure of the corresponding tetramer (O...Te bond length in Å).^[33a]

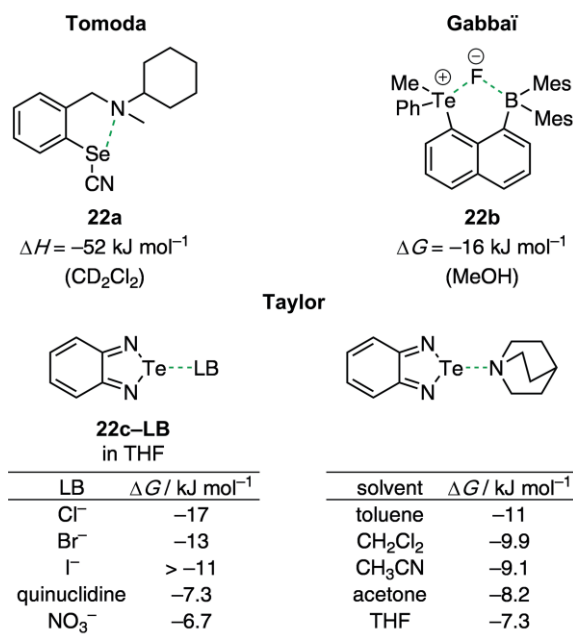
This “unconventional” interaction is also the topic of numerous computational investigations. Already in 1969, Kapecki and Baldwin concluded from extended Hückel calculations that covalent bonds are not important to rationalize the short S...O distances in crystal structures. Subsequent calculations by various groups support this picture and suggest that electron-withdrawing substituents at the chalcogen atom lead to stronger interactions.^[8,34] Gleiter and colleagues have analyzed 12 model systems with chalcogen-chalcogen interactions in 2006.^[5b] While hydrogen bonding significantly contributes to the interactions between O...O species like the dimethyl ether dimer, dispersion is the major contribution to the interactions between heavier chalcogen atoms such as Me₂Se or Me₂Te.

Frontera and colleagues computationally compared the interaction energies of different σ -hole model compounds with benzene and trimethylamine as Lewis bases (Table 2).^[34e] In general, heavier atoms give rise to stronger interactions and interestingly, both chalcogen and pnictogen donors bind slightly stronger to the arene than the amine. In line with their calculations, the authors observed significantly more I...N or Te...N than Br...N or Se...N interactions in the Cambridge Structural Database (CSD), while interactions to pnictogen atoms were scarcely found.

Table 2. Calculated interaction energies (in kJ mol⁻¹, BP86-D3/def2-TZVPD) of two Lewis basis (C₆H₆ and NMe₃) with pnictogen-, chalcogen-, and halogen-bond donors.^[34e]

	AsCl ₃	SbCl ₃	Se(CF ₃) ₂	Te(CF ₃) ₂	BrCF ₃	ICF ₃
C ₆ H ₆	-27	-26	-19	-23	-14	-19
NMe ₃	-21	-24	-15	-24	-32	-46

Similar to the halogen bond discussed above, the strength of the chalcogen bond should depend on the position of the chalcogen atom in the periodic table (Te > Se > S), the nature of the substituents in the chalcogen atom, and the Lewis basicity of the reaction partner. Iwaoka and Tomoda studied the interaction energies for the Se...N chalcogen bond within a series of 2-selenobenzylamine derivatives by NMR spectroscopy (**22a**, Scheme 8). The strength of the interaction strongly depends on the substituent on the Se atom and in combination with computational investigations, the authors estimated interaction energies between 30 and 80 kJ mol⁻¹.^[35] Significantly smaller interaction energies were determined when the amino group was replaced by a less Lewis basic hydroxy or formyl group.^[36]



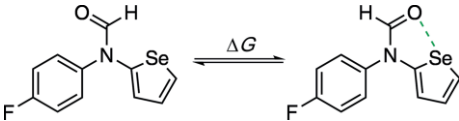
Scheme 8. Selected interaction energies for chalcogen bonds (Mes = mesityl).^[35,37,38]

In 2010, Zhao and Gabbai first reported on anion binding to a tellurium ion (**22b**, Scheme 8) and determined an interaction energy of -16 kJ mol⁻¹ between the telluronium borane and fluoride in methanol.^[37] In a more systematic analysis, Taylor and colleagues determined the interaction energies for a series of Lewis bases to a benzotelluradiazole (**22c**, Scheme 8).^[38] The interaction with the neutral quinuclidine in five different solvents indicates that only moderate changes are observed for this combination. The overall strongest interaction was determined for the combination of chloride as the best Lewis base with a perfluorinated benzotelluradiazole (-29 kJ mol⁻¹ in THF, not shown in Scheme 8). This indicates that chalcogen bonds

can be relatively strong, as this value is comparable to the interaction energy of chloride with an electron-deficient urea.^[39] Interestingly, a bidentate chalcogen-bond donor based on tellurophene resulted in an interaction energy of only -19 kJ mol^{-1} indicating that electron-withdrawing substituents could be more important than a bidentate binding.^[40] Similar values were determined for the interaction of a selenium-based cationic macrocycle and chloride (-15 kJ mol^{-1} in $[\text{D}_6]\text{acetone}$).^[41]

In 2017, Cockroft and colleagues employed different molecular balances to gain a better understanding of $\text{O}\cdots\text{S}$, $\text{O}\cdots\text{Se}$, and $\text{S}\cdots\text{S}$ interactions.^[51] The strongest chalcogen-bond interactions in this study were comparable to conventional hydrogen bonds underlining the potential applicability of these interactions for synthesis and catalysis. Surprisingly, the strength of the chalcogen bond as shown in Table 3 for one example did not depend on the solvent as usually found for hydrogen bonds.^[42] Closer analysis of this unexpected observation indicated that neither electrostatics, solvophobic, nor van-der-Waals forces account for this trend. Instead the authors observed a correlation between the experimental free energies and calculated orbital interactions of the lone pair at the amide oxygen and the antibonding orbital at the chalcogen atom ($n \rightarrow \sigma^*$).

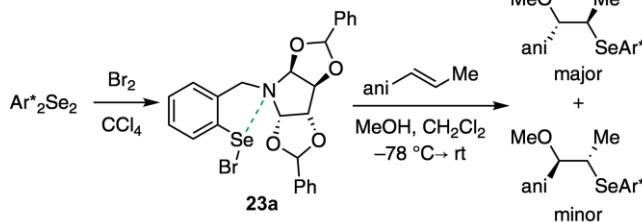
Table 3. Experimental conformational free energies ΔG (in kJ mol^{-1} , 298 K) for a molecular balance.^[51]



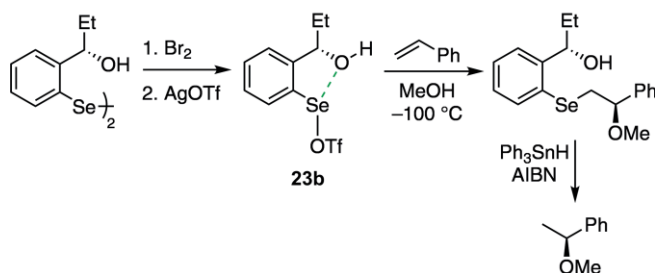
Solvent	ΔG	Solvent	ΔG	Solvent	ΔG
THF	-5.7	CS_2	-5.1	CH_2Cl_2	-4.7
C_6D_6	-5.5	EtOH	-5.1	CDCl_3	-4.1
$(\text{CD}_3)_2\text{CO}$	-5.5	CD_3OD	-5.1	Et_2O	-3.1
EtOAc	-5.5	CD_3CN	-5.1	$\text{C}_4\text{F}_9\text{OH}$	-2.2
$(\text{CD}_3)_2\text{SO}$	-5.3				

In general, organic selenium and tellurium compounds are known for decades and have found various applications on synthesis and catalysis.^[43] However, in many cases, these compounds were used as Lewis bases and will not be discussed here. Intramolecular chalcogen bonds have frequently been used to stabilize organic structures and to obtain preferred structural arrangements.^[43b,43e] Tomoda and colleagues introduced this interaction into asymmetric methoxyselenenylations in 1994 (Scheme 9). In a first step, chiral diaryl diselenides were converted into the corresponding arylselenenyl bromides **23a**. An intramolecular chalcogen-bond interaction within **23a** allowed a stereoselective addition with diastereomeric excesses of up to 60 %.^[44] Shortly after, Wirth relied on $\text{Se}\cdots\text{O}$ interactions (e.g. in **23b**) and was able to show that even small substituents on the oxygen atom (e.g., Me or Et) result in a diastereomeric excess of 88 % (Scheme 9).^[45] Interestingly, the replacement of the OH by a SMe group as the Lewis-basic element by the groups of Tiecco and Temperini did only result in a moderate improvement of the observed selectivity (diastereomeric excess of 96 %).^[46]

Tomoda:

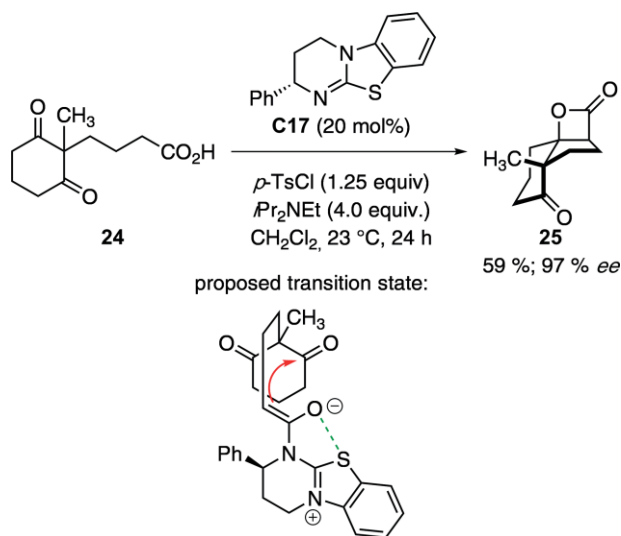


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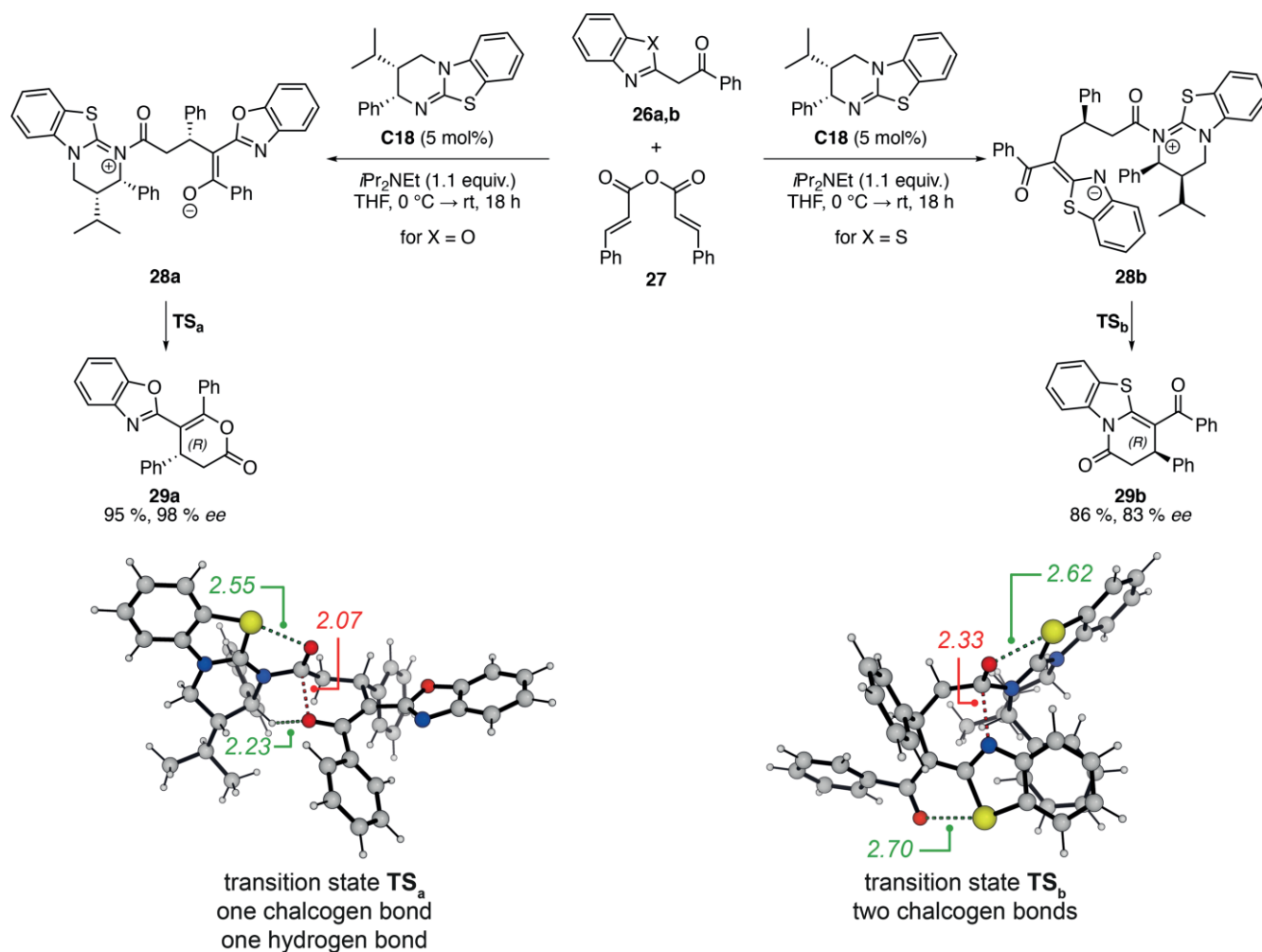
Scheme 9. Intramolecular chalcogen bonds as important interactions for the diastereoselective methoxyselenenylations of alkenes (ani = *p*-MeO- C_6H_4).^[44,45]

Chalcogen-bond motifs have also been used as an additional interaction site within nucleophilic catalysts, e.g., within isothioureas. In 2010, Romo and colleagues reported on intramolecular aldol lactonizations catalyzed by homobenzotetramisole **C17** (Scheme 10).^[47] This catalyst features a sulfur atom in close proximity to the nucleophilic nitrogen atom. The negatively charged amide enolate can then be stabilized through a $\text{S}\cdots\text{O}$ interaction.^[48] This type of interaction had previously been described in crystal structures (see above) and was studied in more detail computationally already in 1998 by Nagao and colleagues.^[49]



Scheme 10. Intramolecular $\text{S}\cdots\text{O}$ chalcogen bonds in aldol lactonizations.^[47]

In 2011, Smith and colleagues postulate a similar interaction for the isothiourea-catalyzed Michael addition-lactonization of enones and carboxylic acids.^[50] Different isothioureas were em-

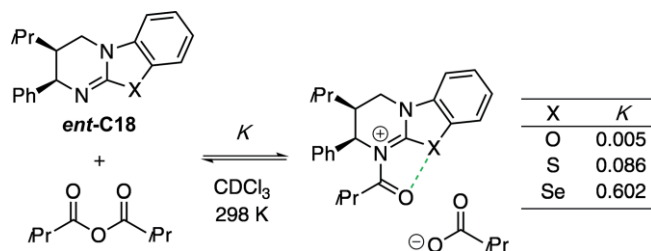


Scheme 11. Role of chalcogen bonding in the isothiurea-catalyzed annulations of benzazoles.^[52]

played for the intra- and intermolecular version of this transformation and excellent stereoselectivities were observed in these reactions. The authors suggest a similar mode of action as discussed in Scheme 10. In subsequent years, the group of Smith explored the potential of this 1,5-S \cdots O interaction in different transformations.^[51] An interesting chemoselectivity was observed in the reaction of isothiurea-catalyzed annulations of benzazoles: while the benzoxazole derivatives like **26a** resulted almost exclusively in the corresponding lactones **29a**, reactions with the related benzothiazoles **26b** furnished the lactams **29b** in high yield (Scheme 11).^[52] DFT calculations indicate that the change in chemoselectivity can be attributed to differences in chalcogen bonds. While two S \cdots O interactions are present in the most favorable transition state for the lactamization, the corresponding transition states for the lactonization feature only one interaction.

The same isothiurea was subsequently employed in [2+2] cycloadditions between symmetric anhydrides and perfluoroalkyl ketones.^[53] Kinetic isotope effects in combination with DFT calculations indicate that this reaction proceeds through a concerted but asynchronous mechanism. Again, the calculations underline the importance of a chalcogen bond for the activation of the substrates.

In 2020, Willoughby, Cockroft, Smith, and colleagues systematically analyze the importance of this interaction in isochalcogenourea catalysis.^[54] Calculations based on crystal structures indicate that the chalcogen bond increases in the series O \rightarrow S \rightarrow Se, as can also be observed in the conformational preferences of the carbonyl group in the solid state. ¹H-NMR investigations as well as equilibrium constants (Scheme 12) further support this trend. Similarly, the reaction half-life for the kinetic resolution of tertiary alcohols increases from 8 to 35 minutes when the selenium catalyst was replaced with the sulfur analog.

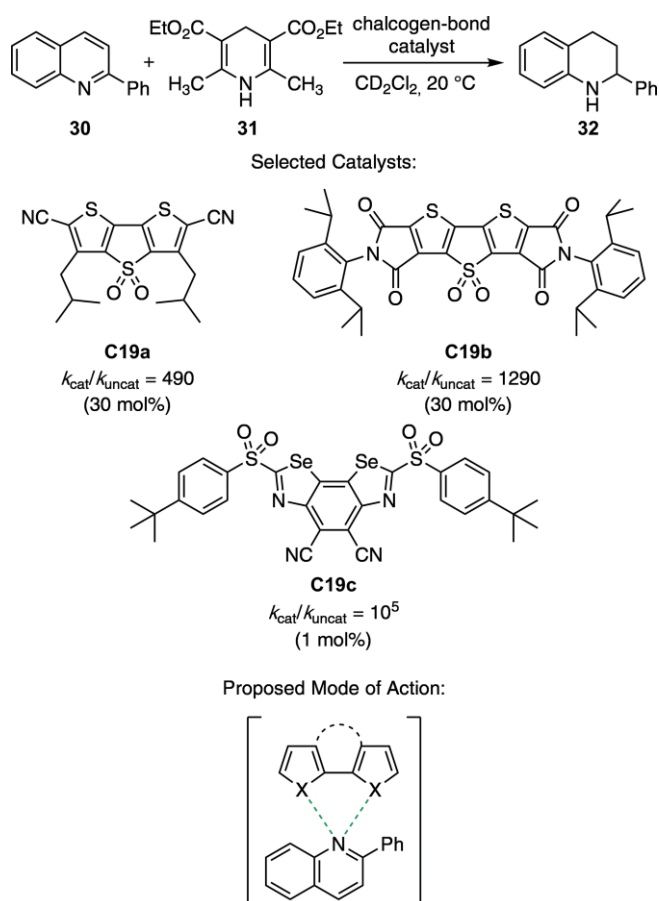


Scheme 12. Equilibrium constants for the reaction between an isochalcogenourea and isobutyric anhydride supporting an intramolecular chalcogen bond.^[54]

Larger effects (up to a 13-fold reactivity increase) were observed in other catalytic reactions involving these isochalcogenoureas. These results impressively show the effect of intramolecular chalcogen bonds in catalytic transformations.

Besides intramolecular interactions, intermolecular chalcogen bonds can also be applied in catalysis. An early application of Lewis-acidic selenium salts was published in 2009 by Lenardão and colleagues. The addition of phenyl butyl ethyl selenonium tetrafluoroborate ($\text{PhBuEtSe}^+\text{BF}_4^-$) resulted in a significant acceleration of the Morita–Baylis–Hillman reaction of aldehydes and electron-deficient alkenes.^[55] Ke, Yeung, and colleagues relied on similar selenonium cations in 2017 to catalyze the electrophilic bromination of arenes and aldol-type reactions.^[56] In both cases, the authors propose a chalcogen-bond activation, but no detailed mechanistic investigations have been reported so far.

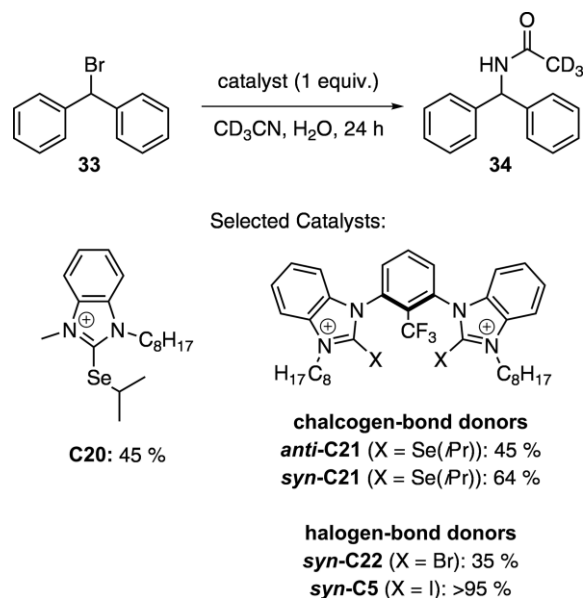
Extending their earlier work on anion transport via chalcogen bonds,^[57] Matile and colleagues reported on the use of different dithieno[3,2-b;2',3'-d]thiophenes (DTTs, **C19**) as chalcogen-bond catalysts in 2017 (Scheme 13).^[58] The most active catalyst in the reduction of quinolines and related imines by a Hantzsch ester showed a rate enhancement of 1290 compared to the uncatalyzed reaction. As the calculated chloride anion affinities correlated well with the observed catalytic activities, the authors concluded that a chalcogen-bond activation



Scheme 13. Chalcogen-bond catalysts for the transfer-hydrogenation of quinolines.^[58,59]

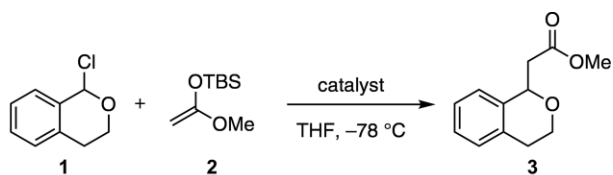
is most likely. Later this year, an improved version of the catalyst was presented that now incorporates selenium instead of sulfur atoms.^[59] The most active benzodiselenazole **C19c** results in a rate enhancement of more than 10^5 over the uncatalyzed process.

In parallel, Huber and colleagues reported on the potential of selenium-based catalysts in the Ritter-type reaction of benzhydryl bromide (**33**) and acetonitrile (Scheme 14).^[60] Stoichiometric amounts of the catalyst are required in this reaction, as the bromide ion binds stronger to the chalcogen-bond donor than to the starting material. While monodentate structures like **C20** only resulted in moderate yields, the preorganized *syn*-isomers of the bidentate structures (*syn*-**C21**) are significantly more active. Although the corresponding iodinated halogen-bond donors (*syn*-**C5**) are significantly more active in both cases, the brominated analogs (*syn*-**C22**) – a much better comparison given their relative position in the periodic table – perform worse. Recently, Matile and colleagues also employed their benzodiselenazole structures in this reaction.^[61] In general, these structures seem to be less active in this transformation and the most active catalyst, a dicationic version of the benzo-diselenazole, afforded approx. 60 % conversion after 800 h.

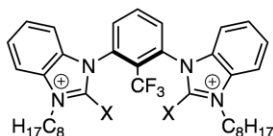


Scheme 14. Application of selenium-based catalysts (counter anion OTf^-) in the Ritter-type reaction of benzhydryl bromide and acetonitrile.^[60]

A similar comparison of chalcogen- and halogen-bond donors is also possible for another C–Cl bond activation: The reaction between chloroisochroman (**1**) and silyl ketene acetals is catalyzed by 10 mol% of the bidentate chalcogen-bond donor (Scheme 15, see also Scheme 1).^[62] Again, chalcogen-bond catalysts like *syn*-**C23** show a much better activity than the corresponding halogen-bond donors (e.g., *syn*-**C22**). Subsequent investigations by the Matile group indicate that bis(pentafluorophenyl)tellurium (albeit with a higher catalyst loading) shows a remarkable catalytic activity in this reaction (48 % after 24 h) while the corresponding pentafluoro-iodobenzene is less reactive (15 % after 24 h, not shown in Scheme 15).



Selected Catalysts:



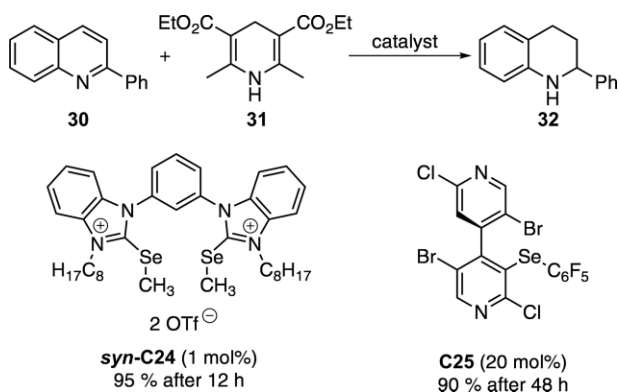
chalcogen-bond donor
syn-C23 (X = Se(C₈H₁₇))
10 mol%
92 % after 118 h

halogen-bond donor
syn-C22 (X = Br)
10 mol%
40 % after 118 h

20 mol%
48 % after 24 h

Scheme 15. Chalcogen-bond catalysts in the reaction of 1-chloroisochroman and a silyl ketene acetal (OTf[−] counteranions are not shown, TBS = *tert*-butyldimethylsilyl).^[62]

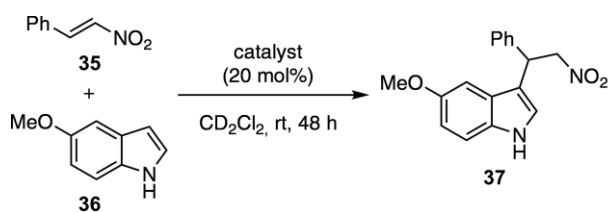
In 2019, Huber and colleagues were able to extend the concept of chalcogen-bond activation also to reductions of quinolines (Scheme 16, see also Scheme 13).^[63] Very low catalyst loadings of only 1 mol% for the preorganized **syn-C24** were sufficient to provide the product **32** in excellent yields after 12 hours. Attempts by Peluso, Mamane, and colleagues to use axially-chiral monodentate chalcogen-bond donors (**C25**) as catalysts in these transformations resulted only in racemic mixtures.^[64] As discussed for halogen bonding above, a monodentate catalyst might still be too flexible to induce chirality in these reactions.



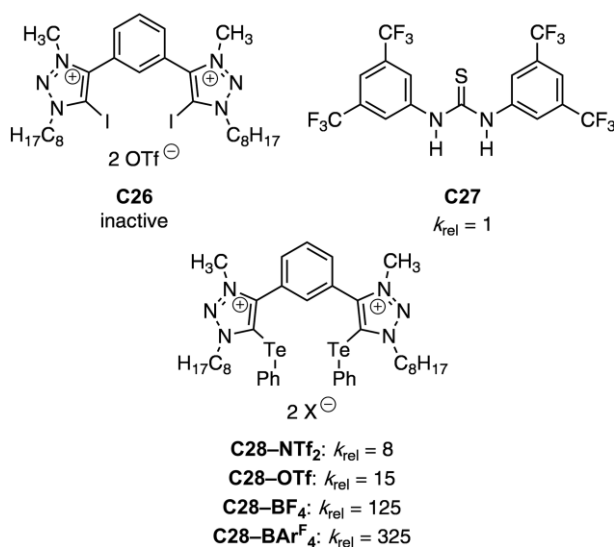
Scheme 16. Reduction of quinolines catalysed by chalcogen-bond catalysts.^[63]

A dicationic tellurium-based catalyst was for the first time successfully employed in a nitro-Michael reaction (Scheme 17).^[65] While the corresponding halogen-bond donor **C26** did not result in any product formation after 120 hours, a typical hydrogen-bond donor like Schreiner's thiourea (**C27**) showed a very weak activity (approx. 2 % after 48 h). In contrast, the tellurium-based catalyst **C28** displayed a significant catalytic effect resulting in an acceleration of more than 300 compared to the reference thiourea. As observed for halogen-bond donors,

weakly coordinating anions like BARF₄[−] are highly beneficial for a high catalytic activity (**C28**–BARF₄). These catalysts even outperform typical metal catalysts like AlCl₃ or strong Brønsted acids like HBF₄. DFT calculations for smaller model systems indicate that both oxygen atoms of the nitro group form chalcogen bonds with the tellurium atoms and activate the nitroolefin accordingly. Furthermore, the authors also determined association constants for the reactions of chloride ions and nitrostyrene with the chalcogen- and halogen-bond donors shown in Scheme 17. As nitrostyrene binds similarly strong to both Lewis acids, and Cl[−] binds even stronger to the halogen-bond donor, thermodynamic data cannot be considered as a good predictor for the catalytic activity.



Relative Reactivity of Selected Catalysts:



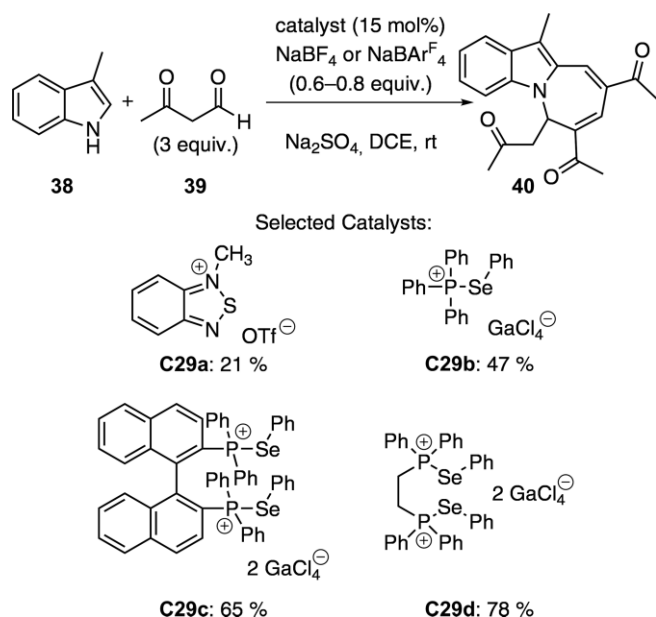
Scheme 17. First application of tellurium-based chalcogen-bond donors in nitro-Michael additions (BARF₄[−] = B[3,5-(CF₃)₂C₆H₃]₄[−]).^[65]

The same catalyst system was subsequently also applied in the Michael addition of indoles to *trans*-crotonophenone.^[66] Again, the tellurium-based chalcogen-bond donor showed the highest catalytic activity. Compared to the analogous iodinated halogen-bond-donor, the chalcogen-bond donor is 10⁴-times more reactive. When changing the chalcogen atom (Te → Se), the catalytic activity decreases significantly. The tellurium catalyst is roughly one order of magnitude more reactive than the selenium derivative, while the sulfur-based catalyst was completely inactive.

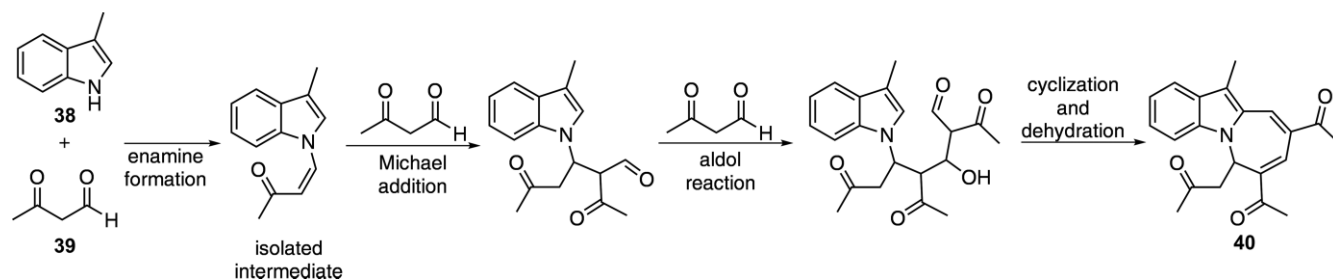
Very recently, Wang and colleagues reported on the application of dual chalcogen-chalcogen bonding catalysis.^[67] Initially,

the authors describe the reaction of 3-methylindole (**38**) with 3 equivalents of β -ketoaldehydes yielding the corresponding heterocycles (Scheme 18) in the presence of a bidentate selenium catalyst. All steps of the proposed reaction mechanisms of Scheme 19 are amenable to chalcogen-bond activation through $\text{Se}\cdots\text{O}$ interactions. To support the hypothesis of a chalcogen-bond activation, the authors performed a series of control experiments. The addition of stronger Lewis bases (e.g., Cl^- , N -oxides, PPh_3) led to a significant reduction or even a complete loss of the catalytic activity. Similarly, GaCl_3 resulted only in a yield of 8 % and $n\text{Bu}_4\text{NGaCl}_4$ was found to be catalytically inactive. Addition of a Brønsted base (K_2CO_3 or sodium 3-oxobut-1-en-1-olate) did not quench the reactivity which excludes Brønsted-acid catalysis as the underlying cause. Consequently, a chalcogen-bond activation seems to be the most likely explanation. Similar results were subsequently reported by the same group in a Rauhut–Currier-type reaction proceeding under very mild conditions.^[67b]

In conclusion, chalcogen bonding has stepped out from under the shadow of halogen bonding. Many proof-of-principle reactions relying on Lewis-acidic chalcogen atoms have been reported that reveal the potential of this noncovalent interaction for future applications.



Scheme 18. Application of chalcogen-bond donors in a cascade synthesis of N-heterocycles.^[67a]



Scheme 19. Proposed reaction mechanism for the cascade synthesis of N-heterocycles.^[67a]

4. Pnictogen Bonding

Similar to halogen and chalcogen bonding discussed above, also elements from group 15 can act as Lewis acids in pnictogen (or also pnictogen) bonds.^[68] These interactions are known for a long time in the solid state and Alcock summarized early investigations particularly on arsenic and antimony compounds.^[3] The selected examples shown in Figure 5 all feature distances significantly shorter than the van-der-Waals radii: SbCl_3 forms interactions with aniline^[69] or can interact with the π -system of naphthalene in an η^3 -fashion.^[70] The nature of this pnictogen bond (a combination of electrostatics and dispersion) was later studied in detail theoretically by Hobza and colleagues.^[71]

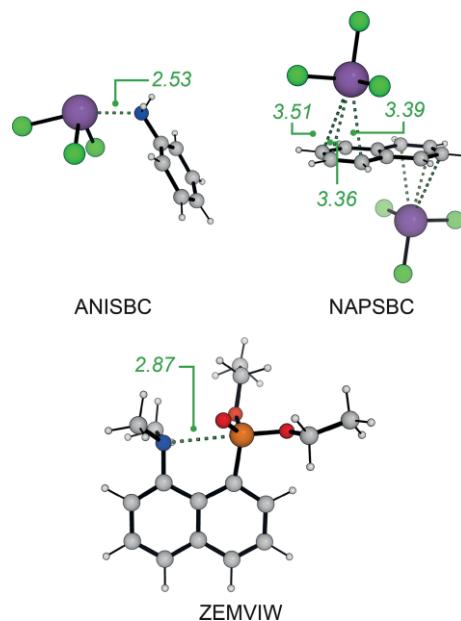


Figure 5. Selected crystal structures highlighting pnictogen bonds in the solid state. Hydrogen atoms have been added manually.^[69,70,72]

Comparable $\text{P}\cdots\text{N}$ interactions can also be observed in the solid-state structure of $\text{P}(\text{CN})_3$ or $\text{As}(\text{CN})_3$.^[73] For the latter, the authors conclude that the “bonding in this interaction is presumably between the lone pair of electrons on the CN and an empty d orbital on the As. Nevertheless, it does indicate that one or two kilocalories per mole more than the normal van der Waal’s forces are involved in holding the crystal together.”^[74] Intramolecular pnictogen bonds are also known e.g., in the amino-substituted phosphonate shown in Figure 5.^[72] Cozzolino and colleagues

recently compared the stability of different pnictogen-containing alkoxide cages,^[75] while pnictogen atoms could engage in up to three noncovalent interactions (cf. the 3 σ -holes in Figure 1), this bonding pattern was only observed for the larger antimony cages. The authors furthermore concluded that antimony cages display the best balance between strength and directionality. Recent high-resolution X-ray diffraction data by Nelyubina and colleagues provide experimental evidence for a weak σ -hole in ammonium ions in crystals.^[76] Similarly, spectroscopic investigations have been employed to detect and better understand pnictogen bonds.^[77]

The Lewis acidic properties of trihalophosphanes are known since the 1960s.^[78] ³¹P and ¹³C NMR investigations of the adduct formed between P(CN)₃ and pyridine indicated noncovalent P...N interactions. Wilkie and Parry realized in 1980 that the substituent at the phosphorus atom plays an important role in its reactivity: P(CN)₃ acts as an acid, while P(CN)₂Ph is a neutral compound, and P(CN)Ph₂ reacts slightly basic.^[79] Similarly, Menjón and colleagues concluded based on their calculated fluoride anion affinities (FIAs) that Sb(C₆Cl₅)₃ is a mild Lewis acid.^[80] Recently, Greb and colleagues computationally determined the FIAs of a large variety of different Lewis acids at the DLPNO-CCSD(T)/aug-cc-pVQZ (Table 4).^[81] Based on these values, antimony(III) compounds are considerably weaker Lewis acids than AlCl₃ or BCl₃.

Table 4. Calculated Fluoride Anion Affinities (FIA, in kJ mol⁻¹, DLPNO-CCSD(T)/aug-cc-pVQZ//PBEh-3c/def2-mSVP) for Selected Lewis Acids.^[81]

Acid	FIA	Acid	FIA	Acid	FIA
BF ₃	346	AlMe ₃	369	SbCl ₃	309
BCl ₃	404	SnCl ₄	360	Sb(C ₆ F ₅) ₅	384 ^[b]
B(C ₂ F ₅) ₃	581	PBr ₃	286	Sb(C ₂ F ₅) ₃	315
B(C ₆ F ₅) ₃	448 ^[a]	P(C ₂ F ₅) ₃	274	SbCl ₅	438
AlCl ₃	505	AsBr ₃	286	Sb(C ₂ F ₅) ₅	437

[a] DLPNO-CCSD(T)/cc-pVQZ//PBEh-3c/def2-mSVP. [b] DSD-BLYP-D3BJ/def2-QZVPP//PBEh-3c/def2-mSVP.

Pnictogen bonding was also extensively studied computationally in the last decades.^[82] In 1995, Klinkhammer and Pyykkö employed ab-initio calculations to provide insights into the attractive interactions in dipnictogens.^[83] As a striking example (Figure 6), Scheiner computationally showed that the pnictogen-bonded dimer (H₃P...NH₃) between phosphane and ammonia is more stable than the expected hydrogen-bonded analog (H₂P-H...NH₃).^[84] Based on numerous computational investigations, similar trends can be expected for the pnictogen bond that were already described for halogen and chalcogen bonds: Electron-withdrawing substituents and heavy pnictogen atoms increase the strength of the noncovalent interaction.

In many cases, investigations focused also on the comparison of pnictogen bonding with related noncovalent interactions.^[5d,85] Scheiner relied on the dithieno thiophene framework (see Scheme 12 for an example) to compare chalcogen, pnictogen, and tetrel bonding.^[86] The calculated interaction energies with the fluoride ion follow the same trend as expected based on the atomic polarizabilities of Table 1. Slightly different results were obtained by Frontera and colleagues. They concluded in their analysis of the Cambridge Structural Database

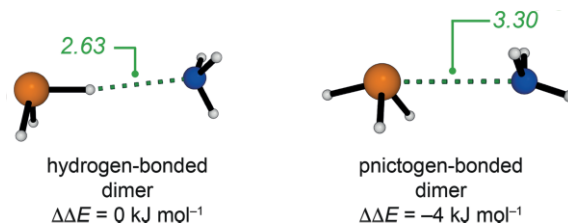


Figure 6. Relative stabilities of phosphane-ammonia dimers with selected bond lengths in Å.^[84]

(CSD) that halogen bonding is the most favorable interaction when the Lewis base is an amine. In contrast, pnictogen bonding is preferred for π -systems like benzene.^[34e] Resnati, Bryce, and colleagues recently showed that pnictogen bonding prevailed over halogen and hydrogen bonding in competitive co-crystallization of 4,4'-dipyridyl *N,N'*-dioxides.^[87]

Starting in 2008, Hey-Hawkins, Kirchner, and colleagues have identified pnictogen bonds between phosphorus atom as a new molecular linker.^[88–90] They observed very close P...P contacts in crystal structures of bis(phosphanyl)carbaborane(12) compounds (Figure 7). NMR investigations as well as computational investigations were employed to further study this interaction. The authors analyzed a series of pnictogen-bonded complexes and found that the dissociation energy can be as high as 28 kJ mol⁻¹, which is comparable to a moderately strong hydrogen bond.^[91] As expected, electron-withdrawing substituents result in the strongest interactions. In parallel to these investigations, Tuononen and colleagues employed high-level calculations (LCCSD(T)/aug-cc-pVQZ) to better understand the nature of the weak interactions between X₃E...EX₃ pnictogen-bond dimers.^[92] These investigations clearly demonstrate the suitability of this noncovalent interaction for subsequent practical applications.

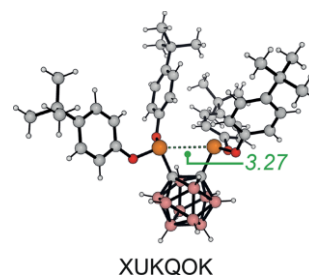
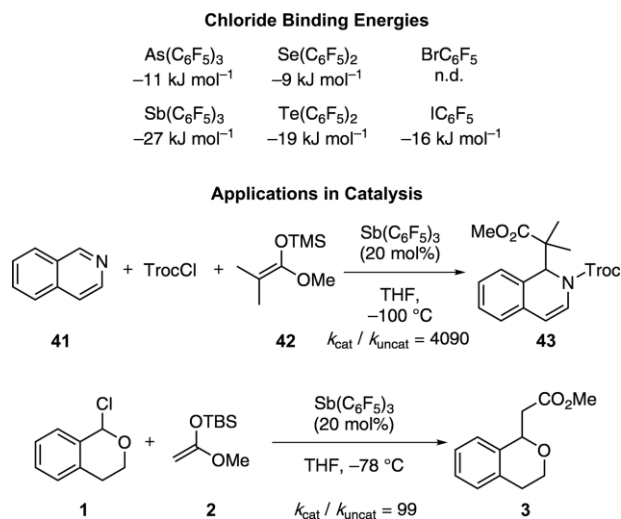


Figure 7. P...P Pnictogen bonding in a bis(phosphanyl)carbaborane(12) with selected bond lengths in Å.^[88]

However, catalytic applications of pnictogen bonds are still relatively scarce. In 2017, Schmauck and Breugst computationally investigated the catalytic potential of different pnictogen-bond donors in a series of organic reactions.^[93] Although only model compounds were included in the theoretical investigations, the results indicate that pnictogen-bond catalysis should be possible even with phosphorus compounds. Similar conclusions were derived by Yaghoobi and Sohrabi-Mahboub in a related reaction in 2018.^[94]

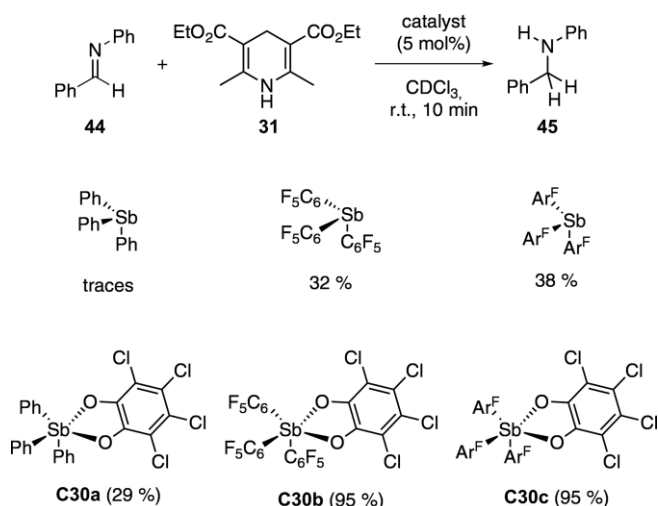
The first catalytic application of pnictogen bonds was reported in 2018 by Matile and colleagues.^[95] Dissociation constants determined for a series of pnictogen-containing mol-

ecules revealed that tris(pentafluorophenyl) stibane resulted in the strongest interaction with chloride ions (Scheme 20). Subsequently, this compound was applied in anion-binding catalysis (Scheme 20). For the Reissert-type substitution of isoquinoline (**41**), a rate enhancement of more than 4000 was observed compared to the uncatalyzed reaction. A slightly smaller acceleration of 99 was determined for the chloride abstraction in 1-chloroisochroman (**1**). In comparison to the related chalcogen- and halogen-bond donors, pnictogen-bond donors were found to be significantly more active. Computational investigations in 2020 by Sun, Zeng, and colleagues further support the experimentally observed reactivity series.^[96]



Scheme 20. Comparison of chloride binding energies (top) and first applications of pnictogen-bond donors as catalysts in organic reactions (Troc = 2,2,2-trichloroethoxycarbonyl).^[95]

Shortly after, Gabbaï and colleagues compared the catalytic activities of antimony(III) and antimony(V) compounds in different transformations.^[97] Oxidation results in a deeper σ -hole and an increased catalytic activity can be expected. In fact, the employed antimony(V) catalysts (**C30**) displayed a much better catalytic activity in the reduction of an imine than their anti-



Scheme 21. Differences in the catalytic activity for antimony(V) and antimony(III) compounds in the reduction of benzylideneaniline.^[97]

mony(III) analogs and resulted in almost quantitative reactions within 10 minutes (Scheme 21).

In summary, different proof-of-principle investigations have revealed the potential of pnictogen bonding for catalytic applications. Given the many computational investigations, it can be envisioned that the number of catalytic applications will increase in the near future.

5. Conclusions

σ -Hole interactions have clearly stepped out from under the shadow of hydrogen bonding for catalytic applications. Halogen, chalcogen, and pnictogen bonding cannot only be comparable in strength to this classical noncovalent interaction. In many cases, these modes of activation can even be more effective for catalytic applications. Initially, these “unconventional” interactions were considered as curiosities for crystallographers or theoreticians. Nowadays, multiple applications in many different fields of chemistry and catalysis in particular are known. While halogen bonding can already be considered to be an accepted mode of action in organocatalysis, further investigations for chalcogen and pnictogen bonding are certainly needed. The selected examples presented above clearly demonstrate the potential of these interactions for future applications.

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Keywords: Reaction mechanisms · Noncovalent interactions · Organocatalysis · Synthesis · Calculations

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