Organocatalysis

International Edition: DOI: 10.1002/anie.201910639
German Edition: DOI: 10.1002/ange.201910639

Chalcogen Bonding Catalysis of a Nitro-Michael Reaction

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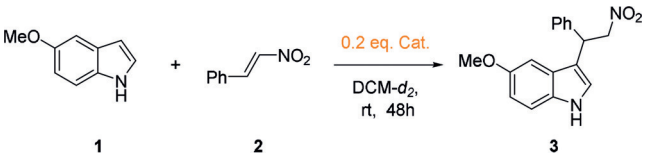
Abstract: *Chalcogen bonding is the non-covalent interaction between Lewis acidic chalcogen substituents and Lewis bases. Herein, we present the first application of dicationic tellurium-based chalcogen bond donors in the nitro-Michael reaction between trans-β-nitrostyrene and indoles. This also constitutes the first activation of nitro derivatives by chalcogen bonding (and halogen bonding). The catalysts showed rate accelerations of more than a factor of 300 compared to strongly Lewis acidic hydrogen bond donors. Several comparison experiments, titrations, and DFT calculations support a chalcogen-bonding-based mode of activation of β-nitrostyrene.*

Non-covalent organocatalysis has thus far been dominated by hydrogen bonding (HB), with primarily (thio)urea derivatives being used as catalyst backbones.[1] Nonetheless, other weak interactions such as anion–π interactions,[2] halogen bonding (XB),[3] and chalcogen bonding (ChB)[4] have attracted ever-increasing interest lately, and particularly the first two modes are now also established in organocatalysis.[5] In contrast, the application of ChB donors as intermolecular Lewis acidic catalysts is a hardly explored concept, and first examples were only published in 2017.[6] This is somewhat surprising as ChB offers several potential advantages such as its high directionality (with interaction angles of ca. 180°)[7] and manifold options to fine-tune the binding strength (by variation of the chalcogen substituent, the core structure, and/or the second substituent on the chalcogen). Still, most reports on ChB have thus far focused on its intramolecular use,[8] on applications in supramolecular[9] and solid-state chemistry,[10] as well as on anion recognition processes.[11]

ChB-based catalysts and activators were previously mainly employed in halide abstraction reactions, in which very Lewis basic anions act as substrates.[6a,b,12] The coordination of ChB donors to neutral compounds is surely weaker in strength, and so their activation is more challenging (even though the transition state may of course still be charged). Indeed, this concept has hitherto been limited to a handful of examples in which ChB donors enable the reduction of quinolines,[6c,d,13] and to a very recent report on the activation of carbonyl compounds.[14] In particular, the activation of nitro compounds has not been reported thus far for XB[15] or ChB organocatalysis.

Herein, we present the first such activation of a nitro derivative by ChB. To this end, the Michael addition of 5-methoxyindole to *trans*-β-nitrostyrene (Scheme 1) was chosen as a robust benchmark reaction.[16]



Scheme 1. Benchmark reaction for catalyst activity: The reaction of indole **1** with *trans*-β-nitrostyrene (**2**). DCM = dichloromethane.

In XB organocatalysis, neutral molecule activation has mostly been achieved with iodine-based catalysts,[17] and the heavier chalcogens are similarly known to produce stronger noncovalent Lewis acids (Te > Se > S).[4,18] Interestingly, previous ChB catalysts were mostly based on S and Se, with the very few examples of Te-based catalysts[11c,d,12b] being restricted to neutral compounds[12b] or derivatives in which the Te substituent is bound to a neutral moiety (in an overall monocationic compound).[11c,d] In this study, we decided to focus on dicationic bidentate selenium- and especially tellurium-based compounds, to achieve maximum Lewis acidity. Charged backbone structures are provided by triazolium units as 1) their neutral analogues are stable compounds and already strong anion acceptors[11c] and 2) the synthesis of their cationic analogues should be feasible by simple alkylation.[11d] The second substituent on the chalcogen was chosen to be phenyl in order to prevent a possible dealkylation of this group by nucleophilic attack.[6a]

The synthesis of all compounds followed the same strategy: Commercially available 1,3-diethynylbenzene (**4**) was converted into 1,3-bis(triazole)benzene derivative **5** by an azide–alkyne 1,3-dipolar cycloaddition reaction in quantitative yield (Scheme 2).[19] Deprotonation with LDA in the presence of the corresponding diphenyldichalcogenide provided neutral compounds $\mathbf{6}^{Ch}$ and—in the case of tellurium—also the mono-chalcogenated analogue $\mathbf{8}^{Ch}$.[20] In the final alkylation step, several different counterions were introduced to allow for a systematic investigation of their effect on catalytic activity: $Me_3OBF_4{\cdot}Et_2O$, MeOTf, and $MeNTf_2$ led directly to the respective dicationic chalcogen bond donors $\mathbf{7}^{Ch\text{-}X}$,[6a,21] whereas $BAr^F{}_4$ derivative $\mathbf{7}^{Te\text{-}BAr^F{}_4}$ was obtained by anion exchange from $\mathbf{7}^{Te\text{-}BF_4}$ with $TMABAr^F{}_4$.[16d,21,22] To the best of our knowledge, this is the first report on dicationic

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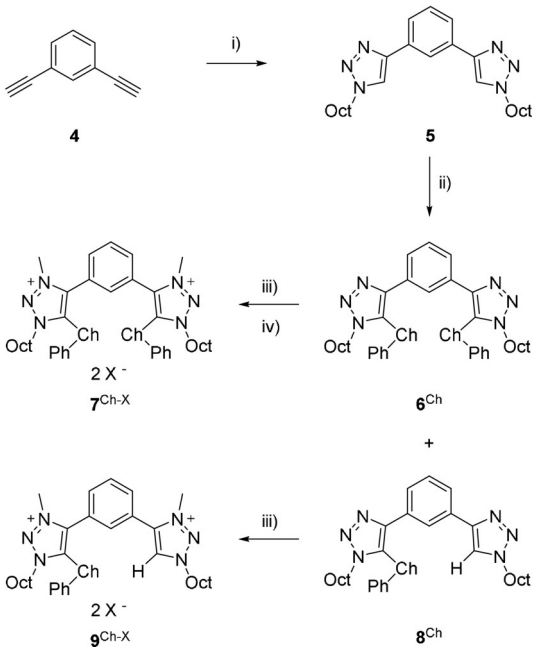
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201910639.



Scheme 2. Synthesis of chalcogen bond donors $\mathbf{7}^{Ch\text{-}X}$ and $\mathbf{9}^{Ch\text{-}X}$. i) CuI, TBTA, $OctN_3$, THF, dark, rt, 48 h; ii) LDA, THF, $(PhCh)_2$, −78→25 °C, 24 h; iii) for Me_3OBF_4 or MeOTf: DCM, rt, 24 h; for $MeNTf_2$: toluene, reflux, 24 h; iv) $TMABAr^F{}_4$, $CHCl_3$, rt, 24 h. TBTA = tris((1-benzyl-4-triazolyl)methyl)amine, Oct = octyl, THF = tetrahydrofuran; LDA = lithium diisopropylamide; Tf = trifluoromethanesulfonyl, TMA = tetramethylammonium; $BAr^F{}_4$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

tellurium-based chalcogen bond donors that are stable under ambient conditions. X-ray structural analysis of single crystals of compound $\mathbf{7}^{Te\text{-}OTf}$ (Figure 1) confirmed the strong Lewis acidity of the Te substituents, which were coordinated by triflate and by water.

First, the benchmark nitro-Michael reaction (Scheme 1; overall concentration: 36 mM) was run in the presence of various reference compounds to exclude other modes of activation than chalcogen bonding (Table 1). Under the reaction conditions shown in Scheme 1, there was virtually

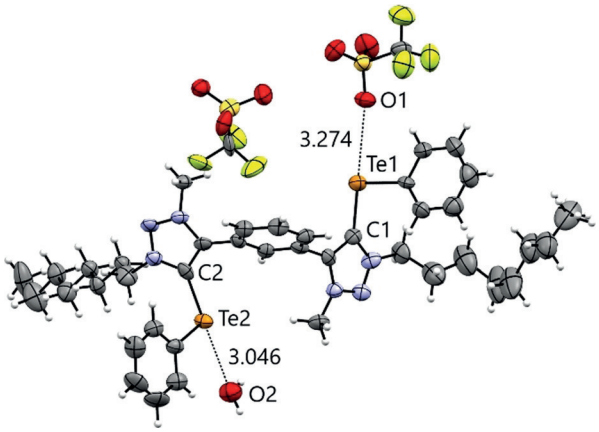


Figure 1. X-ray crystal structure of $\mathbf{7}^{Te\text{-}OTf}$.[31] The bond angles are 177° (C2-Te2-O2) and 171° (C1-Te1-O1). The sum of the Te—O van der Waals radii is 3.58 Å.

Table 1: ^{1}H NMR yields of product **3** (Scheme 1) in the presence of several reference compounds as catalyst candidates. For further data see the Supporting Information.

Entry	Catalyst	Cat. loading [mol %]	Yield of **3** [%]
1	–	–	< 5
2	**10**	20	5
3	$\mathbf{6}^{S}$	20	< 5
4	$\mathbf{6}^{Se}$	20	< 5
5	$\mathbf{6}^{Te}$	20	< 5
6	$\mathbf{12}^{H\text{-}BF_4}$	20	< 5
7	$\mathbf{13}^{I\text{-}BF_4}$	20	< 5

no background reaction even after 120 h (Table 1, entry 1). This allowed us to follow the reaction at room temperature by ^{1}H NMR spectroscopy and to easily monitor catalyst stability. As hydrogen bonding catalysis has been reported for this reaction,[16b] we then tested thiourea derivative **10** (Figure 2), which did not produce noticeable yields of product **3** (Table 1, entry 2) under these more diluted conditions.

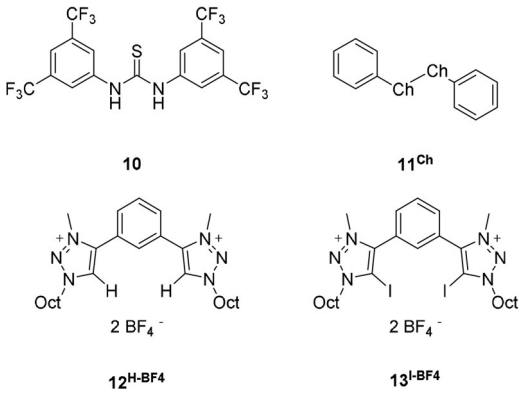


Figure 2. Lewis acidic reference compounds **10**, $\mathbf{11}^{Ch}$, $\mathbf{12}^{H\text{-}BF_4}$, and $\mathbf{13}^{I\text{-}BF_4}$.

Next, elemental chalcogens (S, Se, Te) and all corresponding variants of chalcogen compounds $\mathbf{6}^{Ch}$ and $\mathbf{11}^{Ch}$ (Ch = S, Se, Te) were applied in the reaction to rule out any chalcogen-based activation not related to ChB, but none of the catalyst candidates led to any product formation (see Table 1, entries 3–5 and the Supporting Information). The same was true for the hydrogen and iodine analogues $\mathbf{12}^{H\text{-}BF_4}$ and $\mathbf{13}^{I\text{-}BF_4}$ of ChB donors $\mathbf{7}^{Ch\text{-}X}$ (Table 1, entries 6 and 7). While this is somewhat surprising with regard to XB donor $\mathbf{13}^{I\text{-}BF_4}$, it also clearly demonstrates that neither the triazolium units nor the BF_4^- counterion are catalytically active.

These findings were further corroborated by comparison experiments with $NaBF_4$, NEt_4OTf, and $NMe_4BAr^F{}_4$, all of which showed no conversion into product **3** (see the Supporting Information). Even strong Lewis or Brønsted acids such as $AlCl_3$ or $HBF_4{\cdot}Et_2O$ exhibited only (very) weak activity even with a loading of 40 mol % (see the Supporting Information), which confirms that hidden acid catalysis can be excluded in the ChB catalysis discussed below.

With these results in hand, ChB donors $\mathbf{7}^{S\text{-}BF_4}$, $\mathbf{7}^{Se\text{-}BF_4}$, and $\mathbf{7}^{Te\text{-}BF_4}$ were applied in the benchmark reaction at a catalyst

loading of 20 mol%. For all three compounds, no indications of catalyst decomposition were observed by ^{1}H NMR spectroscopy. With tellurium-based catalyst $\mathbf{7}^{\text{Te-BF}_4}$, compound **3** was obtained in 78% yield after 48 h (Table 2, entry 3)

Table 2: ^{1}H NMR yields of product **3** (Scheme 1) in the presence of 20 mol% of chalcogen bond donors $\mathbf{7}^{\text{Ch-X}}$.

Entry	Catalyst	Yield of **3** [%]
1	$\mathbf{7}^{\text{S-BF}_4}$	< 5
2	$\mathbf{7}^{\text{Se-BF}_4}$	< 5
3	$\mathbf{7}^{\text{Te-BF}_4}$	78
4	$\mathbf{7}^{\text{Te-OTf}}$	7
5	$\mathbf{7}^{\text{Te-NTf}_2}$	< 5
6	$\mathbf{7}^{\text{Te-BAr}^F{}_4}$	81
7	$\mathbf{9}^{\text{Te-BF}_4}$	20

whereas the sulfur- and selenium-based catalysts $\mathbf{7}^{\text{S-BF}_4}$ and $\mathbf{7}^{\text{Se-BF}_4}$ were virtually inactive (Table 2, entries 1 and 2). Even though sulfur and selenium derivatives have been successfully used as ChB catalysts before,[6,12,13] the order of activity observed here is surely well in line with ChB theory (see above). To confirm the aspired bidentate mode of activation of $\mathbf{7}^{\text{Te-BF}_4}$, its mono-chalcogenated analogue $\mathbf{9}^{\text{Te-BF}_4}$ was subsequently also investigated. The fact that the latter is markedly less active (20% yield of **3**, Table 2, entry 7) clearly points towards a twofold coordination of the nitro group of the substrate by $\mathbf{7}^{\text{Te-BF}_4}$.

The influence of the counterion on the catalytic potency was studied with $\mathbf{7}^{\text{Te-OTf}}$, $\mathbf{7}^{\text{Te-NTf}_2}$, and $\mathbf{7}^{\text{Te-BAr}^F{}_4}$ (Table 2, entries 4–6). While the OTf and NTf_2 salts worked very poorly (7% and < 5% yield), the $BAr^F{}_4$ salt (with 81% yield) was comparable (or even slightly superior) in performance to $\mathbf{7}^{\text{Te-BF}_4}$. These observations are in good agreement with previous results for the counterion dependency in XB catalysis (with less coordinating anions leading to more accessible/Lewis acidic substituents).[17a–c]

Next, rate accelerations were determined for selected catalysts (Table 3) based on kinetic profiles (Figure 3). As the background reactivity is very slow, thiourea compound **10** was used as a reference with $k_{rel} = 1$ (2% yield after 48 h). The OTf and NTf_2 salts of $\mathbf{7}^{\text{Te}}$ as well as the acids $AlCl_3$ and $HBF_4{\cdot}Et_2O$ provided only relatively modest accelerations, whereas the stronger catalysts $\mathbf{7}^{\text{Te-BAr}^F{}_4}$ and $\mathbf{7}^{\text{Te-BF}_4}$ added

Table 3: Initial rate accelerations for selected catalysts (relative to catalyst **10**).[a]

Entry	Catalyst	k_{rel}
1	**10**	1
2	$\mathbf{7}^{\text{Te-NTf}_2}$	8
3	$HBF_4{\cdot}Et_2O$	13
4	$\mathbf{7}^{\text{Te-OTf}}$	15
5	$AlCl_3$	20
6	$\mathbf{7}^{\text{Te-BF}_4}$	125
7	$\mathbf{7}^{\text{Te-BAr}^F{}_4}$	325

[a] After 3 h reaction time. All catalysts were used in 20 mol% except for $AlCl_3$ and $HBF_4{\cdot}Et_2O$ (40 mol%).

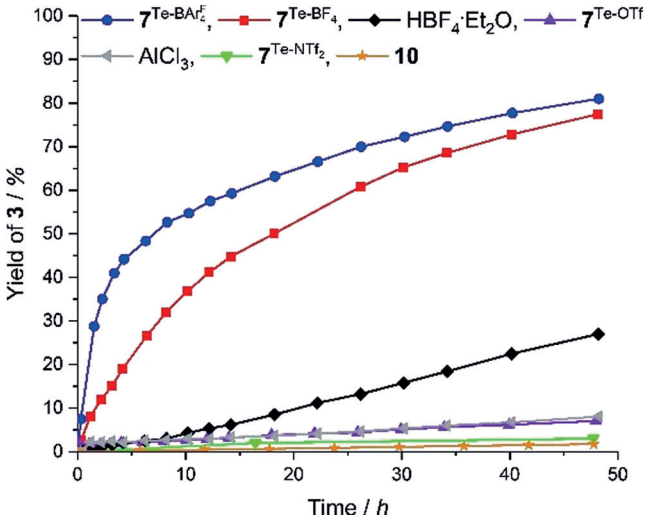


Figure 3. Time versus yield profile for the formation of **3** in the presence of different catalysts.

a further order of magnitude and accelerated the reaction by more than 300-fold.

In addition, binding constants for catalysts $\mathbf{7}^{\text{Te-BF}_4}$ and $\mathbf{7}^{\text{Te-BAr}^F{}_4}$ with *trans*-β-nitrostyrene (**2**) were determined by ^{1}H NMR titrations[23] in DCM-d_2, and values of 0.4 M^{-1} and 0.6 M^{-1} were obtained, respectively (Table 4, entries 4 and 2).

Table 4: Binding constants *K* for catalysts $\mathbf{7}^{\text{Te-BAr}^F{}_4}$, $\mathbf{7}^{\text{Te-BF}_4}$, and $\mathbf{13}^{\text{I-BF}_4}$ with *trans*-β-nitrostyrene (**2**) and chloride in DCM.

Entry	Host	Guest	Solvent	K [M^{-1}]
1	$\mathbf{7}^{\text{Te-BAr}^F{}_4}$	TBACl	DCM	2.7×10^4
2	$\mathbf{7}^{\text{Te-BAr}^F{}_4}$	**2**	DCM-d_2	0.6
3	$\mathbf{7}^{\text{Te-BF}_4}$	TBACl	DCM	7.5×10^3
4	$\mathbf{7}^{\text{Te-BF}_4}$	**2**	DCM-d_2	0.4
5	$\mathbf{13}^{\text{I-BF}_4}$	TBACl	DCM	4.2×10^5
6	$\mathbf{13}^{\text{I-BF}_4}$	**2**	DCM-d_2	0.2

TBA = tetrabutylammonium.

This data indicates that at the overall concentrations mentioned above, only a small amount of substrate **2** is coordinated by the ChB donors (less than 1%). As the action of the catalysts is likely based on the coordination to a partially anionic transition state or an anionic intermediate (see below), we also determined the binding constants to NBu_4Cl in DCM by ITC (isothermal titration calorimetry) measurements.[24] As expected, the binding is overall much stronger compared to that to the neutral substrate, and in agreement with the previous experiments, the more active catalyst $\mathbf{7}^{\text{Te-BAr}^F{}_4}$ ($K = 2.7\times10^4\ M^{-1}$, Table 4, entry 1) also binds slightly more strongly than the BF_4 salt ($K = 7.5\times10^3\ M^{-1}$, Table 4, entry 3).

For comparison, the same binding data was also acquired for the catalytically inactive XB donor $\mathbf{13}^{\text{I-BF}_4}$ (Table 4, entries 5 and 6). The coordination to *trans*-β-nitrostyrene ($K = 0.2\ M^{-1}$) was of similar strength as with the ChB donors, while the complexation of chloride ($K = 4.2\times10^5\ M^{-1}$) was an order of magnitude stronger. This disagreement with the

catalytic performance means that either the transferability of this binding data to catalysis is quite limited or that there is a sweet spot in Lewis acidity that is ideal for catalysis.

Previous studies on nitro-Michael[25] (and Michael)[26] addition reactions, typically involving enolate-type nucleophiles, have indicated that the initial carbon–carbon bond-forming step is an equilibrium process and that the subsequent proton transfer is rate-determining. Thus, it is plausible that the ChB donors coordinate to the nitronate intermediate and shift the equilibrium of its formation to the product side. The following proton transfer step will likely be negatively affected by coordination of the ChB Lewis acid to the nitronate so that the ChB donors would exert opposing influences on the mechanism. This is one possible explanation why the apparently stronger Lewis acid $\mathbf{13}^{I-BF_4}$ did not accelerate the reaction.

Finally, first insight into the nature of the complex between the nitronate and the ChB donors was obtained by density functional theory (DFT) calculations in the gas phase. To this end, the M062X[27] functional with D3 dispersion corrections[28] and the def2-TZVP[29] basis set was used. The optimized minimum featured two very short ChBs between one Te substituent and one oxygen atom of the nitronate, respectively (Figure 4), which strongly corroborates a bidentate mode of activation.

In conclusion, the first dicationic tellurium-based chalcogen bond donors that are stable under ambient conditions have been synthesized and successfully used as noncovalent (in)organocatalysts in a nitro-Michael addition reaction. Comparison experiments indicated that the corresponding S and Se derivatives are inactive and that the mode of action can very likely be ascribed to chalcogen bonding. Similar to halogen bonding, non-coordinating counterions such as BF_4 and BAr^F_4 are crucial for catalytic activity. The relative Lewis acidities of these ChB donors were further investigated by titration experiments, and the proposed bidentate mode of activation was supported by DFT calculations. Future work in our group will deal with a detailed mechanistic study of this and related mechanisms as well as with the activation of further neutral compounds such as carbonyl derivatives.

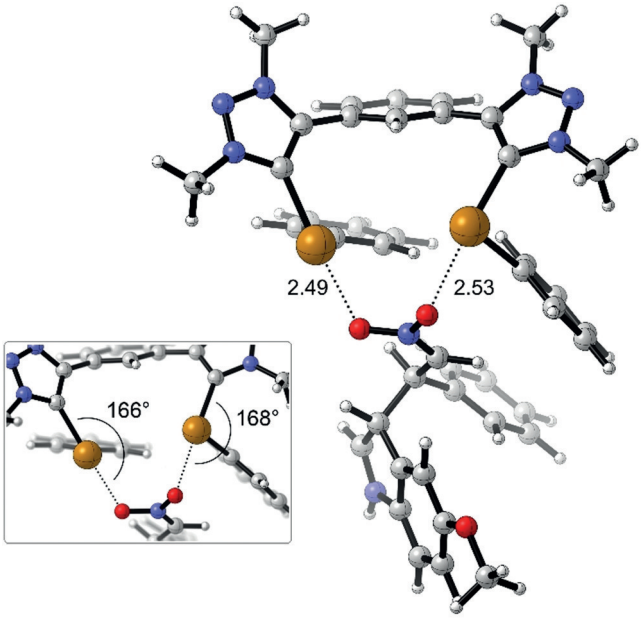


Figure 4. Simplified complex between ChB donor $\mathbf{7}^{Te}$ (all-methylated) and the nitronate formed from **1** and **2**, as obtained by DFT calculations (distances in Å; zoomed inset: C–Te···O bond angles). Graphics by CYLview.[30]

Acknowledgements

We thank the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (638337) for financial support. This work was further funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy (EXC-2033, Projektnummer 390677874).

Conflict of interest

The authors declare no conflict of interest.

Keywords: chalcogen bonding · Lewis acids · Michael addition · non-covalent interactions · organocatalysis

How to cite: *Angew. Chem. Int. Ed.* **2019**, *58*, 16923–16927
Angew. Chem. **2019**, *131*, 17079–17083

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[31] CCDC 1946498 (**7**$^{Te\text{-}OTf}$) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Manuscript received: August 20, 2019
Accepted manuscript online: September 19, 2019
Version of record online: October 23, 2019

