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Chiral isotellurourea Lewis base catalysts

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Highlights:

- Synthesis and development of highly nucleophilic chiral isotellurourea Lewis base catalysts.
- Elucidation of the kinetic and thermodynamic properties of isotelluroureas.
- Establishing isotelluroureas for asymmetric transformations.

Abstract: Our group has recently introduced chiral isotelluroureas as a new class of Lewis base catalysts, which show increased nucleophilicity and basicity as compared to the lighter chalcogen-based congeners within the family of isochalcogenoureas. This short perspective article aims to introduce the readers to these novel catalysts which show promising reactivity profiles and allow for increased reaction rates, thus making them particularly appealing for applications where some of the established isothioureas or isoselenoureas may not be nucleophilic enough and thus reach their limits.

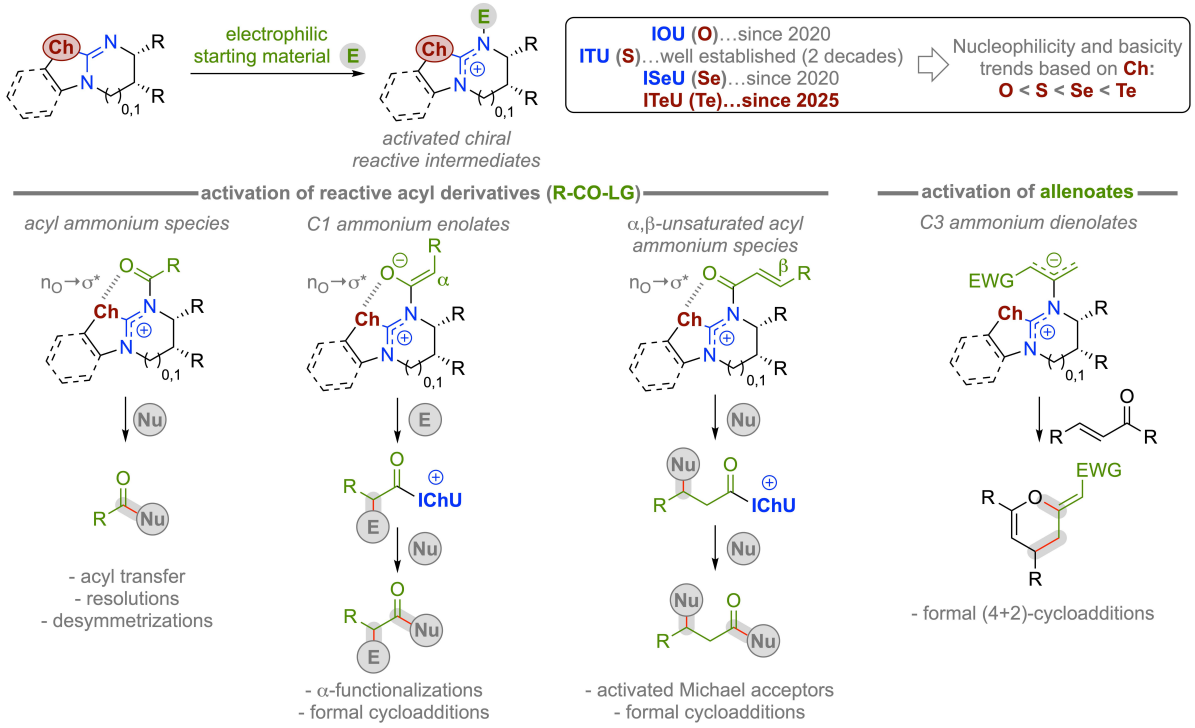
Keywords: organocatalysis; asymmetric catalysis; Lewis bases; organotellurium compounds; cycloadditions; C-C bond formations

1. Introduction and motivation

Chiral isochalcogenoureas (IChUs) have found widespread use as covalently interacting Lewis base (LB) organocatalysts for asymmetric organic synthesis (Scheme 1) [1–5]. Pioneering work by Birman's group revealed the high potential of easily accessible and bench stable isothioureas (ITUs) as chiral acyl transfer-reagents [6,7] and over the years a multitude of asymmetric acyl transfer-based reactions using ITU catalysis has been developed (e.g., kinetic or dynamic kinetic resolutions or desymmetrization reactions) [6–9]. Furthermore, ITUs have been very successfully used for the generation and utilization of chiral C1 ammonium enolates, which can be successfully engaged in α-functionalization and formal cycloaddition reactions [10,11] and chiral α,β-unsaturated acyl ammonium species that can be utilized for asymmetric conjugate addition process [12,13]. These established activation modes and applications rely on the initial addition of the ITU to an activated carboxylic acid derivative (e.g., acylhalides,

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anhydrides, electron-deficient esters) and the formed ammonium species adopt a very well-defined conformation because of stabilizing 1,5-O···S ($n_O \rightarrow \sigma^*$) interactions, thus allowing for stereochemically predictable follow up transformations [14,15]. In addition, our group has recently also shown that ITUs serve well for the activation and utilization of allenoates in formal (4+2)-cycloadditions, proceeding via chiral C3 ammonium dienolate species (Scheme 1) [16–19]. Furthermore, ITUs were also very successfully used for silyl-transfer reactions [20–22] but, although synthetically very powerful, this concept will not be discussed in further detail in this contribution as our own focus was so far only on applications where the catalyst acts via addition to a carbon center.



Scheme 1. Overview of the established IChU activation modes.

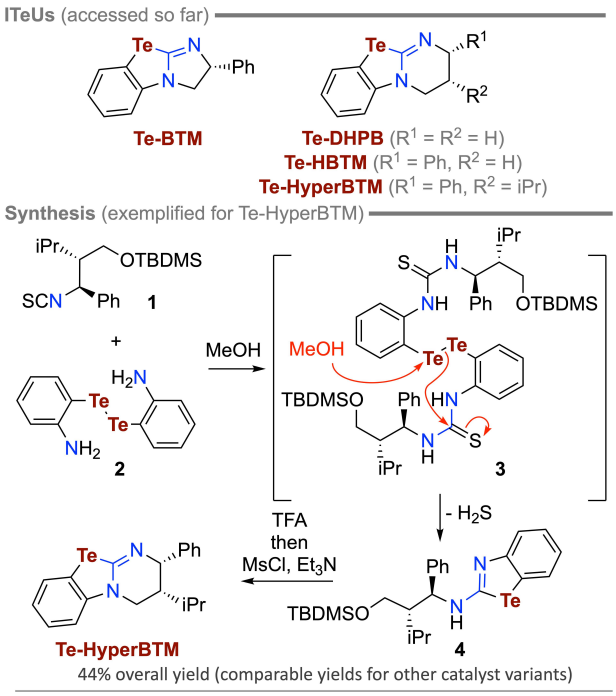
In 2020 [23], Smith's group introduced and utilized first derivatives of analogous O- and Se-based isochalcogenoureas (IOUs and ISeUs) as LB catalysts and a pronounced effect of the chalcogen on reactivity, catalytic activity, and the 1,5-O···Ch interaction was observed in this seminal contribution, as well as follow up investigations [23–26]. Noteworthy, ISeUs show a stronger $n_O \rightarrow \sigma^*$ interaction and often higher catalytic reactivity as compared to ITUs (with usually similar levels of enantioselectivities), while IOUs are the least reactive and also do not show any pronounced $n_O \rightarrow \sigma^*$ stabilization, thus resulting in lower levels of enantioselectivities [23]. Detailed recent kinetic, thermodynamic, and computational collaborative studies of our team (with the groups of Smith and Ofial) [27–30] as well as Wiskur's group [31,32] showed that the chalcogen atom has a pronounced impact on the nucleophilicity (*N*-parameter determined according to Mayr's methodology [33]) and Lewis [34] and Bronsted basicity of the reactive nitrogen atom. More specifically, the *N*-parameter follows the order ISeU > ITU > IOU and the same comes true for the basicity, while the leaving group quality (nucleofugality) is the highest for IOUs (and lowest for ISeUs) [29]. Overall, this strong chalcogen impact, which can be rationalized by the lower electronegativity of the heavier chalcogens, thus paves the way to a conceptually unique and powerful tool to tune the reactivity of these Lewis base catalysts (besides modifying the catalyst

backbone itself). Benefitting on these effects the use of more nucleophilic IChUs thus becomes appealing for applications where the initial addition of the catalyst to the reagent may be the rate-determining step, which is for example the case in our allenoate cycloaddition reactions where we observed a superior performance of ISeUs in most case studies [16–19].

Based on the knowledge gathered in all these previous experimental and computational studies and considering the fact that sometimes the established IChUs clearly come to their limits (long reaction times, high catalyst loadings, insufficient activation of less electrophilic starting materials, …), we rationalized that analogous, until recently unprecedented, isotelluroureas (ITeUs) may represent a new generation of even more reactive chiral IChUs [29]. As discussed in this perspective, we have succeeded in developing robust and flexible syntheses routes to access this novel class of chiral IChUs and found them to be highly nucleophilic and basic catalysts, which, in our opinion, hold much promise for future Lewis base catalysis applications [35–37].

2. Syntheses of isotelluroureas

Focusing on the development of a robust and flexible general synthesis route to access various (chiral) isotelluroureas, we initially investigated and optimized the synthesis of the achiral derivative **Te-DHPB** [29]. Once a successful protocol for this parent derivative had been established, we extended this strategy to the chiral variants **Te-BTM**, **Te-HBTM**, and **Te-HyperBTM** (these chiral core structures have emerged as the most privileged and well-established scaffolds in ITU chemistry and were therefore our primary motifs of interest for ITeUs as well) [35–37]. After several unsuccessful attempts where we tested different strategies to incorporate the tellurium in the N-heterocyclic framework we managed to identify the route exemplified for **Te-HyperBTM** in Scheme 2 as being well suited to access all four derivatives of interest. Very generally, by starting from the described ditelluride **2** [38] and reacting it with (chiral) isothiocyanate-containing O-protected alcohols such as compound **1** in MeOH the intermediate benzotellurazole **4** can be directly accessed. This transformation is postulated to proceed via formation of the bisthiourea-containing ditelluride **3** first, which immediately reacts with MeOH resulting in a cleavage of the Te-Te-bond and subsequent benzotellurazole formation (release of H_2S). Following OTBDMS-deprotection and activation of the alcohol by mesylation a final cyclization gives the targeted **Te-HyperBTM**. Accessing the other catalyst derivatives required some subtle variations of the reaction conditions only (especially for the late deprotection-cyclization sequence), thus giving access to these ITeUs in a straightforward manner (with practical overall yields of around 40% in all cases) [29,35–37]. It should be emphasized that all ITeUs accessed so far were found to be bench stable and not sensitive to an oxygen atmosphere or when dissolved in classical organic solvents or in the presence of water. Only when carrying out prolonged reactions at temperatures clearly above 100 °C sometimes some decomposition could be observed.



Scheme 2. ITeUs accessed so far and their synthesis exemplified for **Te-HyperBTM**.

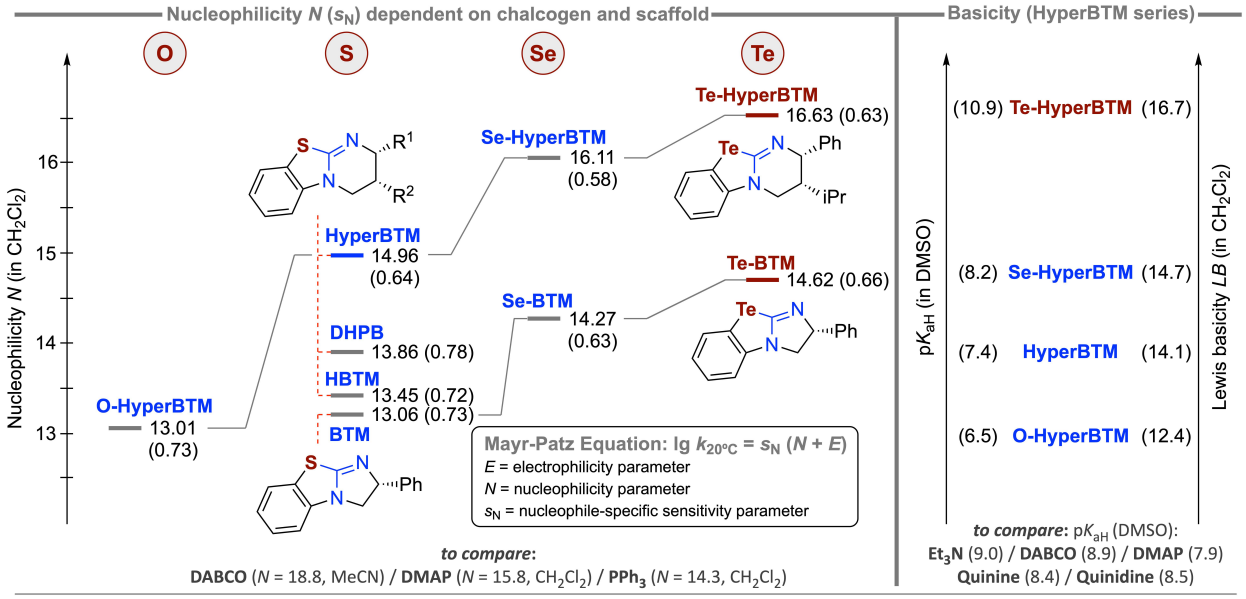
3. Kinetic and thermodynamic properties of isotelluroureas

To gather a deeper understanding of the factors that influence and steer the reactivity of different classes of IChUs, we recently carried out detailed collaborative studies with the groups of Ofial and Smith to determine the key kinetic and thermodynamic properties of IChUs in dependency of their parent skeleton and the nature of the chalcogen [29,30] One reliable methodology to quantify the nucleophilicity of a reaction partner in a bimolecular transformation is the Mayr-Patz approach, which allows for the description of the reaction rate by means of the well-established Mayr-Patz equation ($\lg k_{20\,°C} = s_N (N + E)$) [33,39,40]. Hereby the parameter N describes the nucleophilicity of the employed nucleophile, while E is the electrophilicity parameter of the reaction partner, and s_N the nucleophile-specific sensitivity parameter. Experimental determination of the N parameters for various IChUs showed interesting trends and relationships (Scheme 3). Focusing on the parent S-based ITUs first, showed that the 5-ring derivative **BTM** is the least nucleophilic one, while the 6-ring fused systems **HBTM**, **DHPB** and **HyperBTM** show increased N parameters (with **HyperBTM** (N = 14.96) being the clearly the most nucleophilic species in the series) [27,29]. Investigating selected variants with different chalcogens next revealed that IOUs are clearly less nucleophilic, while the heavier chalcogens significantly enhance the nucleophilicities of the catalysts and especially the novel ITeUs were found to be highly nucleophilic, with **Te-HyperBTM** (N = 16.63) standing out as the most nucleophilic chiral derivative (please note that the achiral **Te-DHPB** shows the same nucleophilicity (N = 16.63) but for reasons of simplicity it is not given in Scheme 3). Interestingly, the nucleophile-specific sensitivity parameter s_N is not significantly changed by the Te-incorporation as compared to the lighter chalcogen derivatives [29,35].

Noteworthy, a conceptually similar quantification approach can also be used to describe equilibrium reactions between a nucleophilic and an electrophilic species, which thus allows for the determination of the corresponding Lewis basicities (LB) and Lewis acidities (LA) [34]. We have done this for a series of IChU derivatives as well and, as exemplified for the HyperBTM scaffold, the chalcogen again has a

very pronounced effect on the Lewis basicities, with **Te-HyperBTM** being clearly the strongest Lewis base in the series [29,35]. Similarly, also the Brønsted basicity, given by the pK_{aH} value (the pK_a of the protonated conjugated acid) [41,42], shows the same trend and chalcogen impact, with **Te-HyperBTM** (pK_{aH} in DMSO = 10.9) [43] being almost two orders of magnitude more basic than **Se-HyperBTM** and also for example Et_3N.

These different kinetic and thermodynamic properties of the different IChUs and especially the high nucleophilicity and basicity of the ITeUs will have a strong implication on their use as catalysts. On one hand ITeUs are significantly stronger nucleophiles and bases than the other members of the IChU family [29,35], which implies that they should be the catalysts of choice for less reactive (less electrophilic) starting materials. On the other hand, their strong basicity will make them prone to protonation (which can thus lead to catalyst deactivation). Also, their leaving group ability is expected to be weaker than that of the lighter chalcogen analogues [35,44,45], which will make them less-suited catalysts for applications where catalyst release may be the rate limiting step.



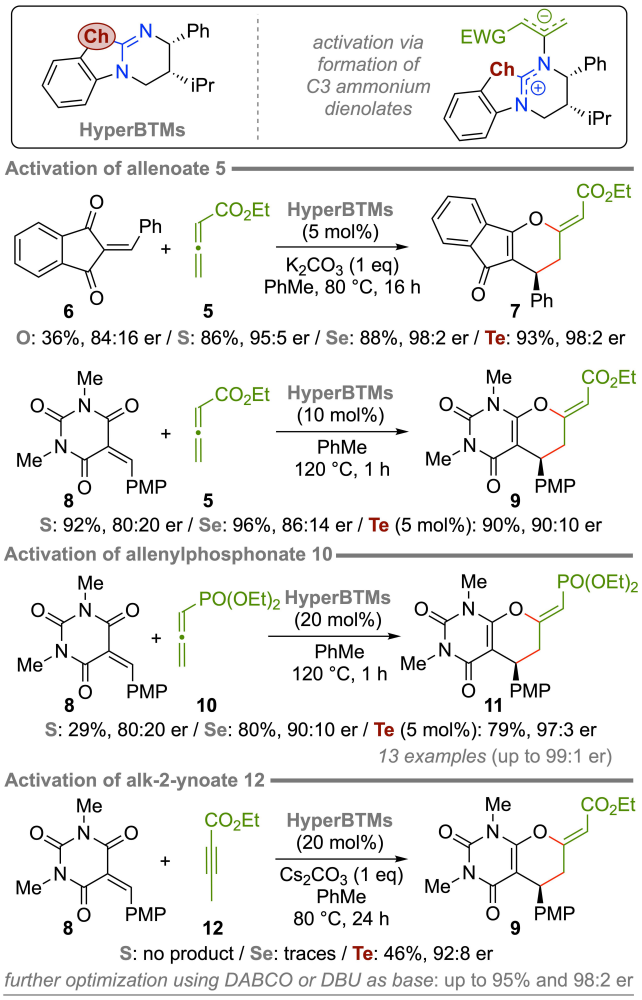
Scheme 3. Kinetic (nucleophilicity N (s_N in parentheses)) and thermodynamic (Lewis and Brønsted basicity) properties of IChUs.

4. Isotelluroureas as chiral Lewis base catalysts

Once we had a robust synthesis route for chiral ITeUs and a proper understanding of their kinetic and thermodynamic properties at hand, we set out to benchmark them as catalysts in prototypical ITU and ISeU applications. Considering our own experience with allenoate-based (4+2)-cycloadditions using the HyperBTM series [16–19] we first investigated **Te-HyperBTM** as a catalyst for some of our previously reported cycloadditions of allenoates (Scheme 4) [35]. As can be seen for the reactions of **5** with the Michael acceptors **6** and **8**, the use of **Te-HyperBTM** allowed for increased reactivities as compared to the Se- and S-analogous. This resulted in higher yields while preserving or even improving the levels of enantioselectivities and, as demonstrated for the synthesis of the barbiturate-based product **9**, also allowed for a lowering of the catalyst loading without compromising the outcome. Once the beneficial effect of the Te-incorporation for established allenoate cycloadditions was proven, we then targeted to exploit the higher nucleophilicity of **Te-HyperBTM** for reactions of less reactive building blocks

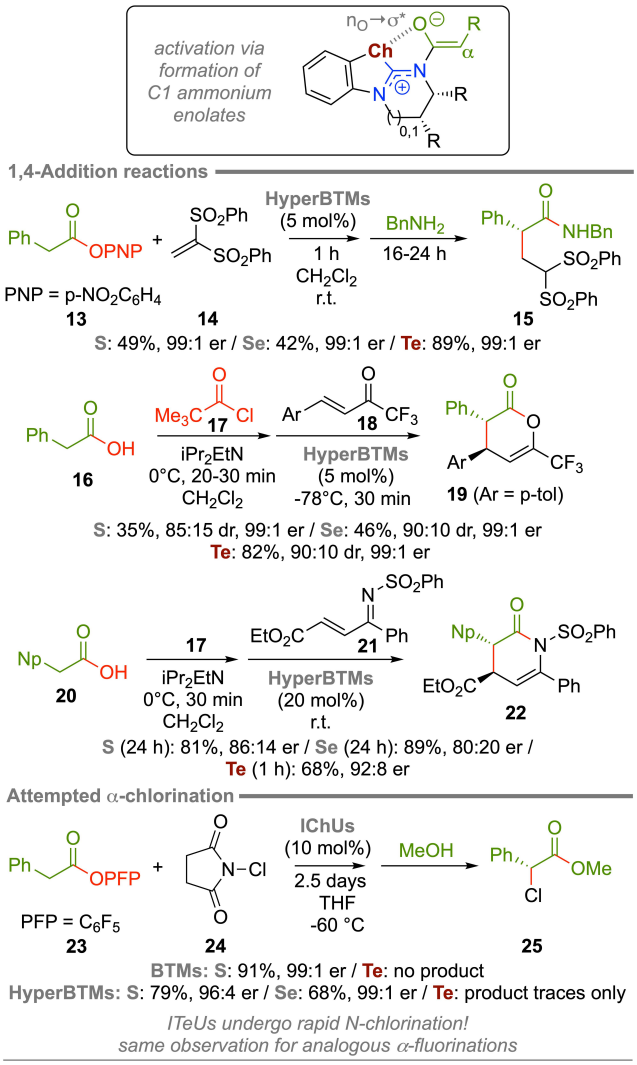
(Scheme 4, lower two reactions). First, we screened the cycloaddition of allenylphosphonate **10** with arylidene barbiturate **8**. While the parent **HyperBTM** (Ch = S) clearly came to its limits, resulting in low yield and moderate er only, the more nucleophilic **Se-HyperBTM** performed better but still not fully satisfactorily. Gratifyingly, as anticipated **Te-HyperBTM** proved to be much better suited, allowing for high yields and enantioselectivities, even when reducing the catalyst loading to 5 mol% [35]. An even more pronounced chalcogen-depending trend in reactivity was observed when employing alk-2-ynoate **12** in the reaction with **8**. In principle this cycloaddition should give access to product **9**, in analogy to the use of allenoate **5**. However, S- and Se-based HyperBTMs did not allow for any product formation [35], which can be rationalized by the fact that alkynoate **12** is approximately two orders of magnitude less electrophilic in its β-position as compared to allenoate **5** [46]. Benefitting from **Te-HyperBTM**'s higher nucleophilicity and basicity it was then possible to successfully engage alkyne **12** in the target cycloaddition (approx. 50% yield under the initial conditions) [35] and after some optimization of the reaction conditions (*i.e.* changing for an organic amine-based achiral stoichiometric base instead of Cs_2CO_3) high yields and high levels of enantioselectivities could be achieved [36]. Overall these results obtained when using **Te-HyperBTM** for these types of (4+2)-cycloadditions clearly underscore the potential of this highly nucleophilic catalyst for asymmetric applications, especially when facing a scenario where the initial attack of the catalyst to a reaction partner is supposed to be the rate limiting step (it should be stated that we also had test reactions with some more sensitive vinylogous acceptors such as quinone methides [19] where the higher reactivity of ITeUs was found to be somewhat detrimental [35], resulting in competing attack to the acceptors and their decomposition).

Having identified the potential of ITeUs for allenoate-type cycloadditions (Scheme 4), we next investigated their suitability for reactions proceeding via chiral C1 ammonium enolates [10,11,37]. Hereby we first benchmarked them for established conjugated addition reactions by either using activated aryl esters (such as compound **13**) or by starting from free carboxylic acids (**16** or **20**) and carrying out an *in situ* activation via formation of a mixed anhydride with acyl chloride **17** [37]. First the 1,4-addition of the p-nitrophenyl ester **13** to the bissulfone-based acceptor **14** followed by direct amidation of the primary reaction product with $BnNH_2$ was investigated. Noteworthy, when the initial IChU-catalyzed addition step was limited to 1 h reaction time, a clearly increased reactivity rate of **Te-HyperBTM** as compared to **HyperBTM** and **Se-HyperBTM** was observed (the same came true when testing the BTM series). A similarly increased reaction rate, without compromising the stereoselectivity, was observed when starting from either acid **16** and engaging it in a lactonization reaction with **18** (product **19**), or when employing **20** and carrying out a conceptually similar lactamization to access product **22** (in all these cases the HyperBTM scaffold was found to be the best suited one) [37]. Hereby it should however also be stated that a careful monitoring of the reaction time was found to be crucial, as prolonged times lead to retro reactions and decomposition of the products because of the capability of the ITeUs to add to the products as well.



Scheme 4. Increasing reactivities and reaction rates in IChU-catalyzed (4+2)-cycloadditions of allenoates and similar building blocks by using **Te-HyperBTM**.

Moving to α-halogenation reactions next resulted in unexpected results (lower part of Scheme 5). While we have recently shown that ITUs and ISeUs are well-suited to facilitate the asymmetric α-chlorination of the activated ester **23** [47], ITeUs were however not tolerated at all (the same trend was observed for the analogous α-fluorination [48]). Hereby we instead observed more or less quantitative N-chlorination of the catalyst, leading to its complete deactivation. When carrying out NMR control experiments where the IChUs were mixed with NCS we found that this N-chlorination is a fast process for ITeUs, while ISeUs undergo this process significantly slower and ITUs do show almost no N-chlorination, a trend which is well in line with their nucleophilicities and Lewis basicities.

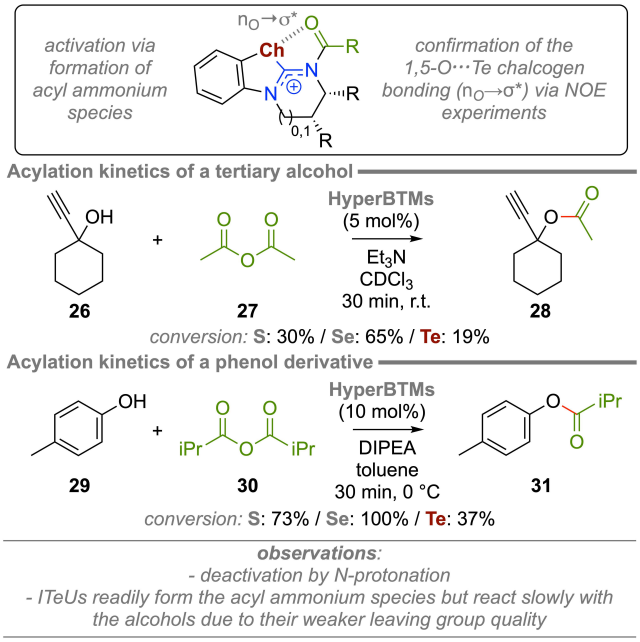


Scheme 5. Effect of ITeUs for C1 ammonium enolate chemistry in comparison to ITUs and ISeUs.

Maybe the most classical application of chiral ITUs is their use as chiral acyl transfer reagents [9], allowing for (dynamic) kinetic resolution and desymmetrization approaches. It was recently shown by Smith's group that ISeUs possess increased acyl-transfer potential as compared to ITUs [23] and we thus of course also tested our ITeUs for such transformations. Interestingly, in initial experiments using the achiral **Te-DHPB** we found a significantly reduced catalytic activity as compared to the lighter chalcogen congeners [29]. Moreover, the more basic ITeU was found to undergo N-protonation rather quickly hereby. Investigating this in more detail [49], we systematically checked the acylation of the tertiary alcohol **26** [50] and the phenol derivative **29** (Scheme 6). In both cases we found **Te-HyperBTM** being catalytically clearly less active than **HyperBTM** and **Se-HyperBTM** (general reactivity order for acyl transfer: Se > S > Te). Besides the competing N-protonation (deactivation) another fact that explains this reactivity trend is the reduced leaving group quality of ITeUs. While we found them to rapidly add to acylating agents like anhydrides **27** or **30** (or analogous carboxylic acid halides) these N-acyl-ITeU species turned out to be rather stable and thus the acyl transfer to the alcohol nucleophiles is a slow process when using the less nucleofugal ITeUs as leaving groups [35,44,45].

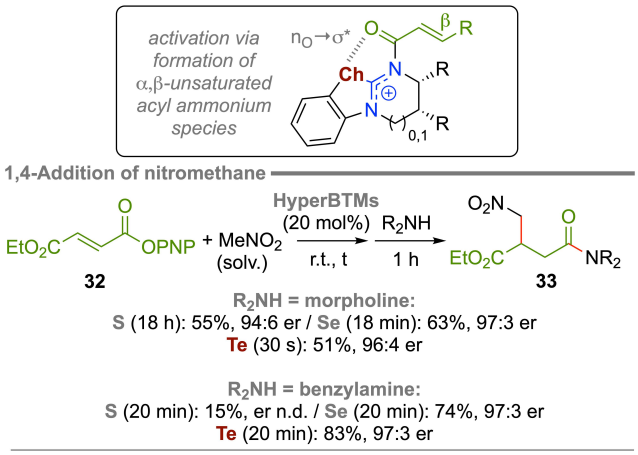
Another point that should be noted is the fact that we so far did not succeed in obtaining single crystals suited for X-ray analysis of acylated ITeUs and thus we could not directly prove the crucial

1,5-O···Te ($n_O \rightarrow \sigma^*$) interaction. However, NOE NMR experiments (as described recently for other IChUs [23]) clearly support the presence of these chalcogen bonding interactions when using ITeUs as well [51].



Scheme 6. Limited applicability of ITeUs for acyl transfer reactions.

Finally, to obtain a full picture of the catalytic potential of ITeUs, we also briefly investigated their suitability to activate α,β-unsaturated Michael acceptors via formation of chiral α,β-unsaturated acyl ammonium species (Scheme 7) [12,13]. Hereby we so far only tested the HyperBTM series for the well-described conjugate addition of nitromethane to the diester **32**, followed by subsequent amidation with either morpholine or benzylamine (giving amides **33**) [52]. The superior performance of **Se-HyperBTM** compared to **HyperBTM** was already described previously [23] and we were delighted to see that also for this class of transformations the use of **Te-HyperBTM** resulted in significantly increased reaction rates again [53] While a reaction time of 18 h for the conjugate addition step were required to achieve 55% NMR yield when using **HyperBTM**, approximately the same result was obtained after 18 min with **Se-HyperBTM** already and within only 30 seconds when using **Te-HyperBTM** (without any noteworthy deviation in er). Alternatively, when carrying out the reaction for 20 min only, followed by a benzylamine quench, **HyperBTM** yielded only small amounts of the product, while **Se-HyperBTM** (74%) and **Te-HyperBTM** (83%) significantly boosted the rate of the conjugate addition reaction, thus proving the potential of ITeUs for future conceptually similar applications as well.



Scheme 7. Increased reactivity of Michael acceptors activated by **Te-HyperBTM** (NMR yields).

5. Conclusion

Chiral isothioureas, and more recently also analogous isoselenoureas, have been established as highly potent and versatile Lewis base catalysts which are capable of facilitating a broad variety of different transformations. Over the course of the last two years, our group has succeeded in extending the family of isochalcogenoureas to include the so far unprecedented tellurium-based derivatives (isotelluroureas) as well. These Lewis bases show an even higher nucleophilicity and basicity as compared to the lighter chalcogen-containing established congeners, thus allowing for enhanced catalytic performance in several reactions. As discussed in this short perspective article, ITeUs are especially powerful for reactions where the initial attack of the catalyst on a reagent is energetically demanding (may even be rate limiting), as is the case in cycloadditions of allenoates or isomeric alkynoates. Furthermore, we also found increased reaction rates in C1 ammonium enolate-based C-C bond forming reactions as well as the activation of α,β-unsaturated activated esters. On the other hand, their increased nucleophilicity also makes them prone to undergo undesired side-reactions with electrophilic reagents, as observed in the attempted α-chlorination of C1 ammonium enolates. Furthermore, their leaving group quality (nucleofugality) is weaker as compared to ITUs and ISeUs. Accordingly, based on our current understanding, ITeUs may thus be very promising catalysts for applications where the nucleophilicity and basicity of the established ITUs and ISeUs is not sufficient, while the lighter chalcogen-based IChUs will rather be the catalysts of choice when the catalyst release is the crucial (maybe rate-limiting) step.

Declaration of generative AI and AI-assisted technologies

The authors did not use generative AI or AI-assisted technologies in the writing of this manuscript.

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Authors' contribution

Conceptualization, M.W., L.S.; methodology, L.S., M.P., S.A., F.K., A.K., F.B., L.S.V., A.S., M.H. and M.B., investigation, L.S., M.P., S.A., F.K., A.K., F.B., L.S.V., A.S., M.H. and M.B.; data curation, L.S., M.P., S.A., F.K., A.K., F.B., L.S.V., A.S., M.H. and M.B.; writing—original draft preparation, M.W.; writing—review and editing, M.W., L.S., M.P., S.A., F.K., A.K., F.B., L.S.V., A.S., M.H. and M.B.; visualization, M.W.; supervision, M.W.; project administration, M.W.; funding acquisition, M.W. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Mario Waser holds the position of Associate Editor and Guest Editor of the Special Issue "Advances in Asymmetric Catalysis: From Mechanisms to Applications" for *Asymmetry* and has not peer reviewed or made any editorial decisions for this paper. The authors declare no other conflicts of interest associated with this manuscript.

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