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Critical Review

N,N'-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea: a Privileged Motif for Catalyst Development

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Dedicated to Professor Peter R. Schreiner

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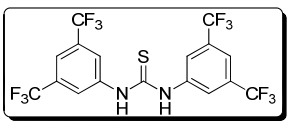
Over the last decade, the use of (thio)urea derivatives as organocatalysts in organic chemistry has increased rapidly. One of the key features is their ability to activate substrates and subsequently stabilize partially developing negative charges (e.g., oxyanions) in the transition states employing explicit double hydrogen bonding. Among (thio)urea-based catalysts, *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea developed by Schreiner's group (abbreviated here as Schreiner's thiourea) has played a very important role in the development of H-bond organocatalysts. Nowadays it has found wide utilities in promoting organic transformations, and the 3,5-bis(trifluoromethyl)phenyl motif thereof is used ubiquitously in H-bond catalysts. This review summarizes the key developments of Schreiner's thiourea-mediated reactions with aim to further expand the applications of (thio)urea-based catalysts.

Introduction

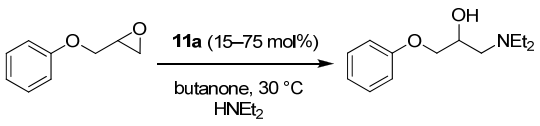
The last decade has seen the increasing use of (thio)urea derivatives as catalysts in synthetic chemistry, in large part due to their hydrogen-bonding interactions with partially developing negatively charged atoms in the substrates as well as in the transition states.[1-3] In parallel with well appreciated knowledge that hydrogen bonding plays a key role in the mode of action of various enzymes, well-defined hydrogen-bonding donors have started to serve as efficient catalysts for various organic transformations.[4,5] Among others, *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (abbreviated as *Schreiner's thiourea* or **T1**) developed by Schreiner and coworkers possesses privileged catalytic properties and has been applied to a wide range of organic transformations (Scheme 1).[6-8] In addition, incorporation of the 3,5-bis(trifluoromethyl)phenyl moiety into a chiral module has also become a common strategy for the design of novel chiral (thio)urea-based catalysts.[9] Nowadays, merging Schreiner's thiourea with another achiral or chiral catalytic species has paved a new way to further explore its potential applications.[10] This review summarizes the key developments of Schreiner's thiourea including its proof-of-principle studies as well as its applications as catalyst and cocatalyst.

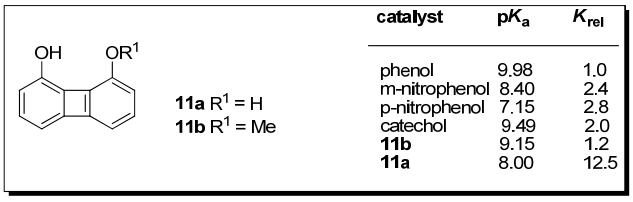


Scheme 1. *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (*Schreiner's thiourea* or **T1**)

Historical development of T1

In pioneer studies, Hine *et al.* identified that conformationally rigid biphenylenediols were efficient catalysts for addition of diethylamine to phenyl glycidyl ether, in which simultaneous donation of two H-bonds to the electrophile is essential for high catalytic activities (Scheme 2).[11-14]



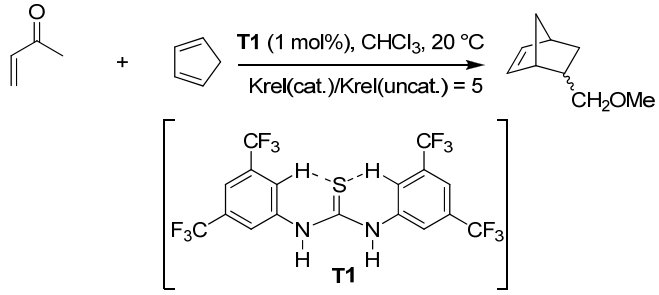


Scheme 2. Biphenylenediol-promoted epoxide-opening reactions.

Later, Kelly and co-workers reported the promotion of the Diels-Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes and ketones by biphenylenediol derivatives and proposed double hydrogen-bond donation to the dienophile as an explanation for the catalysis observed.[15] This was consistent with a theory proposed by Jorgensen based on computational studies to rationalize the observed acceleration of Diels-Alder reactions and Claisen rearrangements in H_2O relative to nonprotic solvents.[16] Around the same time, Etter *et al.* observed that *N,N'*-diarylureas cocrystallize with a variety of Lewis basic functional groups via hydrogen-bonding directed interactions.[17, 18] Although

these catalysts had only moderate catalytic activities, they laid the basis for rational consideration of diaryl (thio)urea derivatives as potential catalysts. The first such example was reported by Curran *et al.* who found that diarylurea enhanced both the yield and diastereoselectivity of the allylation of cyclic α–sulfinyl radicals with allyltributylstannane.[19] Later on, the same group demonstrated that the promotion of the Claisen rearrangement by using a stoichiometric amount of urea.[20] For the first time, thiourea derivatives were also shown to hold promise as hydrogen-bonding reaction promoters.

In 1998, Schreiner's group took these ideas together and settled for using thiourea derivatives as catalysts because they have several advantages over urea a)more soluble in a variety of solvents; b)easier to prepare; c) less favorable self association.[21] In a systematic study, *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**T1**) was identified as the most active species for the promotion of Diels-Alder and dipolar cycloaddition reactions, even with water as the reaction solvent, in which thioureas are in a similar fashion of Lewis acids in the activation of carbonyl compounds (Scheme 3).[6, 8]



Scheme 3. Thiourea-catalyzed Diels-Alder reaction

In view of the generally low binding energies between thioureas and carbonyl substrates, the high catalytic effects are ascribed partially to entropic effects, in which an attractive interaction between the ortho-hydrogen atoms with sulfur heteroatom significantly increases the rotational barrier of **T1**. This rigidifying interaction minimizes entropy loss upon binding of the substrate and thus facilitates catalysis. Mediating through bidentate hydrogen bonding interaction, Schreiner's thiourea has become a powerful tool in organocatalytic field since its advent as catalyst in Diels-Alder reaction introduced by Schreiner and Wittkopp. To date, a large number of applications of **T1** to various reaction types and substrates has been explored.

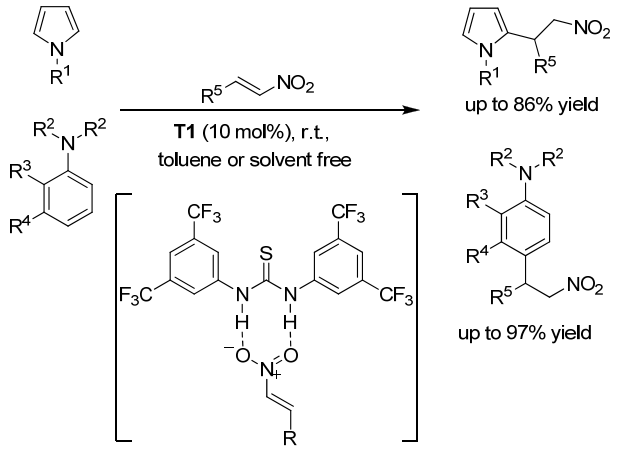
T1 as organocatalyst

Diels-Alder Reaction

In 2000, Schreiner and coworker took up the investigation of thiourea derivatives as catalysts for Diels-Alder reactions.[22] A combination of NMR, IR, and *ab initio* techniques reveals the striking structural similarities of an exemplary H-bonded complex of an *N*-acyloxazolidinone with an *N,N'*-disubstituted electron-poor thiourea and the corresponding Lewis acid complex.[8] The Diels-Alder reaction of *N*-acyloxazolidinone with cyclopentadiene was used to examine the catalytic effect of thioureas, which shows the apparent similarities of thiourea derivatives and Lewis acids in terms of yields and diastereoselectivities. Later on, Schreiner et al. performed systematic studies on the catalytic activity of substituted thioureas in a series of Diels-Alder reactions and 1,3-dipolar cycloadditions.[6, 8] They found that the relative effectiveness of these catalysts depends more on their substituents than on the reactants or solvent. Symmetrically rigid aryl thiourea bearing electron-withdrawing groups bind more favourably, as a consequence, **T1** was found to be the most active catalyst. Soon afterwards, **T1** started to serve as an efficient catalyst for other transformations, i.e., Friedel-Crafts alkylation[23], addition to nitrones[24], Baylis-Hillman reaction[25], etc.. Recently, **T1** catalyzed Diels-Alder reaction was further extended to the cycloaddition of the sterically hindered naphthoquinone monoketal dienophile with diene by Kramer et al., providing a synthetic access to the natural product beticolin 0.[26]

Friedel-Crafts Alkylation

The addition of aromatic substrates to electron deficient alkenes, Friedel-Crafts-type alkylation, represents an important reaction in synthetic organic chemistry for the formation of new C-C bonds. In the presence of 10 mol% of **T1**, Ricci and coworkers found that the Friedel-Crafts alkylation of electron rich aromatic e.g. substituted anilines and heteroaromatic substrates, e.g., substituted pyrroles or indoles with nitroolefins proceeded smoothly (Scheme 4).[23] A consistent improvement of the reaction efficiency was observed by performing the reactions under solvent-free conditions. In the cases of indoles as substrates, **T1** shows apparent advantages in terms of much milder reaction conditions and higher yields than alkylation of indoles catalyzed by $Yb(OTf)_3$ or $Sc(OTf)_3$.

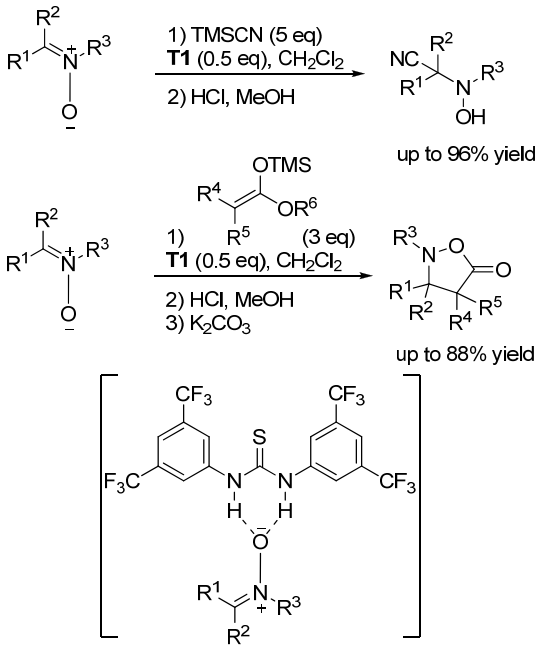


Scheme 4. Friedel-Craft alkylation of electron-rich aromatic substrates with nitroolefins.

Nucleophilic Addition to Nitrones

Takemoto and co-workers reported that **T1** promoted the addition of TMSCN and ketene silyl acetals to various nitrones, giving the corresponding hydroxyamines in good yields (Scheme 5).[24] Consistent with Schreiner's report, a positive correlation was observed between the acidity of the N-H bond of thioureas and their catalytic activity, simultaneously, bidentate coordination of the thiourea to nitrones is also critical for catalytic activation. The

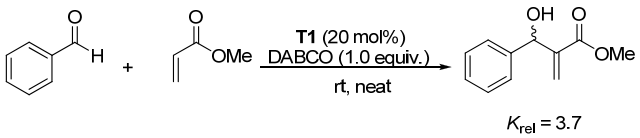
postulated bidentate hydrogen-bonding interaction mode between **T1** and nitrones was further supported by ^{1}H and ^{13}C NMR experiments.



Scheme 5. Nucleophilic addition of TMSCN and ketene silyl acetals to nitrones.

Baylis-Hillman reaction

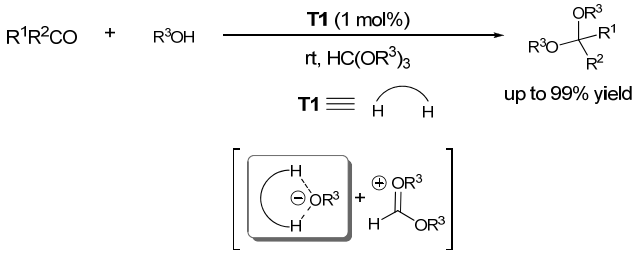
The Baylis-Hillman reaction, also known as the Morita-Baylis-Hillman reaction, is an atom economic carbon-carbon bond forming process that furnishes products of high functional-group density from relatively simple starting materials. The main drawback of the Baylis-Hillmann reaction is the extremely low reaction rate. The reaction can take from days to weeks to complete. Numerous efforts have been made towards the development of different catalytic systems. In 2004, Maher and Connon developed a dual activation for this reaction using a combination of DABCO and (thio)urea derivatives (Scheme 6).[25] Significant acceleration was observed in the presence of (thio)urea derivatives relative to the "uncatalyzed" process. Unexpectedly, the urea analogue was superior to more acidic **T1** in reaction efficiency, probably due to **T1**'s partial decomposition under these conditions. In general, these preliminary results show that (thio)urea derivatives hold promise as efficient cocatalysts for tertiary-amine-promoted Baylis-Hillman reactions.



Scheme 6. Baylis-Hillman reaction of bezaldehyde and methyl acrylate.

Acetalization

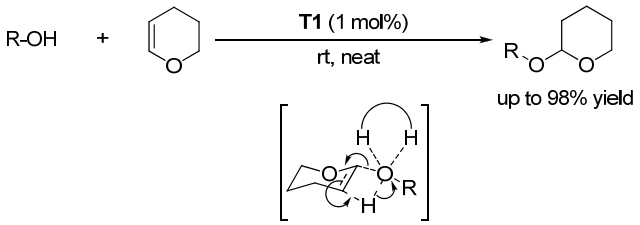
Acetals are masked carbonyl derivatives that are important intermediates in synthetic as well as carbohydrate chemistry. Kotke and Schreiner reported a highly efficient **T1** catalyzed acetalization of various aliphatic and aromatic carbonyl compounds i.e. saturated, aromatic as well as unsaturated aldehydes and ketones (Scheme 7).[27] This reaction proceeds at considerably high turnover frequencies (around 600 h^{-1}). In contrast to widely accepted carbonyl activation, they proposed that the role of **T1** is to facilitate the heterolysis of orthoester and subsequently stabilize multiple oxyanion intermediates. This work provided the first link between hydrogen-bonding catalysis and oxyanion binding and the strategy that recognizes oxyanion with hydrogen bonding donors is further extended to the synthesis of oligosaccharides by McGarrigle, et al.[28] and Friedel-Crafts reaction by Kass, et al.[29]



Scheme 7. Acetalization of aromatic and aliphatic carbonyl compounds.

Tetrahydropyranylation of hydroxyl functionalities

The acid-catalyzed reaction of alcohols and phenols with 3,4-dihydro-2H-pyran (DHP) to tetrahydropyranyl-substituted ethers is a prevalent strategy for the protection of hydroxyl functions (tetrahydropyranylation). Based on the observation that **T1** assists the heterolysis of orthoester in acetalization reactions, Schreiner and Kotke successfully extended this strategy to the tetrahydropyranation of hydroxyl functionalities (Scheme 8).[30] This reaction is broadly applicable to a variety of alcohols, phenols, and other ROH derivatives, in particular, to acid-labile substrates such as aldol products, hydroxyl ethers, acetals, silyl-protected alcohols and cyanohydrins. It is noteworthy that **T1** is remarkably active in this reaction and its loading can be reduced to as low as 0.001 mol%, giving a maximum turnover frequency of up to 5700 h^{-1}, which represents the most efficient organocatalytic reaction reported to date. Mechanistic investigations by DFT computations revealed that **T1** aids the generation of the nucleophile (RO^{-}) and preferentially stabilizes the developing oxyanion in the transition state through double hydrogen bonding, which correlates well to the concept of "oxyanion stabilization" developed by Schreiner *et al.* in the design of hydrogen-bonding mediated transformations.

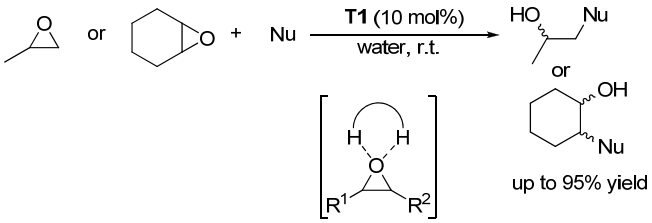


Scheme 8. Tetrahydropyranylation of hydroxyl functionalities.

Epoxides opening

Water has long being recognized as a key medium in sustaining intricate protein structures and promoting organic transformations.

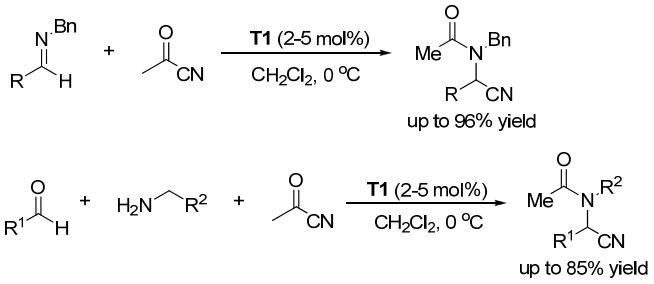
Kleiner and Schreiner found that **T1** catalyzes epoxide openings with a variety of nucleophiles giving the highest yields using water as solvent (Scheme 9).[31] The postulated rationale behind is that water brings the solutes together so that this so called "hydrophobic hydration" can lead to rate enhancements of reactions in an enzyme-like fashion through minimization of the solute's volume. The relative rate acceleration in water is 200-fold larger than in CH_2Cl_2, which thus led to a novel concept "hydrophobic amplification" in organocatalytic reactions. Based on this study, Chimni et al. extended this method to aminolysis of epoxides catalyzed by **T1** under solvent free conditions, which reveals the electronic control of regioselective ring opening of substituted styrene oxides.[32]



Scheme 9. Epoxides opening in water.

Strecker reaction

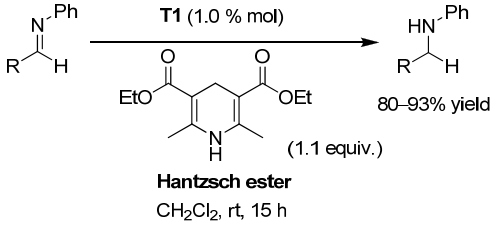
Discovered in 1850, the reaction of aldehyde, ammonia, and hydrogen cyanide known as Strecker reaction provides one of the most efficient methods for the preparation of α-amino nitriles, which serve as useful intermediates in the synthesis of α-amino acids. In 2006, List and co-workers presented a modified version of Strecker reaction, in which aldimines react with acetyl cyanide in the presence of **T1** as catalyst (Scheme 10).[33] Both aromatic and aliphatic aldimines proceed smoothly to give the corresponding *N*-acetylated amino nitriles in high yields. Quickly thereafter, the same group extended the reaction of imines with acetylcyanide to a three-component acyl-Strecker reaction of aldehydes, amines, and acetylcyanide.[34] This reaction is applicable to a broad range of aldehyde and amine substrates. Later on, in the studies of a general method for the catalytic asymmetric Strecker reaction of both α-CF_2H and α-CF_3 ketoimines with TMSCN, Zhou and co-workers obtained an unexpected result in the presence of **T1** as catalyst.[35] **T1** could catalyze the Strecker reaction of non-fluorinated ketimines, while failed to promote the reaction of α-difluoromethyl or trifluoromethyl analogues, which was hard to understand since both CF_2H and CF_3 groups enhanced the electrophilicity of ketimines toward cyanide addition. Based on theoretical calculations, they proposed a new recognition model of **T1** with fluorinated ketimines, in which imine nitrogen interacted with one thiourea hydrogen and one of the α-fluorine atoms with the other thiourea hydrogen. Recently, during the investigation of enantioselective Strecker-type reaction of aliphatic *N,N*-dialkylhydrazones using TMSCN as the cyanide source, Lassaletta and co-workers found that **T1** efficiently accelerated the model reactions with respect to the background reaction in several solvents, thereby leading to the development of an asymmetric version.[36]



Scheme 10. Acyl-Strecker reactions.

Transfer hydrogenation of aldimines

The organocatalytic hydrogenation of imines represents a contemporary challenge. Currently most accessed approaches for the preparation of amines rely on metal-based catalysts and molecular hydrogen as the reductant. Encouraged by the work reported by Menche et al. on the reductive amination of ketones[37] and aldehydes[38] with thiourea itself as the catalyst and Hantzsch 1,4-dihydropyridine as the reductant, Zhang and Schreiner envisaged that **T1** would be more effective catalyst than thiourea itself. Much to their surprise, Menche's protocols were unable to be reproduced and the reaction occurs only in the presence of unactivated 5Å MS as the dehydrating agent. After detailed investigation, Zhang and Schreiner found that the catalytic species in Menche's report are from relatively volatile components that were contained in unactivated 5Å MS. Simultaneously, Zhang and Schreiner reported a practical **T1**-catalyzed transfer hydrogenation of imines with Hantzsch 1,4-dihydropyridine (Hantzsch ester) as the hydrogen source (Scheme 11).[39] **T1** proved to be an effective catalyst (the catalyst loading of **T1** can be reduced to as low as 0.1 mol%) in promoting the reduction of aromatic as well as aliphatic aldimines with Hantzsch ester as the hydrogen source, giving the respective secondary amine in good to excellent yields.

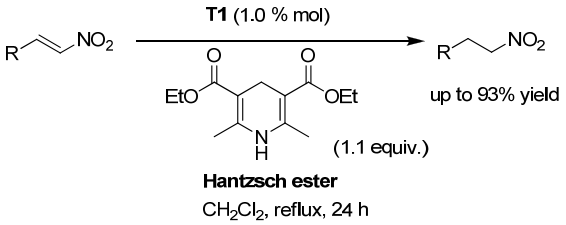


Scheme 11. T1-catalyzed transfer hydrogenation of aldimines.

Biomimetic reduction of nitroolefins

Biological redox transformations have served as a stimulus for the development of a wide range of reductions in synthetic chemistry. Among others, Hantzsch esters are one of the most investigated biomimetic reductants. In a systematic study on the reduction of NADPH-linked nitroolefins with isolated enzymes from baker's yeast or Old Yellow Enzyme (OYE), a catalytic mechanism was proposed in which the nitrocyclohexene was activated by nitro-oxygen hydrogen bonds to His-191 and Asn-194. A hydride is then transferred to the β-position from the reduced flavin which, ultimately, originated from NADPH.

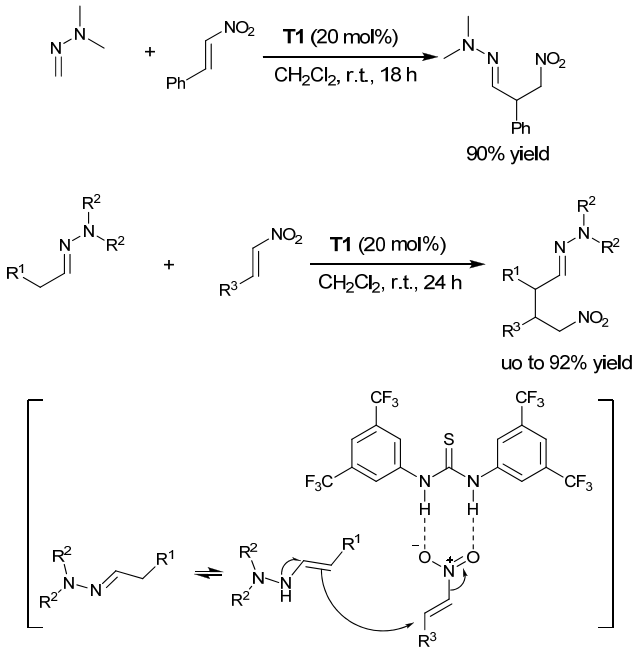
Inspired by this biological system, Zhang and Schreiner developed a biomimetic procedure by using **T1** as the "reductase" and Hantzsch ester as a NADPH analogue (Scheme12).[40] A variety of aromatic and aliphatic conjugated nitroalkenes can be reduced to the corresponding nitroalkanes with good yields under mild conditions. This protocol is not only practical, but may also provide insights into redox transformations through hydrogen-bond activation in biological systems.



Scheme 12. T1-catalyzed biomimetic reduction of nitroolefins.

Nucleophilic addition of hydrazones to nitroalkenes

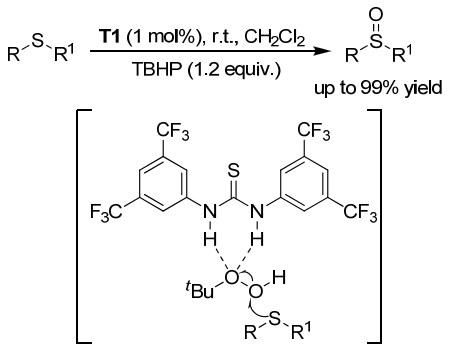
In line with the early report that nitroalkenes were activated by **T1** for the Friedel-Crafts alkylation, Herrera and co-workers developed an organocatalytic conjugate addition of hydrazones to nitroalkenes (Scheme 13).[41] In 2006, the same group successfully applied **T1** to promote the addition of formaldehyde hydrazone to nitrostyrene, leading to azo-methine carbon attacked products. In the presence of 20 mol% **T1**, enolizable hydrazones afforded the products by the nucleophilic attack at the $\alpha-$position of the hydrazone rather than at the azo-methine carbon. When hydrazones without hydrogen at the α-carbon were used as substrates, no reactions were observed under the same conditions. To rationally explain the experimental results, a mechanism that the equilibrium between hydrazone and its ene-hydrazine form, which subsequently attacked the **T1**-activated nitroalkene on the electrophilic β-position was proposed. Solvent screening revealed that apolar solvents are superior to polar solvents for this transformation and the combination of **T1** with ionic liquids was not applicable. In contrast, Lewis acids such as $Sc(OTf)_3$, $In(OTf)_3$, InF_3 or $Cu(OTf)_3$ resulted in no or little product formation accompanied by decomposition of the starting material.



Scheme 13. Nucleophilic addition of hydrazones to nitroalkenes.

Oxidation of sulfides

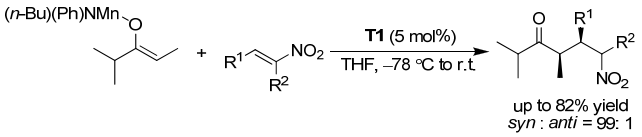
Departing from conventional **T1**-catalyzed carbon-carbon forming reactions, Russo and Lattanzi first reported that **T1** was also a very effective catalyst for the oxidation of sulfides with *tert*-butyl hydroperoxide (TBHP) as an oxidant, affording the corresponding sulfoxides in high yield, excellent chemoselectivity, and good diastereoselectivity (Scheme 14).[42] **T1** showed better catalytic activities in apolar solvents, e.g., CH_2Cl_2, toluene, and $CHCl_3$, than in polar solvents, e.g., THF. The urea analogue of **T1** was inefficient to promote this transformation, giving sulfoxide in low yield after 22 h, but with complete chemoselectivity, since no traces of sulfone were detected. Loadings of **T1** can be reduced to as low as 0.1 mol%, although at the expense of longer reaction time. Different types of phenyl substitution in the methyl aryl sulfides are well tolerated although sulfides bearing electron-withdrawing groups at *para*-position needed longer reaction time. Note that the catalytic performance of **T1** was comparable with transition metal complexes generally used in the oxidation of sulfide with alkyl hydroperoxides in terms of turnover numbers (TON up to 990). They assumed that **T1** activates TBHP operating through double hydrogen-bonding, which was obseved by downfield shift of NH proton of **T1** from 7.96 to 8.12 ppm upon addition of 1.0 equivalent of TBHP into $CDCl_3$ solution of **T1**.



Scheme 14. Oxidation of sulfides.

Addition of manganese enolates to nitroolefins

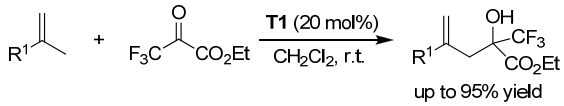
During the investigation of conjugate addition of Mn enolates to nitroolefins, Ricci and co-workers found that in the presence of catalytic loading such as 5 mol% **T1**, the reaction outcomes were remarkably improved in terms of reduced reaction times and slightly increased yields with contrast to uncatalyzed reactions (Scheme 15).[43] Simultaneously, this transformation catalyzed by **T1** offered a major advantage in overcoming poor selectivity frequently encountered in these Michael additions. The corresponding adducts obtained are in almost pure *syn* form.



Scheme 15. Addition of manganese enolates to nitroolefins

Carbonyl-ene reaction

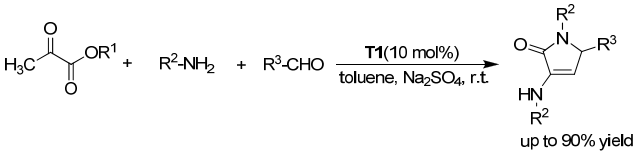
The carbonyl-ene reaction is a useful and completely atom-economic C-C bond forming reaction. Clarke and co-workers developed the first organocatalytic carbonyl ene reaction using **T1** as catalyst, although turnover frequency and substrate scope were very moderate (Scheme 16).[44] The reaction is limited to activated ethyl pyruvate, e.g., ethyl trifluoropyruvate as substrate, in which 1,1'-disubstituted alkenes are more effective than terminal alkenes in terms of reaction time and yield.



Scheme 16. Carbonylene reaction

Three-component reactions of pyruvate, aldehydes, and aniline

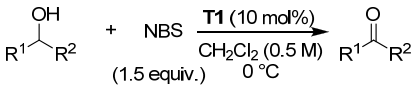
Multicomponent reactions (MCRs) are convergent reactions in which three or more starting materials react to form products with a high degree of structural diversities. Helped by the finding that the reaction of pyruvate and aldehydes in the presence primary amine as catalyst afforded trace amounts of the three-component-coupling product, Li *et al.* investigated the use of hydrogen-bonding donors such as phosphoric acids and thioureas as catalyst for this one-pot three-component reactions of pyruvate, anilines and aldehydes (Scheme 17).[45] Both phosphoric acid and **T1** are found to be efficient catalysts, giving the corresponding 3-amino-1,5-dihydro-2*H*-pyrrol-2-one in high yields. Among different thioureas tested, a correlation between the catalytic activity of the thiourea and its respective p*K*a is evident; **T1** with the lowest p*K*a gives the best results. Further improvement in the reaction was achieved by the addition of drying agents such as molecular sieves or Na_2SO_4.



Scheme 17. Three-component reactions of pyruvate, aldehyde and aniline.

N-Bromosuccinimide-mediated oxidation of alcohols

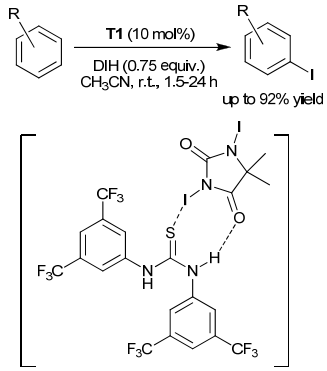
In contrast to the well appreciated hydrogen bonding donor ability of **T1**, Tripathi and Mukherjee described another activation mode based on Lewis basic sulfur center of thioureas. In the presence of 10 mol% **T1**, the oxidation of 1-phenylethanol with *N*-Bromosuccinimide (NBS) proceeded smoothly, giving the corresponding acetophenone in excellent yield (Scheme 18).[46] Without **T1**, the reaction was rather sluggish together with the formation of a significant amount of α-bromoacetophenone and a trace amount of α,α-dibromoacetophenone. The remaining catalytic efficiency of *N*-methylated **T1** clearly demonstrated that this NBS-mediated oxidation of alcohol was independent with hydrogen bonding activation mode. Using **T1** as catalyst, a wide range of secondary alcohols with different steric and electronic substituents underwent smooth oxidation to the corresponding ketones in good yields. Note that this protocol provides remarkably chemoselective oxidation of secondary alcohols in the presence of primary alcohols.



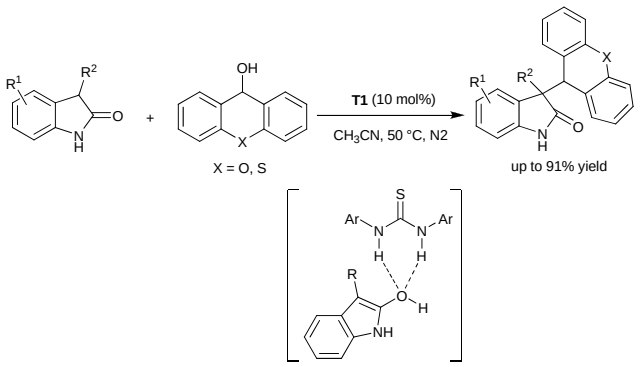
Scheme 18. *N*-Bromosuccinimide-mediated oxidation of alcohols.

Organocatalytic iodination of activated aromatic compounds

In accordance to the nucleophilicity of the sulphur atom of **T1**, Schreiner and co-workers developed a convenient and direct iodination of activated aromatic compounds using 1,3-diiodo-5,5-dimethylhydantoin (DIH) as the iodine source with **T1** as the catalyst in acetonitrile (Scheme 19).[47] The protocol is applicable to a number of aromatic substrates with significantly different steric and electronic properties, generally affording the products with high regioselectivity and yields. NMR kinetic studies underlined the role of sulphur in the thiourea motif as a nucleophile that is assisted by H-bonding in the key steps of the reaction.



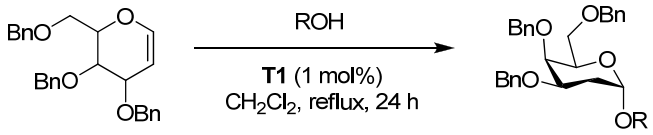
Scheme 19. Organocatalytic iodination of activated aromatic compounds



Scheme 21. Nucleophilic substitution reaction of 3-substituted oxindoles with xanthydrols

Organocatalytic synthesis of 2-deoxygalactosides

The synthesis of oligosaccharides containing 2-dexoysugars is generally considered to be a formidable task. Recently, inspired by the work of **T1**-catalyzed protection of alcohols with dihydropyran, McGarrigle and coworkers successfully extended this method to glycosylation reaction, in which tetrahydropyran was replaced with glycols (Scheme 20).[28] **T1** proved to be an efficient and mild catalyst for such type of transformation. Galactals bearing a range of protecting groups gave the corresponding products in high yields and excellent selectivities. Encouraged by these results, the scope of other common glycosyl acceptors was investigated. Using perbenzylated galactal as a model donor, a range of glycosyl acceptors with a primary alcohol and either benzyl or benzoyl protecting groups, as well as either methoxy or thiophenyl as the anomeric substituents gave yields of the isolated products in good yields and complete α-selectivity. This method is also capable of synthesis of trisaccharide in a three-component, one-pot way.



Scheme 20. Organocatalytic synthesis of 2-deoxygalactosides.

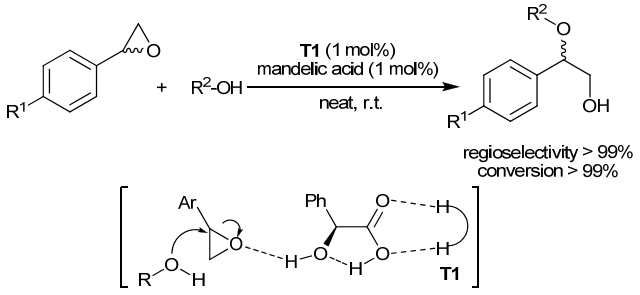
Nucleophilic substitution reaction of 3-substituted oxindoles with xanthydrols

The dehydrative nucleophilic substitution of alcohols is an important atom economical C-C bond forming reaction. Zhou and co-workers reported that **T1** catalyzed the alkylation of 3-substituted oxindoles with xanthydrols to furnish quaternary oxindoles in high yield (Scheme 21).[48] To illustrate the role of **T1** in this reaction, the ESI-MS analysis of the reaction process was undertaken, which clearly shows the interaction of 3-substituted oxindole with **T1**. This finding suggests that **T1** might facilitate the oxindole-hydroxindole tautomerization for the alkylation.

T1 as cocatalyst

Alcoholysis of styrene oxides

In view of the cooperative effect of **T1** with water in the epoxide aminolysis ("hydrophobic amplification")[31], Schreiner and co-workers presented an alternative method for the completely regioselective alcoholysis of styrene oxides utilizing **T1** (1 mol%) as catalyst and mandelic acid (1 mol%) as cocatalyst (Scheme 22).[49] Various styrene oxides are readily transformed into their corresponding β-alkoxy alcohols in good to excellent yields. The experimental findings and DFT computations suggested an H-bonding-mediated cooperative Brønsted acid catalysis mechanism, in which the epoxide is activated by a single-point hydrogen bond of **T1**-coodinated mandelic acid.

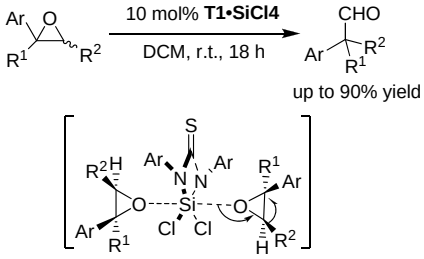


Scheme 22. Alcoholysis of styrene oxides.

Rearrangement of epoxides to quaternary carbaldehydes

While both (thio)urea and silicon-based catalysts have been individually applied to a large variety of reactions, the combination of them has not been explored in the realm of catalysis. Schreiner and coworkers developed a new strategy by using silicon-(thio)urea complex as a cooperative catalyst for the rearrangement of epoxides to quaternary carbaldehydes (Scheme 23).[10] After various combinations of (thio)urea derivatives and halosilanes were tested, **T1**·$SiCl_4$ proved to be the most reactive, giving the corresponding products in good yields. Typically, the *trans*-alkyl shift to the aryl moiety was considerably faster than for the *cis* configuration (1 h vs 18 h reaction time). A planar

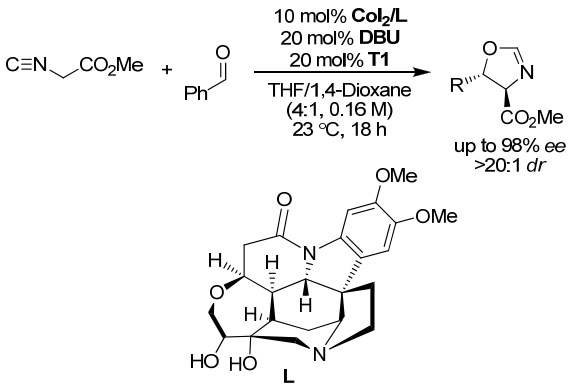
four-membered central ring was proposed to be the catalytically active species, which was underlined by a combination of NMR and IR spectroscopy, mass spectrometry and density functional theory (DFT) computations. Using 5 mol% **T1**·$SiCl_4$ as catalyst, the enantioenriched (*E*)-epoxides rearranged stereospecifically to the corresponding aldehydes. Note that the enantiopurity of the starting epoxides increased over time, which resembles a kinetic resolution of nonracemic starting materials. The rationale behind is probably due to the formation of diastereomeric transition structures through complexation of **T1**·$SiCl_4$ with the starting material.



Scheme 23. Rearrangement of epoxides to quanternary carbaldehydes.

Aldol reaction of methyl α-isocyanoacetate

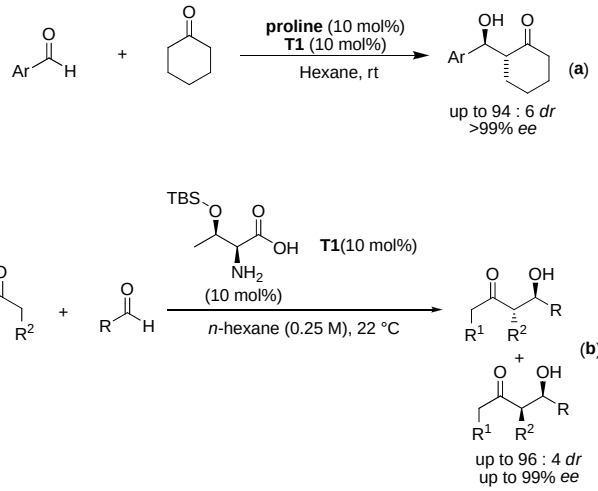
Inspired by biocatalysts utilizing metals and H-bonding interactions synergistically for chemical transformations, Kim and Oh developed a cooperative catalyst system for the highly diastereo- and enantioselective aldol reaction of methyl α-isocyanoacetate (Scheme 24).[50] The optimized catalytic system included four components, e.g., CoI_2, brucine amino diol, DBU and **T1**. **T1** was superior for the improvement of the reaction outcomes in comparison to other H-bonding donors, ascribing by its strong anion-binding abilities. Under optimal reaction conditions, the reaction was applicable to a range of aromatic, heteroaromatic, and aliphatic aldehydes, giving the corresponding products in excellent diastereo- and enantioselectivities (> 20:1 *dr*, 90−98% *ee*).



Scheme 24. Aldol reaction of methyl α-isocyanoacetate.

Direct aldol reactions

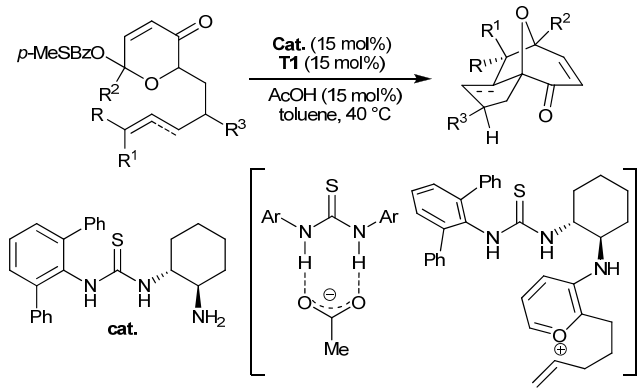
The direct asymmetric aldol reaction is a powerful C-C bond forming transformation in nature and synthetic chemistry. Inspired by the mode of action of the aldolases, the proline-catalyzed enantioselective aldol reactions have been dominated in the past decade since the work reported by List, Barbas and Lerner.[51] Although proline is a rather good catalyst, some drawbacks inherent with it have to be considered, such as low solubility in typical organic solvents, potential side reactions, and low selectivities with planar aromatic aldehydes in direct aldol reactions. In view of the crucial role of some suitable additives, or cocatalysts, Demir and coworkers developed proline-catalyzed direct aldol reactions between cyclic ketones and aldehydes using **T1** as the cocatalyst, giving the aldol products with high diastereo- and enantioselectivities (up to 94 : 6 *dr* and >99% *ee*), which are much better than proline alone (Scheme 25, eq. a).[52] These results clearly demonstrate the enormous effect of **T1** on the reactivity and selectivity, even in an unconventional non-polar reaction medium. Recently, Córdova and co-workers reported an alternative type of cocatalytic system, namely primary amino acids and H-bonding donors, for enantioselective direct aldol reaction (Scheme 25, eq. b).[53] Among the investigated cocatalytic systems, TBS protected threonine in combination with co-catalyst **T1** exhibited the highest reaction rate as well as stereoselectivity. Under optimized reaction conditions, the corresponding aldol products were generally obtained in high yields, *drs* and *ers*. It is noteworthy that the reactions with acyclic ketones were *syn*-selective, which was complementary to the reactions with the cyclic six-membered ketones as well as proline-catalyzed aldol reactions with linear ketones that are *anti*-selective. In addition, the catalyst loading as low as 2 mol% was sufficient for this transformation.



Scheme 25. Direct aldol reactions.

Eantioselective oxidopyrylium-based [5 + 2] cycloadditions

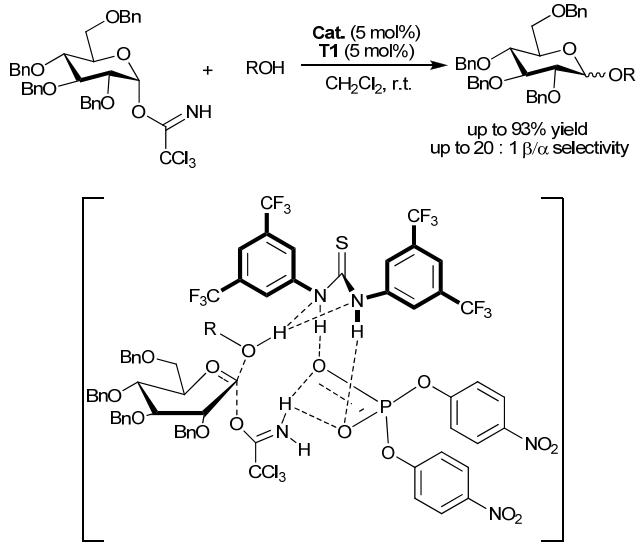
In 2011, Jacobsen and co-workers developed an elegant dual thiourea catalyst system for intramolecular oxidopyrylium [5 + 2] cycloadditions that provides enantioselective access to valuable tricyclic structures, in which **T1** is supposed to be a carboxylate-binding agent, acting cooperatively with Jacobsen's catalyst to generate the reactive ion pair (Scheme 26).[54] This dual catalysis system is viable to a variety of substrates, e. g. terminus substituted olefins, allens, diallyl substrate, et al., giving the corresponding products in moderate yields (37-77%) and good to high enantioselectivities (80-95%).



Scheme 26. Eantioselective oxidopyrylium-based [5 + 2] cycloadditions

Glycosidation reactions with *O*-glycosyl trichloroacetimidates as glycosyl donors

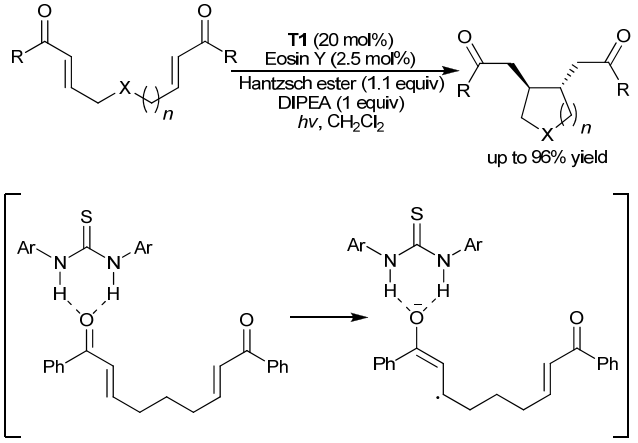
In line with the cooperative catalysis between Brønsted acids and hydrogen-bonding donors developed by the Schreiner group[49,55], Jacobsen group[56], and others[57], Schmidt and co-workers applied this strategy to the glycoside bond formation with *O*-glycosyl trichloroacetimidates as glycosyl donors using phosphorous acids as catalysts and **T1** as cocatalyst (Scheme 27).[58] It turned out that this dual catalysis system not only improved the reaction rate and the product yield but also the anomeric selectivity, leading to overwhelmingly β-selective products in the absence of directing groups. Based on the experimental observation and analysis, a plausible mechanism was proposed in which **T1** effects together with catalyst and acceptor the hydrogen-bond-mediated formation of a complex and functions as a relay for proton transfer, thus enabling an acid-base catalysed S_N2-type glycoside bond formation.



Scheme 27. Glycosidation reactions with *O*-glycosyl trichloroacetimidates as glycosyl donors

Cooperative hydrogen-bond-promoted organophotoredox catalysis

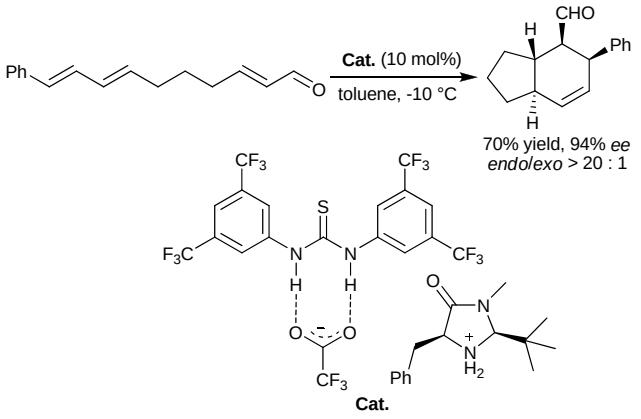
In view of environmental concern, the combination of organocatalytic activation modes with other sustainable methods, especially multicatalysis concepts[59] begun to evolve.[60] In this context, Neumann and Zeitler described a highly diastereoselective hydrogen-bond-promoted reductive cyclization of bisenones by using Eosin Y as organic photoredox catalyst and **T1** as cocatalyst (Scheme 28).[61] This protocol allows the rapid and highly diastereoselective construction of various *trans*-1,2-substituted cycloalkanes and heterocycles. Preliminary mechanistic studies showed that **T1** acts to activate unsaturated (aryl) ketone and subsequently to stabilize the active radical anion generated by visible light, Eosin Y, DIPEA and Hantzsch ester.



Scheme 28. Cooperative hydrogen-bond-promoted organophotoredox catalysis

Hydrogen-bond-mediated supramolecular iminium ion catalysis

Over the past decade, iminium catalysis involving an amine catalyst and an acid cocatalyst has grown to be a prevalent tool for asymmetric synthesis. In consideration of thiourea-anion binding ability, Xu and co-workers sought an appropriate thiourea as cocatalyst to disperse the negative charge of imimiun and consequently separate the ion pair by interaction with the counteranion. This supramolecular iminium based catalytic system might promote asymmetric transformations with higher reactivity, better efficiency, and greater turnover. They found that the combination of MacMillan's imidazolinone with **T1** can significantly accelerate the reaction rate, giving the Diels-Alder addition product with 75% yield after 1 h, without compromising the enantioselectivity (94% *ee*) and diastereoselectivity (*endo*/*exo* > 20 : 1) (Scheme 29).[62] In contrast, only 28% conversion was obtained in the presence of imidazolinone alone after 1 h. This strategy might be applicable to a iminium- as well as hydrogen-bond-catalyzed processes and pave a new way for the design and development of chiral catalysts.



Scheme 29. Hydrogen-bond-mediated supramolecular iminium ion catalysis

Conclusions

As the development of urea- and thiourea-based organocatalysts flourishes, *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**T1**) ranks inter alia one of the most popular hydrogen-bonding catalysts since its first introduction in 2002. The present work describes the use of **T1** as an organocatalyst or a cocatalyst in a large variety of chemical transformations. Lewis basic functionalities such as carbonyls, imines, epoxides et al. have been effectively applied in **T1**-promoting transformations such as Diels-Alder, Friedel-Crafts, epoxide opening, Strecker, transfer hydrogenation and so on. Later on, oxyanion recognition and activation with **T1** resulted in acetalization and tetrahydropyranylation of hydroxyl functionalities with impressive TOF. Departing from the well-appreciated hydrogen-bonding donor ability, **T1** also acts as an effective catalyst for the NBS-mediated oxidation of secondary alcohols through the Lewis basic sulfur center. It is also noteworthy that 3,5-bis(trifluoromethyl)phenyl group has found wide applications in the design of chiral thiourea-based catalysts, in which it was placed appropriately into a chiral scaffold with a Lewis basic moiety. The p*K*a value measurements[63] and the investigation of *ortho*-proton effect of Schreiner's thiourea[64] provide deeper insights into thiourea-based noncovalent organocatalysts. Owing to its good compatibility and tolerance, **T1** was also utilized as a cocatalyst in metal- or organocatalytic reactions. In general, the ability of **T1** to participate in various processes maintains its prominent position as a privileged catalyst and contributes to the development of nonconvalent catalysts. It is our belief that much more applications of **T1** will be certainly explored in the near future. In addition, the cooperative effect of **T1** with metal- and organocatalysts will result in a number of important transformations and eventually pave a new avenue for the design of novel catalysts.

Acknowledgements

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Notes and references

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Critical Review

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