Chapter 2

Isothiouronium Organocatalysts Through Hydrogen Bonding

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Additional information is available at the end of the chapter

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Abstract

The field of small-molecule organocatalysis via noncovalent interactions has attracted the attention of an increasing number of research groups from the academic as well as industrial sectors. Isothiouronium salts have been explored quite recently as a new class of hydrogen-bonding subunit for the purpose of molecular recognition of anions in supramolecular chemistry. The chemical modification of isothiouroniums is readily varied using synthetic methods to make several types of functional molecular systems. This chapter, for the first time, describes the research on hydrogen-bonding isothiouronium organocatalysts considering their designed concepts and synthetic applications in both nonstereoselective and stereoselective reactions.

Keywords: asymmetric aldol reactions, hydrogen-bonding organocatalysts, isothiouronium, reduction, reductive amination

1. Introduction

Organocatalyst has emerged as one of the hot topics in advanced organic chemistry. Although chemical transformations that use organocatalysts have been studied broadly, the field of organocatalyst was not a key area of research until the late 1990s [1]. Organocatalysts consist of small, low-molecular-weight organic compounds containing carbon, hydrogen, nitrogen, sulfur, and phosphorus and acting as catalysts without any metal. The popularity of this word is due to the notion of green chemistry as opposed to dirty organometallic chemistry. The advantages of using organocatalysts include their lack of sensitivity to moisture and oxy-

easy availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with (transition) metal catalysts. In addition, organocatalysts are also more readily amenable than both metal-based catalysts and biocatalysts to anchor on a support with the aim of facilitating catalyst recovery and recycling [2].

The development of acid- and metal-free organocatalysts still remains a challenging task. As investigated, organocatalysts can be considered as minimal versions of metal-free enzymes, and the mechanisms and categorizations of enzyme catalysis are applied to the action of organocatalyst as well. In biological systems, hydrogen bonding plays a key role in many enzymatic reactions, both in orienting the substrate molecules and lowering barriers to reaction. Therefore, in many cases noncovalent organocatalysts depend on the formation of hydrogen-bonding adducts between the substrate and catalyst [3]. Hydrogen bonding can promote reactions by different mechanisms such as stabilizing anionic intermediates and transition states. It can also bind small anions for the formation of reactive electrophilic cations or more acidic donors can actively electrophile by protonation. Especially, for simultaneous activation of both partners, for example, nucleophile and electrophile, in a reaction, bifunctional organocatalysis has been developed so far. In this case, the close association between the organocatalyst molecule and the substrate makes the hydrogen-bonding catalysis a powerful method for inducing enantioselectivity [4].

2. Designed concepts of hydrogen-bonding isothiouronium organocatalysts

2.1. Hydrogen-bonding thiourea organocatalysts [5, 6]

Thioureas are widely recognized as highly useful templates using them powerful organocatalytic systems can be constructed. They result in a considerable acceleration of the reaction rate through hydrogen-bonding interaction. The scope of these small-molecule H-bond donors, termed thiourea organocatalysts, covers both nonstereoselective and stereoselective applications in organic synthesis. The reader may get an idea about the variety of this research field that is generally based on (thio)urea organocatalysts for "*hydrogen bonding in organic synthesis.*"

2.2. Hydrogen bonding in anion recognitions: isothiouronium versus thiourea derivatives

Thioureas have also been thoroughly investigated in the field of molecular recognition [7]. Isothiouronium salts have been explored quite recently as a new class of hydrogen-bonding subunit for the purpose of molecular recognition of anions in supramolecular chemistry. Isothiouroniums were proven as prospective replacements of thioureas because such groups would enhance the acidicity of the NH moieties and therefore can function as a better binder. The examples of hydrogen-bonding isothiouronium derivatives in anion recognitions were described in **Figure 1** [8–15].

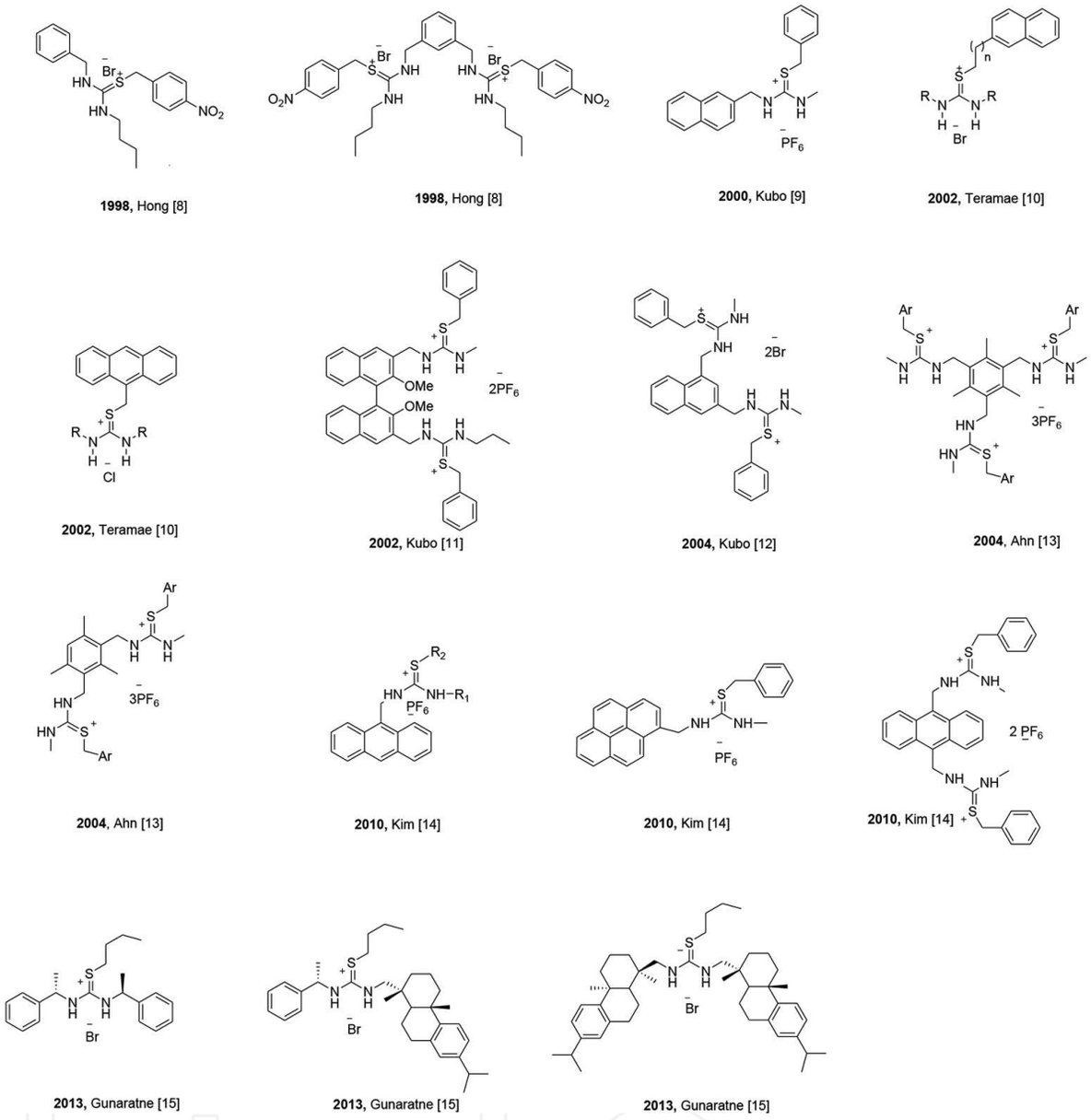


Figure 1. Isothiouronium-based anion recognitions.

2.3. Hydrogen-bonding isothiouronium organocatalysts

As previously explored, there is a close relationship and mutual interplay between molecular recognition, active site consideration in enzyme catalysis involving anions, and organocatalysis utilizing explicit hydrogen bonding. Molecular recognition is the central component of bio- and organocatalysis. Indeed, the concepts of anion bindings are the key to designing new organocatalytic transformations [16, 17]. Keeping this fact in mind, in organocatalysts, isothiouroniums can be used to improve the catalytic property of thioureas because they are better binder than anion recognitions. In addition, the chemical modification of isothiouroniums is readily varied using synthetic methods to make several types of functional molecular

systems. Consequently, isothiouronium-derived catalysts have been explored as a new field in hydrogen-bonding organocatalysts (**Figure 2**) [18–23].

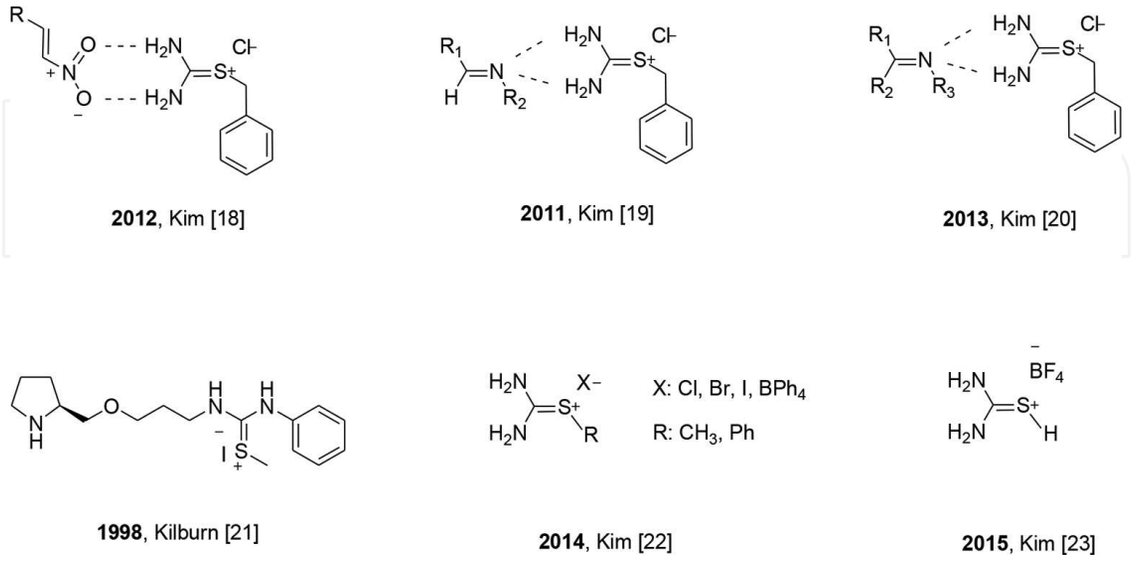
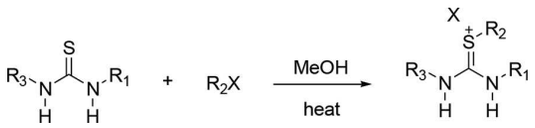


Figure 2. Hydrogen-bonding isothiouronium organocatalysts.

2.4. Synthesis of isothiouronium salts

Isothiouronium salts are typically obtained by the displacement reaction of alkyl halides with thioureas (**Scheme 1**) [24].



Scheme 1. Synthesis of isothiouronium salts.

It should be noted that the configurational and electronic structures of isothiouronium salts presented complexities and remained a subject for investigation (**Figure 3**) [15, 25]. The following three possibilities of isomerism have been reported ($R_1 \neq R_3$):

I. The oscillation of the carbon–nitrogen (CN) double bond (Eq. 1).

(1)

II. Hindered rotation at the CN bond (Eq. 2).

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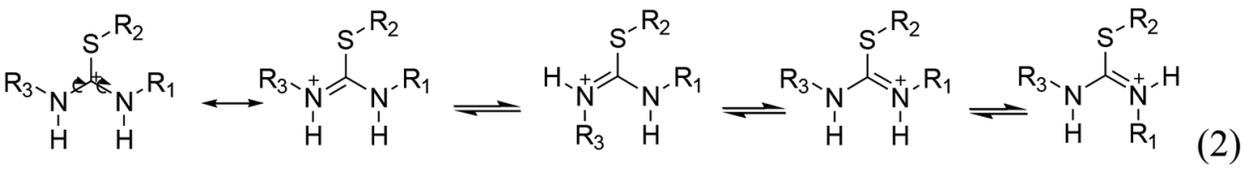
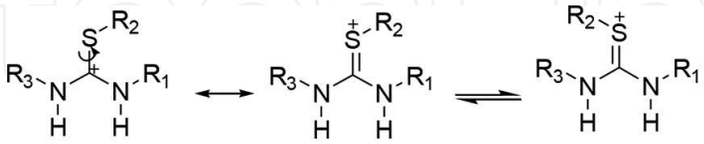


(2)

III. Syn–anti isomerism from restricted rotation at the carbon–sulfur (CS) bond (Eq. 3).



(3)

Among the above isomerisms, the *cis–trans* isomerism at the CN double bond in amides is easily detected; however, the possibility of isomerism at the CS double bond in thioketonium ions has only been examined at low temperature.

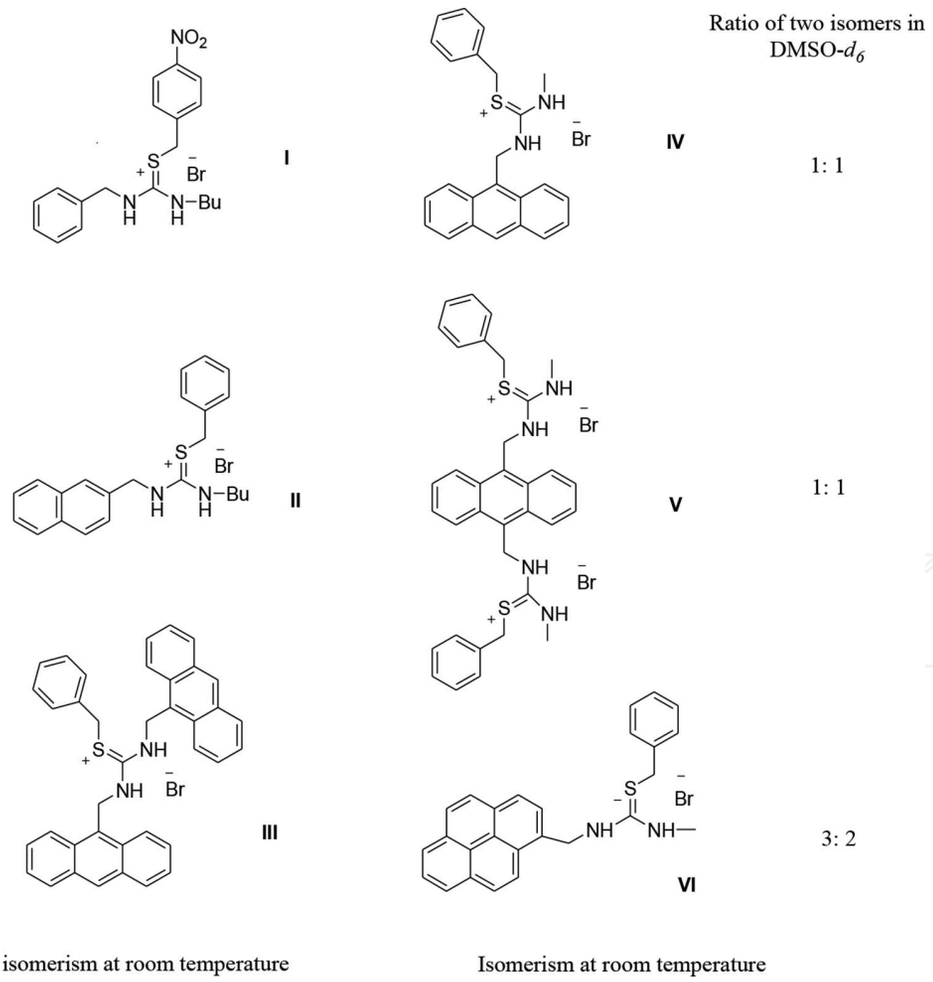


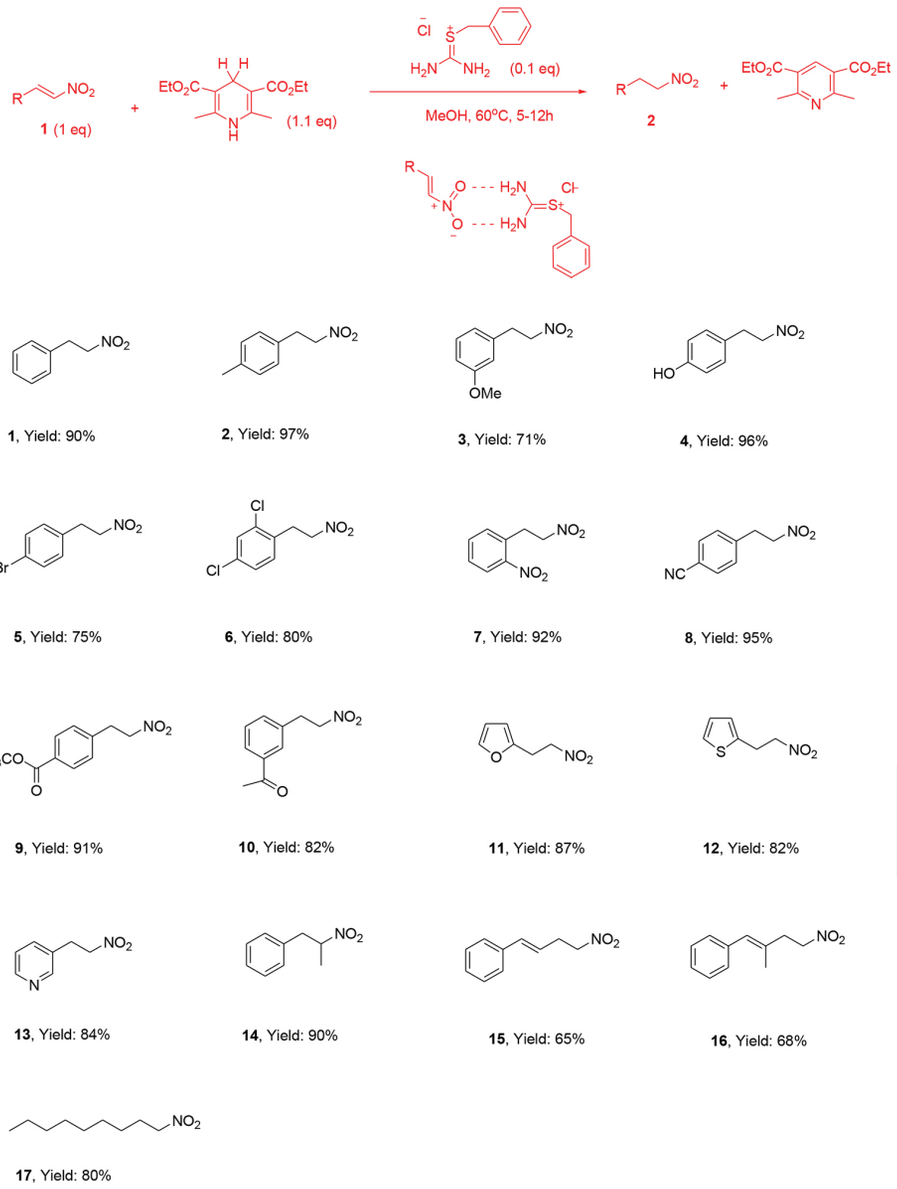
Figure 3. Isomerism in several structures of isothiouronium salts detected by NMR [14].

3. Synthetic applications of hydrogen-bonding isothiouronium organocatalysts

3.1. Nonstereoselective *S*-benzyl isothiouronium chloride organocatalyst

3.1.1. Reduction of conjugated nitroalkenes [18]

Kim et al. introduced the simple *S*-benzyl isothiouronium chloride as an efficient hydrogen-bonding organocatalyst in a series of reduction of conjugated nitroalkenes (**Scheme 2**). The mechanism of *S*-benzyl isothiouronium chloride catalyst for the activation of the reaction was assumed to be quite similar to that of the thiourea catalyst. Because of the formation of the

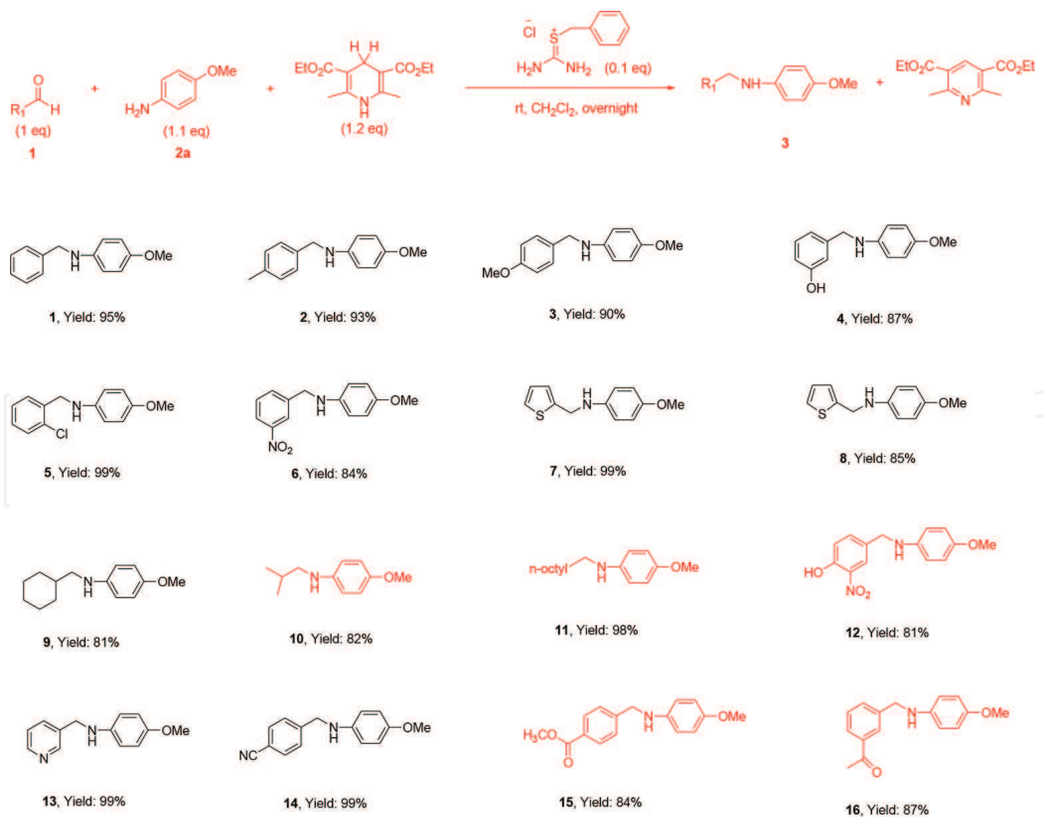


Scheme 2. Reaction scope of reduction of conjugated nitroalkenes using *S*-benzyl isothiouronium chloride catalyst.

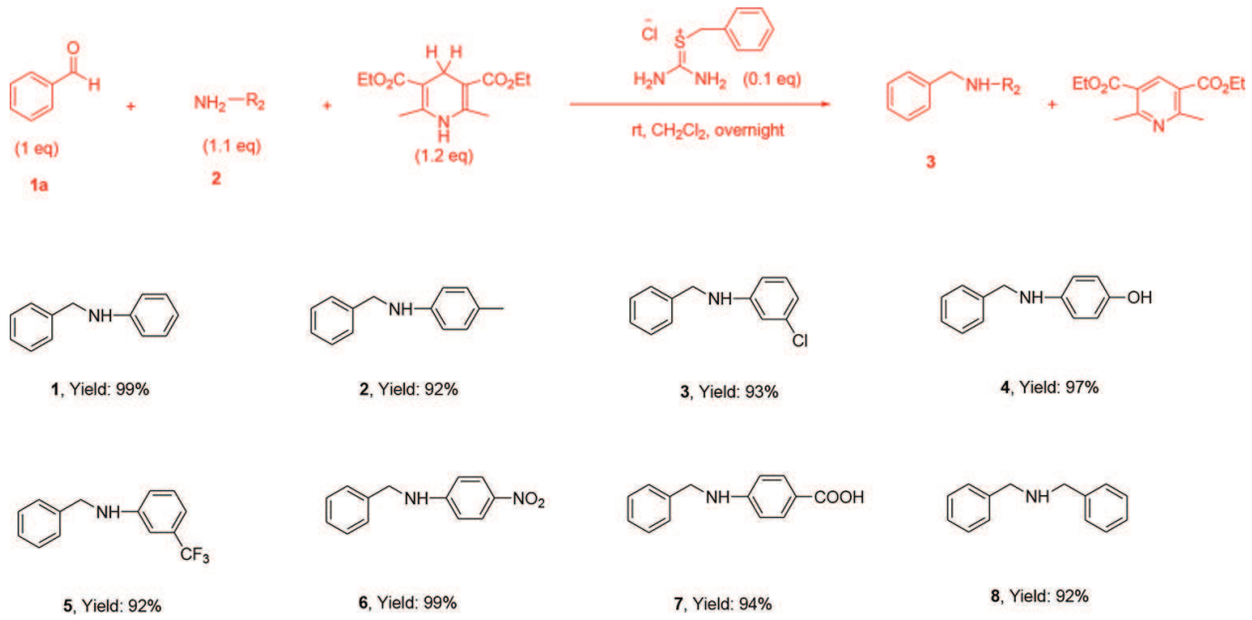
strong hydrogen bonding between the nitro group and the isothiouronium moiety of the catalyst, the lowest uncccupied molecular orbital (LUMO) energy of alkenes is lower and then the reaction is accelerated. The reduction of conjugated nitroalkenes using *S*-benzyl isothiouronium chloride as a recoverable organocatalyst was successfully accomplished with high yields (65–97%) and excellent chemoselectivities. Some valuable characteristics such as the possibilities of working in the protic solvents (MeOH) and recycling (first cycle: 85%; second cycle: 88%; and third cycle: 87% yields) after converting the thiourea organocatalyst into the corresponding isothiouronium salt are the key features of this method (**Scheme 2**).

3.1.2. Reductive amination of aldehydes [19]

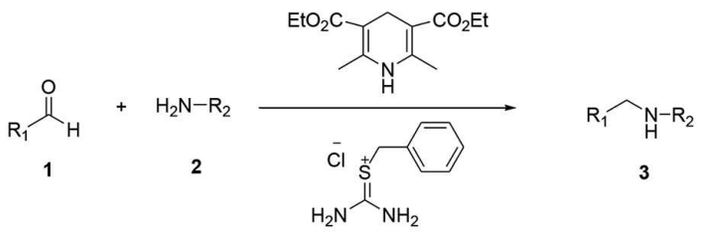
The authors also reported *S*-benzyl isothiouronium chloride as a novel organocatalyst with high efficiency, selectivity, and easy recovery for the direct reductive amination of aldehydes using Hantzsch ester. A mild and operationally simple fragment coupling procedure was developed, which functions with a wide range of aldehydes and amines with good-to-excellent yields (81–99%). The *S*-benzyl isothiouronium chloride catalyst can be easily recovered by simple filtration and reused with no drop in its efficiency (first cycle: 97%; second cycle: 98%; and third cycle: 95% yields). Compared with the same model based on thiourea, the isothiouronium catalyst showed higher yield and milder reaction conditions as well as easier recovery and reuse (**Schemes 3** and **4**, and **Figure 4**).



Scheme 3. Reductive amination of aldehyde scope using a variety of aldehydes.



Scheme 4. Reductive amination of aldehyde scope using a variety of amines.



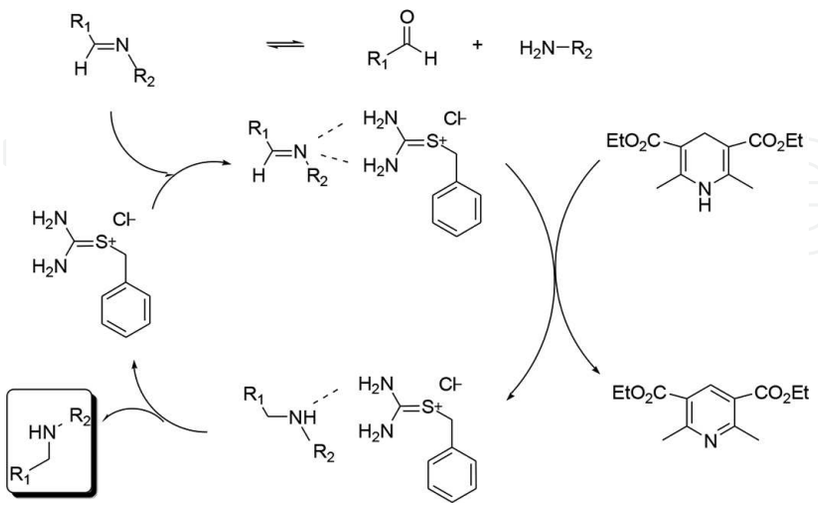
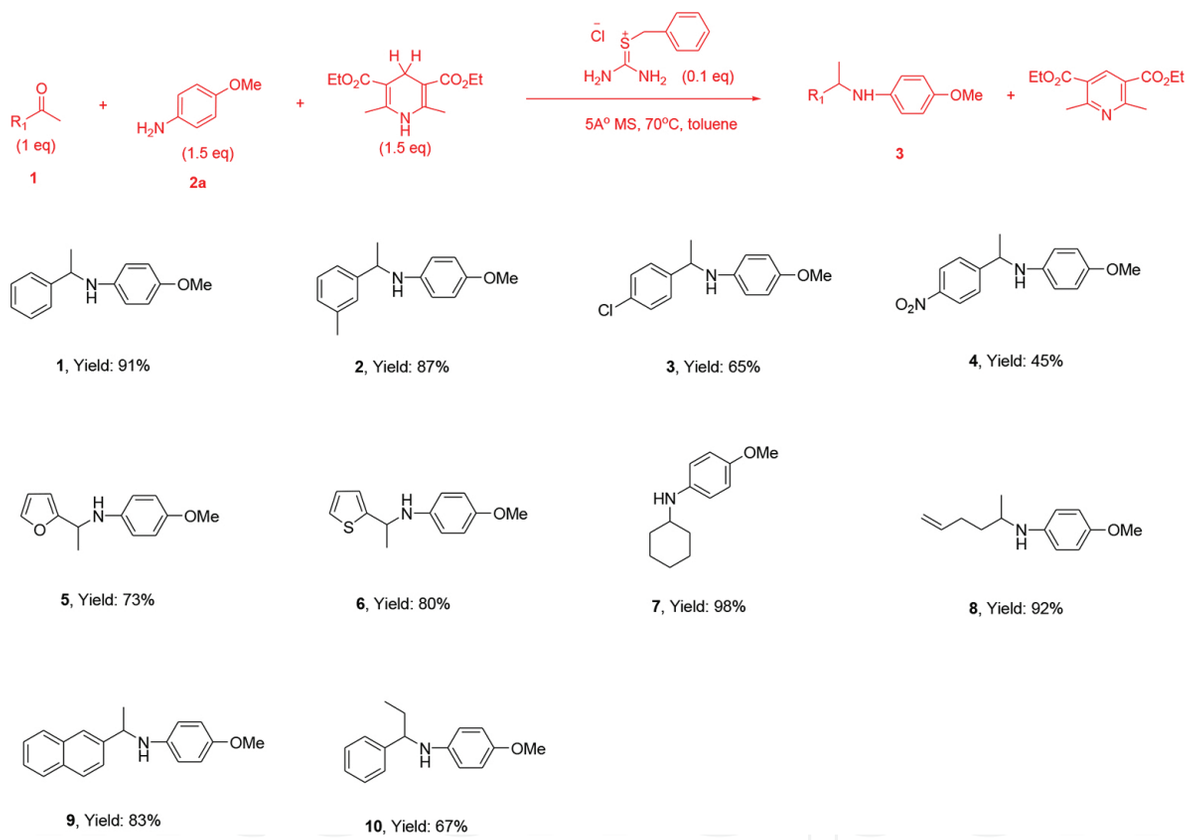


Figure 4. Proposed mechanism of the hydrogen-bond catalyzed direct reductive amination of aldehydes using *S*-benzyl isothiouronium chloride.

3.1.3. Reductive amination of ketones [20]

As part of an ongoing study of the Hantzsch ester and *S*-benzyl isothiouronium chloride system, the authors continuously reported *S*-benzyl isothiouronium chloride as a new class of noncovalent organocatalysts for the direct reductive amination of ketones (**Schemes 5** and **6**). This reaction exclusively relies on the hydrogen-bond activation by the catalyst. A wide range of ketones and amines were found to provide the expected products with moderate-to-excellent yields (45–98%). With simple modification of converting thiourea to its corresponding isothiouronium salt through alkylation, the isothiouronium catalyst acquires certain valuable characteristics such as high hydrogen-bonding propensity, the possibility of working in protic solvents (MeOH), and the ability to be recycled and reused (first cycle: 88%; second cycle: 86%; and third cycle: 85% yields).



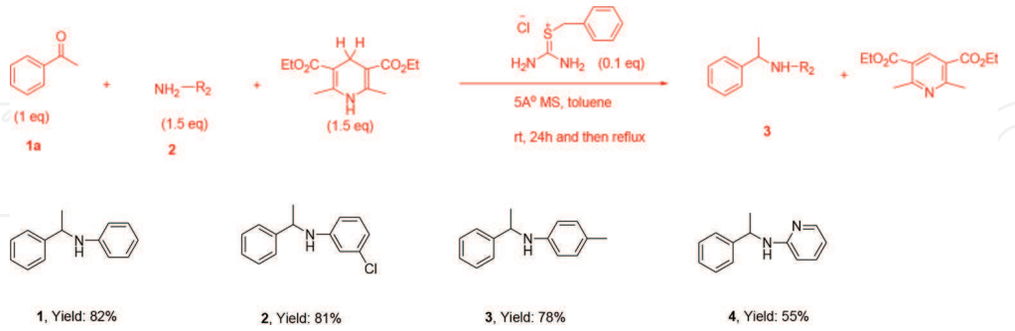
Scheme 5. Reductive amination of ketone scope using a variety of ketones.

3.2. Stereoselective isothiouronium organocatalysts

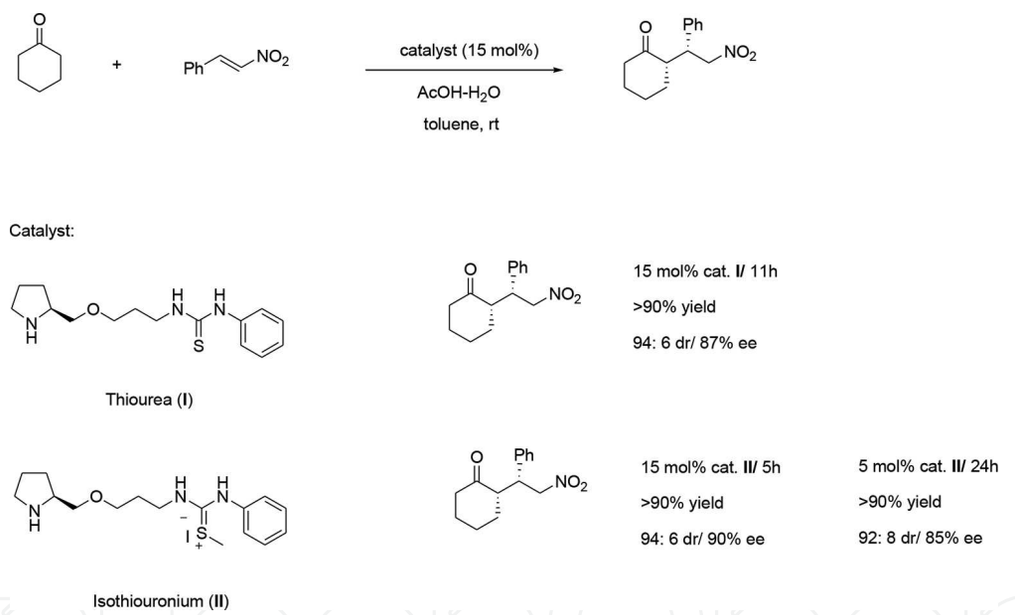
3.2.1. Enantioselective Michael addition reaction [21]

In 2009, Kilburn et al. first synthesized L-proline-based bifunctional organocatalyst containing tethered isothiouronium salt and then applied it to promote the Michael addition reaction of cyclohexanone to *trans*-β-nitrostyrene (**Scheme 7** and **Figure 5**). As compared with the

same model based on thiourea, isothiouronium-substituted organocatalyst showed some enhancement of enantiocontrol (87% ee vs. 90% ee) and significant enhancement in the reaction rate (11 h vs. 5 h). Reduced catalyst loading was also tolerated (from 15 to 5%).



Scheme 6. Reductive amination of ketone scope using a variety of amines.



Scheme 7. Enantioselective addition of cyclohexanone to *trans*-β-nitrostyrene.

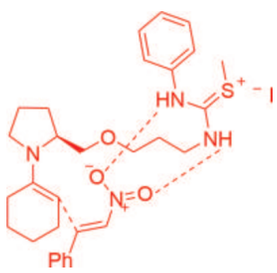
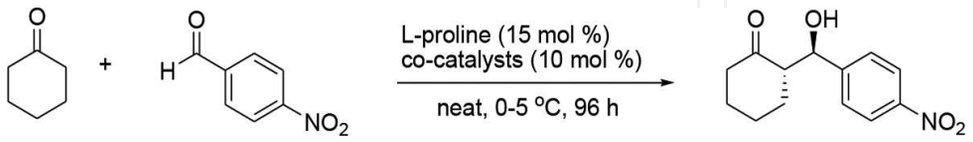


Figure 5. Proposed transition state for conjugate addition catalysis by isothiournium-functionalized organocatalyst.

3.2.2. Asymmetric aldol reaction [22, 23]

With a keen interest in organocatalyst systems based on isothiouronium derivatives, Kim et al. introduced isothiouronium iodide salt as an efficient cocatalyst with L-proline in the direct asymmetric aldol reactions between cyclohexanone and aromatic aldehydes [22]. This method produced good-to-excellent yields (up to 93%) with good stereoselectivities (up to 93:7 dr and 99% ee). This aldol protocol includes a solvent-free catalytic system inside a refrigerator without stirring in the hunt for an inexpensive and green process (**Table 1**, **Scheme 8**, and **Figure 6**).



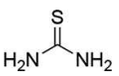
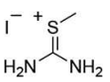
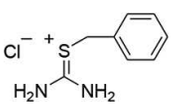
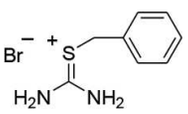
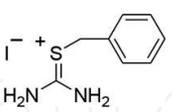
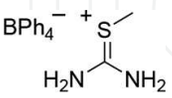
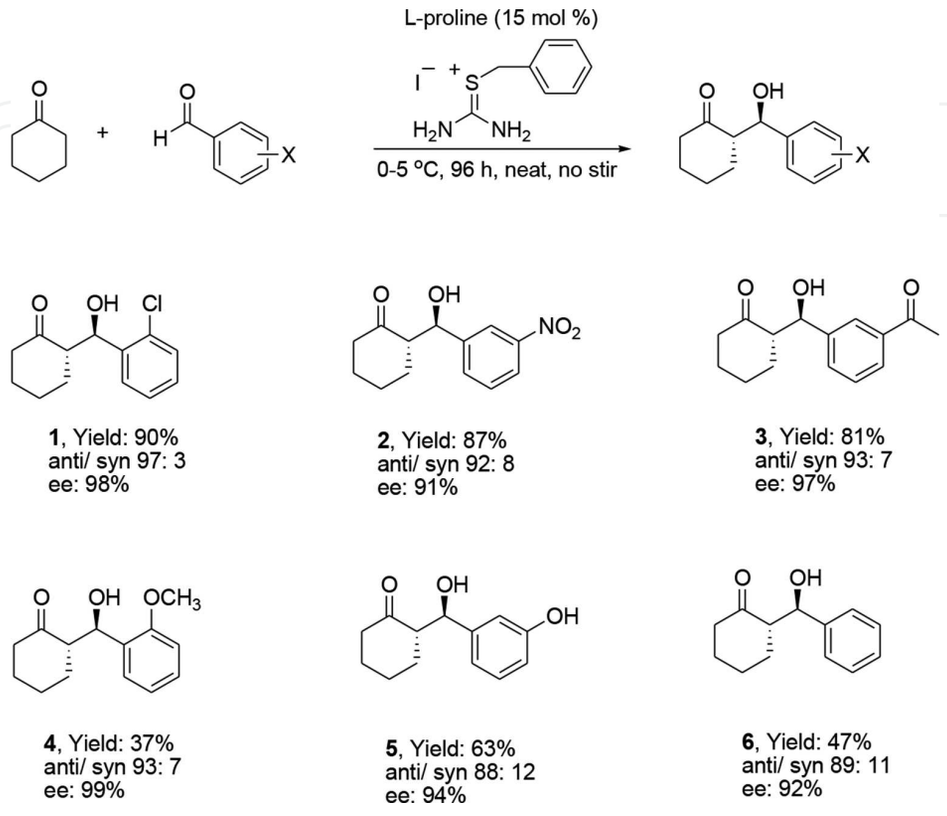
Entry	Cocatalyst	Yield (%)	*anti*:*syn*	ee (%)
1	None	78	81:19	56
2		81	89:11	78
3		90	89:11	92
4		86	88:12	88
5		95	93:7	94
6		93	93:7	97
7		90	92:8	97

Table 1. Screening of isothiouronium cocatalysts for the L-proline-catalyzed aldol reaction.

When exploring an asymmetric aldol reaction, the authors also introduced the mimic system of isothiouronium salts which were prepared indirectly by adding acids to thiourea (**Table 2**) [23]. The isothiouronium core of salts from thiourea and acids could form a network of H-bonding interactions with the carboxylate of proline as well as with the carbonyl moieties of cyclohexanone and aromatic aldehyde, thus enhancing their electrophilicity (**Figure 7**). Asymmetric aldol reactions between cyclohexanone and aromatic aldehydes using these

mimic isothiouronium systems as additives provided products with high yields (40–93%) and good stereoselectivities (up to 95:5 dr and 99% ee). This aldol protocol also enclosed a solvent-free catalytic system inside a refrigerator without stirring (**Scheme 9**).



Scheme 8. Asymmetric aldol reaction between various aldehydes and cyclohexanone with isothiouronium iodide.

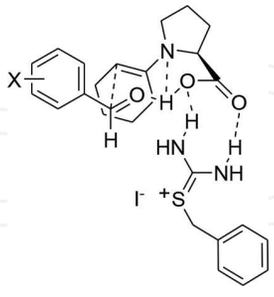
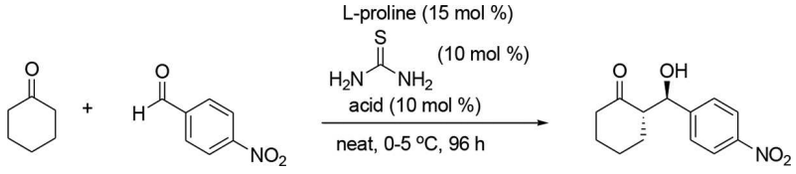


Figure 6. Proposed transition state model for asymmetric aldol reaction.



Entry	Acid	Yield (%)	*anti*:*syn*	ee (%)
1	None	81	89:11	78
2	None	78	81:19	56
3	$PhCO_2H$	82	93:7	92
4	CF_3CO_2H	92	95:5	98
5	HBF_4	93	95:5	99
6	HPF_6	85	96:4	99

Table 2. Screening of acids for the L-proline/thiourea-catalyzed aldol reaction.

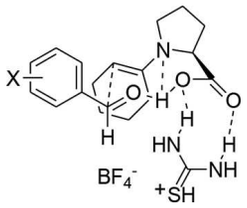
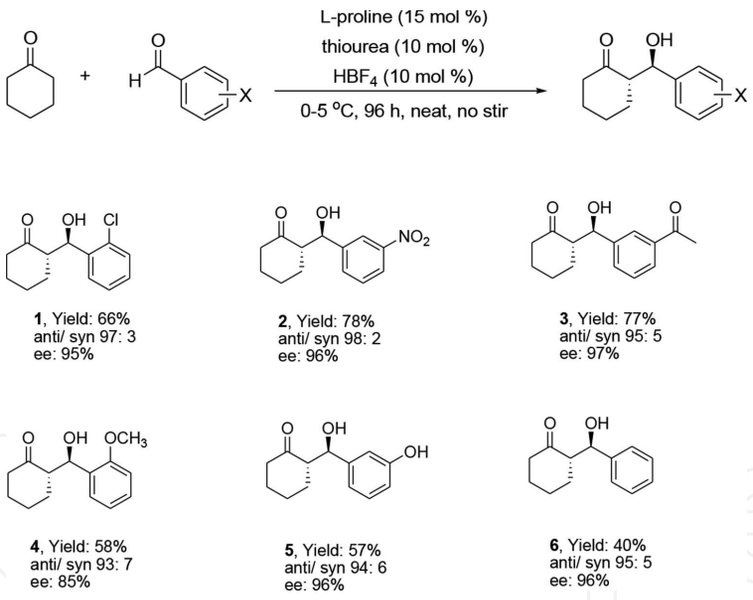


Figure 7. Proposed transition state model for asymmetric aldol reaction by adding acid to thiourea.



Scheme 9. Asymmetric aldol reaction with the mimic system of isothiouronium salts using thiourea/HBF_4.

4. Summary and outlook

This chapter reviews the novel research on hydrogen-bonding isothiouronium organocatalysts considering their designed concepts and synthetic applications in nonstereoselective and stereoselective reactions. From that isothiouroniums were proven to be the prospective

replacements of thioureas in improving the catalytic properties because such groups would enhance the acidicity of the NH moieties for better hydrogen bonding. The milestone achievement and blooming research on thiourea catalysts have paved the avenue for further research efforts in this field. Since the chemical modification of isothiouroniums readily varies using synthetic methods to produce several types of functional molecular systems, hydrogen-bonding isothiouronium derivatives have been expected to open new approaches for the discovery of a wide range of new organocatalytic reactions.

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References

[1] Walvoord RR, Huynh PNH, Kozlowski MC. Quantification of electrophilic activation by hydrogen-bonding organocatalysts. J. Am. Chem. Soc. 2014; 136: 16055-16065.

[2] MacMillan DWC. The advent and development of organocatalyst. Nature. 2008; 455: 304–308.

[3] Zhang Z, Schreiner PR. (Thio)urea organocatalysis—what can be learnt from anion recognition? Chem. Soc. Rev. 2009; 38: 1187–1198.

[4] Zabka M, Sebesta R. Experimental and theoretical studies in hydrogen-bonding organocatalysis. Molecules. 2015; 20: 15500–15524.

[5] Pihko PM (Ed.). Hydrogen bonding in organic synthesis–(thio)urea organocatalysts. Wiley-VCH: Weinheim/Germany; 2009. p. 395.

[6] Fang X, Wang CJ. Recent advances in asymmetric organocatalysis mediated by bifunctional amine-thioureas bearing multiple hydrogen-bonding donors. Chem. Commun. 2015; 51: 1185–1197.

[7] Evans NH, Beer PD. Advances in anion supramolecular chemistry: from recognition to chemical applications. Angew. Chem. Int. Ed. 2014; 53: 11716–11754.

[8] Yeo WS, Hong JI. Oxoanion recognition by a thiouronium receptor. Tetrahedron Lett. 1998; 39: 8137–8140.

[9] Kubo Y, Tsukahara M, Ishihara S, Tokita S. A simple anion chemosensor based on a naphthalene–thiouronium dyad. Chem. Commun. 2000; 653–654.

[10] Nishizawa S, Cui YY, Minagawa M, Morita K, Kato Y, Taniguchi S, Kato R, Teramae N. Conversion of thioureas to fluorescent isothiouronium-based photoinduced electron transfer sensors for oxoanion sensing. J. Chem. Soc. Perkin Trans. 2. 2002; 866–870.

[11] Kubo Y, Ishihara S, Tsukahara M, Tokita S. Isothiouronium-derived simple fluorescent chemosensors of anions. J. Chem. Soc. Perkin Trans. 2. 2002; 1455–1460.

[12] Kobo Y, Kato M, Misawa Y, Tokita S. A fluorescene-active 1,3-bis(isothiouronium)-derived naphthalene exhibiting versatile binding modes toward oxoanions in aqueous MeCN solution: new technology for sensing oxoanions. Tetrahedron Lett. 2004; 45: 3769–3773.

[13] Seong HR, Kim DS, Kim SG, Choi HJ, Ahn KH. Benzene-based tripodal isothiouronium compounds as sulphate ion receptors. Tetrahedron Lett. 2004; 45: 723–727.

[14] Nguyen QPB, Kim TH. Isothiouronium salts based on anthracene and pyrene as anion sensors. Bull. Korean Chem. Soc. 2010; 31: 712–715.

[15] Foreiter MB, Gunaratne HQN, Nockemann P, Seddon KR, Stevenson PJ, Wassell DF. Chiral thiouronium salts: synthesis, characterisation and application in NMR enantiodiscrimination of chiral oxoanions. New J. Chem. 2013; 37: 515–533.

[16] Steed JW, Gale PA. Supramolecular chemistry: from molecules to nanomaterials. John Wiley & Sons: Chichester, UK; 2012. p. 4014.

[17] Phipps RJ, Hamilton GL, Toste FD. The progression of chiral anions from concepts to applications in asymmetric catalysis. Nat. Chem. 2012; 4: 603–614.

[18] Nguyen QPB, Kim JN, Kim TH. S-Benzyl isothiouronium chloride as recoverable organocatalyst for the reduction of conjugated nitroalkenes with Hantzsch ester. Tetrahedron. 2012; 68: 6513–6516.

[19] Nguyen QPB, Kim TH. S-Benzyl isothiouronium chloride as recoverable organocatalyst for the direct reductive amination of aldehydes. Tetrahedron Lett. 2011; 52: 5004–5007.

[20] Nguyen QPB, Kim TH. S-Benzyl isothiouronium chloride as recoverable organocatalyst for the direct reductive amination of ketones with Hantzsch ester. Synthesis. 2012; 44: 1977–1982.

[21] Carley AP, Dixon S, Kilburn JD. Pyrrolidine-based organocatalysts for enantioselective Michael addition of cyclohexanone to trans-β-nitrostyrene. Synthesis. 2009; 15: 2509–2516.

[22] Cho E, Kim TH. Direct asymmetric aldol reaction co-catalyzed by L-proline and isothiouronium salts. Tetrahedron Lett. 2014; 55: 6470–6473.

[23] Cho E, Lee H, Kim TH. Asymmetric aldol reaction catalyzed by L-proline and achiral thiourea fluoroboric acid salt. Bull. Korean Chem. 2015; 36: 410–412.

[24] Sa MM, Ferreira M, Bortoluzzi AJ, Fernandes L, Cunha S. Exploring the reaction of multifunctional allylic bromides with N,S-dinucleophiles: isothiouronium salts and analogs as useful motifs to assemble the 1,3-thiazine core. Arkivoc. 2010; 11: 303–321.

[25] Nguyen QPB, Kim JN, Kim TH. Investigation of isomerism in anthracene-isothiouronium salts and application of these salts for anion sensing. Bull. Korean Chem. 2009; 30: 2093–2097.