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Structure–activity relationship of dihydroimidazo-, dihydropyrimido, tetrahydrodiazepino-[2,1-*b*]-thiazoles, and -benzothiazoles as an acylation catalyst

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ABSTRACT

Cyclic isothioureas **1**, **2**, **3**, and **4** were synthesized through a four-step procedure from the corresponding *ortho*-bromoanilines **10** via Pd- or Cu-catalyzed cyclization–benzothiazole formation. Nonbenzo analogues **7**, **8**, and **9** were synthesized by a condensation reaction of cyclic thioureas **15** and α-bromoacetophenones **14**. Investigations of the acylation reactions of 1-phenylethanol with acid anhydrides in the presence of these cyclic isothiourea catalysts revealed their structure–activity relationships. Remarkable electronic effects resulting from substituent(s) on a benzo or phenyl moiety and the influence of the size of the annulating ring were observed. Introduction of an electron-donating substituent(s) enhanced the reaction rate. A few substitution effects on chiral catalysts of type **3** and **7** were also studied.

Recently, cyclic isothioureas such as **1**–**4** (Fig. 1) have received considerable attention in research studies on organic catalysts and asymmetric synthesis.[1] In 2006, Birman et al. developed **3a** (BTM) as a very efficient asymmetric catalyst for acylative kinetic resolution of racemic secondary alcohols.[2] In the same year, we independently found that 2,3-dihydroimidazo[2,1-*b*]benzothiazole (**1a**, DHIB) and 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (**2a**, DHPB) work well as a good catalyst for acyl transfer reactions. It is noteworthy that **2a** can catalyze the reactions quite efficiently.[3] For instance, **2a** catalyzed the acylation of alcohols with an anhydride at a high rate, which was more than that of 4-dimethylaminopyridine (DMAP). Smith and co-workers pointed out that **2a** efficiently catalyzed Steglich rearrangement reactions and that the analogous **1a** was not effective.[4] From 2006 to 2013, chiral derivatives of **1a** and **2a** involving **3a** and **4a** attracted increasing interests, and have been widely used to develop efficient asymmetric reactions such as kinetic resolution of alcohols,[2,5] acids,[6] lactams[7] and 2-oxazolidinones,[8] desymmetrization of meso diols,[9] dynamic kinetic resolution of α-thioalkanoic acids and azlactons,[10] Steglich rearrangement and related reactions,[11] aldol-lactonization reaction,[12] Michael addition-cyclization reaction,[13] and α-amination of carboxylic acids.[14,15] During this period, the reactivity (basicity and nucleophilicity) of cyclic isothioureas has been investigated primarily for the corresponding nonbenzo saturated compounds, 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole and 3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*a*]pyrimidine, and their derivatives.[16,17]

Herein we report the development of a new method for synthesizing **1**, **2**, **3**, and **4** derivatives bearing a substituent(s) on the benzene ring, **6**, and nonbenzo analogues **7**, **8**, and **9**. The experimental results of the acylation reactions using these analogues as catalysts are discussed to elucidate their structure–activity relationship.

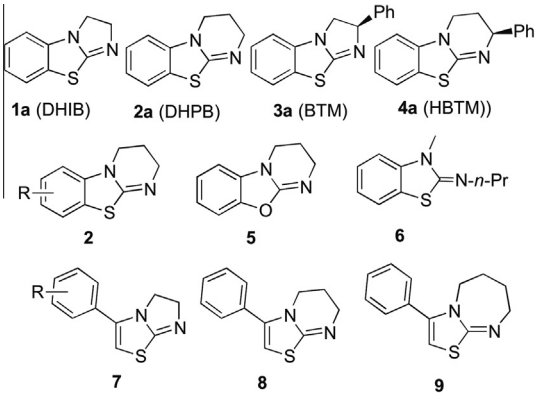

Figure 1. Various cyclic isothioureas.

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Various isothioureas **2** were synthesized according to the procedure involving Pd- or Cu-catalyzed cyclization of thiourea-alcohols **12** derived from *ortho*-bromoanilines **10** as a key reaction (Scheme 1). After converting bromoanilines **10** to the corresponding isothiacyanates **11**, the reaction with 3-aminopropanol gave thioureas **12**, which were cyclized to benzothiazoles **13** in the presence of $Pd(PPh_3)_4$ or CuI/1,10-phenanthroline as a catalyst and Cs_2CO_3.[18] Finally, the resulting benzothiazoles **13** were cyclized by treatment with MsCl and Et_3N and isothioureas **2** was obtained in moderate to good yields through four steps.

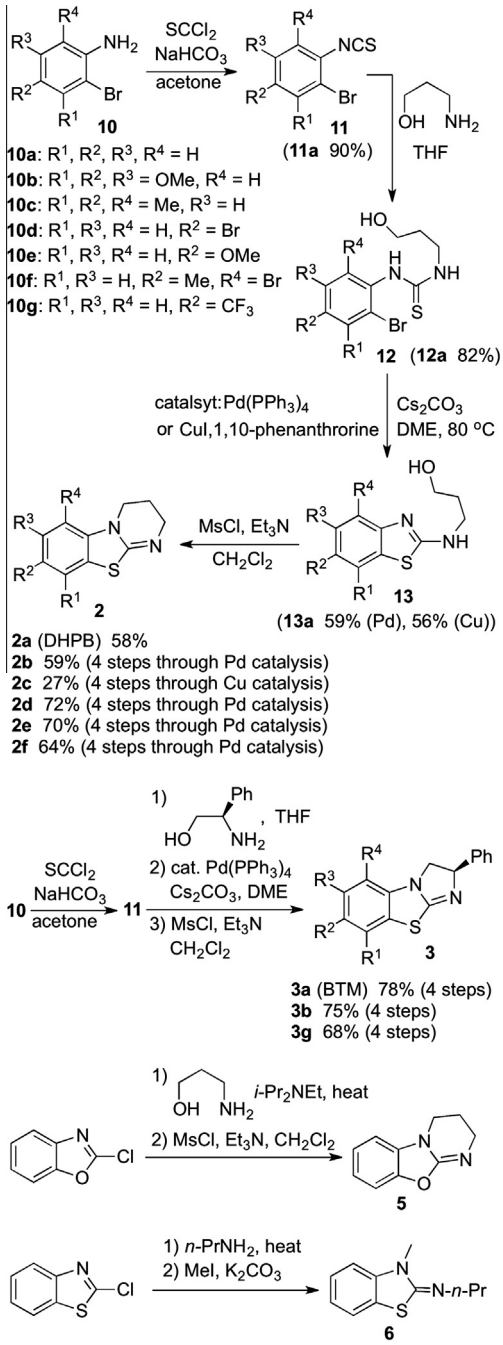
Similarly, BTM (**3a**) and its derivatives **3b** and **3g** were readily synthesized from the corresponding *ortho*-bromoanilines and (*R*)-2-phenyl-2-aminoethanol (Scheme 1). Oxa analogue **5** of HBTM and noncyclic benzothiazole-amine **6**[19] were synthesized from chlorobenzo-oxazole and chlorobenzothiazole by treatment with the corresponding amine followed by cyclization or methylation on the ring nitrogen (Scheme 1).

Nonbenzo derivatives **7a**–**d**, **8**, and **9** were readily synthesized by the corresponding α-bromoacetophenone derivatives **14** and cyclic thioureas **15** by heating in EtOH, followed by neutralization (Scheme 2).[20] Similarly, chiral 2-phenyl substituted **7e**–**h** were obtained from **14** and (*R*)-4-phenylimidazolidine-2-thione; production of a possible regioisomer **16** was not observed presumably because of the steric repulsion in an intermediate **A**.

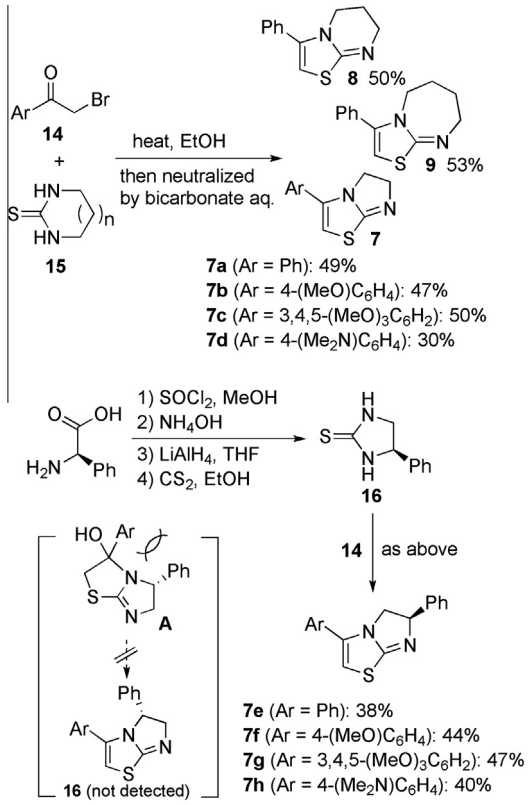
With cyclic isothioureas **2**, **5**, **6**, **7**, **8**, and **9** in hand, we evaluated their catalytic activity in the acylation reaction of 1-phenylethanol with acid anhydride (Scheme 3).

First, we performed the reactions using DHPB (**2a**) and its substituted analogues **2b**–**e** as a catalyst (0.5 mol %), isobutyric anhydride (1.0 equiv), and Et_3N (1.5 equiv) in CH_2Cl_2 (0.25 M) at 20 °C. The time course of the reaction was traced by TLC analysis. Digitized stained TLC images were analyzed using image processing and analysis software (NIH-image).[21] The amounts of alcohol and ester were quantified to determine the conversion. The calculated rate constant *k* for each catalyst[22,23] and the relative activity (100 for DHPB) are summarized in Table 1. It was found that substitution on the benzene ring electronically affected the catalytic ability. Thus, the introduction of an electron-donating substituent(s) increased the reaction rate (**2b**, **2e**, **2c**); in contrast, an electron-withdrawing substituent (Br) decreased the activity (**2d**).

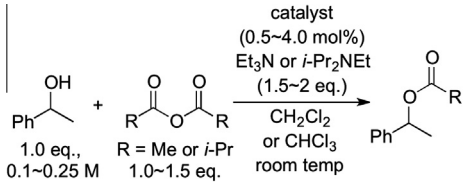
In a similar way, activities of **1a**, **2a**, oxa analogue **5**, open structure **6**, and nonbenzo derivatives **7a**, **8**, and **9** were compared by measuring conversions at each reaction time and calculating rate constants in the reactions of 1-phenylethanol with a catalyst (1 mol %), acetic anhydride (1.5 equiv), and Et_3N (2 equiv) in CH_2Cl_2 (0.2 M) at 20 °C.[22,23] The calculated relative activities (100 for DHPB) are shown in Table 2. Among nonbenzo derivatives **7a**, **8**,



Scheme 1. Synthesis of **2**, **3**, **5**, and **6**.

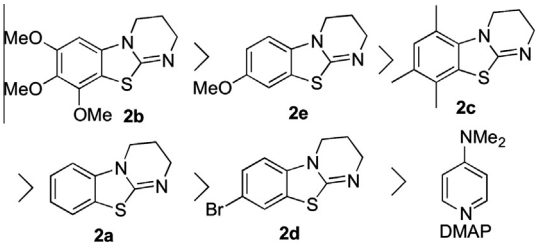


Scheme 2. Synthesis of **7**, **8**, and **9**.



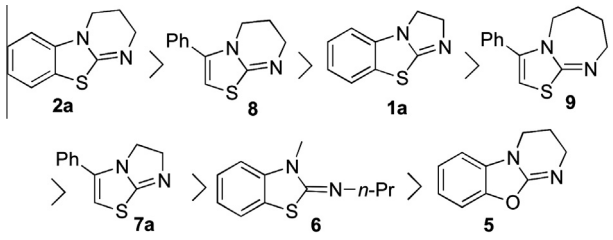
Scheme 3. Acylation reactions for evaluating catalytic activity.

Table 1
Relative acylation activity of catalysts **2a**–**e**



	2b	2e	2c	2a	2d	DMAP
k ($min^{-1}M^{-2}$)	536	500	400	272	172	124
Relative activity	197	184	147	100	63	46

Table 2
Relative acylation activity of catalysts **1a**, **2a**, and **5**–**9**



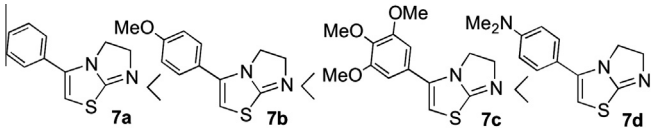
	2a	8	1a	9	7a	6	5
Relative activity	100	89	20	15	3.3	3.0	2.3

and **9**, which have a different annulating ring, six-membered compound **8** was more active than five-membered **7a** and seven-membered **9**. Compound **6**, which has an open structure, was much less reactive than **1a** and **2a**. Accordingly, in both series of benzo and nonbenzo analogues, the compounds comprised with a six-membered ring were the most active catalysts. Oxa analogue **5** showed very low activity because of a higher electronegativity of *O* (3.5) than *S* (2.4).[24]

The catalytic activities of **7a**–**d** which have a differently substituted phenyl group were compared in the reactions of 1-phenylethanol with a catalyst (4 mol %), isobutyric anhydride (1.5 equiv), and Et_3N (2 equiv) in $CHCl_3$ (0.25 M) at 20 °C. The calculated relative activities (1.0 for **7a**) are shown in Table 3. Introduction of an electron-rich substituent(s) increased the reactivity. In particular, introducing a NMe_2 group at the *p*-position greatly enhanced the reaction rate.

Introducing an electron-donating group(s) *R* to **i** and **ii** can increase the electron density of the sp^2 N by a positive inductive effect, which enhances the nucleophilicity (Fig. 2). In addition, the electron-donating R may stabilize the iminium cation in the acylated intermediates **iii** and **iv** and increase their existence ratio. The size of the annulating ring of **i** and **ii** is smaller, nucleophilicity of sp.[2] N may become higher, similar to saturated N-heterocycles

Table 3
Relative acylation activity of catalysts **7a**–**d**



	7a	7b	7c	7d
Relative activity	1.0	2.5	4.4	8.2

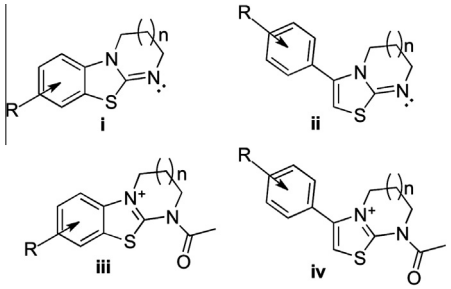


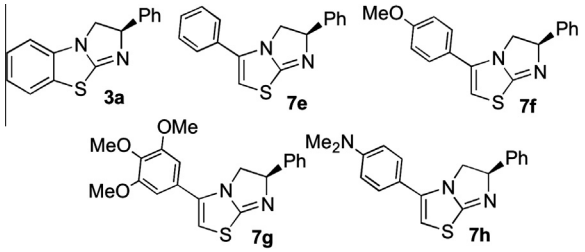
Figure 2. Structure for electronic effects and ring strains.

such as pyrrolidine, piperidine, and azepane. However, in the acylated intermediates, a compound comprised with a smaller ring has higher strain enegy, which could destabilize **iii** or **iv**. Considering a balance of these factors, it would be reasonable to conclude that six-membered derivatives such as **2** and **8** would exhibit the highest activity.

Table 4 summarizes the results of kinetic resolution of 1-phenylethanol with isobutyric anhydride in the presence of a chiral catalyst **3a** (BTM) or **7e**–**h**. It is evident that lack of benzo structure decreased the *S* value. Interestingly, introducing an electron-donating group on the phenyl substituent improved the selectivity.

The effect of the substituent(s) on the benzene ring of BTM (**3a**) was studied (Table 5). Compared to **3a**, selectivity factor *S*[25] for **3b**, which has a trimethoxybenzo structure, decreased; however, it remained similar to that of **3a**. The introduction of an electron-withdrawing CF_3 greatly decreased both the reaction rate and *S*.

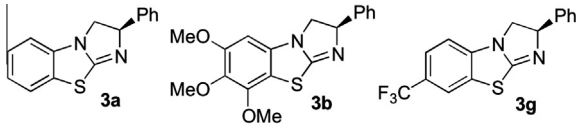
Table 4
Kinetic resolution of 1-phenylethanol with **3a** or **7e**–**h** catalysts[a]



Catalyst	Time (h)	C_{HPLC}[b] (%)	*S*
3a	44	21.3	13.9
7e	26	26.7	3.5
7f	3	30.0	6.6
7g	5	38.9	5.8
7h	3	46.3	8.4

[a] Evaluated by the reaction of 1-phenylethanol with isobutyric anhydride (0.75 equiv), *i*-Pr_2NEt (0.75 equiv), and a catalyst (4 mol %) in $CHCl_3$ (0.25 M) at room temperature.
[b] Conversion.

Table 5
Kinetic resolution of 1-phenylethanol with **3a**, **3b**, and **3g** catalysts[a]



Catalyst	Time (h)	C_{HPLC}[b] (%)	*S*
3a	1.5	60.2	16.5
3b	1	54.1	11.3
3g	18	45.4	5.6

[a] Evaluated by the reaction of 1-phenylethanol with acetic anhydride (1.0 equiv), *i*-Pr_2NEt (1.0 equiv), and a catalyst (5 mol %) in $CHCl_3$ (0.25 M) at room temperature.
[b] Conversion.

In summary, cyclic isothioureas **1**, **2**, **3**, and **4** have been synthesized in four steps from the corresponding *ortho*-bromoanilines **10** via Pd- or Cu-catalyzed cyclization–benzothiazole formation. In addition, nonbenzo analogues **7**, **8**, and **9** were synthesized by a condensation reaction of cyclic thioureas **15** and α-bromoacetophenones **14**. Investigation of the acylation reactions of 1-phenylethanol with acid anhydrides in the presence of these cyclic isothiourea catalysts revealed their structure–activity relationships. Remarkable electronic effects resulting from substituent(s) on a benzo or phenyl moiety and the influence of the size of the annulating ring were observed. A few substitution effects on chiral catalysts of type **3** and **7** were also studied.

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21. Version 1.63 for Macintosh was used. This is available via the internet at http://rsb.info.nih.gov/nih-image/download.html. See Ref. 3.
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