

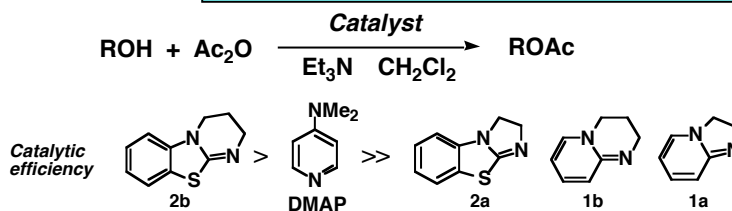
Graphical Abstract

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Unexpected reactivity of annulated 3*H*-benzothiazol-2-ylideneamines as an acyl transfer catalyst

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Unexpected reactivity of annulated 3*H*-benzothiazol-2-ylideneamines as an acyl transfer catalyst

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Abstract—Catalytic ability of annulated 3*H*-benzothiazol-2-ylideneamines and 1*H*-pyridin-2-ylideneamines for acylation of alcohols was investigated and 3,4-dihydro-2*H*-9-thia-1,4a-diazafluorene (**2b**) was found to be an extremely effective catalyst, the reaction with which was faster than that with DMAP. © 2011 Elsevier Science. All rights reserved

Acylation or esterification of alcohols is an important, basic transformation in organic and bioorganic chemistry. Non-peptide small organic molecules such as pyridine and imidazole derivatives are well known as an effective catalyst for the transformation. Recently, an enantioselective variant catalyzed by non-peptide compounds has been of great interest as a versatile means for acylative kinetic resolution and asymmetric desymmetrization.¹ Many of the effective catalysts developed so far have a 4-aminopyridine nucleus as a reactive core, achiral derivatives of which such as 4-*N,N*-dimethylaminopyridine (DMAP) have been used in a wide range of organic reactions.¹ A new aspect has been shown by Birman *et al.* who introduced a new class of acyl transfer catalysts, 2,3-dihydroimidazo[1,2-*a*]pyridines, **1a** and its derivatives, and elegantly applied their optically active derivatives such as **1c** as a catalyst to kinetic resolution of racemic aryl alcohols (Figure 1).² The results prompted us to investigate the possibility of annulated benzothiazol-2-ylideneamines **2** as a catalyst, expecting that they might have a more nucleophilic nitrogen atom than compounds of the type **1** and could exhibit good catalytic activity. In the course of the study we found that 3,4-dihydro-2*H*-9-thia-1,4a-diazafluorene (**2b**) was an unexpectedly effective catalyst for acyl transfer reaction, the efficiency of which was higher than that of the compounds illustrated in Figure 1, including 4-*N,N*-dimethylaminopyridine (DMAP, **4**). Herein we report the results of investigation on catalytic reactivity and the mechanism of annulated benzothiazol-2-ylideneamines **2** and pyridin-2-ylideneamines **1** as a reactive core of the

catalyst. During these investigations, quite recently Birman *et al.* have reported that Tetramisole (**3**) and its benzo derivative **2c** were efficient enantioselective acyl transfer catalysts, the latter of which exhibited a high selectivity factor in the 100-350 range in the kinetic resolution of secondary benzylic alcohols.

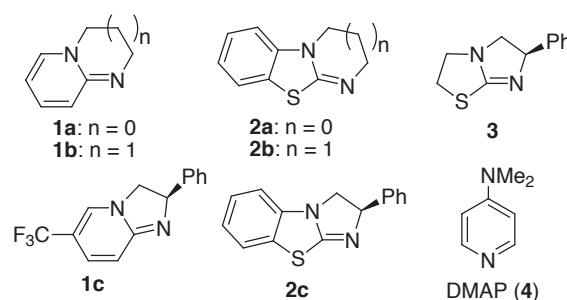
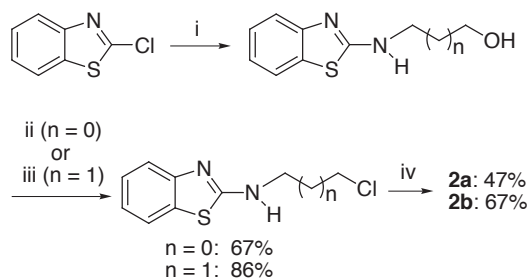


Figure 1. Structures of compounds **1**, **2**, **3** and **4**.

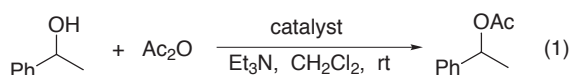
Annulated benzothiazol-2-ylideneamines **2a** and **2b** were synthesized according to the procedure illustrated in Scheme 1.^{4,5} Thus, 2-chlorobenzthiazoles were substituted with 1,2- or 1,3-aminoalcohols followed by chlorination of the resulting alcohols and cyclization under basic conditions. 2,3-Dihydroimidazo[1,2-*a*]pyridine **1a** and **1b** were prepared by the procedure reported with minor modification.²

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Scheme 1. Synthesis of **2**: (i) $\text{HOCH}_2(\text{CH}_2)_n\text{CH}_2\text{NH}_2$, neat, 130°C ; (ii) SOCl_2 , DMF, reflux; (iii) SOCl_2 , CHCl_3 , reflux; (iv) K_2CO_3 , CHCl_3 .

First, we carried out the reaction of 1-phenylethylalcohol with acetic anhydride (Ac_2O) in the presence of **1a**, **1b**, **2a**, **2b** or DMAP under the identical reaction conditions (Eq 1). Thus, to a solution of 1-phenylethylalcohol (1.0 mmol), Et_3N (1.5 mmol) and the catalyst (5 mol%) in CH_2Cl_2 (5 mL) was added Ac_2O (1.5 mmol) at $22\text{--}24^\circ\text{C}$. The TLC analysis of the reaction showed the approximate reaction time for consumption of the substrate alcohol to be >40 , >40 , 15, <0.25 and <0.25 h, respectively, with **1a**, **1b**, **2a**, **2b** and DMAP (**4**).



To confirm the relative efficiency of catalysts, the reaction with **1a**, **1b** or **2a** was performed with 1-phenylethylalcohol (1.0 mmol), Ac_2O (1.0 mmol), Et_3N (1.5 mmol) and a catalyst (5 mol%) in 1 mL of CH_2Cl_2 , while that with **2a** or DMAP was carried out with 1-phenylethylalcohol (1.0 mmol), Ac_2O (1.0 mmol), Et_3N (1.5 mmol) and a catalyst (1 mol%) in 10 mL of CH_2Cl_2 . The time course of the reaction was traced by TLC analysis: thus, images of stained TLC were allowed to be imported as digital data to computer by image-scanning and analyzed by the image processing and analysis software (**NIH image**)⁶ and the amounts of the alcohol and the acetate were quantified to determine the conversion. The results are illustrated in Figure 2. As revealed in Figure 2(a), pyridine derivatives **1a**, **1b** and dihydroimidazo derivative of benzothiazole **2a** have similar catalytic activity and the reactions with them were much slower than that with DMAP and, surprisingly, a dihydropyrimido derivative of benzothiazole **2b** was found to be an extremely effective catalyst and the activity was higher than that of DMAP. These reactions could be treated as a pseudo-second order kinetics (Figure 2(b)). From the time vs. $1/(1-x)$ plots (x = conversion, $0 \leq x \leq 1$) shown in Figure 2(b), TOF_{50} [turnover factor at 50% conversion, h^{-1} (mol of product/(mol of catalyst \times h))]⁹ was calculated for each catalyst: 3.04 for **1a**, 3.61 for **1b**, 3.57 for **2a**, 531 for **2b** and 278 for DMAP. Although a similar trend that the dihydropyrimido derivative was more active than the dihydroimidazo derivative was observed for **1** and **2**, it was noteworthy that the difference between **2a** and **2b** was much larger than that between **1a** and **1b**.

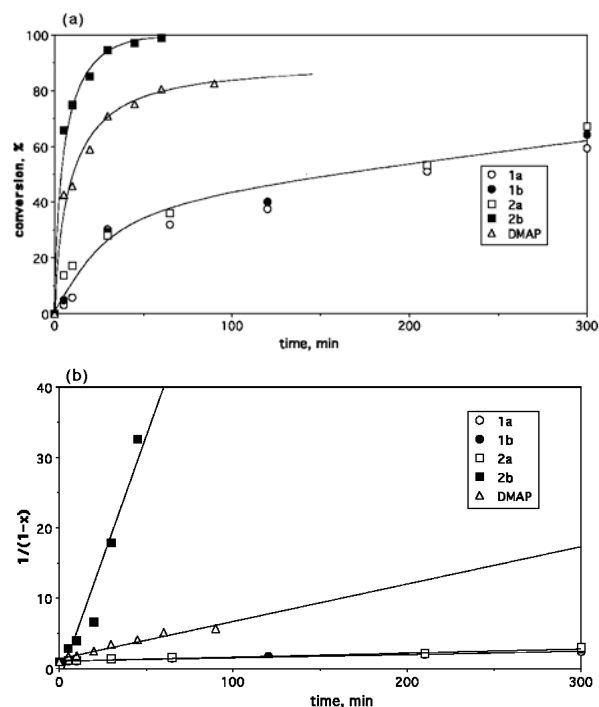
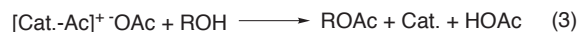
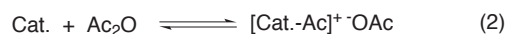


Figure 2. Kinetic study: The reaction was carried out with 5 mol % of **1a**, **1b** or **2a** in a 1.0 M solution, or with 1 mol % of **2b** or DMAP in a 0.1 M solution (see text). (a) time-course of conversion, (b) time vs. $1/(1-x)$ plots.

With these results in hand, we next carried out the stoichiometric reaction of catalyst compounds in CDCl_3 which were analyzed by 500MHz ^1H NMR. The reaction shown in Eq 1 might consist of the following reactions shown in Eqs 2-4, where the reactions of Eqs 5 and 6 among catalyst compound, AcOH and Et_3N may be involved. Regarding Eqs 5 and 6, in all cases, NMR spectra of the 1:1:1 mixture of the catalyst compound, AcOH and Et_3N in CDCl_3 showed peaks of a neutral catalyst compound and acetic acid salt of triethylamine quantitatively.



Next, NMR experiments of the reaction of catalyst compounds and Ac_2O were carried out. The addition of 1 equiv of Ac_2O to DMAP in CDCl_3 at room temperature gave no new peak other than DMAP and Ac_2O (data not shown), the results of which indicate that an acylated intermediate $[\text{DMAP-Ac}]^+ \cdot \text{OAc}$ becomes thermodynamically much less stable than DMAP, due to loss of aromaticity of the pyridine ring. Meanwhile, as shown in Figure 3, the mixture of benzothiazole derivatives

2 and 1 equiv of Ac₂O generated a considerable amount of the corresponding acylated compounds [Cat.-Ac]⁺OAc. It can be explained by assuming that the acylated compounds of **2a** and **2b** may be stabilized by aromaticity of the newly formed thiazole structure and resonance effect of the nitrogen cation by the benzene ring. Interestingly, although the spectra of a mixture of **2b** and Ac₂O involved one set of peaks corresponding to an acylated intermediate, those of a mixture of **2a** and Ac₂O were much more complicated. The different behaviors thus observed for **2a** and **2b** cannot be explained at this time but may reflect the difference of their relative catalytic activity.

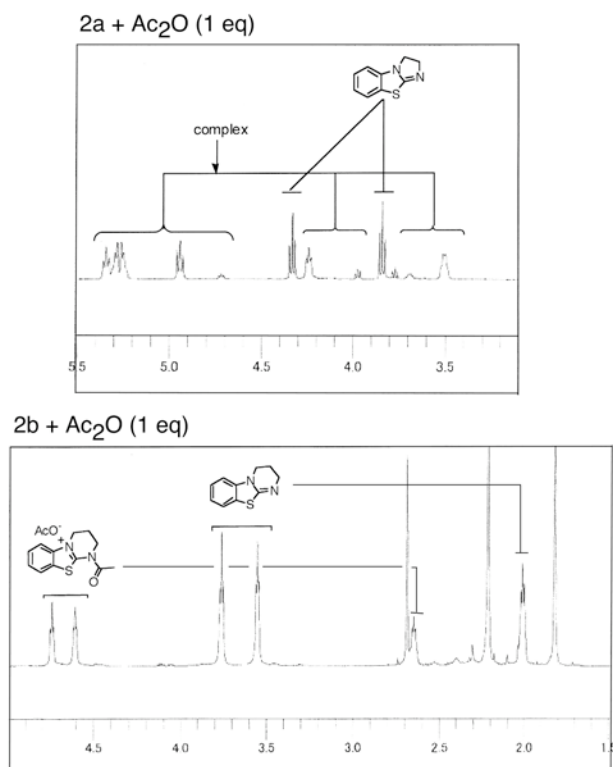


Figure 3. 500MHz ¹H NMR spectra for a 1:1 mixture of **2a** and Ac₂O (the upper spectra) or for a 1:1 mixture of **2b** and Ac₂O (the lower spectra) in CDCl₃ at room temperature.

To consider the large difference of catalytic reactivity between **2a** and **2b**, we tried to estimate energy differences among catalyst compounds and their acylated intermediates by calculation using molecular mechanics (MM2).¹⁰ From the results shown in Figure 4, acylation of **2b** seems to be much easier than that of other compounds, and [DMAP-Ac]⁺ may be expected to be relatively less stable. These assumptions are in good agreement with the results of NMR experiments for Eq 2 mentioned above. Moreover, it may be considered that pyrimido derivatives **1b** and **2b** could be acylated easier than the corresponding imidazo derivatives **1a** and **2a**, respectively. Acylated **2b** is much more stable than acylated **2a**, presumably due to a larger ring strain of acylated **2a** than that of acylated **2b**. Although confirmation of details of the mechanism must

await further study, it may totally be assumed that easy generation of the acylated intermediate from **2b** due to a large energy gain by delocalizing stabilization of the generated positive charge might mainly affect the catalytic activity of **2b**.

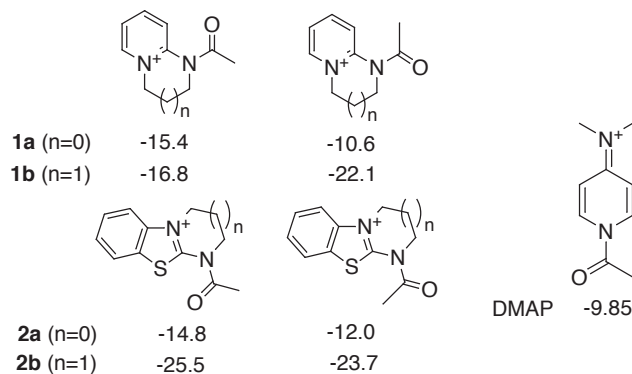


Figure 4. The preliminary results of calculation of energy differences between catalyst compound and the acylated derivative: Cat. to [Cat.-Ac]⁺ (kcal/mol).

In summary, we have investigated the reactivity of annulated benzothiazol-2-ylidenamines **2** as an acyl transfer catalyst and found that the dihydropyrimido derivative of benzothiazole **2b** exhibited extremely high activity, which might be a good candidate as a reactive core for development of an asymmetric catalyst.

Acknowledgement

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- 2a**: ¹H NMR (600 MHz, CDCl₃) δ 7.26 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 4.35 (t, *J* = 8.9 Hz, 2H), 3.85 (t, *J* = 8.9 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 162.7, 138.2, 127.3, 124.7, 122.8, 122.5, 110.7, 42.6, 40.9. **2b**: ¹H NMR (600 MHz, CDCl₃) δ 7.27 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 7.6, 8.2 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 3.79 (t, *J* = 6.2 Hz, 2H), 3.55 (t, *J* = 5.7 Hz, 2H), 2.01 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 159.2, 140.0, 126.2, 122.4(2C),

- 121.9, 108.1, 44.1, 42.6, 19.3. **1b**: ^1H NMR (500 MHz, CDCl_3) δ 6.85 (d, $J = 6.9$ Hz, 1H), 6.67 (t, $J = 6.3$ Hz, 1H), 6.04 (d, $J = 9.8$ Hz, 1H), 5.57 (t, $J = 6.9$ Hz, 1H), 3.74 (t, $J = 6.3$ Hz, 2H), 3.28 (t, $J = 6.3$ Hz, 2H), 1.77 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.0, 136.8, 132.9, 122.7, 103.2, 49.5, 43.3, 20.0.
6. Version 1.63 for Macintosh was used. This is available *via* the Internet at <http://rsb.info.nih.gov/nih-image/download.html>.
7. $d[\text{ROH}]/dt = k[\text{ROH}][\text{Ac}_2\text{O}]$. When $[\text{ROH}]_0 = [\text{Ac}_2\text{O}]_0 = a$ and $x = \text{conversion}$ ($0 \leq x \leq 1$), $1/[a(1-x)] = kt + 1/a$. If $k' = ak$ (constant), $1/(1-x) = k't + 1$.
8. 0.50 mmol / [time (h) for 50% conversion][mmol of catalyst]
9. Line-fitting was performed using a graph software Cricket Graph 1.3.2 for Macintosh.
10. The MM2 calculations resulting in the data in Figure 4 were performed using CAChe software (Quantum 4.9 for Macintosh, Fujitsu Ltd.).