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Dramatic Acceleration of an Acyl Transfer-Initiated Cascade by Using Electron-Rich Amidine-Based Catalysts

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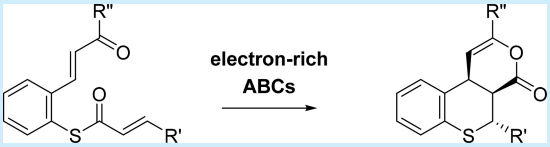
Supporting Information

ABSTRACT: A tandem rearrangement of α,β-unsaturated thioesters into tricyclic ene-lactones fails with conventional amidine-based catalysts, but becomes possible when their electron-rich analogs are employed. A highly diastereo- and enantioselective version of this process has been developed using H-PIP **1b**, a chiral catalyst prepared over a decade ago, but never utilized since its disclosure.



Enantioselective acyl transfer catalysis has become an indispensable tool of asymmetric synthesis.[1] Amidine-based catalysts (ABCs) introduced by our group in 2004 (cf. **1a**, Figure 1)[2a] have demonstrated their efficacy in a variety of transformations employing this mode of catalysis.[3] Among the many structural variations of the basic catalyst design, catalysts **2**,[2b] **3**,[2c] and **4a**−**c**[2d−f] have enjoyed the highest success rate. However, even they are not without their limitations. Most of their reported applications rely on the use of relatively reactive acyl donors, such as anhydrides or activated esters. In this letter, we demonstrate that electron-rich ABCs succeed in activating substrates that remain out of reach of their "conventional" counterparts.

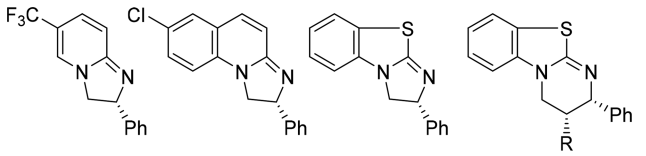
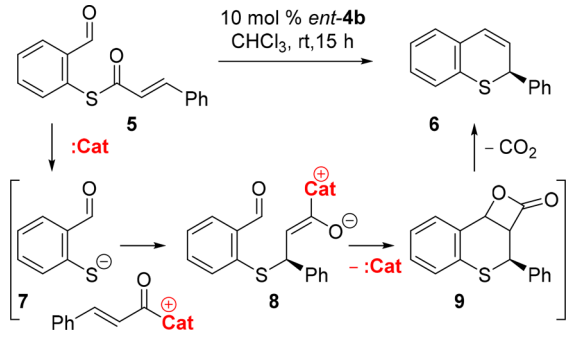


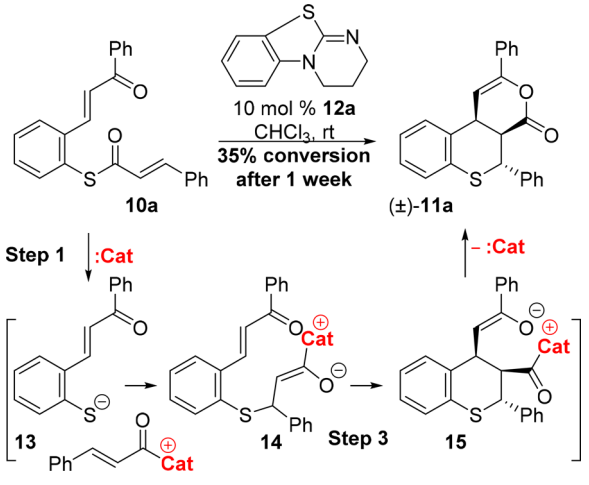
Figure 1. Representative chiral ABCs.[3]

Recently, we reported a highly enantioselective synthesis of 2-substituted thiochromenes **6** from *o*-(acylthio)benzaldehydes **5** (Scheme 1).[4] Encouraged by its success, we set out to explore a related process that would proceed via a formal [4 + 2] cycloaddition (Scheme 2). When the enone substrate **10a** was subjected to acyl transfer catalysis by the achiral catalyst DHPB **12a**,[5] the expected tricyclic ene-lactone **11a** formed with good diastereoselectivity. To our dismay, however, the reaction proceeded excruciatingly slowly, reaching only 35% conversion in 7 days. This did not bode well for the development of the asymmetric version of the new process. Indeed, in the presence of the chiral catalyst **4b**[2e] no signs of the desired reaction could be discerned after 1 week.

Scheme 1. Synthesis of Thiochromenes



Scheme 2. New Tandem Transformation



We reasoned that two steps in the new tandem may be responsible for the drastically diminished overall reaction rate: activation of the thioester (Step 1) and the Michael addition of

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the zwitterionic enolate to the enone moiety (Step 3). Employing a more Lewis basic catalyst was expected to accelerate both of the problematic steps. With this in mind, we performed a DFT study using a nonpolar solvent model[6] to compute the enthalpies of the isodesmic acyl transfer reaction between the *N*-acetyl-DHPB cation and several types of achiral ABCs (Figure 2).[7] As expected, derivatives of DHPB bearing

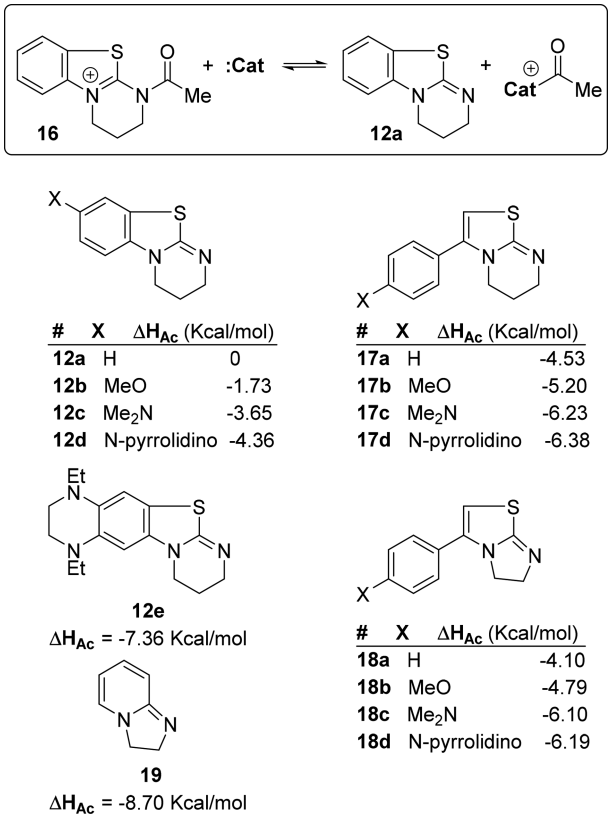
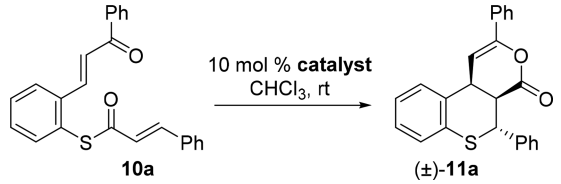


Figure 2. Relative acylation enthalpies of some achiral ABCs.

electron-donating substituents on the benzene ring (**12b–e**) produced strongly negative values. More interestingly, bicyclic isothioureas **17a** and **18a** disclosed recently by Okamoto et al.[8] displayed considerably higher intrinsic Lewis basicities than DHPB itself and were further enhanced by substitution on the phenyl group (**17b–d**, **18b–d**). Finally, the highest Lewis basicity was predicted for DHIP **19**—the very first ABC that served as the starting point for designing this whole class of catalysts.[3a] With these results in hand, we synthesized the catalysts shown in Figure 2 and tested their activity in the rearrangement of thioester **10a**.[9]

Electron-rich derivatives of DHPB **12b–e** produced considerably increased reaction rates compared to that of the parent compound (Table 1, entries 2–5 vs 1). Bicyclic isothioureas **17** and **18** (entries 6–13) were even more active—much more than DHPB derivatives with similar computed acylation enthalpies (see, e.g., **17a** and **18a** vs **12d** or **17d** and **18d** vs **12e**). These results were all the more remarkable given the fact that catalysts **17a–c** and **18a** performed slower than DHPB **12a** in the acylation of 1-phenylethanol with anhydrides in Okamoto's study.[8] Finally, DHIP **19** displayed catalytic activity comparable to the fastest bicyclic isothioureas (entry 14). This was in sharp contrast to its poor performance in the acetylation of alcohols observed in

Table 1. Achiral Catalyst Survey[a]



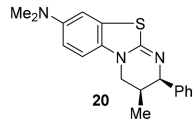
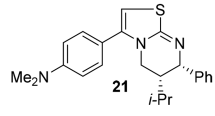
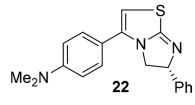
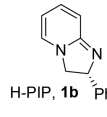
entry	catalyst	$t_{1/2}$, min	relative rate	dr
1	**12a**	ND[b]	1	ND
2	**12b**	7600	3.20	ND
3	**12c**	998	22.6	ND
4	**12d**	841	31.3	ND
5	**12e**	77	221	97:3
6	**17a**	92	210	95:5
7	**17b**	54	308	96:4
8	**17c**	27	574	96:4
9	**17d**	28	537	96:4
10	**18a**	184	98	93:7
11	**18b**	96	180	93:7
12	**18c**	40	392	92:8
13	**18d**	33	509	91:9
14	**19**	38	431	96:4

[a]Conditions: 0.1 M **10a**, 0.01 M catalyst, $CDCl_3$, rt. [b]The reaction stalled after 7 days at 35% conversion.

our early studies: several hundred times slower than DHPB![5b] Even though this dramatic reversal in the relative activity of the two catalysts was easy to rationalize mechanistically, given the much lower reactivity of the thioester moiety compared to an anhydride, we were nevertheless surprised by the magnitude of this effect.

Encouraged by these findings, we synthesized chiral catalysts **20–22** and **1b** and tested them in the enantioselective variant of the rearrangement (Table 2). Catalyst **20**, the dimethylamino derivative of HBTM-2 **4b**, provided the highest enantioselectivity, but required 5 days to reach completion (entry 1). Surpisingly, **21** gave only poor ee and displayed the lowest activity (entry 2), despite the fact that its analog **17c** was

Table 2. Chiral Catalyst Survey[a]

entry	catalyst	time	yield (%)	dr	ee (%)
1		5d	77	97:3	–99
2		4d	32	ND	–42
3		17h	83	98:2	96
4		17h	93	97:3	95

[a]Conditions: 0.2 M **10a**, 0.02 M catalyst, $CDCl_3$, rt.

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the fastest among the achiral catalysts tested (Table 1, entry 8). Gratifyingly, both **22**[8] and H-PIP **1b**[2a] produced excellent enantioselectivity and good activity (entries 3 and 4). Because **1b** was the easiest of the four catalysts to prepare, we selected it to test the substrate scope of our new transformation (Figure 3).

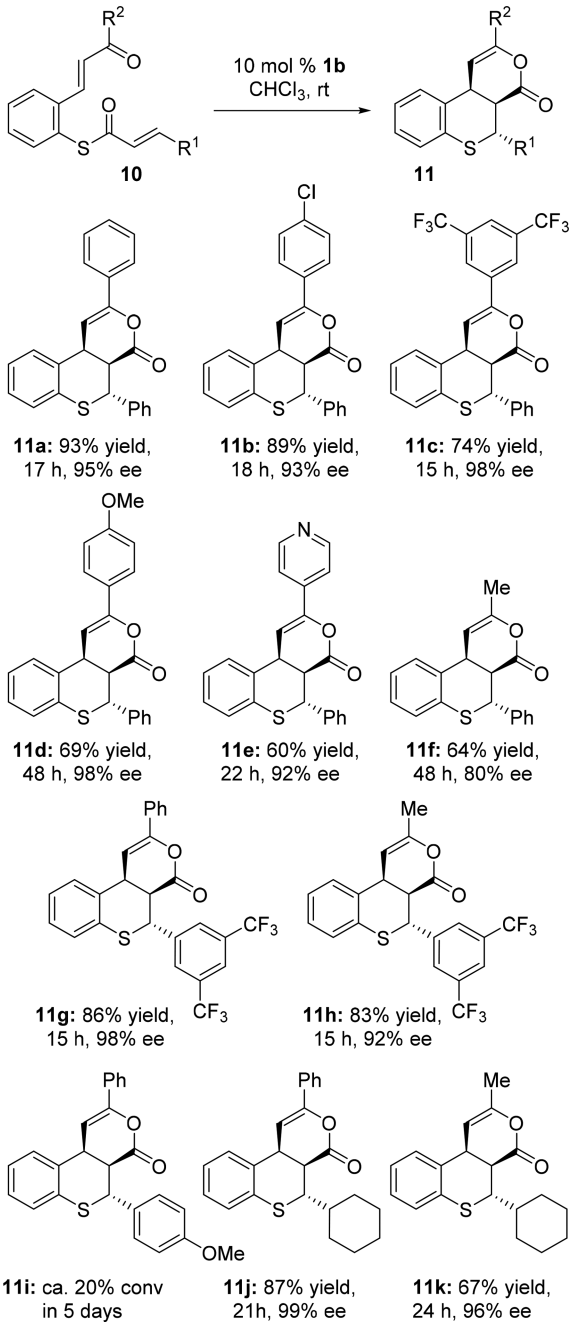

Figure 3. Substrate scope.

Substrates with both electron-deficient and -rich aryl R^2 substituents on the enone moiety (**11a**–**e**, **g**, **j**), as well those with a methyl group (**11f**, **h**, **k**), reacted successfully. Unsubstituted phenyl (**11a**–**f**) or an electron-deficient aryl (**11g** and **h**), as well as a cyclohexyl group (**11j** and **k**) at the R^1 position, were also well-tolerated. A *p*-methoxyphenyl group, however, resulted in a significant loss of reactivity (cf. **11i**), evidently due to its deactivating effect on the thioester carbonyl group. Excellent diastereoselectivities (dr ca. 20:1) were observed in all thiochromanes produced in the reaction. Enantioselectivities above 90% ee were obtained in all cases but one (**11f**). Finally, to demonstrate the scalability of the rearrangement, we carried it out on 1 g (2.7 mmol) of substrate **10a** and obtained an 86% yield and 95% ee.

In conclusion, we have developed a new highly enantioselective and waste-free tandem transformation of thioesters into fused thiochromanes. A simple DFT study has enabled us to identify the most promising classes of catalysts to test and thus greatly facilitated our undertaking. It is somewhat ironic that the best results were achieved with H-PIP **1b**, the very first chiral ABC to be synthesized. In our original study 13 years ago, which focused on the acylation of benzylic alcohols with anhydrides, H-PIP proved to be considerably inferior to its more electron-deficient derivatives (e.g., CF_3–PIP **1a**, Figure 1) and, as a result, has been completely neglected by the asymmetric catalysis community since its disclosure. Its success in the present study underscores the potential of H-PIP and other electron-rich ABCs in activating moderately reactive acyl donors, such as thioesters. Studies in this direction are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03044.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(9) See Supporting Information for the synthesis of all catalysts and substrates.
(10) While this manuscript was under consideration, a paper was published describing the same transformation promoted by an NHC catalyst: Lu, H.; Zhang, J.-L.; Liu, J.-Y.; Li, H.-Y.; Xu, P.-F. *ACS Catal.* **2017**, *7*, 7797.

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