Urea-catalyzed transthioesterification: towards a new kinetic resolution methodology

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Dedicated to Professor Siegfried Blechert on the occasion of his 65th birthday

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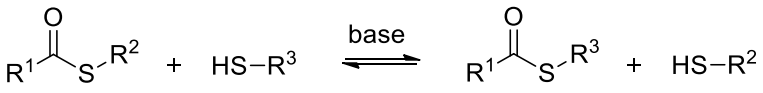
Abstract

The efficient catalysis of transthioesterification reactions by a urea-based (but not thiourea-based) hydrogen bond donor in the presence of an amine co-catalyst has been demonstrated for the first time. The process is of wide substrate scope and the efficient exchange between unhindered achiral thiols and bulkier chiral thioesters is possible in the presence of the catalyst, which is a key first milestone towards the development of kinetic resolution processes based on transthioesterification processes.

Keywords: Organocatalysis, thioester, transthioesterification, urea, hydrogen bonding

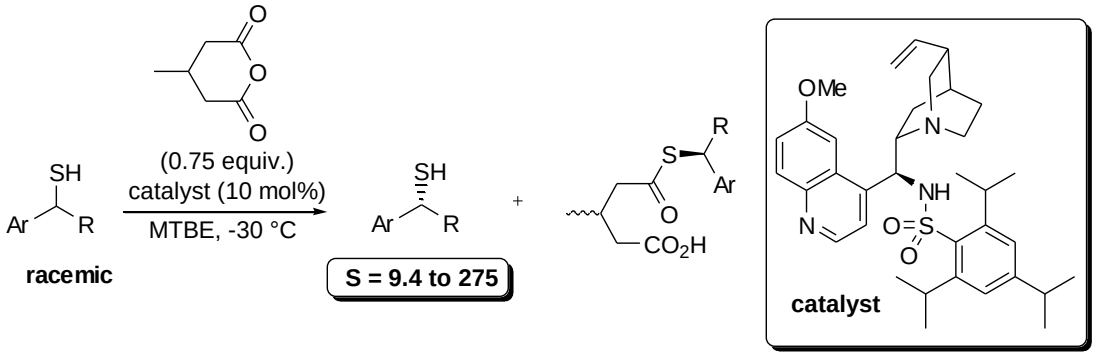
Introduction

Transthioesterification is a reversible process involving the reaction of a thioester with a thiol in the presence of base (Scheme 1).[1,2] This exchange process is an essential component of fatty acid biosynthesis[3] and also constitutes the rate-determining step of the powerful Native Chemical Ligation (NCL)[4,5] peptide coupling methodology. These processes are often slow in the absence of a strong base and/ or strongly activated thiolate leaving group, which makes the design of catalysts for this reaction potentially desirable. To the best of our knowledge, efforts thusfar from a catalyst design standpoint have been confined to the use of a substituted thiophenol-based nucleophilic catalyst, which, when utilized in large excess, exchanges with a thioester derived from an alkyl thiol and participates in relatively fast thioesterification.[6,7]



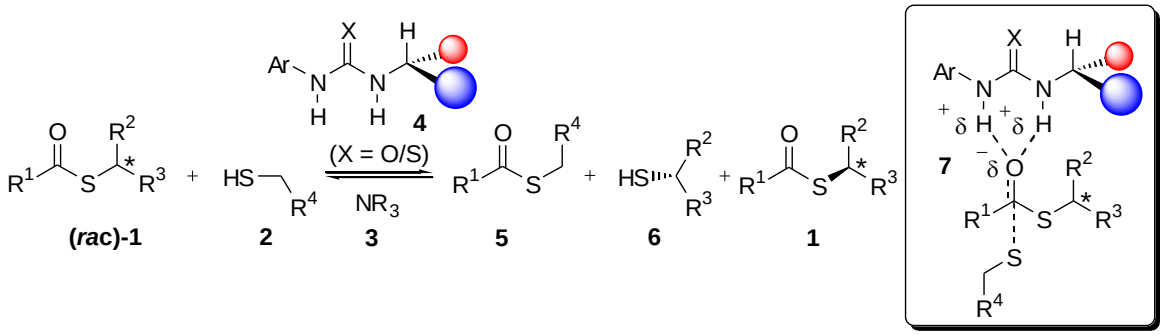
Scheme 1. Transthioesterification.

We recently reported the first examples of the organocatalytic acylative kinetic resolution of *sec*-thiols (Scheme 2).[8] In this reaction, a thiol is treated with substoichiometric amounts of 3-methyl glutaric anhydride in the presence of a cinchona alkaloid-derived organic bifunctional organocatalyst. High selectivity (S = k_{fast}/k_{slow}) could be obtained if the *sec*-thiol was benzylic in nature, however, when the thiol stereogenic centre does not incorporate an aromatic substituent almost racemic acylation results.



Scheme 2. Organocatalytic acylative kinetic resolution of thiols.

In an attempt to widen the scope of this new organocatalytic process we have been searching for alternative methods of bringing the acyl-transfer step under the influence of an organic catalyst. Our group have reported several examples of the use of (thio)urea catalysts to stablise developing negative charge in the transition states of both 1,2-[9] and 1,4-addition[10] reactions (in addition to processes acting on sp^3 centres[11]), and we therefore postulated that it could be possible to promote thiol acylation *via* transthioesterification in the presence of a hydrogen-bond donating catalyst and a base (Scheme 3). For instance, if it could be demonstrated that (thio)ureas could intervene in a thioesterification process, it could be subsequently feasible to design a process whereby the reaction of a chiral thioester **1** with an achiral (relatively unhindered) thiol **2** in the presence of an amine base **3** and a (thio)urea catalyst **4** would furnish the achiral thioester **5** and the resolved, exchanged products **1** and **6** (*e.g. via* a transition state assembly such as **7**, Scheme 3).



Scheme 3. Proposed kinetic resolution of thiols *via* transthioesterification.

We thus set out to conduct a study of transthioesterification *with the objective of first developing an achiral (thio)urea-catalyzed variant of the process*. Specifically, we wished to ascertain if: a) a (thio)urea catalyst system could promote the reaction, b) a base co-catalyst is required and c) conditions could be identified under which the exchange could proceeded exclusively *via* a (thio)urea catalyzed pathway.

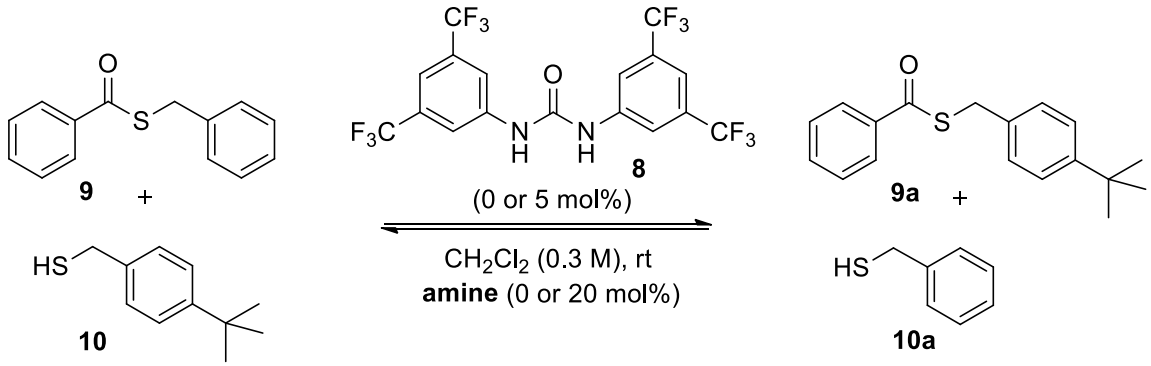
Results and Discussion

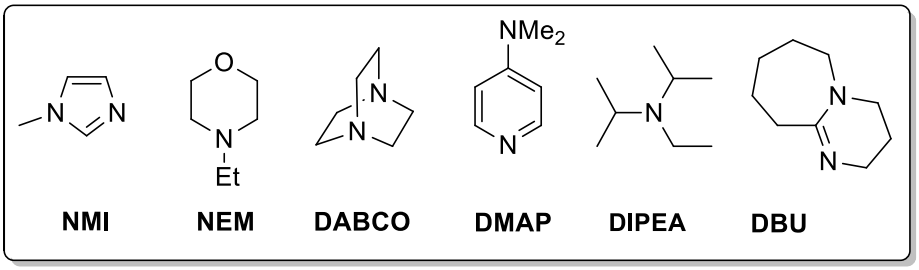
Our preliminary experiments were focused on establishing the catalytic competence of a urea catalyst (**8** - which we have shown to be useful in a variety of catalytic processes previously) in a simple thioester exchange reaction. The results of this study are outlined in Table 1 below. We chose to study the exchange between thioester **9** and thiol **10**. In this reaction the attacking nucleophile and the thiol leaving group possess very similar steric and electronic characteristics, thus we would expect a finely balanced catalyzed reversible process with equal ratios of exchanged products (*i.e.* **9a** and **10a**) and starting materials (*i.e.* **9** and **10**) at equilibrium.

In the absence of any additive, no reaction occurs (entry 1). The addition of urea **8** (at 5 mol% levels) also failed to result in any detectable exchange (entry 2). Next, the effect of adding amines of variable basicity was evaluated. While the mildly basic *N*-methyl imidazole (NMI) proved ineffectual alone (at 20 mol% levels), its use in conjunction with **8** (5 mol%) led to the formation of trace amounts of **9a** after 44 h reaction time (entries 3 and 4). The marginally more basic *N*-ethyl morpholine was also unable to mediate the reaction in the absence of **8** (entry 5), while slightly elevated levels of product could be observed in its presence (entry 6). Increasing the basicity of the amines further led to faster rates of exchange: DABCO, DMAP and DIPEA all promoted the reaction almost to equilibrium inside 44 h in conjunction with the urea catalyst, while promoting the formation of less than 3% exchange in the same time period in the absence of **8** (entries 7-12). The considerably more basic catalyst DBU (estimated pK_a = *ca*. 13) is active enough to promote rapid equilibration of the system even in the absence of the urea co-catalyst (entries 13-14). We would suggest that in this case specific-base catalysis (involving the formation of significant levels of the cleanly deprotonated thiol) is likely to be in operation.

These findings were encouraging: it is clear that a binary catalyst system involving the use of low loadings of urea **8** and an amine co-catalyst (the pK_a of the conjugate acid of which should be closely matched to that of the attacking nucleophile – *e.g*. benzyl mercaptan pK_a = 9.4[12]) can efficiently promote the exchange under conditions where use of the amine co-catalyst alone fails.

Table 1. Preliminary studies on the urea-catalyzed transthioesterification process





Entry	Amine	pK_a[a]	Cat. **8** Loading (mol%)	t = 0 h	Yield **9a**/**10a** (%)[b] t = 1.5 h	t = 20 h	t = 44 h	**9** : **9a**
1	-	-	0	0	0	0	0	100:0
2	-	-	5	0	0	0	0	100:0
3	NMI	7.1	0	0	0	0	0	100:0
4	NMI	7.1	5	0	0	0	1.2	99:1
5	NEM	7.8	0	0	0	0	0	100:0
6	NEM	7.8	5	0	0	<2	2.7	96:4
7	DABCO	8.8	0	0	2.3	7.2	8.1	90:10
8	DABCO	8.8	5	0	10.6	27.4	32.1	66:34
9	DMAP	9.7	0	0	0	1.5	2.7	96:4
10	DMAP	9.7	5	0	2.1	22.4	32.8	65:35
11	DIPEA	11.4	0	0	0	1.1	2.4	98:2
12	DIPEA	11.4	5	0	4.0	42.0	38.1	50:50
13	DBU	N/A	0	45.0	45.2	44.0	44.3	50:50
14	DBU	N/A	5	45.1	46.2	43.8	44.6	50:50

[a]Refers to the pK_a of the corresponding conjugate acid in H_2O at 25 °C.[13] [b]Determined by ^1H NMR spectroscopy using (*E*)-stilbene as an internal standard.

The strong performance of DABCO in these reactions is noteworthy, which exhibited an activity profile reproducibly similar to that associated with the use of DMAP – a catalyst

approximately 10 times as basic (Table 1, entries 7-10). We ascribe this effect to a somewhat unexpected source: the existence of a nucleophilic catalysis pathway in reactions mediated by DABCO. While monitoring these reactions using ^{1}H NMR spectroscopy, we observed two sets of triplets (δ = 3.30 ppm and 3.85 ppm) which seemed consistent with the formation of an acyl-ammonium ion from reaction between DABCO and **9**. To investigate this possibility we treated DABCO with one equivalent of benzoyl chloride in dichloromethane to generate the benzoylated DABCO (**DABCO-Bz**, Figure 1A), which possesses very similar[14] spectral characteristics to the intermediate identified in the exchange reaction promoted by DABCO (see Figure 1B). This supports the theory that DABCO is able to (at least partially) promote this reaction *via* a nucleophilic catalysis mechanism.[15]

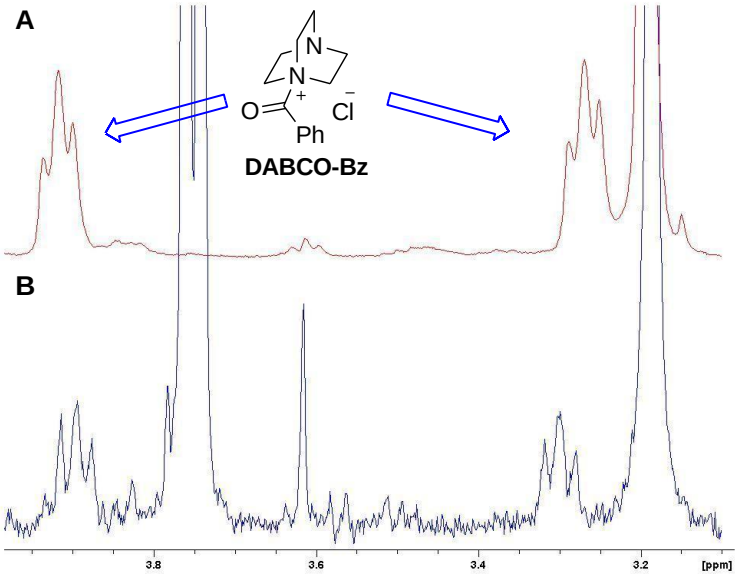
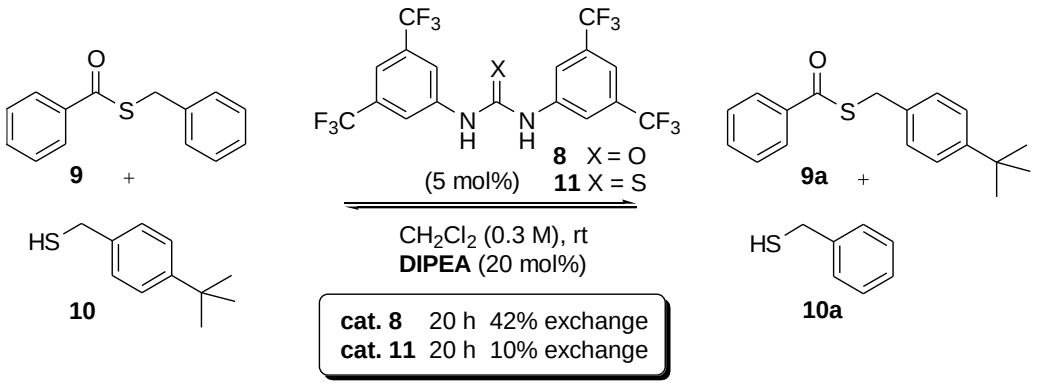


Figure 1. A: ^{1}H NMR spectrum obtained after addition of benzoyl chloride (1.0 equiv.) to DABCO. **B:** ^{1}H NMR spectrum of the transesterification reaction catalyzed by **8** and DABCO (Table 1, entry 8).

In many (but not all) transformations promoted by (thio)urea-based catalysts the thiourea proves a superior catalyst than its urea analogue. In this case we found the **11**, the thiourea analogue of **8**, to be a particularly poor promoter of the reaction.[16]

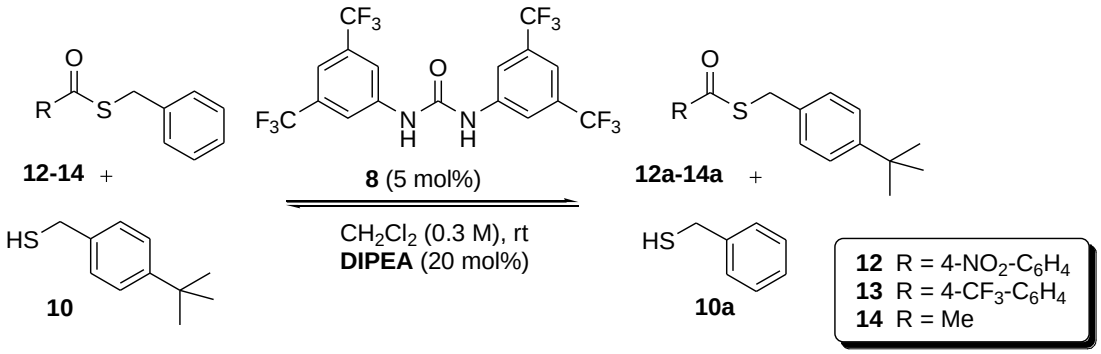
We next examined the effect of the thioester acyl group on reaction rate (Table 2). While the use of activated benzoyl moieties (*i.e.* **12** and **13**) led to faster reactions rates, predictably the rate of the reaction catalyzed by DIPEA alone also increased (entries 1-4). Since the objective of this study is to identify conditions under which the catalysis proceeds only in the presence of the urea, these substrates were not evaluated further. Gratifyingly, the thioester bearing an *S*-acetyl group (*i.e.* **14**) underwent no exchange in the presence of DIPEA alone, but would participate in the transthioesterification process in the presence of **8**. This is an ideal situation from a practicality standpoint: the background amine-catalyzed reaction was now eliminated through the use of *S*-

acetyl compounds; which are undoubtedly the most conveniently prepared class of thioester *via* either Mitsunobu or S_N2 substitution chemistry.



Scheme 4. Comparison of urea and thiourea-mediated transthioesterification.

Table 2. Evaluation of the influence of the thioester acyl-moiety



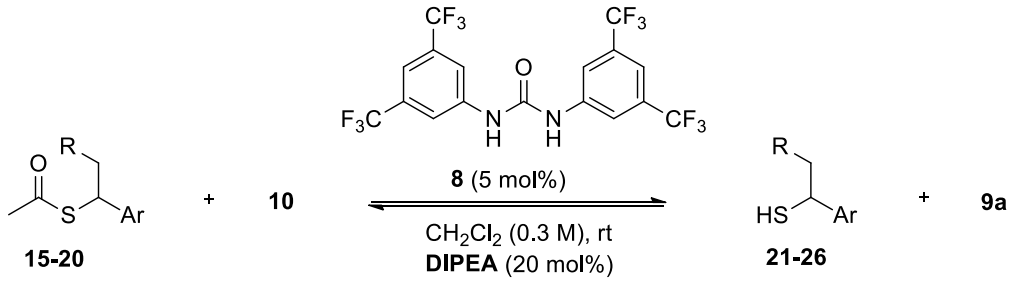
Entry	Thioester	Cat. **8** Loading (mol%)	t = 0 h	Yield **12a-14a** t = 1.5 h	(%)[a] t = 20 h	**12-14 : 12a-14a**
1	**12**	0	0	9.9	25.1	64:36
2	**12**	5	3.6	44.2	41.1	50:50
3	**13**	0	0	0	3.0	95:5
4	**13**	5	<2	44.9	43.1	50:50
5	**14**	0	0	0	0	100:0
6	**14**	5	0	3.6	33.4	43:57

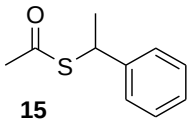
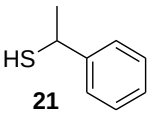
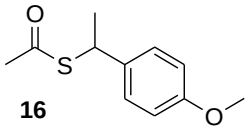
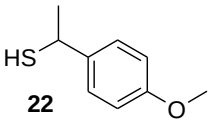
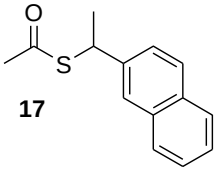
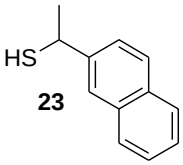
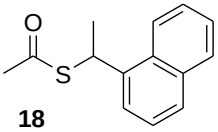
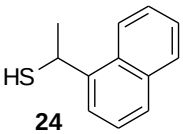
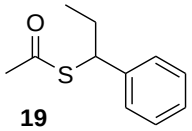
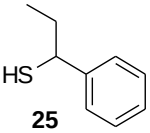
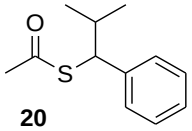
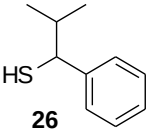
[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard.

With a view towards the eventual application of this process as a platform upon which to develop kinetic resolution methodologies, it was necessary to establish if urea-catalyzed transthioesterification involving chiral substrates is possible. To this end, we reacted thioesters **15-20** with achiral thiol **10** in the presence of urea **8**. We were pleased to observe the catalyzed

exchange reaction proceed in all cases to form thiols **21-26** (Table 3). The relatively unhindered chiral thioesters **15**, **16** and **17** underwent smooth exchange (entries 1-3). Substrate **18** - characterized by a bulkier aromatic substituent - also participated in thioester exchange to yield thiol **24** in good yield[17] (entry 4). Augmenting the size of the aliphatic substituent at the chiral centre (*i.e.* substrates **19** and **20**, entries 5-6) unsurprisingly retards the rate of exchange; however the hindered thiols **25** and **26** are formed in appreciable amounts.

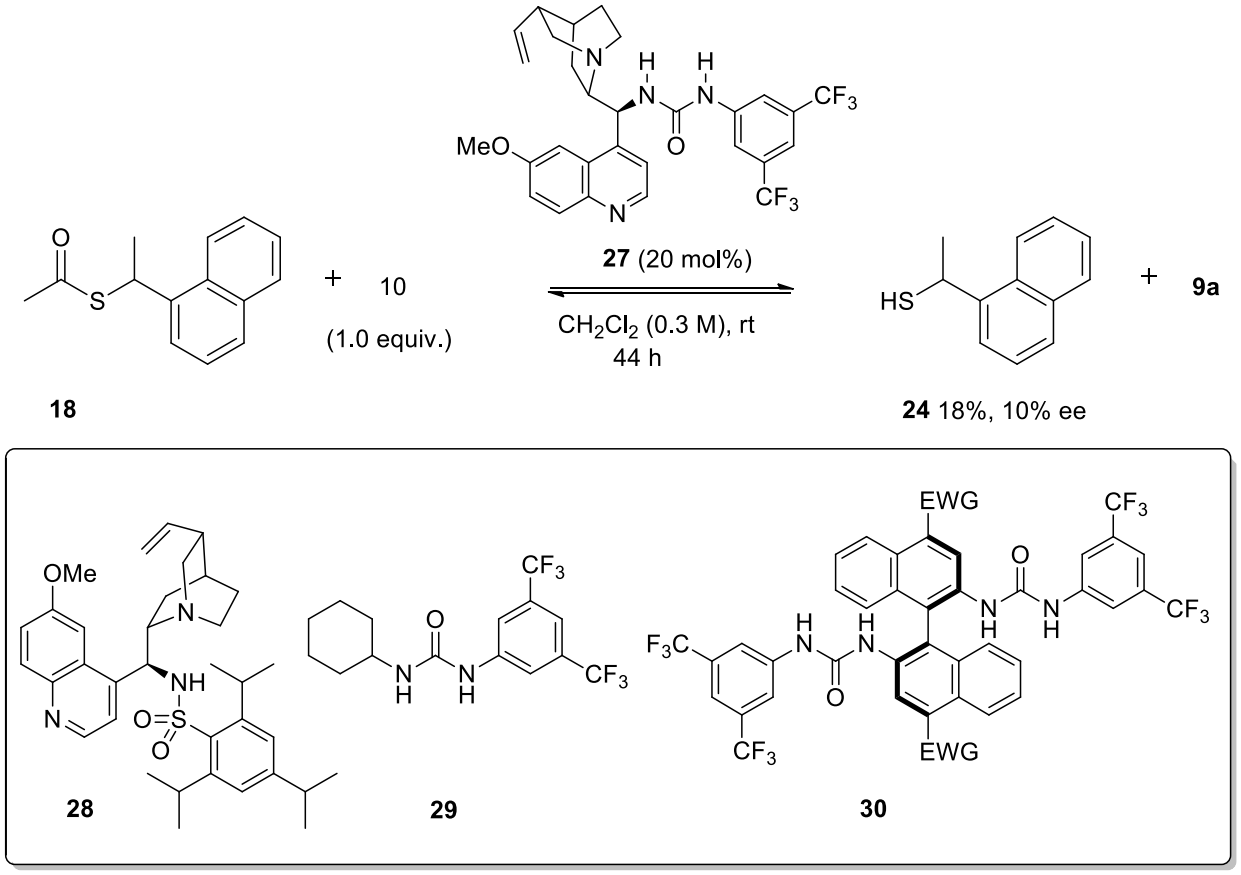
Table 3. Urea catalyzed transthioesterification of chiral thioester substrates



Entry	Thioester	Thiol	Yield (%)[a] t = 20 h	t = 44 h
1	 **15**	 **21**	35	50
2	 **16**	 **22**	40	52
3	 **17**	 **23**	21[b]	32
4	 **18**	 **24**	41	54
5	 **19**	 **25**	33	40
6	 **20**	 **26**	24	37

[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b]Average of two experiments

Finally, we carried out preliminary investigations into the development of a kinetic resolution protocol based on transthioesterification (Scheme 5). The racemic chiral thioester **18** was treated with achiral thiol **10** in the presence of the chiral bifunctional catalyst **27** at 20 mol% loading (Scheme 5).[18] The transthioesterification proceeded slowly – reaching only 18% conversion after 44 h – however thiol **24** was formed in 10% *ee* (after trapping with acrylonitrile and CSP-HPLC analysis). While it is clear that this catalyst does not represent an optimal system, these preliminary experiments demonstrate that the design of an artificial catalyst to bring about the kinetic resolution of thiols *via* enantioselective transthioesterification is potentially feasible. The low catalytic activity of the bifunctional urea-based catalyst is of interest, we would suggest that the basicity of the quinuclidine nitrogen atom in the presence of the β-urea substituent is not high enough to allow fast catalysis (see Table 1). In addition, it is noteworthy that we found that **29**, which incorporates a single activating *N*-*bis*-3,5-trifluoromethylphenyl unit to be completely inactive as a catalyst. This would imply that catalyst **27** also does not possess the thioester-activating characteristics for the mediation of efficient transthioesterification. The sulfonamide-based catalyst **28** also failed to produce appreciable levels of product in these reactions. At this early juncture it would appear that the design of a binary catalyst system involving a tertiary amine base of sufficient basicity and a chiral *N,N'*-diarylurea (*e.g*. **30**, Scheme 5) would be the way to proceed if fast, enantioselective catalysis is the goal.



Scheme 5. Prototype kinetic resolution process based on transthioesterification.

Conclusions

In summary, we have demonstrated the first examples of urea-catalyzed transthioesterification. A binary catalyst system consisting of the readily available urea **8** (at low loadings) serving as a hydrogen bond donor and DIPEA acting as a base can efficiently mediate the reaction at room temperature. Interestingly, thioureas (which often outperform their urea analogues in hydrogen-bond accelerated reactions) are poor catalysts for this process. A strong correlation between amine basicity and catalyst competency was observed, except in the case of DABCO. Using this amine - which catalyses the equilibrium considerably more efficiently than its conjugate acid pK_a would suggest - evidence was found to support the presence of a concurrent nucleophilic catalysis pathway. Simple *S*-acetyl thioesters are ideal substrates for the reaction, and catalyzed exchange between unhindered achiral thiols and bulkier chiral thioesters has been demonstrated in the absence of any background (uncatalyzed) reaction, which may facilitate the development of kinetic resolution protocols based on this new catalyzed process in the future. A prototype system for such a reaction was developed which furnished an exchanged thiol from a racemic chiral thioester in 10% *ee* at 18% conversion.

Experimental Section

General. Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ (to prevent oxidation of the thiols, $CDCl_3$ was purified by distillation and stored under argon over molecular sieves) referenced relative to residual $CHCl_3$ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F254 slides, and visualized by UV irradiation and $KMnO_4$ staining. Methylene chloride was distilled over calcium hydride and stored under argon. CH_2Cl_2 was distilled over CaH_2 and stored under nitrogen. All reactions were carried out under a protective nitrogen or argon gas atmosphere. In the case of thiol **24**, the absolute configuration was confirmed by comparison of the optical rotation and HPLC retention time with the literature data.[8] Catalysts **8**,[9] **11**,[8] **27**,[19] and thioesters **15**,[8] **16**,[8] **17**,[8] **18**,[8] **19**,[8] **20**,[8] were prepared according to literature procedures. Thiols **10** and **10a**, were obtained from commercial sources and used without further purification.

General procedure for the (thio)urea mediated transthioesterification

An oven-dried 5 mL round bottom flask equipped with a magnetic stirrer was charged with the appropriate thioester (0.3 mmol), (*E*)-stilbene (54 mg, 0.3 mmol), (thio)urea (0.015 mmol) and the appropriate amine (0.06 mmol) under a atmosphere of nitrogen. CH_2Cl_2 (1 mL) and **10** (56 µL, 0.3 mmol) were then added *via* syringe. The reaction was stirred at room temperature and analyzed periodically by ^1H NMR spectroscopic analysis.

General procedure for the preperation of thioesters.

Benzyl mercaptan (434 µL, 3.7 mmol) was added dropwise *via* syringe to an ice-cooled solution of triethylamine (529 µL, 3.8 mmol), 4-*N*,*N*-dimethylaminopyridine (90 mg, 0.74 mmol) and the appropriate acid chloride (3.7 mmol) in dichloromethane (15 mL). The reaction mixture was allowed to warm to room temperature with continuous stirring. After 12 h the solvent was removed *in vacuo* and the crude residue was purified by flash chromatography on silica gel.

***S*-benzyl benzothioate (9).** Following the general procedure outlined above the product was isolated as a white solid (708 mg, 84% yield), mp 42-43 ºC; (lit.[20] 38 ºC). ^{1}H NMR ($CDCl_3$, 400.13 MHz) 7.97 (d, *J* = 7.7 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48-7.23 (m, 7H), 4.33 (s, 2H).

***S*-benzyl 4-nitrobenzothioate (12).** Following the general procedure outlined above the product was isolated as a pale yellow (414 mg, 41% yield), mp 87-89 ºC. IR ν 3112, 1644, 1599, 1515, 1368, 1345, 1318, 1193, 1106, 920, 844, 768, 708, 690; ^{1}H NMR ($CDCl_3$, 400.13 MHz) 8.29 (d, *J* = 8.5 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.40-7.26 (m, 5H), 4.37 (s, 2H); ^{13}C NMR ($CDCl_3$ 100.61 MHz) 189.9, 150.6, 141.4, 136.7, 129.1, 128.9, 128.4, 127.8, 124.0, 33.9; HRMS calcd. for $C_{14}H_{11}NO_3S$ (M^+): 273.0460. Found: 273.0460.

***S*-benzyl 4-(trifluoromethyl)benzothioate (13).** Following the general procedure outlined above the product was isolated as a white solid (470 mg, 43% yield), mp 47-49 ºC. IR ν 3068, 1947, 1656, 1582, 1496, 1454, 1405, 1315, 1205, 1171, 1112, 1062, 1011, 916, 842, 767, 691; ^{1}H NMR ($CDCl_3$, 400.13 MHz) 8.07 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.41-7.26 (m, 5H), 4.36 (s, 2H); ^{13}C NMR ($CDCl_3$ 100.61 MHz) 190.5, 139.6, 137.4, 134.8 (q, *J* = 33.1 Hz), 129.1, 128.9, 127.8, 127.7, 125.8 (q, *J* = 3.8 Hz), 123.6 (q, 272.1 Hz), 33.7; HRMS calcd. for $C_{15}H_{11}OF_3S$ (M^+): 296.0483. Found: 296.0486.

***S*-benzyl ethanethioate (14).**[21] Following the general procedure outlined above the product was isolated as a colourless oil (320 mg, 52% yield). ^{1}H NMR ($CDCl_3$, 400.13 MHz) 7.33-7.25 (m, 5H), 4.16 (s, 2H), 2.38 (s, 3H); HRMS calcd. for $C_9H_{10}OS$ (M^+): 166.0452. Found: 166.0453.

Enantioselective transthioesterification

A 5 mL round bottom flask with a magnetic stirrer was charged with **18** (138 mg, 0.6 mmol), (*E*)-stilbene (108 mg, 0.6 mmol) and, **27** (69.4 mg, 0.12 mmol). The flask was evacuated and flushed with nitrogen and a nitrogen atmosphere was maintained using a septum and balloon. CH_2Cl_2 (2 mL) was added *via* syringe and the resulting mixture was stirred until all reagents dissolved. The reaction was initiated by the addition of **10** (112 µL, 0.6 mmol) *via* syringe. The reaction was stirred at room temperature and analyzed periodically by ^{1}H NMR spectroscopic analysis. After 44 h, the reaction had proceeded to 18% conversion. Acrylonitrile (394 µL, 6.0 mmol) and triethylamine (417 µL, 3.0 mmol) were added *via* syringe and the reaction mixture was stirred at room temperature. After 3 h the solvents were removed *in vacuo* and the crude residue passed through a plug of silica gel (9:1, hexane:ethyl acetate) to remove the catalyst and yield a micture of a) the thioacetates and b) the Michael adducts from the reaction between the thiols and acrylonitrile. CSP-HPLC analysis of this mixture indicated that **(*R*)-24** (analysed as its adduct with acrylonitrile) was formed in 10% *ee*. HPLC conditions: Chiralcel OD-H column (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min-1, RT, UV detection at 220 nm, retention times: 28.8 min ((*S*)-enantiomer) and 36.9

min ((*R*)-enantiomer). The unreacted thioester **18** (marginally enriched in the (*S*)-enantiomer) was present in 3% *ee*: HPLC conditions: Chiralcel OD-H column (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min-1, RT, UV detection at 220 nm, retention times: 5.8 min ((*S*)-enantiomer) and 8.9 min ((*R*)-enantiomer).

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13. pK_a values (25 °C) are taken from: (a) (DABCO) Hine, J.; Kaufmann, C.; Cholod, S. *J. Am. Chem. Soc*. **1987**, *52*, 2091. (b) (DMAP) Chrystuik, E.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 3040. (c) (DIPEA) Fujii, T.; Nishida, H.; Abiru, Y.; Yamamoto, M.; Kise, M. *Chem. Pharm. Bull*. **1995**, *43*, 1872. (d) (NMI) Appleton, D. W.; Sarkar, B. *Proc. Nat. Acad. Sci. USA* **1974**, *71*, 1686. (e) (NEM) Metzler, D. E.; Metzler, C. M. *Biochemistry: The Chemical Reactions of Living Cells*, Vol. 2, Academic Press, 2001, pp 99-100.
14. Since **DABCO-Bz** possesses a different counteranion to that associated with the putative intermediate in the DABCO-catalyzed process it is perhaps not surprising that the chemical shifts are marginally different. We could show that the putative intermediate is not the conjugate acid of DABCO by comparing the spectrum shown in Figure 1B with that obtained following addition of one equivalent of TFA to DABCO in dichloromethane.
15. It is certainly unexpected that discernible nucleophilic catalysis can be observed using DABCO, but not using the 'hypernucleophilic' DMAP as a catalyst. One possible explanation is that since the pK_a of DMAP is much more closely matched to that of the attacking nucleophile, so a general base-catalyzed process may predominate.
16. It seems likely that the decomposition of **11** under these conditions is problematic.
17. It is noteworthy that the ideal yield for this process from a kinetic resolution perspective is 50%).
18. A separate experiment using 5 mol% catalyst loading conversion reached only 12% conversion after 44 h.
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