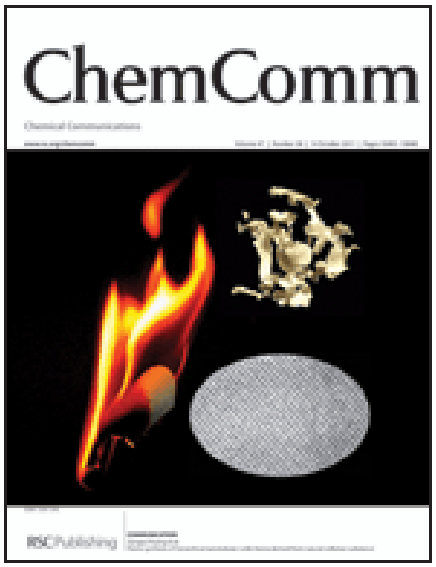

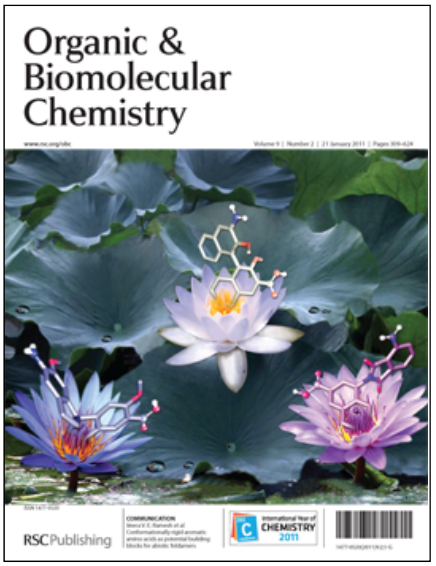

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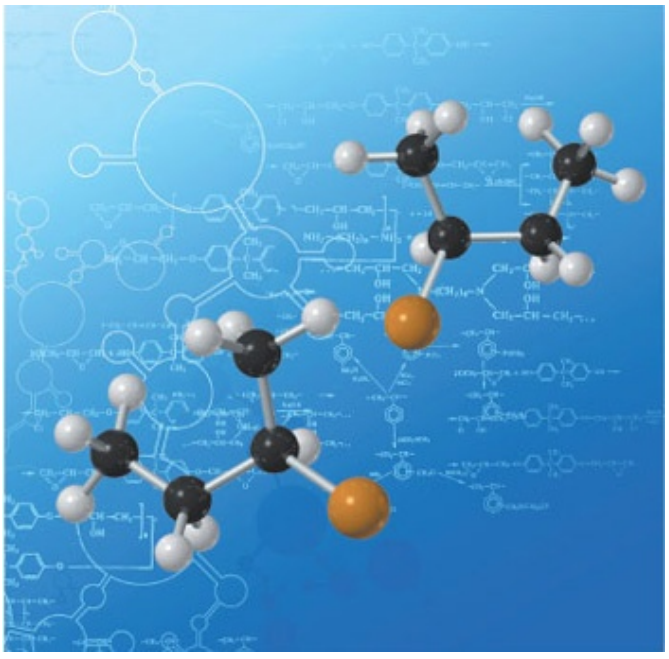

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COMMUNICATION

Organocatalytic asymmetric tandem condensation–intramolecular rearrangement–protonation: an approach to optically active α-amino thioester derivatives†‡

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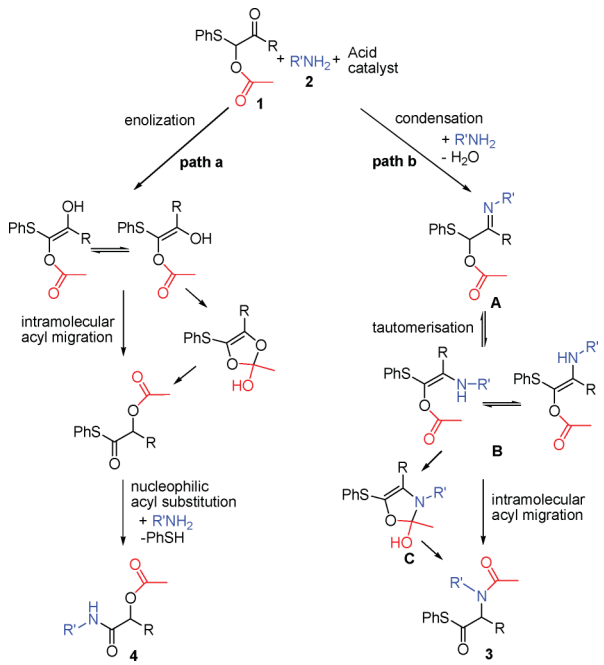
An unprecedented and conceptually novel chiral Brønsted base/Brønsted acid catalytic method for the enantioselective synthesis of α-amino thioesters through a tandem condensation–intramolecular rearrangement–protonation has been developed which provides a number of important synthetic building blocks in good yield and with moderate to good enantioselectivities.

Asymmetric protonations of prochiral enolates have received great attention as efficient methods for the construction of optically active α-substituted carbonyl compounds.[1] The majority of such reactions have been conducted with preformed enolates and a stoichiometric amount of chiral proton source.[2] Recent research witnesses an increasing application of organocatalysis[3] in enantioselective protonation reactions[4] and notably, some enantioselective protonations have been successfully incorporated into tandem or cascade processes to give access to structurally complex molecules.[5] These methods are based on the use of an enol or enolate prepared *in situ* from a suitable precursor in the absence of metal components. In particular, only a few examples of organocatalytic tandem intramolecular rearrangement–enantioselective protonation have been reported.

In pioneering work, Bolm and co-workers developed the enantioselective protonation of an enediol prepared by a base-promoted rearrangement yielding chiral α-hydroxy esters with up to 83% ee.[6] In 2011, Nakamura and Hayashi disclosed a highly enantioselective protonation of ester enolates prepared through the phospha-Brook rearrangement.[7] Recently, we reported an enantioselective organocatalytic rearrangement of α-acyloxy-β-ketosulfides to α-acyloxy thioesters[8] which involves the generation of a transient enolate through a proton abstraction from terminal carbon by a chiral base (cinchona alkaloid),[9] followed by an *in situ* enantioselective protonation. Thus, as a logical extension of our work, we planned the application of this concept to the preparation of chiral α-amino thioesters (Scheme 1, path b). In this respect, it was hypothesized that catalytic asymmetric synthesis of α-amino thioesters could be achieved through an enantioselective protonation-terminated chiral acid-catalyzed intramolecular rearrangement,[10] initiated by an *in situ* imine formation from an α-acyloxy-β-ketosulfide and a primary amine.



Scheme 1 Competitive reaction pathways leading to α-amino thioester **3** and α-acyloxy amide **4** adducts.

Anyway, in planning our synthetic approach, that would start with the formation of the necessary intermediate imine **A**, by the acid catalyzed reaction of **1** with **2**, it was evident that two reaction paths were possible (Scheme 1, path a and b). As a matter of fact, the acid catalyzed reaction of **1** with **2** could lead either to the corresponding α-acyloxy amide **4**, *via* a nucleophilic acyl substitution terminated intramolecular acyl migration (path a), or to the desired α-amino thioesters **3**. This last transformation can occur through the intermediacy of the imine

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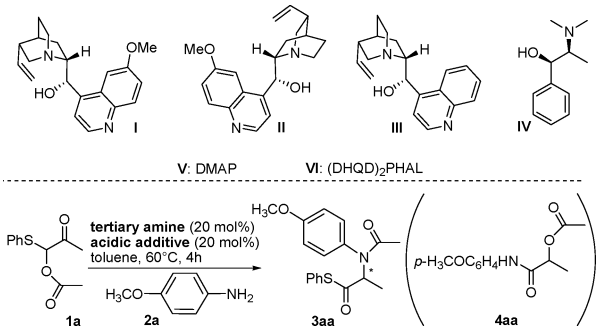
‡ Electronic supplementary information (ESI) available: Experimental protocols, proof of the absolute stereochemical configuration, copies of NMR spectra and HPLC chromatograms. See DOI: 10.1039/c1ob06623d

Table 1 Selected screening results[a]



Entry	Tertiary amine	Acidic additive	Ratio **3aa** :**4aa**[b]	Yield **3aa**(%)[c]	*ee* **3aa**(%)[d]
1	I	TsOH	>20 : 1.0	66	66
2[e]	I	(*R*)-BDHP	2.3 : 1.0	40	74
3	I	(*R*)-TRIP	>20 : 1.0	47	68
4	I	(–)-CSA	>20 : 1.0	48	50
5	I	HCl	>20 : 1.0	79	16
6[f]	I	HBr	>20 : 1.0	20	10
7[g]	I	BzOH	1.0 : 2.8	7	56
8[h]	I	AcOH	1.0 : 8.2	6	50
9[i]	I	*p*-NO_2PhOH	1.0 : 3.3	5	n.d.
10	II	(*R*)-BDHP	>20 : 1.0	34	–70
11	III	(*R*)-BDHP	>20 : 1.0	33	74
12	IV	(*R*)-BDHP	>20 : 1.0	72	–60
13[j]	V	(*R*)-BDHP	10.1 : 1.0	30	rac
14[k,l]	VI	(*R*)-BDHP	7.3 : 1.0	62	–82
15[m,n]	I	(*S*)-BDHP	>20 : 1.0	66	76
16	none	(*R*)-BDHP	>20 : 1.0	49	rac
17[o]	I	none	1.0 : >20	—	—

[a] Conditions: 0.22 mmol of **1a**, 0.27 mmol of **2a**, 0.044 mmol of tertiary amine and 0.044 mmol of acidic additive, 0.5 mL toluene. [b] Determined by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield after chromatography. [d] Determined by HPLC analysis using a chiral stationary column. [e] 16% yield of **4aa** was obtained. [f] At room temperature, 16 h. [g] 19% yield of **4aa** was obtained. [h] 64% yield of **4aa** was obtained. [i] 75% yield of **4aa** was obtained. [j] Reaction carried out over 8h. [k] 8% yield of **4aa** was obtained. [l] Reaction carried out over 24 h. [m] 76% of yield after 24h. [n] When decreasing the amount of catalyst to 10 mol%, a drop in both the reaction rate (27% yield) and ee value of the product **3aa** (72% ee) was observed. [o] 50% yield of **4aa** (78% ee) was obtained. BDHP: 1,1′-Binaphthyl-2,2′-diylhydrogenphosphate; TRIP: 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate. n.d. = not determined.

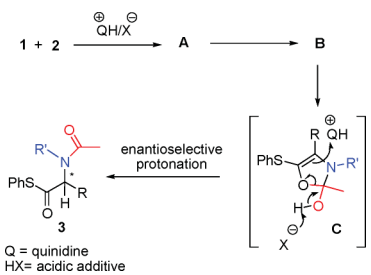
A, its tautomerisation to the corresponding enamines **B** and final intramolecular rearrangement of the *E* geometric isomer (path b).

To test our hypothesis, the reaction between α-acyloxy-β-ketosulfide **1a** and *p*-anisidine **2a** was chosen as a model reaction, for catalyst screening and evaluation (Table 1).

We began our investigations by examining the ability of two organic acids (results not shown in Table 1) to promote the organocatalytic tandem reaction. Pleasingly, when we carried out the reaction with TsOH (10 mol%, in CH_2Cl_2, 40 °C, 16 h) the only isolated compound from the reaction was the α-amino thioester **3aa** (45% yield), and no trace of the corresponding α-acyloxy amide **4aa** was observed. (–)-CSA (20 mol%, in CH_2Cl_2, 40 °C, 16 h) was equally effective, affording the desired adduct **3aa** in good yields (64%) but as a racemate.

On the basis of these observations we decided to develop an asymmetric version of this new reaction and envisioned that a chiral Brønsted base/Brønsted acid combined salt catalyst (bifunctional catalytic system),[11,12] made by reacting the easily available quinidine **I** with an acidic additive, could be an effective catalyst for the enantioselective tandem reaction.

In fact, we speculated that protonation of quinidine **I** by an acid derivative would generate a chiral ion pair as the active catalytic species wherein the anion, provided by the acid component of the



Scheme 2 Working mechanistic hypothesis of cooperative catalysis for the asymmetric synthesis of α-amino thioesters **3**.

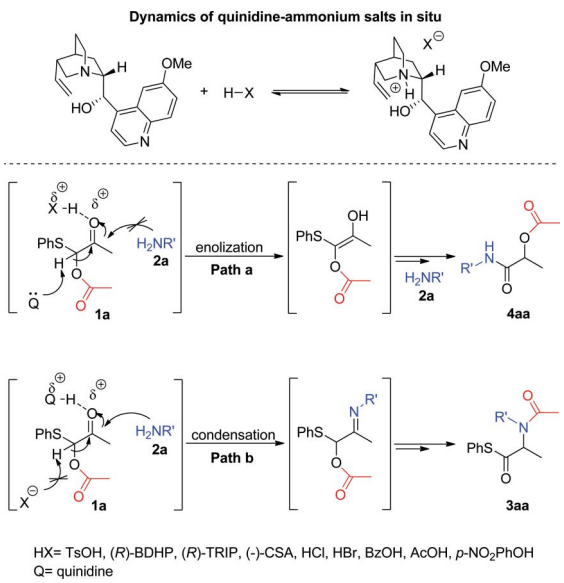
base/acid combined salt, would activate the transient intermediate **C** toward an *in situ* transfer of the proton, in a stereoselective manner, from the quinidine ammonium counterion (Scheme 2).[4f,g]

To our delight, quinidine **I** in combination with TsOH, in toluene at 60 °C, was found to be effective (Table 1, entry 1), affording the product **3aa** in good yield (66%) and with moderate enantioselectivity (66% ee). Encouraged by this result, we decided to examine the importance of the counteranion for what concerns its role in the asymmetric induction using different acidic additives (entries 2–9).

Gratifyingly, the expected product **3aa** was formed with good enantioselectivity (74% ee), although, with low chemical yield (40%) and associated with a significant amount of **4aa** (16% yield) when the (*R*)-BDHP salt of quinidine **I** was used (entry 2). The results obtained with (*R*)-TRIP, (–)-CSA, HCl, HBr, BzOH, AcOH, and *p*-NO_2PhOH did not bring any appreciable improvement but deserve some comment (entries 3–9).

As it can be seen from the data shown in Table 1, it is interesting that the selectivity (**3**:**4** ratio) of the reaction seemed to be dependent on the pK_a differences of the acidic additive. As a matter of fact, it is well-known that ammonium salts behave as a dynamic complex, and are equilibrated with "free amines" and "free acids" in solution.[11a–c] Depending upon the nature of the amine and the acid from which the salt is derived, its concentration and the nature of the organic solvent employed, the ion pairs may either "dissociate" or "associate" into a tighter ion-pair.

The observed difference in selectivity may be, therefore, related to the capacity of the amine salt used as catalyst to dissociate to its "free amine" and "free acid". Indeed, as a general trend, for a given tertiary amine (*e.g.* quinidine **I**) acidic additives with strong Brønsted acidity induced higher selectivity toward the formation of **3aa** (Table 1, entries 1–6) while less acidic additives offered better **4aa** selectivity (entries 7–9). In these cases, probably, the "free amine" and "free acid" rather than the corresponding ammonium salt may be the catalytic active species in solution (Scheme 3) and it is reasonable to expect that the preferential formation of **4aa** is promoted by the protonation of the carbonyl group *via* the "free acid" and subsequent α-proton abstraction by the "free base" (a more strongly basic base compared to the anion provided by the acid component of the base/acid combined salt catalyst).



Scheme 3 Path a *versus* Path b.

The subsequent optimization of our protocol has been carried out by screening the catalytic performance of different tertiary amines (entries 10–14) with (*R*)-BDHP as a fixed acidic additive. Access to *ent*-**3aa** (34% yield and –70% ee) could be achieved using quinine **II** (*pseudo*-enantiomer of **I**) as catalyst (entry 10). Cinchonine **III** (entry 11) gave satisfying ee (74%) albeit with low conversion (33% yield), whereas (–)-*N*-methylephedrine **IV** (entry 12) displayed good reactivity (72% yield) and moderate enantioselectivity (–60% ee) giving, as expected, the desired product with opposite configuration.[13] DMAP **V** was catalytically active, but provided **3aa** in 30% yield as a racemate (entry 13).

It is worth noting that the reaction stereoselection appears to be affected essentially by the nature of the tertiary amine, as further demonstrated by the fact that either the (*R*)-BDHP or the (*S*)-BDHP ammonium salt of **I** (entry 2 and entry 15) gave the same product **3aa**, with comparable enantiomeric excess (74% and 76% ee respectively). Anyway, using (*S*)-BDHP, **3aa** was obtained as the sole product in 66% yield showing a higher catalytic activity and a better selectivity (**3**:**4** ratio).

Further catalyst evaluation screened a series of commercially available biscinchona alkaloids under similar reaction conditions (entry 14, see also the ESI‡). Satisfyingly, $(DHQD)_2$PHAL **VI** proved to be superior to quinine **II** in terms of yield (62%) and enantioinduction, and *ent*-**3aa** was obtained with up to –82% ee.

Remarkably, (*R*)-BDHP alone was much less active than the corresponding ammonium salts and afforded the product **3aa** (49% yield) with almost no enantioselectivity (entry 16), whereas quinidine **I**, used as a free base, furnished the α-acyloxy amide **4aa** in moderate conversion (50% yield and 78% ee) through a base-mediated intramolecular acyl migration[8] followed by a nucleophilic acyl substitution (entry 17).

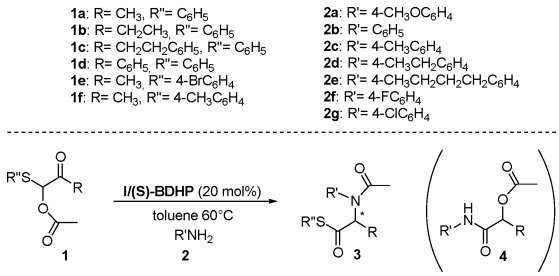
Based on the above optimization studies, we next examined the scope and limitation of the reaction using the catalyst **I**/(*S*)-BDHP (the results are reported in Table 2). With regard to the substituent at the 2 position of **1**, not only a methyl group but also ethyl and ethylphenyl (Table 2, entries 2–3) can be successfully utilized to afford derivatives **3ba** and **3ca** with good yields (62–75%) although with concomitant decreasing enantioselectivities (22 and 16% ee respectively). Notably, the reaction of **1d**, bearing a phenyl substituent at the 2 position, occurred preferentially *via* a nucleophilic acyl substitution terminated intramolecular acyl migration mechanism, affording, as a major product (67% yield and 26% ee), the corresponding α-acyloxy amide **4da** (entry 4).

In this case, the impressive reversal of selectivity between **3da** and **4da** observed is likely due to the enhanced α-proton acidity (provided by phenyl substitution) of the methine position of **1d**, which allows deprotonation by the weakly basic phosphate anion leading to the enol and, subsequently *via* path a, the corresponding α-acyloxy amide **4da**.

The protocol was efficient in the presence of aromatic substituents in the phenylthio group (*e.g.* bromine in **1e** and a methyl group in **1f**) providing the expected products in good yield (entries 5 and 6, 47% and 62% respectively) and optical purity (54–62% ee). Moreover, there appears to be significant tolerance toward structural and electronic variations of the primary amines **2** (entries 7–12, 52–77% yield and 54–70% ee), to enable access to a broad variety of densely functionalized α-amino thioester derivatives.

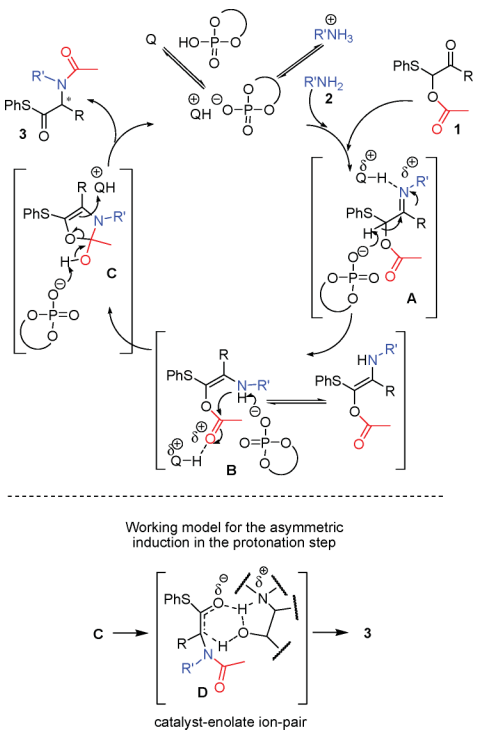
The reaction can be rationalized by assuming the mechanism shown in Scheme 4. The chiral ammonium salt catalyzes the generation of enamine **B** from **1** and **2**. An acyl migration may reasonably be expected to furnish a transient 2,3-dihydro-oxazol-2-ol **C** followed by an *in situ* enantioselective protonation. Proton transfer from the protonated quinidine **I** to transient enolate **D** provides the product **3** and releases the catalyst back into the cycle. The protonation can occur within the catalyst–enolate ion pair.[14]

Table 2 Preliminary scope of the reaction[a]



Entry	Substrates	Products	Ratio **3** : **4**[b]	Product yield **3** : **4** (%)[c]	*ee* **3**(%)[d]
1	**1a**; **2a**	**3aa**	>20 : 1.0	76 : —	76 (*S*)[e]
2[f]	**1b**; **2a**	**3ba**	>20 : 1.0	75 : —	22
3[g]	**1c**; **2a**	**3ca**	>20 : 1.0	62 : —	16
4	**1d**; **2a**	**3da** : **4da**	1.0 : 5.3	10 : 67	rac
5	**1e**; **2a**	**3ea** : **4aa**	2.7 : 1.0	47 : 17	54
6	**1f**; **2a**	**3fa** : **4aa**	11.4 : 1.0	62 : 5	62
7[h]	**1a**; **2b**	**3ab**	>20 : 1.0	60 : —	70
8[i]	**1a**; **2c**	**3ac** : **4ac**	3.3 : 1.0	60 : 18	64
9[i]	**1a**; **2d**	**3ad** : **4ad**	10.0 : 1.0	70 : 7	56
10[i]	**1a**; **2e**	**3ae** : **4ae**	1.6 : 1.0	53 : 34	58
11[i]	**1a**; **2f**	**3af** : **4af**	13.0 : 1.0	77 : 6	62
12[i]	**1a**; **2g**	**3ag** : **4ag**	5.5 : 1.0	52 : 9	54

[a] Conditions: 0.22 mmol of **1**, 0.27 mmol of **2**, 0.044 mmol of **I/(*S*)-BDHP**, 0.5 mL toluene, 24 h, 60 °C. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield after chromatography. [d] Determined by HPLC analysis using a chiral stationary column. [e] For proof of the absolute stereochemical configuration, see the ESI.‡ [f] 36% yield of **3ba** (**3** : **4** ratio = 3.1 : 1.0) with –64% ee, using **VI/(*R*)-BDHP** as catalyst. [g] 18% yield of **3ca** (**3** : **4** ratio = 1.0 : 1.3) with –64% ee, using **VI/(*R*)-BDHP** as catalyst. [h] Reaction carried out over 4 h. [i] Reaction carried out over 48 h.



Scheme 4 Proposed mechanism for the tandem reaction.

In summary, we have developed an unprecedented and conceptually novel chiral Brønsted base/Brønsted acid catalytic method for the enantioselective synthesis of α-amino thioesters through a tandem condensation–intramolecular rearrangement–protonation. Although the enantioselectivities are still moderate, these preliminary results obtained form the basis for further developments.

The optimisation and extension of this reaction, as well as studies aimed at increasing the enantioselectivity are currently under investigation in our laboratories.

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