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Phase-transfer catalysed asymmetric synthesis of α-chiral tetrasubstituted α-aminothioesters†

Yasushi Yoshida, * Reina Kasuya, Takashi Mino and Masami Sakamoto

Chiral amino thioesters are important scaffolds owing to their widespread use in organic synthesis and biosynthesis. Despite their usefulness, their asymmetric synthesis, especially the catalytic asymmetric synthesis of α-chiral tetrasubstituted α-aminothioesters, is limited, with only one example reported so far. Herein, we report the first phase-transfer catalysed asymmetric synthesis of α-chiral tetrasubstituted α-aminothioesters to afford the corresponding products in up to 81% ee.

The synthesis of amino thioesters is of great importance because of their widespread use in the biosynthesis of non-ribosomal peptides[1] and because of their application as useful substrates in the Fukuyama reaction[2] to obtain further functionalised molecules (Fig. 1). The chiral amino thioesters have also been used as activated derivatives of important chiral amino acids as they serve as useful building blocks in organic synthesis and foldamer chemistry.[3] Therefore, their catalytic asymmetric syntheses have attracted significant research interest.[4] In 2007, Ricci and Pettersen *et al.* reported the β-ICD catalysed asymmetric decarboxylative addition of malonic half thioesters into aldimines to afford the corresponding amino thioesters in high yields with up to 79% ee (Fig. 2).[4a] In 2014, Wennemers *et al.* developed the highly enantioselective catalytic synthesis of several classes of β-amino thioesters with tertiary or quaternary stereogenic centres through the addition reaction of malonic acid half thioesters with aldimines, affording the desired products in up to 99% ee (Fig. 2).[4b] Although the catalytic asymmetric synthesis of β-amino thioesters could be smoothly accomplished through these routes, the catalytic asymmetric synthesis of α-tetrasubstituted-α-amino thioesters still remains unexplored. In 2017, Palomo *et al.* reported the first catalytic asymmetric synthesis of α-tetrasubstituted-α-amino thioester derivatives through the Michael reaction of α-alkyl isocyanothioacetates with enones. The reaction was catalysed by *Cinchona*-derived chiral squaramides to give the corresponding products in up to 99% ee (Fig. 2).[5] Nevertheless, the seminal discovery of the enantioselective synthesis of their α-aryl candidates has been much sought-after.

The phase-transfer catalysed asymmetric syntheses of unnatural amino acids have been researched mainly through the α-alkylation of imines.[6] Maruoka *et al.* reported the enantioselective α-alkylation of glycine-derived benzophenone imines by using their originally developed chiral binaphthyl-based catalyst (Maruoka catalyst), which provided the corresponding products with excellent stereoselectivities (Fig. 2).[6c]

The organocatalytic asymmetric umpolung reaction of imines has been utilised as an efficient method for synthesizing chiral amines.[7] We also recently developed the chiral phase-transfer catalysed umpolung reaction of α-imino carbonyl compounds with enones to afford chiral α-tetrasubstituted-α-amino esters and amides in high yields with excellent enantioselectivities (Fig. 2).[8] From the above information, we speculated that the use of aldimino thioesters as the substrate of the phase-transfer catalysed asymmetric alkylation reaction could afford the corresponding unprecedent α-aryl-tetrasubsti-

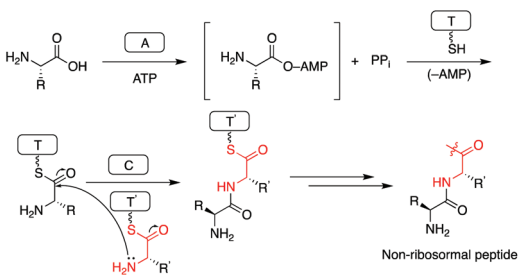

Fig. 1 Biosynthesis of non-ribosomal peptides through the thioester intermediate. ATP = adenosine triphosphate, AMP = adenosine monophosphate, PP_i = pyrophosphate, A domain = adenylation domain, T domain = thiolation (peptidyl carrier protein) domain, and C domain = condensation domain.

Molecular Chirality Research Center, Graduate School of Engineering, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba-shi, Chiba 263-8522, Japan. E-mail: yoshiday@chiba-u.jp

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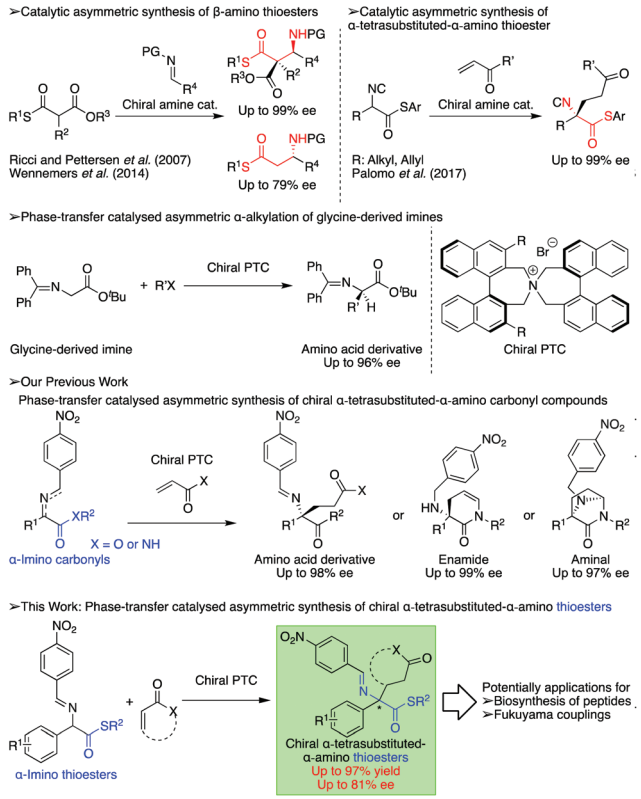


Fig. 2 Catalytic asymmetric synthesis of amino thioesters.

tuted-α-amino thioesters in an enantioselective manner. Herein, we report the catalytic asymmetric synthesis of α-tetrasubstituted-α-amino thioesters through the Michael reaction of aldimino thioesters with enones; the desired products were obtained in high yields with good enantioselectivities (Fig. 2).

First, aldimino thioesters **1** were synthesised through the dehydrative imination of the corresponding ketones with 4-nitrobenzyl amine and subsequent isomerisation with DBU in moderate yields (see the ESI for more details†). With the substrate in hand, the reaction conditions for the catalytic asymmetric synthesis of **4a** were optimised (Fig. 3, Table 1). The reaction of **1a** with methyl vinyl ketone **2a** was carried out in toluene at −10 °C, and the catalyst and base were screened.

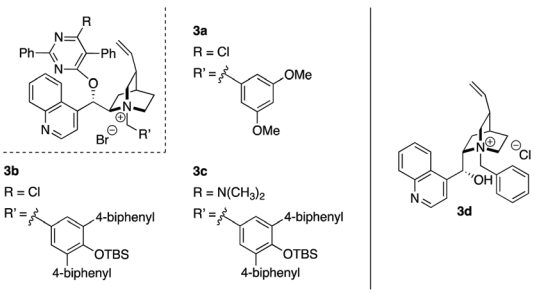
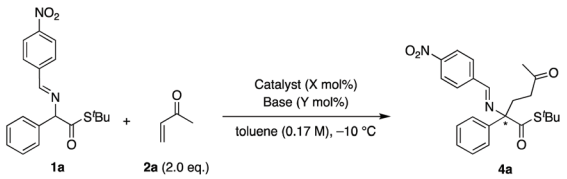


Fig. 3 Catalysts employed in this study.

Table 1 Catalyst and base optimisation for the catalytic asymmetric synthesis of α-chiral tetrasubstituted α-aminothioesters **4a**[a]



Entry	Catalyst	*X*	Base	*Y*	Time (h)	Yield[b] (%)	ee[c] (%)
1	**3a**	20	K_2CO_3 aq.	200	20	67	2
2	**3a**	20	KOH aq.	100	20	57	2
3	**3a**	20	KOH aq.	50	20	69	2
4	**3b**	20	K_2CO_3 aq.	200	20	43	48
5	**3b**	20	KOH aq.	50	20	38	57
6	**3b**	2	KOH aq.	50	1.5	74	53
7	**3c**	2	KOH aq.	50	1.5	70	61
8	**3d**	2	KOH aq.	50	1.5	51	−2

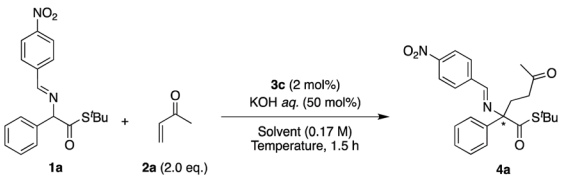
[a] Reactions were conducted with **1a** (1.0 eq.), **2a** (2.0 eq.), catalyst (*X* mol%), and base (*Y* mol%) in toluene (0.17 M) at −10 °C, unless otherwise stated. [b] ^{1}H NMR yields using 1,3,5-trimethoxy benzene as an internal standard. [c] Determined by HPLC analysis.

First, the reaction was conducted in the presence of 20 mol% of **3a**[7a] and 200 mol% of aq. potassium carbonate. The desired product was obtained in 67% yield and with 2% ee (Table 1, entry 1). Following this, the base was screened with catalyst **3a**. The desired product **4a** was obtained in moderate yields with all the bases, although the enantioselectivity was almost nil (entries 1–3). The same bases were screened with the catalyst **3b**,[8a] and a drastic increase in the enantioselectivities was observed, with potassium hydroxide being the optimal base (entries 4 and 5). The product yield with only 2 mol% of **3b** was higher than that with 20 mol% of **3a** or **3b**, probably due to the inhibition of the decomposition of imines, and most importantly, there was no decrease in the enantioselectivity (entry 6). Finally, the use of the catalyst **3c**[8b] with a dimethylamino group afforded **4a** in 70% yield with 61% ee (entry 7). Further investigations of catalysts such as *N*-benzyl cinchonidinium chloride (**3d**), which is widely used as a phase-transfer catalyst, provided **4a** in 51% yield with almost no selectivity (entry 8). Thus, 2 mol% of catalyst **3c** and 50 mol% of aq. potassium hydroxide were determined to be the optimal conditions.

The solvent and temperature were optimised next (Table 2). When the reaction temperature was decreased to −30 °C in toluene, the enantioselectivity of **4a** increased to 74% ee (entry 2). Solvent screening at this temperature revealed that the yields were better in non-polar solvents, with *m*-xylene being the optimal solvent, and **4a** was obtained in 79% yield with 76% ee (entries 3–5). A further decrease in the reaction temperature to −45 °C in *m*-xylene afforded **4a** in 77% yield with 81% ee (entries 6 and 7).

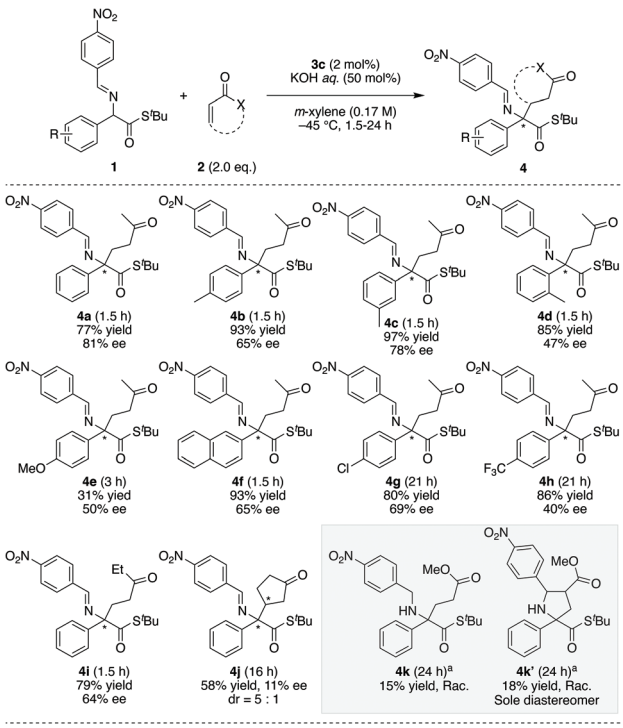
With the optimal conditions in hand, the substrate scope of the present asymmetric transformation was investigated (Scheme 1). The scope of the aldimino thioester revealed that

Table 2 Solvent and temperature optimisation for the catalytic asymmetric synthesis of **4a**[a]



Entry	Solvent	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	Toluene	−20	68	69
2	Toluene	−30	82	74
3	DCM	−30	68	27
4	MeCN	−30	44	1
5	*m*-Xylene	−30	79	76
6	*m*-Xylene	−40	75	78
7	*m*-Xylene	−45	77	81

[a] Reactions were conducted with **1a** (1.0 eq.), **2a** (2.0 eq.), **3c** (2 mol%), and aq. KOH (50 mol%) in solvent (0.17 M) at an appropriate temperature for 1.5 hours, unless otherwise stated. [b] ^{1}H NMR yields using 1,3,5-trimethoxy benzene as an internal standard. [c] Determined by HPLC analysis.



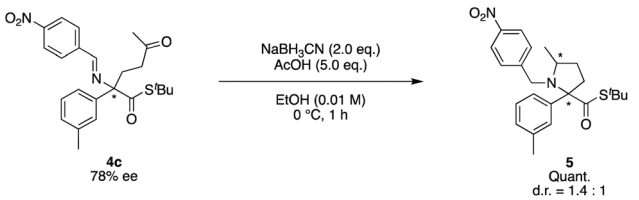
Scheme 1 Substrate scope for the asymmetric synthesis of α-chiral tetrasubstituted α-aminothioester **4**. Reactions were conducted with **1** (1.0 eq.), **2** (2.0 eq.), aq. KOH (50 mol%), and **3c** (2 mol%) in *m*-xylene (0.17 M) at −45 °C for 1.5–24 h, unless otherwise stated. Yields of isolated products are shown. [a]Isolated after $NaBH_4$ reduction in EtOH at −20 °C.

the electron-donating group substituted **4a–4f** were obtained in high yields with moderate to good enantioselectivities (47–81% ee). Compound **4e** was obtained in only 31% yield due to substrate decomposition. The substrate decomposition occurs due to the higher solubility to the aqueous layer, which is caused by the highly polar methoxy group. The electron-withdrawing group substituted **4g** and **4h** were also isolated in high yields with moderate ees. From the substrate scope results for imines, the electron-deficient substrate was found to slowly react with enones, maybe due to the lower nucleophilicity of their anion intermediate compared to that of the electron-rich one. Next, the scope of the Michael acceptor was investigated. Substituted enones such as ethyl vinyl ketone and cyclopentenone provided the corresponding adducts **4i** and **4j** in good yields with moderate to low enantioselectivities. The use of methyl acrylate also gave the desired product **4k** and its cyclised product **4k′** in 15% and 18% yield, respectively, which could not be achieved in our previous study (Michael reaction of α-imino esters).[8b] This suggested the higher reactivity of the α-imino thioesters employed in this study.

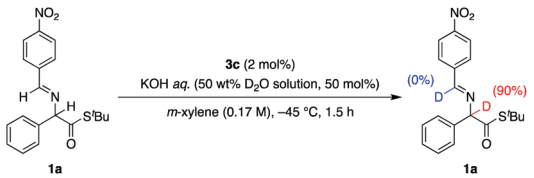
To demonstrate the usefulness of the present reaction, the α-chiral tetrasubstituted α-aminothioester **4** was derivatised (Scheme 2). The reduction of **4c** with sodium cyanoborohydride ($NaBH_3CN$) under acidic conditions afforded the chiral pyrrolidine derivative **5** through the reduction of the imine moiety, followed by the reductive amination, in quantitative yields. **5** bears a proline-like core skeleton and has potential usefulness as artificial amino acids[9] and organocatalysts.[10]

Next, the reaction mechanism was investigated (Scheme 3). When **1a** was stirred with 2 mol% of **3c** and 50 mol% of potassium hydroxide (50 wt% deuterium oxide solution) in *m*-xylene at −45 °C for 1.5 h, substrate **1a** was recovered with 90% deuterium incorporation at the α-position of the thioester moiety. However, no deuteration occurred at the imine proton. This result suggested that the negative charge of the ionic intermediates for the present reaction were not delocalised on the imine moiety.

The plausible reaction mechanism is shown in Fig. 4. Aldimino thioester **1** was deprotonated by potassium hydroxide to form the enolate intermediate **A**, which underwent a



Scheme 2 Derivatisation of chiral thioester **4c**.



Scheme 3 Deuterium incorporation of **1a**.

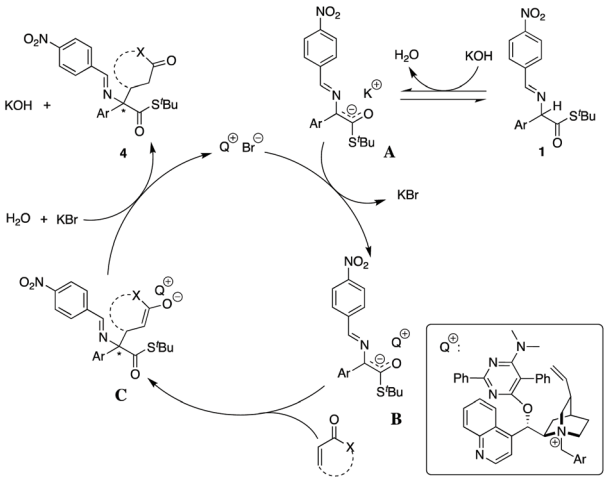


Fig. 4 Plausible reaction mechanism.

counter cation exchange with a chiral phase-transfer catalyst to give intermediate **B**. Then, the Michael addition of **B** with enone proceeded to give the chiral enolate **C**. This was followed by protonation to give the corresponding product **4**, along with the regeneration of the catalyst. In this mechanism, the conversion of intermediate **B** to **C** is the enantioselective carbon–carbon bond forming step. Therefore, the structure of **B** is crucial for both the enantioselectivity of the product and reactivity with the unactivated reactant such as methyl acrylate. The *tert*-butylthio moiety behaved as a strong electron-donating group, thereby increasing the electron density and nucleophilicity of **B** and enabling the reaction with various reactants.[11]

In conclusion, the phase-transfer catalysed asymmetric synthesis of α-chiral tetrasubstituted α-aminothioesters was achieved using various enones. The corresponding products were obtained in high yields with up to 81% ee. Mechanistic studies revealed that the negative charges of the ionic intermediates for the present reaction were not delocalised on the imine moiety but were delocalised only on the thioester part. The derivatisation reactions demonstrated the wide applicability of the products for the synthesis of more functionalised molecules. Further investigations on the application of chiral products in asymmetric catalysis are ongoing.

Conflicts of interest

There are no conflicts to declare.

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