Monatsh Chem
DOI 10.1007/s00706-016-1744-4

ORIGINAL PAPER

One-pot multicomponent asymmetric synthesis of α-amidosulfides from thiophenol and *N*-acylimines generated in situ from α-amidosulfones

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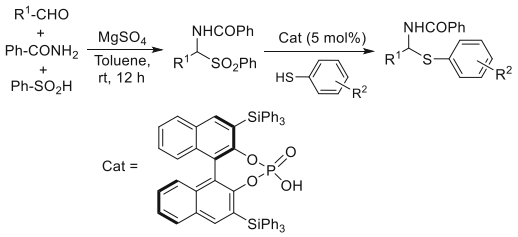
Received: 27 January 2016 / Accepted: 15 March 2016

Abstract A novel one-pot, multicomponent asymmetric synthesis of α-amidosulfides was described. By employing chiral phosphoric acid as Brønsted acid and catalyst, α-amidosulfides were obtained in excellent yields with high to excellent enantioselectivities via reaction of thiophenol and *N*-acylimines generated in situ from α-amidosulfones.

Graphical abstract



Keywords α-Amidosulfide · α-Amidosulfone · Chiral phosphoric acid · Thiophenol

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Introduction

α-Amidosulfides are an important class of structural motifs found in a large of pharmaceutical agents and heterocycles [1, 2]. In particular, because α-amidosulfides and α-amidosulfones can generate intermediate imine in the presence of Brønsted acid [3] or Lewis acid [4], they are widely used in the synthesis of important compounds. For example, 2-indolylmethanamines can be obtained from indoles by nucleophilic addition of imine generated from α-amidosulfides catalyzed by phosphoric acid [3]. For another example, 1,3-diamine derivatives can be prepared from enecarbamates and imine generated from hemiaminal ethers in presence of chiral phosphoric acid [5].

However, few methods are known for the preparation of α-amidosulfides and most of them involve multistep processes that have limited application scope [6]. Therefore, the development of simple and convenient methods for preparing the α-amidosulfides, especially for the optically active ones, is particularly important. Recently, George reported a method for obtaining α-amidosulfides in high yields by nucleophilic addition of thiols to α-amidosulfones in basic media [3]. Fang demonstrated asymmetric addition of thiols to trifluoromethylaldimine catalyzed by a bifunctional squaramide-based organocatalyst for the construction of chiral trifluoromethylated α-amidosulfides [7]. Wang also described the synthesis of chiral α-amidosulfides from thiols and α-amidosulfones by using amino acid-based bifunctional thiourea-ammonium salt as catalysts [8]. Herein, we reported an effective asymmetric synthesis of α-amidosulfides from thiophenol and *N*-acylimines generated in situ from α-amidosulfones in presence of chiral phosphoric acid.

Published online: 04 April 2016

Results and discussion

Initially, we examined the reaction of 4-cholorothiophenol (**1a**, 1.2 mmol), chiral phosphoric acid **3a** (5 mol%) and α-amidosulfone **2a** (1 mmol) [4, 9] in toluene at −40 °C (Scheme 1). To our satisfaction, the reaction was complete in 24 h and yielded 90 % of α-amidosulfide **4a** with 14 % ee. The result indicated that the chiral phosphoric acid is used as a catalyst for both enantioselective addition reaction and formation of *N*-acylimines from α-amidosulfone in quantitative yield [10]. To search for more optimal reaction conditions, we screened a number of structurally related chiral phosphoric acids (Fig. 1), solvents and reaction temperature. Table 1 summarizes these results. **3a** was the most effective catalyst in terms of stereochemical control, providing an excellent enantioselection. Among the chosen solvents toluene was the best one for the synthesis of α-amidosulfide. Upon cooling the reaction, the addition product was obtained with higher enantioselectivity.

To develop a general, simple, and convenient method for construction of α-amidosulfide, we sought to the new technology for the synthesis of α-amidosulfide in one-pot by using **3a** as catalyst and Brønsted acid, benzaldehyde, benzamide, phenylsulfinic acid, and thiophenol as materials. Thus, in the presence of $MgSO_4$, a toluene solution of benzaldehyde (**5a**), benzamide (**6**), and phenylsulfinic acid (**7**) was vigorously stirred at room temperature for 12 h [11]. Upon complete consumption of the benzaldehyde, the mixture was cooled to −78 °C, **3a** and 4-chlorothiophenol was added. The resulting mixture was vigorous stirred for additional 24 h, and the corresponding product **4a** was obtained in 90 % yield with 86 % ee.

We next examined a series of aromatic aldehydes and thiophenols to establish the scope of the novel one-pot sequential multicomponent synthesis of α-amidosulfides (Scheme 2, Table 2). Under our optimized reaction conditions, benzaldehyde bearing electron withdrawing substituents such as chloro, fluoro, and bromo produced excellent yields and enantioselectivities. Similar result was obtained with 2-naphthaldehyde. 3-Methylbenzaldehyde and 4-methylbenzaldehyde were converted into corresponding products in excellent yields with high enantioselectivities. Thiophenol bearing halogen substituent has better yield and enantioselectivity than itself.

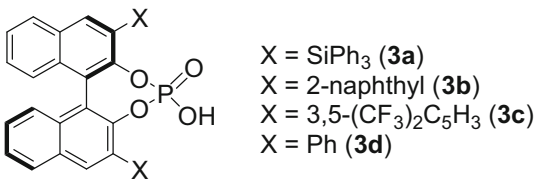

Fig. 1 The structures of catalysts **3**

Conclusion

We have described a new one-pot, sequential multicomponent synthesis of optically active α-amidosulfides from readily accessible starting materials. The method was general, simple, and convenient, the α-amidosulfides were obtained in excellent yields with high to excellent enantioselectivities.

Experimental

^1H and ^{13}C spectra were recorded on a 400 MHz instrument at 400 MHz (^1H) and 100 MHz (^{13}C) with TMS as internal standard. Melting points were measured with micromelting point apparatus. High-performance liquid chromatography (HPLC) was conducted on an Agilent 1100 liquid chromatograph; HPLC analysis using Diacel chiralcel OD-H column (eluent: hexane/2-propanol); IR spectra were performed as KBr pellets on a Bruker VERTEX 70 spectrophotometer; MS spectra were recorded on a. ZAB-HS and ESQUIRE 6000 mass spectrometer.

*General procedure for the preparation of α-amidosulfides **4***

To a solution of benzamide (**6**, 1.2 mmol) and phenylsulfinic acid (**7**, 1.2 mmol) in 4 cm^3 toluene, anhydrous magnesium sulfate (0.9 mmol) was added and the mixture was vigorously stirred at room temperature, and the flask was purged with argon. The aldehydes **5** (1 mmol) was dissolved in 1 cm^3 toluene and the solution was added dropwise, the resulting reaction mixture was vigorous stirred overnight. Then the resulting mixture was cooled to −78 °C, **3a** (0.05 mmol) and thiophenols **1** (1.5 mmol) were then added, and the solution was vigorously stirred for additional 24 h. After warming to room temperature,

Scheme 1

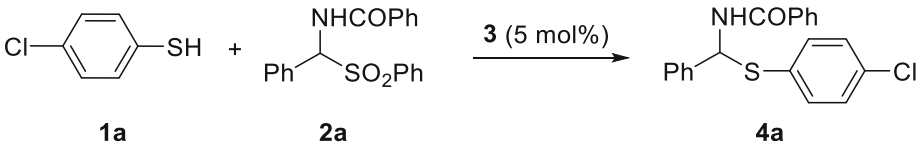

Table 1 Optimization of the reaction conditions

Entry	Catalyst	Solvent	Temp/°C	Yield/%[a]	Ee/%[b]
1	**3a**	Toluene	−40	90	14
2	**3a**	Toluene	−60	91	58
3	**3a**	Toluene	−78	90	86
4	**3b**	Toluene	−78	89	12
5	**3c**	Toluene	−78	93	82
6	**3d**	Toluene	−78	91	78
7	**3a**	DCM	−78	87	53
8	**3a**	THF	−78	85	49

[a] Isolated yield after column purification

[b] Determined by HPLC analysis using Diacel chiralcel OD column (eluent: hexane/2-propanol)

Scheme 2

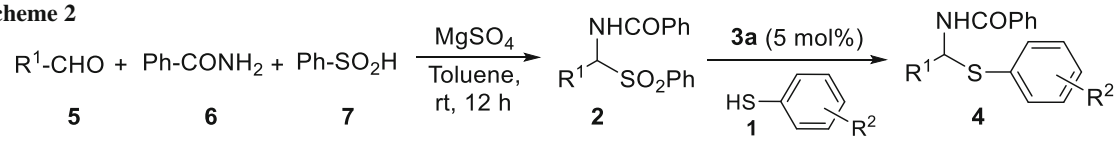

Table 2 Asymmetric synthesis of α-amidosulfides

Entry	R^1	R^2	Product	Yield/%[a]	Ee/%[b]
1	C_6H_5	4-Cl	**4a**	90	86
2	4-FC_6H_4	4-Cl	**4b**	93	91
3	3-ClC_6H_4	4-Cl	**4c**	92	89
4	4-ClC_6H_4	4-Cl	**4d**	95	88
5	4-BrC_6H_4	4-Cl	**4e**	93	90
6	2-$C_{10}H_7$	4-Cl	**4f**	87	83
7	3-MeC_6H_4	4-Cl	**4g**	88	81
8	4-MeC_6H_4	4-Cl	**4h**	90	80
9	C_6H_5	4-Br	**4i**	87	78
10	C_6H_5	H	**4j**	84	70

[a] Isolated yield

[b] Determined by HPLC analysis using Diacel chiralcel OD column (eluent: hexane/2-propanol)

the solid in the reaction mixture was removed by filtration and the filtrate was concentrated in vacuo. The residues was purified by column chromatography on neutral aluminum oxide (hexane/EtOAc = 10:1) to give α-amidosulfides **4**.

N-[(4-Chlorophenylthio)(phenyl)methyl]benzamide (**4a**, $C_{20}H_{16}ClNOS$)

White solid; m.p.: 181–183 °C; 86 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 10.6 min, t_{major} = 17.7 -min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.2 Hz, 2H), 7.52–7.47 (m, 3H), 7.42–7.24 (m, 7H), 7.30–7.22 (m, 2H), 6.77–6.73 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 138.3, 134.2, 133.8, 133.6, 131.9, 131.4, 129.2, 128.9, 128.7, 128.6, 126.8, 126.6, 59.8 ppm; ESI–MS: *m/z* = 376.0 ($[M + Na]^+$); IR (KBr): $\overline{v}$: = 3303, 2966, 1682, 1579, 1434, 1305, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}ClNOS$ ($[M+Na]^+$) 376.0533, found 376.0528.

N-[(4-Chlorophenylthio)(4-fluorophenyl)methyl]benzamide (**4b**, $C_{20}H_{15}ClFNOS$)
White solid; m.p.: 186–189 °C; 91 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 8.7 min, t_{major} = 14.4 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.6 Hz, 2H), 7.53–7.36 (m, 7H), 7.26–7.20 (m, 2H), 7.08–7.04 (m, 2H), 6.73–6.66 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 163.8, 116.4, 134.5, 134.3, 134.2, 133.8, 133.5, 132.0, 131.2, 129.3, 128.7, 128.5, 128.4, 126.9, 115.9, 115.7, 59.2 ppm; ESI–MS: *m/z* = 394.8 ($[M+Na]^+$); IR (KBr): $\overline{v}$ = 3306, 2970, 1525, 1490, 1150, 801, 747, 514, 494, 396 cm^{-1}.

N-[(4-Chlorophenylthio)(3-chlorophenyl)methyl]benzamide (**4c**, $C_{20}H_{15}Cl_2NOS$)
White solid; m.p.: 165–167 °C; 89 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 9.0 min, t_{major} = 15.0 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.2 Hz, 2H), 7.65–7.50 (m, 2H), 7.249–7.29 (m, 5H), 7.26–7.20 (m, 4H), 6.73–6.68 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 140.3, 134.8, 134.6, 133.9, 133.3, 132.1, 130.9, 130.1, 126.9, 126.8, 124.9, 59.3 ppm; ESI–MS: *m/z* = 410.0 ($[M+Na]^+$); IR (KBr): $\overline{v}$ = 3326, 3063, 1668, 1601, 1573, 1432, 1303, 1094, 824, 759 cm^{-1}.

N-[(4-Chlorophenylthio)(4-chlorophenyl)methyl]benzamide (**4d**, $C_{20}H_{15}Cl_2NOS$)
White solid; m.p.: 195–197 °C; 88 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 9.6 min, t_{major} = 13.6 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.2 Hz, 2H), 7.64–7.50 (m, 1H), 7.44–7.33 (m, 7H), 7.26–7.24 (m, 3H), 6.70–6.63 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 163.8, 116.4, 134.5, 134.3, 134.2, 137.8, 133.5, 132.0, 131.1, 129.3, 128.7, 128.5, 128.4, 126.9, 155.9, 155.7, 59.2 ppm; ESI–MS: *m/z* = 410.0 ($[M+Na]^+$); IR (KBr): $\overline{v}$ = 3308, 3064, 1660, 1570, 1435, 1010, 960, 775, 701 cm^{-1}.

N-[(4-Chlorophenylthio)(4-bromophenyl)methyl]benzamide (**4e**, *$C_{20}H_{15}BrClNOS$)*
White solid; m.p.: 202–205 °C; 90 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 11.1 min, t_{major} = 14.2 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.6 Hz, 2H), 7.54–7.49 (m, 3H), 7.44–7.36 (m, 6H), 7.25–7.21 (m, 2H), 6.68–6.61 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 134.4, 134.6, 133.9, 133.4, 132.0, 130.9, 129.4, 128.8, 128.3, 126.9, 122.6, 59.3 ppm; ESI–MS: *m/z* = 453.9 ($[M+Na]^+$); IR (KBr): $\overline{v}$ = 3303, 3055, 1665, 1578, 1473, 1067, 803, 732, 683, 671, 459 cm^{-1}.

N-[(4-Chlorophenylthio)(2-naphthalenyl)methyl]benzamide (**4f**, $C_{24}H_{18}ClNOS$)
White solid; m.p.: 190–193 °C; 83 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 22.1 min, t_{major} = 27.0 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.70 (m, 4H), 7.67–7.60 (m, 2H), 7.54–7.50 (m, 1H), 7.45–7.41 (m, 7H), 7.26–7.22 (m, 2H), 6.90 (d, J = 9.2 Hz, 1H), 6.79 (d, J = 9.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 135.6, 134.4, 133.9, 133.7, 133.2, 133.1, 132.0, 131.4, 129.3, 128.9, 128.7, 128.1, 127.7, 126.9, 126.6, 125.5, 124.5, 60.1 ppm; ESI–MS: *m/z* = 426.1 ($[M+Na]^+$); IR (KBr): $\overline{v}$ = 3310, 3049, 3001, 1669, 1561, 1384, 840, 743, 615, 471 cm^{-1}.

N-[(4-Chlorophenylthio)(m-tolyl)methyl]benzamide (**4g**, $C_{21}H_{18}ClNOS$)
White solid; m.p.: 173–176 °C; 81 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 7.5 min, t_{major} = 14.2 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.6 Hz, 2H), 7.50–7.48 (m, 1H), 7.41–7.37 (m, 4H), 7.27–7.21 (m, 5H), 7.13 (d, J = 6.4 Hz, 1H), 6.76–6.70 (m, 2H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 138.7, 138.2, 134.0, 133.6, 131.8, 129.2, 128.8, 128.6, 127.3, 126.9, 123.6, 21.5 ppm; ESI–MS: *m/z* = 390.1 ($[M+Na]^+$); IR (KBr): $\overline{v}$ = 3309, 3079, 3050, 3022, 1680, 1575, 1492, 1027, 801, 728, 693, 465 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}ClNOS$ ($[M+Na]^+$) 390.0690, found 390.0681.

N-[(4-Chlorophenylthio)(p-tolyl)methyl]benzamide (**4h**, $C_{21}H_{18}ClNOS$)
White solid; m.p.: 198–199 °C; 80 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 8.5 min, t_{major} = 11.9 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 6.8 Hz, 2H), 7.64–7.50 (m, 1H), 7.47–7.36 (m, 6H), 7.26–7.17 (m, 4H), 6.73–6.66 (m, 2H), 2.35 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 138.5, 135.3, 134.1, 133.6, 131.9, 131.6, 129.5, 129.2, 128.8, 128.7, 126.5, 126.0, 59.6, 21.3 ppm; ESI–MS: *m/z* = 390.1 ($[M+Na]^+$); IR (KBr): $\overline{v}$ = 3311, 3054, 1676, 1580, 1500, 1030, 806, 730, 691, 463 cm^{-1}.

N-[(4-Bromophenylthio)(phenyl)methyl]benzamide (**4i**, $C_{20}H_{16}BrNOS$)
White solid; m.p.: 187–189 °C; 78 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 9.5 min, t_{major} = 15.0 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 6.8 Hz, 2H), 7.65–7.47 (m, 3H), 7.43–7.30 (m, 9H), 7.77–7.71 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): δ = 166.3, 138.3, 133.9, 132.6, 132.1, 132.0, 128.9, 128.9, 128.7, 128.6, 126.6, 122.2, 59.5 ppm; ESI–MS: *m/z* = 420.0 ($[M+Na]^+$); IR (KBr): $\overline{v}$

= 3304, 2966, 1680, 1579, 1436, 1307, 801, 732, 671, 459 cm^{-1}.

N-[(Phenylthio)(phenyl)methyl]benzamide
(**4j**, $C_{20}H_{17}NOS$)
White solid; m.p.: 166–169 °C; 70 % ee determined by HPLC analysis (chiralpak OD-H, hexane/*i*-PrOH = 90:10, 1.0 cm^3/min, 228 nm), t_{minor} = 9.1 min, t_{major} = 10.7 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 6.8 Hz, 2H), 7.50–7.45 (m, 5H), 7.40–7.30 (m, 5H), 7.29–7.25 (m, 5H), 6.77 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 138.6, 133.7, 133.0, 132.5, 131.8, 129.0, 128.8, 128.6, 128.4, 128.0, 126.9, 126.5, 59.6 ppm; ESI–MS: *m/z* = 342.1 ($[M+Na]^+$); IR (KBr): $\overline{\nu}$ = 3311, 2960, 1681, 1585, 1450, 688, 672 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}NOS$ ($[M+Na]^+$) 342.0923, found 342.0925.

Acknowledgments We thank the Hebei province of china science and technology support programs (Grant No. 15226601D).

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