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Indium(III) chloride-catalyzed thiolysis of *meso*-aziridines

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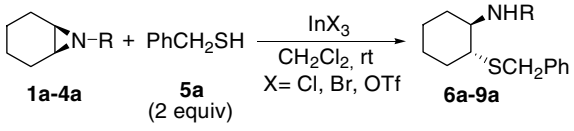
Abstract—Indium(III) chloride efficiently catalyzed the thiol addition to *meso*-aziridines at very low substrate-catalyst ratios giving rise to 1,2-amino sulfides in excellent yields and complete diastereocontrol.

Aziridines are reactive small-ring heterocycles, which may be readily ring-opened with nucleophiles to furnish valuable 1,2-difunctionalized fine chemicals.[1] Depending upon the nitrogen substituent they are divided into activated aziridines carrying an electron-withdrawing N-substituent and nonactivated aziridines with an *N*-alkyl or *N*-aryl group. In contrast to the ring-opening of epoxides[2] comparably few catalytic processes have been developed for the addition of amines,[3] azides,[4] alcohols,[5] thiols,[6] and carbon nucleophiles[7] to aziridines, which may be due to their attenuated reactivity and less convenient accessibility. Among the Lewis acid catalysts employed for the thiolysis of aziridines $ZnCl_2$[6e] and $Bi(OTf)_3$[6c] are most prominent and deliver the corresponding 1,2-amino sulfides in good yields. In addition, Lewis bases such as PBu_3[6d] and DABCO[6b] have been successfully employed for the thiolysis of aziridines as well as a chiral ammonium salt constituting the first enantioselective catalyst for this reaction.[6g] In all of these processes, however, 5–10 mol % of catalyst was required for full conversion and typically activated aziridines were employed to facilitate the ring-opening event.

Based on our experience with catalytic, enantioselective ring-opening of *meso*-epoxides with alcohols,[8] amines,[8a,9] and thiols[10] we wish to report here that indium(III) chloride is a highly efficient catalyst for the addition of aliphatic thiols to nonactivated *meso*-aziridines furnishing 1,2-amino sulfides in excellent yields with only 1 mol % of catalyst necessary for full conversion within typically 1–2 h at rt.[11,12]

Table 1. Optimatization of the thiolysis



1a-4a **5a** (2 equiv) **6a-9a**

Entry	Aziridines	Lewis acids	Time	Yield[a]
1	**1a**, R = Ts	$InCl_3$ (10 mol %)	24 h	**6a**, R = Ts, 65%
2	**2a**, R = COPh	$InCl_3$ (10 mol %)	3 h	**7a**, R = COPh, 75%
3	**3a**, R = Bn	$InCl_3$ (10 mol %)	15 min	**8a**, R = Bn, 60%
4	**4a**, R = Ph	$InCl_3$ (10 mol %)	15 min	**9a**, R = Ph, 88%
5	**4a**, R = Ph	$InBr_3$ (10 mol %)	15 min	**9a**, R = Ph, 89%
6	**4a**, R = Ph	$In(OTf)_3$ (10 mol %)	15 min	**9a**, R = Ph, 85%
7	**4a**, R = Ph	$InCl_3$ (1 mol %)	30 min	**9a**, R = Ph, 88%[b]

[a] Isolated yields of chromatographed product.
[b] 1.5 equiv of benzyl thiol was used.

Keywords: 1,2-Amino sulfide; Aziridine; Catalysis; Indium; Thiol.
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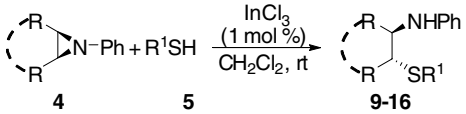
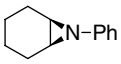
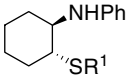
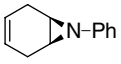
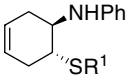
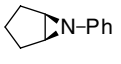
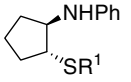
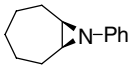
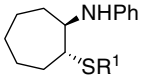
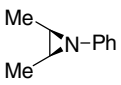
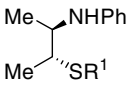
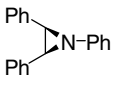
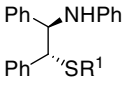
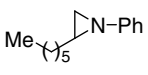
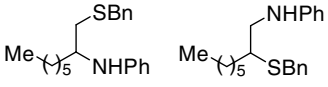
The ring-opening of aziridines strongly depends on the nature of the nitrogen substitutent. Therefore, we started our investigation with the reaction of cyclohexeneimines **1a**–**4a** carrying different substituents on the nitrogen atom and benzyl thiol (**5a**) in the presence of $InCl_3$ (10 mol %) in CH_2Cl_2 (Table 1). Whereas 1,2-amino sulfides **6a**–**8a** were obtained in moderate to good yields (entries 1–3), ring-opening of aziridine **4a** (R = Ph) furnished 1,2-amino sulfide **9a** in excellent yield within 15 minutes (entry 4). To further optimize this process other indium salts were screened. Thus, $InBr_3$ and $In(OTf)_3$ were equally effective in the thiolysis of aziridine **4a** (entries 5–6). $InCl_3$, however, turned out to be the only Lewis acid giving rise to complete conversion at a 1 mol % level. Thus, the reaction of *N*-phenylaziridine **4a** with 1.5 equiv benzyl thiol afforded 1,2-

Table 2. $InCl_3$-catalyzed thiolysis of *N*-phenylaziridines **4**



4 **5** (1.5 equiv) **9-16**

Entry	Aziridines	Thiols	Time	Product (yield)[a]
		R^1SH		
1	**4a**	**5a**, $R^1 = Bn$	30 min	**9a**, $R^1 = Bn$, 88%
2	**4a**	**5b**, $R^1 = Ph$	15 min	**9b**, $R^1 = Ph$, 92%[b]
3	**4a**	**5c**, $R^1 = Et$	30 min	**9c**, $R^1 = Et$, 92%
4	**4a**	**5d**, $R^1 = Me_2CH(CH_2)_2$	45 min	**9d**, $R^1 = Me_2CH(CH_2)_2$, 87%
5	**4a**	**5e**, $R^1 = Me_3C$	12 h	**9e**, $R^1 = Me_3C$, 90%[c]
				
6	**4b**	**5a**, $R^1 = Bn$	45 min	**10a**, $R^1 = Bn$, 88%
7	**4b**	**5d**, $R^1 = Me_2CH(CH_2)_2$	15 min	**10d**, $R^1 = Me_2CH(CH_2)_2$, 91%
				
8	**4c**	**5a**, $R^1 = Bn$	120 min	**11a**, $R^1 = Bn$, 79%
9	**4c**	**5d**, $R^1 = Me_2CH(CH_2)_2$	120 min	**11d**, $R^1 = Me_2CH(CH_2)_2$, 85%
				
10	**4d**	**5a**, R^1= Bn	60 min	**12a**, $R^1 = Bn$, 87%
11	**4d**	**5d**, $R^1 = Me_2CH(CH_2)_2$	120 min	**12d**, R^1= $Me_2CH(CH_2)_2$, 90%
				
12	**4e**	**5a**, $R^1 = Bn$	45 min	**13a**, $R^1 = Bn$, 81%
13	**4e**	**5d**, $R^1 = Me_2CH(CH_2)_2$	45 min	**13d**, $R^1 = Me_2CH(CH_2)_2$, 80%
				
14	**4f**	**5a**, $R^1 = Bn$	60 min	**14a**, $R^1 = Bn$, 92%
15	**4f**	**5d**, $R^1 = Me_2CH(CH_2)_2$	60 min	**14d**, $R^1 = Me_2CH(CH_2)_2$, 86%
				
16	**4g**	**5a**, $R^1 = Bn$	60 min	**15a**, **16a**, 65% (4:1)

[a] Isolated yields of chromatographed product.
[b] 30% yield in the absence of catalyst.
[c] 10 mol % of catalyst was used.

amino sulfide **9a** in 88% yield as a single trans-diastereomer in the presence of 1 mol % $InCl_3$ in CH_2Cl_2 at rt for 30 min (entry 7).

Subsequently, employing 1 mol % of $InCl_3$ as catalyst *N*-phenylaziridine **4a** was ring-opened with several aromatic as well as aliphatic thiols furnishing 1,2-amino sulfides **9a–d** in excellent yields irrespective of the thiol component (Table 2, entries 1–4).[13] In the case of thiophenol, however, a significant background reaction was observed delivering **9b** in 30% yield in the absence of the catalyst presumably due to the enhanced acidity of the aromatic thiol serving as its own Brønsted acid catalyst. Even the sterically hindered *t*-butyl thiol (**5e**) gave rise to excellent yield with increased catalyst loading of 10 mol % and extended reaction times of 12 h (entry 5). In all cases examined we observed the trans ring-opened products exclusively.

In order to investigate the scope of the reaction other aziridines **4b–g** were subsequently examined in indium-catalyzed ring-opening reactions. Thus, the reaction of *N*-phenylcyclohex-4-eneimine **4b** with benzyl and 3-methylbutyl thiol afforded the corresponding 1,2-amino sulfides **10a** and **10d**, respectively, in excellent yields (Table 2, entries 6 and 7). Similarly, cyclopentyl and cycloheptyl aziridines **4c** and **4d**, respectively, were smoothly ring-opened with benzyl and 3-methylbutyl thiol and delivered the corresponding 1,2-amino sulfides in good to very good yields within 2 h (entries 8–11). Acyclic *meso*-aziridines such as **4e** and **4f** reacted likewise and gave rise to the products in 80–92% yields with only 1 mol % of $InCl_3$ (entries 12–15). Finally, a mono-substituted aziridine, *N*-phenyl-2-hexylaziridine (**4g**), was also investigated and furnished the regioisomers **15a** and **16a** in good yield and 4:1-isomeric ratio (entry 16). Some uncatalyzed background reaction, however, was observed here under the reaction conditions, which delivered the products in <10% yield.

In conclusion, we have shown that indium(III) chloride is a highly efficient catalyst for the ring-opening of *N*-phenyl aziridines with aliphatic thiols giving rise to 1,2-amino sulfides in typically excellent yields, complete diastereocontrol and with very low catalyst loading. Work is being continued to develop this process into a catalytic, enantioselective reaction through searching for the optimal chiral indium ligand.

Acknowledgments

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12. For previous use of $In(OTf)_3$ as catalyst for aziridine ring-opening with carboxylic acids see: Yadav, J. S.; Subba Reddy, B. V.; Sadashiv, K.; Harikishan, K. *Tetrahedron Lett.* **2002**, *43*, 2099.
13. *General procedure for ring-opening of meso-aziridines*: To a solution of $InCl_3$ (2 mg, 0.01 mmol) in CH_2Cl_2 (5 mL) were added *N*-phenyl aziridine (1.00 mmol) and thiol (1.50 mmol) and the mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC). The solvent was removed in vacuo

and the crude product was purified through flash chromatography using 50:1 petroleum ether–ethyl acetate as eluent. All products gave satisfactory spectroscopic data in full agreement with the assigned structures. Some representative data are as follows: compound **9d**: colorless oil; R_f 0.35 (5% EtOAc–petroleum ether); IR (film): ν_{max} 3373, 2930, 1601, 1503, 1446, 1079 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 7.21 (t, $J = 7.2$ Hz, 2H), 6.72 (t, $J = 7.2$ Hz, 1H), 6.68 (m, 2H), 4.97 (br s, 1H), 3.23 (dt, $J = 4.0$, 9.4 Hz, 1H), 2.73 (dt, $J = 4.0$, 9.4 Hz, 1H), 2.55–2.59 (m, 2H), 2.33–2.38 (m, 1H), 2.17–2.22 (m, 1H), 1.60–1.85 (m, 4H), 1.39–1.50 (m, 4H), 1.25–1.33 (m, 1H), 0.88 (d, $J = 5.6$ Hz, 3H), 0.86 (d, $J = 5.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 147.7, 129.3, 117.5, 113.5, 55.99, 48.79, 39.03, 32.83, 32.72, 27.98, 27.63, 25.50, 24.08, 22.43, 22.33; ESI-MS: $m/z = 278$ (32) $[M+1]^+$, 185 (100) $[M-NHPh]^+$. Compound **11a**: mp 34–35 °C (pentane); R_f 0.28 (5% EtOAc–petroleum ether); IR (KBr): ν_{max} 3314, 3051, 2951, 1601, 1513, 1494, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 7.28–7.34 (m, 5H), 7.16 (t, $J = 7.6$ Hz, 2H), 6.71 (t, $J = 7.6$ Hz, 1H), 6.59 (t, $J = 7.6$ Hz, 2H), 3.82 (d, $J = 13.6$ Hz, 1H), 3.77 (d, $J = 13.6$ Hz, 1H), 3.65 (q, $J = 6.0$ Hz, 1H), 3.60 (br s, 1H), 2.87 (q, $J = 6.0$ Hz, 1H), 2.19–2.28 (m, 1H), 2.05–2.14 (m, 1H), 1.63–1.88 (m, 3H), 1.44–1.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 147.6, 138.6, 129.3, 128.9, 128.6, 127.1, 117.5, 113.5, 61.27, 49.95, 36.35, 32.85, 32.02, 22.82; ESI-MS: $m/z = 284$ (27) $[M+1]^+$, 191 (100) $[M-NHPh]^+$. Compound **12a**: colorless oil; R_f 0.31 (5% EtOAc–petroleum ether); IR (film): ν_{max} 3395, 2926, 2853, 1601, 1503, 1452, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 7.27–7.34 (m, 5H), 7.16 (t, $J = 7.2$ Hz, 2H), 6.69 (t, $J = 7.2$ Hz, 1H), 6.49 (t, $J = 7.6$ Hz, 2H), 3.82 (d, $J = 13.2$ Hz, 1H), 3.73 (d, $J = 13.2$ Hz, 1H), 3.72 (br s, 1H), 3.35–3.38 (m, 1H), 1.99–2.05 (m, 1H), 1.81–1.94 (m, 3H), 1.51–1.71 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): 147.4, 138.7, 129.3, 129.0, 128.7, 127.1, 117.4, 113.6, 58.41, 50.44, 35.74, 31.84, 31.80, 29.29, 25.22, 23.79; ESI-MS: $m/z = 312$ (73) $[M+1]^+$, 219 (100) $[M-NHPh]^+$. Compound **13d**: colorless oil; R_f 0.39 (5% EtOAc–petroleum ether); IR (film): ν_{max} 3403, 2925, 2869, 1601, 1504, 1451, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 7.18 (t, $J = 7.2$ Hz, 2H), 6.69 (t, $J = 7.2$ Hz, 1H), 6.63 (d, $J = 7.2$ Hz, 2H), 3.77 (br s, 1H), 3.71–3.74 (m, 1H), 3.05 (dq, $J = 2.8$, 6.8 Hz, 1H), 2.59–2.63 (m, 2H), 1.65–1.76 (m, 1H), 1.47–1.54 (m, 2H), 1.24–1.27 (m, 6H), 0.95 (d, $J = 3.6$ Hz, 3H), 0.92 (d, $J = 3.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 147.2, 129.5, 117.4, 113.3, 52.27, 43.64, 39.15, 29.64, 27.66, 22.45, 22.42, 16.79, 16.52; ESI-MS: $m/z = 252$ (11) $[M+1]^+$, 159 (100) $[M-NHPh]^+$.