Catalytic asymmetric S-H insertion reaction of carbenoids

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This paper is dedicated to Professor Zhi-Tang Huang on the occasion of his 75th birthday

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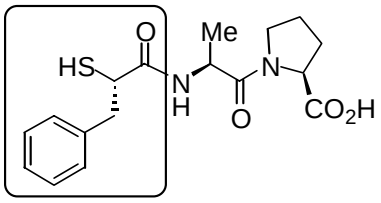
Abstract

Catalytic asymmetric S-H insertion of carbenoids generated from aryldiazoacetates has been investigated with a number of chiral Rh(II) and Cu(I) catalysts. 12 % - 23 % ee enantioselectivity were achieved with chiral Rh(II) catalysts.

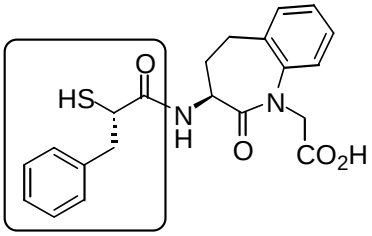
Keywords: S-H Insertion, carbenoids, catalytic asymmetric synthesis

Introduction

Optically active α–mercapto carboxylic acid derivatives are ubiquitous structural subunits in numerous biologically active natural and unnatural compounds. Compounds containing the mercapto or mercaptoacyl moiety often exhibit strong inhibitory effects on metal-containing enzymes (metallozymes). For example, α-mercaptoacyl dipeptides QS-26332 and BMS-182657, as shown in Scheme 1, have been demonstrated to be potent inhibitors of angiotensin converting enzyme (ACE) and neutral endopeptidase.[1] Consequently, the synthesis of enantioenriched α–mercapto carboxylic acids attracted considerable attention.[2] Although some methods have been developed, the stereoselective synthesis of these compounds still remains to be a formidable challenge. To the best of knowledge, so far there has be no highly selective catalytic asymmetric method for preparing enantioenriched α–mercapto carbonyl compounds.



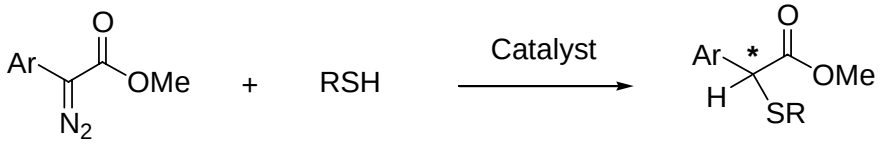
SQ-26332



BMS-182657

Scheme 1

The direct S-H insertion of α–diazocarbonyl compounds with thiol provides an efficient route to α–mercapto carbonyl compounds.[3] It would be highly desirable if the stereochemistry of the S-H insertion can be controlled by the chiral ligands of the metal catalysts. As far as our knowledge is concerned, there is only one report about the investigation in this area. Brunner and Doyle reported the S-H insertion reaction of 3-diazobutan-2-one with thiophenol in the presence of chiral Cu(I) and Rh(II) catalysts. Up to 13.8 % ee was achieved.[4] Since the carbenoids derived from aryldiazoacetate shown exceptionally high enantioselectivity in C-H insertion[5] and moderately high enantioselectivity in sulfur ylide [2,3]sigmatropic rearrangement,[6] we reasoned that it would be worthwhile to investigate the corresponding catalytic asymmetric S-H insertion with aryldiazoacetates. In this paper, we present our investigation along this line (Scheme 2).

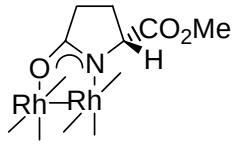


1 **2** **3**

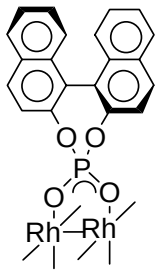
Scheme 2

Results and Discussion

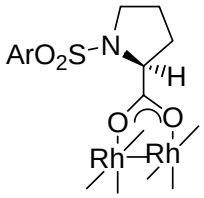
Firstly, the phenyldiazoacetates was employed as the diazo substrate to optimize the reaction conditions. A wide range of chiral catalysts was selected for study (Scheme 3). These chiral catalysts have been demonstrated to be highly effective in asymmetric reaction of carbenoids, such as C-H insertion and cyclopropanation.[7] From the results summarized in Table 1, it can be seen that the decomposition of diazo compounds in the presence of chiral Rh(II) and Cu(I) catalysts gave the expected S-H insertion product in moderate yields, but the enantioselectivities were low. Cu(I) catalysts are generally less effective than Rh(II) catalysts (Table, entries 1-9). The reactions with Cu(I) catalyst were slower and the enantioselectivities were lower. Solvent and temperature have measurable influence over enantioselectivity. It appears that dichloromethane and benzene are better solvents for high enantioselectivity. Ee values could be slightly improved at low temperature. On the other hand, the effect of the structure of thiols on the enantioselectivity was also studied (Table 1, entries 10, 11, 12). Although both aryl and aliphatic thiols were tested, the enantioselectivity was not improved. The optimization experiments concluded that the reaction with thiophenol in CH_2Cl_2 at 0 ^oC with catalyst **7** gives the best enantioselectivity (23 % ee, Table 1, entry 7).



4 $Rh_2(5S\text{-MEPY})_4$

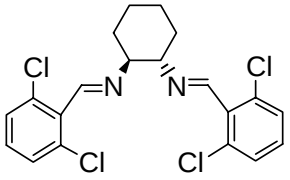


5 $Rh_2(S\text{-BNP})_4$



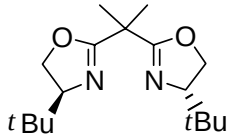
6 $Rh_2(S\text{-TBSP})_4$ (Ar = 4-^{t}BuC$_6$H$_4$)

7 $Rh_2(S\text{-DOSP})_4$ (Ar = 4-$CH_3(CH_2)_{10\text{-}12}C_6H_4$)



$Cu(MeCN)_4PF_6$

8



$Cu(MeCN)_4PF_6$

9

Scheme 3

Table 1. Enantioselectivity of the reaction of phenyldiazoacetate and thiols with chiral Cu(I) or Rh(II) catalysts

Entry	Thiols **2** (R =)	Cat[a]	Solvent	Temp (^{o}C)	Time (h)	ee(%)[b]	Yield (%)[c]
1	Ph	**4**	CH_2Cl_2	rt	8	1	56
2	Ph	**5**	CH_2Cl_2	rt	4	13	49
3	Ph	**5**	PhH	rt	5	10	60
4	Ph	**5**	CH_2Cl_2	0	8	14	52
5	Ph	**5**	n-hexane	rt	12	5	49
6	Ph	**6**	CH_2Cl_2	0	2	21	53
7	Ph	**7**	CH_2Cl_2	0	2	23	61
8	Ph	**8**	CH_2Cl_2	rt	12	7	45
9	Ph	**9**	CH_2Cl_2	rt	12	6	39
10	2-ClPh	**5**	CH_2Cl_2	rt	4	6	47
11	2,6-$(CH_3)_2$Ph	**5**	CH_2Cl_2	rt	4	5	62
12	Cyclohexanyl	**5**	CH_2Cl_2	rt	4	6	72

[a]For Cu(I) catalyst: chiral ligand (11 mol %) was mixed with $Cu(MeCN)_4PF_6$ (10 mol %); for Rh(II) catalyst: 0.5 % mol catalyst is used. [b]Ee's determined by chiral HPLC; Chiracel OJ; hexane/*iso*-propanol. [c]Isolated yields.

Although the enantioselectivity is rather low, we proceeded to apply the best reaction conditions in Table 1 to other aryldiazoacetates. Two Rh(II) catalysts, **5** and **7**, were used, and the results are summarized in Table 2. It demonstrates that moderately low enantioselectivity can be

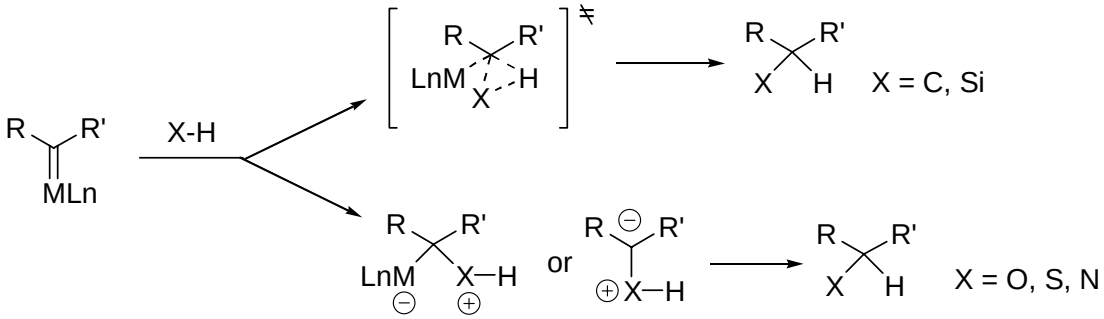
achieved in general with a series of aryl diazoacetates. We could observe a dependence of the enantioselectivity on the substituents in the phenyl ring of the aryldiazoacetate substrates. The Rh(II) catalyst **7** usually works better for the diazo compounds with *para* substituents in the phenyl ring, while the catalyst **5** appeared to be the opposite.

Table 2. Enantioselectivity of the reaction of aryldiazoacetate **1** and thiols **2** (R = Ph) with chiral Rh(II) catalysts **5** and **7**

Entry	Diazo Compound **1** (Ar)	Cat[a]	Time (h)	Ee (%)[b]	Yield[c] (%)
1	C_6H_5	**7**	2	23	61
2	*p*-$MeOC_6H_4$	**5**	3	14	54
3	*p*-$MeOC_6H_4$	**7**	2	13	48
4	*m*-ClC_6H_4	**5**	4	14	62
5	*p*-ClC_6H_4	**7**	2	14	61
6	naphthyl	**5**	4	12	63
7	*p*-BrC_6H_4	**7**	2	18	67

[a]For Rh(II) catalyst: 0.5 % mol catalyst is used. [b]For Rh(II) catalyzed reaction, the temperature is 0 ^oC. Ee's determined by chiral HPLC using the condition given in Table l. [c]Isolated yields.

In contrast to transition metal-catalyzed carbene insertions into C-H or Si-H bonds, in which the catalytic asymmetric induction has reached high level,[7,8] the corresponding insertions into polar X-H bonds (X = O, S, N, etc.) have proved to be much more difficult.[9] This fact may reflect the difference in the reaction mechanism. The insertions into C-H or Si-H bonds follow concerted pathway, while the insertions into polar bonds are believed to follow stepwise process, in which ylide is firstly generated, followed by proton transfer (Scheme 4).[10]



Scheme 4

In summary, we have conducted a systematic investigation on catalytic asymmetric S-H insertion generated from aryldiazoacetates. Unfortunately, the enantioselectivity is not dramatically improved compared with Brunner and Doyle's investigation. Further effort is needed to improve the enantioselectivity to the level that asymmetric S-H insertion reaction can be practically useful.

Experimental Section

General Procedures. All reactions were performed under a nitrogen atmosphere in a flame-dried reaction flask, and the components were added via Syringe. All solvents were distilled prior to use. For chromatography, 100-200 mesh silica gel (Qindao, China) was employed. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz with Varian Mercury 300 spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. IR spectra were recorded with a Nicolet 5MX-S infrared spectrometer. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. Aryl diazoacetates[11] and $Cu(MeCN)_4PF_6$[12] was prepared according to literature procedure. Chiral bisoxazoline ligands, and chiral Rh(II) catalysts Rh_2(*S*-TBSP)$_4$ **6** and Rh_2(*S*-DOSP)$_4$ **7** were purchased from Aldrich. HPLC analysis was performed at HP 1100 apparatus with Chiracel OJ column.

Typical procedure for the reaction of aryldiazoacetate with sulfide catalyzed by Cu(I) complex

In nitrogen atmosphere, $Cu(MeCN)_4PF_6$ (6.25×10^{-3} mmol, 2.2 mg) and ligand **9** (9.4×10^{-3} mmol, 2.3 mg) were added to a 25 mL round-bottom flask. Dry dichloromethane (2 mL) was introduced and the solution was stirred for 1 h. To the slightly blue solution was then added thiols **2** (R = C_6H_4, 1.25×10^{-1} mmol, 14 mg) in dichloromethane (1 mL). The solution turned to light purple and remained homogenous. Methyl phenyldiazoacetate (**1**, Ar = C_6H_4) (6.25×10^{-2} mmol, 11 mg) in dry dichloromethane (10 mL) was added via a syringe over 30 min. The solution was stirred for additional 12 h. Solvent was removed by evaporation and the green oily residue was purified by column chromatography (petroleum ether/ethyl acetate = 20 : 1) to give **3** (Ar = C_6H_4, R = C_6H_4) as oil (6.3 mg, 39 %).

Typical procedure for the reaction of aryldiazoacetate with sulfide catalyzed by Rh(II) complex

In nitrogen atmosphere, catalyst **7** (3.13×10^{-4} mmol, 0.6 mg) was added to a 25 mL round-bottom flask. Dry dichloromethane (4 mL) was introduced and the solution was stirred for 1 h. To the slightly blue solution was then added thiol **2** (Ar' = C_6H_4, 1.25×10^{-1} mmol, 14 mg) in dichloromethane (1 mL). The solution turned to light purple and remained homogenous. The flask was put into an ice bath, then methyl phenyldiazoacetate (**1**, Ar = C_6H_4) (6.25×10^{-2} mmol, 11 mg) in dry dichloromethane (10 mL) was added via a syringe over 30 min. The solution was stirred for additional 2 h. Solvent was removed by evaporation and the green oily residue was purified by column chromatography (petroleum ether/ethyl acetate = 20 : 1) to give **3** (Ar = C_6H_4, R = C_6H_4) as oil (9.8 mg, 61 %).

Methyl 2-thiophenyl-phenylacetate (3, Ar = C_6H_5, R = C_6H_5). IR ($CDCl_3$) 1738 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 3H), 4.91 (s, 1H), 7.20-7.44(m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.53, 56.10, 127.85, 128.17, 128.33, 128.52, 128.71, 128.82, 128.94, 129.01, 129.07, 132.43, 133.49, 135.40, 170.69; MS (*m*/*z*, relative intensity) 258 (M^+, 49), 199 (44), 184 (8), 150 (18), 149 (27), 121 (30), 86 (100), 84 (100), 47 (100), 35 (98); HRMS calcd for $C_{15}H_{14}O_2S$: 258.0714, found 258.0708. HPLC (254 nm) t_R = 20.957 min, t_R = 40.150 min.

Methyl 2-(2-chloro)thiophenyl-phenylacetate (3, Ar = C_6H_5, R = *o*-ClC_6H_4). IR ($CDCl_3$) 1738 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 5.07 (s, 1H), 7.11-7.48 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.75, 54.18, 127.12, 127.25, 128.41, 128.68, 128.84, 128.99, 129.14, 129.82, 133.13, 134.82, 170.41; MS (*m*/*z*, relative intensity) 292 (M^+, 17), 233 (32), 197 (8), 150 (85), 149 (44), 121 (52), 91 (100), 65 (42), 39 (27); HRMS calcd for $C_{15}H_{13}O_2SCl$: 292.0324, found 292.0317. HPLC (254 nm) t_R = 32.876 min, t_R = 56.907 min.

Methyl 2-thiophenyl-*p*-methoxylphenylacetate (3, Ar = *p*-$MeOC_6H_4$, R = C_6H_5). IR ($CDCl_3$) 1737 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.79 (s, 3H), 4.88 (s, 1H), 6.83-6.86 (m, 2H), 7.24-7.27 (m, 4H), 7.35-7.38 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.51, 55.09, 55.47, 113.92, 114.11, 127.30, 127.79, 128.83, 129.55, 132.39, 133.68, 170.04; MS (*m*/*z*, relative intensity) 288 (M^+, 8), 229 (37), 228 (6), 179 (100), 151 (88), 121 (40), 110 (27), 77 (23), 51 (18); HRMS calcd for $C_{16}H_{16}O_2S$: 288.0820, found 288.0813. HPLC (254 nm) t_R = 33.555 min, t_R = 45.345 min.

Methyl 2-thiophenyl-*p*-chlorophenylacetate (3, Ar = *p*-ClC_6H_4, R = C_6H_5). IR ($CDCl_3$) 1738 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 4.85 (s, 1H), 7.25-7.37 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.74, 55.56, 128.24, 128.73, 128.97, 129.81, 132.93, 134.13, 170.41; MS (*m*/*z*, relative intensity) 292 (M^+, 50), 233 (67), 183 (99), 155 (100), 139 (14), 109 (22), 65 (18), 39 (14); HRMS calcd for $C_{15}H_{13}O_2SCl$: 292.0324, found 292.0323. HPLC (254 nm) t_R = 13.507 min, t_R = 17.173 min.

Methyl 2-(2,6-dimethyl)thiophenyl-phenylacetate (3, Ar = C_6H_5, R = 2,6-$(CH_3)_2C_6H_3$). IR ($CDCl_3$) 1732 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 6H), 3.51 (s, 3H), 4.50 (s, 1H), 6.98-7.04 (m, 3H), 7.21-7.22 (m, 3H), 7.30-7.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.76, 29.661, 52.41, 55.02, 128.14, 128.40, 128.46, 129.06, 131.43, 136.04, 143.81, 170.99; MS (*m*/*z*, relative intensity) 286 (M^+, 51), 254 (11), 227 (41), 150 (10), 149 (94), 121 (100), 91 (69), 57 (53), 43 (39); HRMS calcd for $C_{17}H_{18}O_2S$: 286.1027, found 286.1030. HPLC (254 nm) t_R = 16.681 min, t_R = 32.046 min.

Methyl 2-cyclohexanyl -phenylacetate (3, Ar = C_6H_5, R = C_6H_{11}). IR ($CDCl_3$) 1738 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.36 (m, 5H), 1.56-1.72 (m, 1H), 1.91-1.95 (m, 2H), 1.95-1.97 (m, 2H), 2.30-2.66 (m, 1H), 3.72 (s, 3H), 4.66 (s, 1H), 7.23-7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.609, 25.738, 33.126, 43.970, 50.678, 52.632, 127.964, 128.330, 128.552, 136.504, 171.686; MS (*m*/*z*, relative intensity) 265 [$(M+1)^+$, 50], 184 (6), 150 (72), 149 (18), 123 (100), 91 (20), 77 (18), 55 (37), 41 (28); HRMS calcd for $C_{15}H_{20}O_2S$: 264.1184, found 264.1193. HPLC (254 nm) t_R = 9.973 min, t_R = 18.603 min.

Methyl 2-thiophenyl-1-naphthylacetate (3, Ar = Naphthyl, R = C_6H_5). IR ($CDCl_3$) 1739 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 5.67 (s, 1H), 7.22-7.87 (m, 11H), 8.13-8.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.99, 57.14, 123.04, 125.32, 125.85, 126.14, 126.66, 126.79, 127.91, 128.25, 128.97, 130.84, 131.14, 132.36, 133.89, 134.10, 171.22; MS (*m*/*z*, relative intensity) 308 (M^+, 39), 249 (21), 200 (36), 199 (100), 171 (77), 141 (40), 110 (14), 63 (9), 47 (57); HRMS calcd for $C_{19}H_{16}O_2S$: 308.0871, found 308.0861. HPLC (254 nm) t_R = 45.579 min, t_R = 55.289 min.

Methyl 2-thiophenyl-*m*-chlorophenylacetate (3, Ar = *m*-ClC_6H_4, R = C_6H_5). IR ($CDCl_3$) 1738 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 4.84 (s, 1H), 7.23-7.43 (m, 9H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 52.83, 55.80, 126.69, 128.34, 128.46, 128.59, 129.03, 129.80, 132.94, 132.99, 134.42, 137.54, 170.28; MS (*m*/*z*, relative intensity) 292 (M^+, 33), 233 (100), 183 (21), 155 (52), 125 (10), 110 (17), 91 (30), 65 (22), 39 (10); HRMS calcd for $C_{15}H_{13}O_2SCl$: 292.0324, found 292.0317. HPLC (254 nm) t_R = 15.237 min, t_R = 19.157 min.

Methyl 2-thiophenyl-*p*-Bromephenylacetate (3, Ar = *p*-BrC_6H_4, R = C_6H_5). IR ($CDCl_3$) 1738 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 4.84 (s, 1H), 7.26-7.44 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.74, 55.66, 122.36, 128.26, 129.00, 129.54, 130.13, 131.71, 132.94, 134.70, 170.32; MS (*m*/*z*, relative intensity) 336 (M^+, 2), 279 (2), 264 (14), 229 (5), 227 (5), 205 (65), 199 (5), 183 (5), 155 (8), 139 (5), 124 (6), 100 (3), 89 (44), 85 (13), 71 (34), 43 (100), 41 (76), 27 (35); HRMS calcd for $C_{15}H_{13}O_2SBr$: 335.9819, found 335.9824. HPLC (254 nm) t_R = 15.567 min, t_R = 21.933 min.

Acknowledgments

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