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Highly Stereoselective [2,3]-Sigmatropic Rearrangement of Sulfur Ylide Generated through Cu(I) Carbene and Sulfides

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The [2,3]-sigmatropic rearrangement of sulfonium ylide is one of the most versatile bond reorganization processes in organic chemistry and has become a synthetically powerful strategy for simultaneously forming C−C and C−S bonds since their discovery in late 1960s.[1,2] In addition to the base-promoted approach, an alternative and efficient way to generate a sulfonium ylide is by transition metal catalyzed reaction of diazo compounds in the presence of a sulfide, known as the Doyle−Kirmse reaction[3] (Scheme 1). Since Uemura's pioneering work in 1995,[4] asymmetric

**Scheme 1.** The Doyle−Kirmse Reaction with Chiral Catalyst
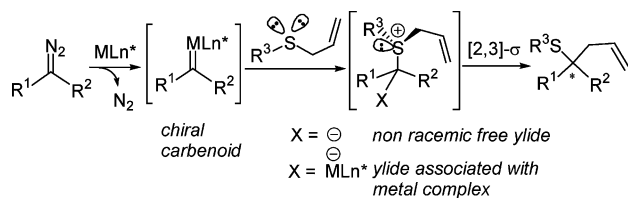
catalysis in [2,3]-sigmatropic rearrangement of sulfur ylides has attracted considerable attention; however, the enantioselectivity for this type of reaction remains mediocre.[5] On the other hand, the transfer of chirality from sulfur to carbon though [2,3]-sigmatropic rearrangement is known to proceed with high selectivity (≥94% ee).[6] Consequently, the generally low enantioselectivity observed in the catalytic reaction may be attributed to the difficulty in the discrimination of heterotopic lone pairs of sulfur in the reaction of chiral carbenoid with allyl sulfide.[5b,7] In this communication, we wish to report the application of a double asymmetric induction approach by combining a chiral camphor sultam auxiliary and Cu(I) catalyst with chiral or achiral ligands.[8] With this approach, the first highly stereoselective [2,3]-sigmatropic rearrangement of sulfur ylide generated through Cu(I) carbene is achieved.

The diazo compounds bearing Oppolzer's camphor sultam auxiliary were prepared,[9] and their reaction with the Cu(I) complex was investigated. Diazo compound **1a** (R = C₆H₅) was used to optimize the reaction conditions (Scheme 2 and Table 1). The Cu(I) complex catalyzed reaction was highly efficient to give product **3a**, from which the chiral auxiliary was removed by reduction with LiAlH₄ to afford **4a** as the final isolated product with good overall yields. First, the effect of sulfide was examined. With chiral diimine (*S,S*)-**7**[10] as the ligand, allyl 2-chlorophenyl sulfide **2d** was found to give the optimal selectivity. Solvent and reaction temperature had only marginal effect on the reaction (entries 5−8). When the reaction was carried out in the absence of ligand, it gave low selectivity (entry 9).

Chiral C₂-symmetric bis(oxazoline) ligands **5** and **6a,b**, which have been successfully utilized in other asymmetric copper-catalyzed carbene transfer reactions,[11] afforded lower enantiomeric excess as compared with that of (*S,S*)-**7** (entries 10−12). Finally, reaction with ligand (*R,R*)-**7** was conducted in order to examine

Scheme 2. Double Asymmetric Induction in [2,3]-Sigmatropic Rearrangement
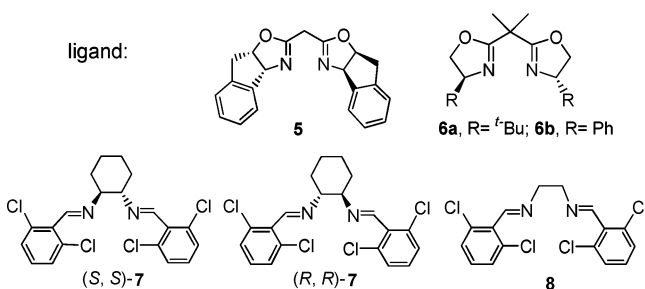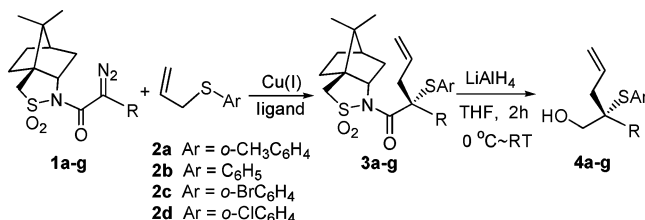
the issue of match and mismatch of the chiral catalysts with the camphor sultam auxiliary (entry 13). The reaction with (*R,R*)-**7** gave slightly lower selectivity as compared to that in the reaction with (*S,S*)-**7**. Furthermore, it was found that both (*R,R*)-**7** and (*S,S*)-**7** afforded the major product **4a** with the same absolute configuration. Thus, the sense of the asymmetric induction was dictated by the chiral auxiliary, rather than the chiral ligand of the Cu(I) catalyst. Interestingly, when achiral ligand **8** was used in the reaction, the enantioselectivity of **4a** could be further improved (entry 14).

Table 1. Optimization of the Reaction Conditions with **1a**

entry	ligand[a]	sulfide	solvent	temp (°C)	reaction time (h)[b]	yield (%)[c]	ee (%)[d]
1	(*S,S*)-**7**	**2a**	CH₂Cl₂	0	10	61	83
2	(*S,S*)-**7**	**2b**	CH₂Cl₂	0	10	64	72
3	(*S,S*)-**7**	**2c**	CH₂Cl₂	0	10	71	88
4	(*S,S*)-**7**	**2d**	CH₂Cl₂	0	10	70	90
5	(*S,S*)-**7**	**2d**	PhCH₃	0	23	51	72
6	(*S,S*)-**7**	**2d**	CH₂Cl₂	−15	16	63	88
7	(*S,S*)-**7**	**2d**	CH₂Cl₂	−35	20	72	87
8	(*S,S*)-**7**	**2d**	CH₂Cl₂	40	1	73	80
9	*e*	**2d**	CH₂Cl₂	0	24	55	30
10	**5**	**2d**	CH₂Cl₂	0	10	82	23
11	**6a**	**2d**	CH₂Cl₂	0	20	79	87
12	**6b**	**2d**	CH₂Cl₂	0	20	84	86
13	(*R,R*)-**7**	**2d**	CH₂Cl₂	0	10	70	80
14	**8**	**2d**	CH₂Cl₂	0	10	72	92

[a] Chiral or achiral ligand (22 mol %) was mixed with Cu(CH₃CN)₄PF₆ (20 mol %). Reaction with 10 mol % catalyst loading gave essentially the same results, with a slightly longer reaction time. *[b]* Refer to the first step only. *[c]* Isolated yields for two steps unless otherwise noted. *[d]* Enantiomeric excess values determined by chiral HPLC. *[e]* No ligand is used.

Table 2. Reaction of **1a**−**g** under Optimized Conditions

entry	1 (R =)	ligand[a]	reaction time[a]	yield (%)[b]	ee (%)[c]
1	**a** (C$_6$H$_5$)	(*S,S*)-**7**	10 h	70	90
2	**a** (C$_6$H$_5$)	**8**	10 h	72	92
3	**b** (*p*-BrC$_6$H$_4$)	(*S,S*)-**7**	6 h	82	90
4	**b** (*p*-BrC$_6$H$_4$)	(*S,S*)-**7**	6 h	92[d]	>99[e]
5	**b** (*p*-BrC$_6$H$_4$)	**8**	6 h	82	94
6	**c** (*m,p*-Cl$_2$C$_6$H$_3$)	(*S,S*)-**7**	12 h	53	86
7	**c** (*m,p*-Cl$_2$C$_6$H$_3$)	**8**	12 h	58	90
8	**d** (*p*-NO$_2$C$_6$H$_4$)	(*S,S*)-**7**	48 h	39 (58)[f]	85
9	**d** (*p*-NO$_2$C$_6$H$_4$)	**8**	48 h	43 (55)[f]	70
10	**e** (CH$_3$)	(*S,S*)-**7**	15 min	81	86
11	**e** (CH$_3$)	(*S,S*)-**7**	15 min	95[d]	96[e]
12	**e** (CH$_3$)	**8**	15 min	67	82
13	**f** (CH$_3$CH=CH)	(*S,S*)-**7**	15 min	74	82
14	**f** (CH$_3$CH=CH)	**8**	15 min	76	78
15	**g** (PhCH=CH)	(*S,S*)-**7**	15 min	82	95
16	**g** (PhCH=CH)	**8**	15 min	78	85

[a] Refer to the first step only. [b] Isolated yields for two steps unless otherwise noted. [c] Enantiomeric excess values determined by chiral HPLC. [d] Isolated yield for the first step. [e] After single recrystallization of the first step product. [f] The yield in parentheses refers to recovered starting diazo compound.

Table 3. Reaction of **1a**−**c,e,f** and Propargyl 2-Chlorophenyl Sulfide **9a,b** under Optimized Conditions

entry	diazo substrate	sulfide	ligand	reaction time[a]	yield (%)[b]	ee (%)[c]
1	**1a**	**9a**	(*S,S*)-**7**	5 h	87	94
2	**1a**	**9a**	**8**	5 h	85	82
3	**1b**	**9a**	(*S,S*)-**7**	5 h	92	91
4	**1b**	**9a**	**8**	5 h	90	88
5	**1c**	**9a**	(*S,S*)-**7**	3 h	86	84
6	**1c**	**9a**	**8**	3 h	83	50
7	**1e**	**9a**	(*S,S*)-**7**	15 min	95	93
8	**1e**	**9a**	**8**	15 min	88	92
9	**1f**	**9a**	(*S,S*)-**7**	15 min	70	91
10	**1f**	**9a**	**8**	15 min	65	90
11	**1b**	**9b**	(*S,S*)-**7**	20 h	77	93
12	**1b**	**9b**	**8**	20 h	73	90
13	**1e**	**9b**	(*S,S*)-**7**	2 h	80	96
14	**1e**	**9b**	**8**	2 h	82	94

[a] Refer to the first step only. [b] Isolated yield for two steps. [c] Enantiomeric excess values determined by chiral HPLC.

The optimized reaction condition (sulfide **2d**/ligand **7a** or **8**/CH$_2$Cl$_2$/0 °C to room temperature) was then applied to **1b**−**g**. The results summarized in Table 2 demonstrate that aryldiazoacetamides, as well as methyl, cinnamoyl, and propenyldiazoacetamide, all reacted with sulfide **2d** smoothly in good yields with good to excellent enantioselectivity. The ligands **7a** and **8** gave comparable results in most cases. The reaction of aryldiazoacetamides bearing a *p*-nitro substituent in the aromatic ring gave slightly low enantiomeric excess values (Table 2, entries 8 and 9). It is worthwhile to note that the rearrangement products **3a**−**g** are all crystalline. Therefore, almost optically pure products of **4a**−**g** could be obtained by single recrystallization of the rearrangement products **3a**−**g** before removal of the camphor sultam auxiliary (for examples, entries 4 and 11). The absolute stereochemistry of the newly formed chiral center was determined to be *R* for **4b** and *S*

for **4e**, by X-ray structures of the corresponding rearrangement products **3b** and **3e**.

As an extension of the double asymmetric approach, the reaction of propargyl 2-chlorophenyl sulfide with diazoacetamides **1a**−**c,e,f** under the optimized condition was investigated. The reaction worked well, and a similar level of enantioselectivity could be achieved with ligand (*S,S*)-**7** for the reaction of sulfide **9a** (Table 3). Ligand **8** afforded comparable results, with only one exception (entry 6). It is noted that the reaction works equally well with methyl-substituted sulfide **9b** (entries 11−14). The absolute configuration of **10d** (R = CH$_3$, R′ = H) is determined as *S* by X-ray structure of the corresponding rearrangement product.

In summary, we have developed a highly stereoselective [2,3]-sigmatropic rearrangement of sulfur ylide generated through Cu(I) carbene and allyl and propargyl sulfides by a double asymmetric induction approach. This approach provides an entry to tertiary chiral sulfides, which are difficult to access.[12]

Supporting Information Available: Experimental procedures, spectra data for new compounds, X-ray structures, and mechanistic study. This material is available free of charge via the Internet at http://pubs.acs.org.

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