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ENANTIOCONTROL IN TANDEM ALLYLIC SULFONIUM YLIDE GENERATION AND [2,3] SIGMATROPIC REARRANGEMENT CATALYZED BY CHIRAL DIRHODIUM(II) COMPLEXES†

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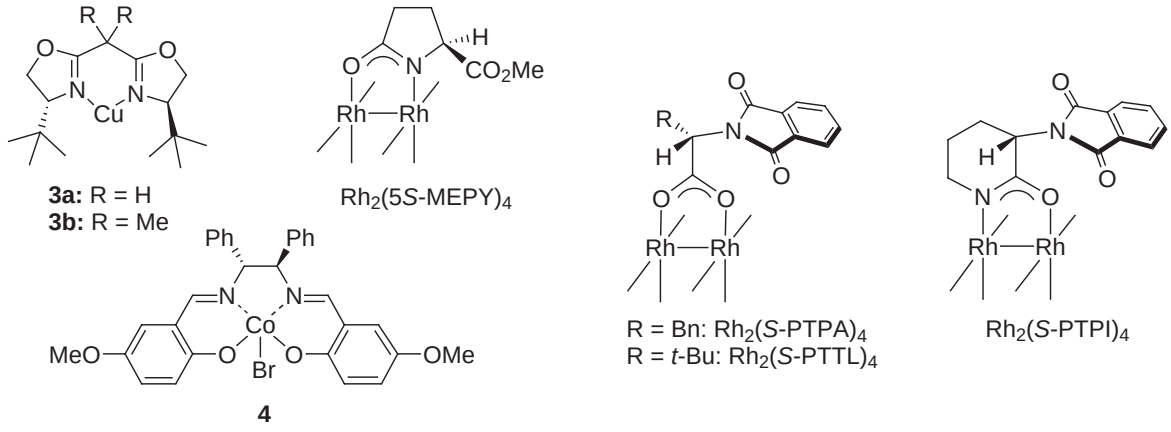
Abstract – Tandem sulfonium ylide formation and [2,3] sigmatropic rearrangement sequence from allylic sulfides and diazoacetates has been effected by using dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinonate], Rh_2(*S*-PTPI)$_4$, as a chiral catalyst, displaying enantioselectivities of up to 58%. It has been demonstrated that the [2,3] sigmatropic rearrangement proceeds through chiral, nonracemic free sulfonium ylides dissociated from the dirhodium(II) complex.

Allylic sulfonium ylides readily undergo a [2,3] sigmatropic rearrangement which features a carbon-carbon bond formation with a high degree of stereocontrol.[1] Considering that catalytic generation and [2,3] sigmatropic rearrangement of sulfonium ylides from allylic sulfides and a variety of metal carbenes have recently enjoyed widespread attention as an alternative to the process *via* deprotonation or desilylation of the corresponding sulfonium salts,[2] the development of an enantioselective version of this sequence mediated by chiral catalysts should be a significant addition to the field of asymmetric synthesis.[3]

Uemura and co-workers were the first to demonstrate asymmetric induction (up to 20% ee) in the reaction of (*E*)-cinnamyl phenyl sulfide (**1a**) and ethyl diazoacetate (**2a**) employing bis(oxazoline)-Cu(I) complex (**3a**) or Rh_2(5*S*-MEPY)$_4$ as a catalyst.[4] Recently, the bis(oxazoline)-Cu(I)-catalyzed process has been systematically investigated by McMillen and co-workers, in which a significant enhancement of up to 52% ee can be attained by the combinational use of the sterically demanding allyl 2,6-dimethyphenyl sulfide and bis(oxazoline)-Cu(I) complex (**3b**).[5] Katsuki and co-workers have reported that chiral salen-Co(III)-complex (**4**) is an efficient catalyst for the reaction of **1a** with *tert*-butyl diazoacetate (**2b**) to display the highest degree of enantioselectivity (64% ee) known for this type of reactions.[6] They have also demonstrated that the [2,3] sigmatropic rearrangement proceeds through chiral, nonracemic free sulfonium ylides rather than through the Co-salen-associated ylides. In this

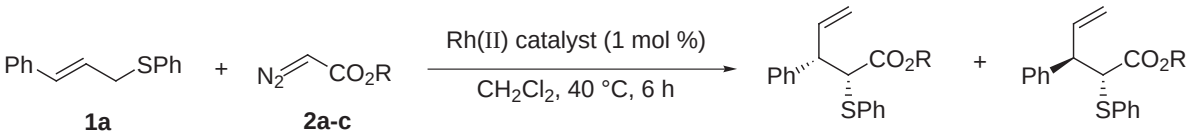
† Dedicated to Professor Shô Itô on the occasion of his 77th birthday.



respect, it has recently been suggested that metal-associated ylides are involved in the rearrangement step with their iodonium and oxonium counterparts.[7,8] We have recently documented that tandem formation and 1,3-dipolar cycloaddition of keto- or ester-carbonyl ylides under the influence of chiral dirhodium(II) carboxylates incorporating *N*-phthaloyl-(*S*)-amino acids as bridging ligands gives cycloadducts in good yields and with up to 93% ee,[9] which provides conclusive evidence for the intermediacy of the chiral rhodium(II)-associated carbonyl ylides in the cycloaddition step. Thus, our interest has now been centered on the mechanistic pathway for asymmetric induction in tandem allylic sulfonium ylide formation and [2,3] sigmatropic rearrangement sequence catalyzed by our dirhodium(II) complexes.

At the outset, we explored the reaction of (*E*)-cinnamyl phenyl sulfide (**1a**) and ethyl diazoacetate (**2a**) in the presence of 1 mol % of chiral dirhodium(II) carboxylates. The use of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate], Rh_2(*S*-PTPA)$_4$, afforded rearrangement products (**5a** and **6a**) as a 62:38

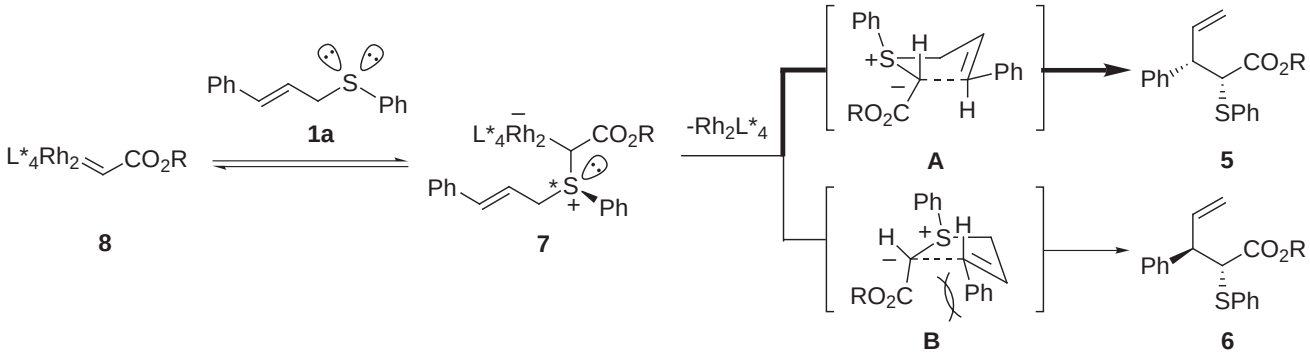
Table 1. Enantioselective Intermolecular Sulfonium Ylide Formation / [2,3] Sigmatropic Rearrangement Catalyzed by Rh(II) Complexes



entry	diazo ester	R	Rh(II) catalyst	% yield of **5**+**6**[a]	ratio of **5** : **6**[b]	% ee **5**	% ee **6**
1	**2a**	Et	Rh_2(*S*-PTPA)$_4$	61	62 : 38	0[c]	0[c]
2	**2a**	Et	Rh_2(*S*-PTTL)$_4$	60	62 : 38	0[c]	0[c]
3	**2a**	Et	Rh_2(*S*-PTPI)$_4$	81	66 : 34	14[c]	14[c]
4	**2b**	*t*-Bu	Rh_2(*S*-PTPA)$_4$	46	80 : 20	<2[d]	<2[d]
5	**2b**	*t*-Bu	Rh_2(*S*-PTTL)$_4$	42	83 : 17	<2[d]	<2[d]
6	**2b**	*t*-Bu	Rh_2(*S*-PTPI)$_4$	61	83 : 17	23[d]	24[d]
7	**2c**	CH(*i*-Pr)$_2$	Rh_2(*S*-PTPI)$_4$	61	94 : 6	53[d]	-[e]

[a] Isolated yield. Carbene dimers, maleate and fumarate were obtained as the only detectable by products in all cases. [b] Determined by ^{1}H NMR after $LiAlH_4$ reduction and acetylation. [c] Determined by HPLC (Daicel Chiralcel OD). [d] Determined by HPLC (Daicel Chiralcel OJ) after $LiAlH_4$ reduction. [e] Could not be accurately determined due to an exceptionally high order of diastereoselectivity.

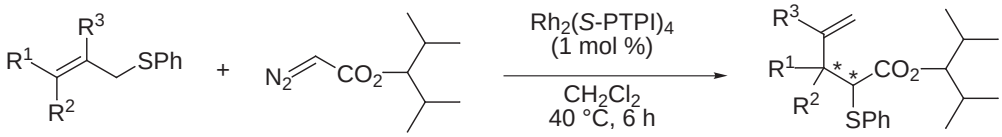
mixture of *erythro* and *threo* isomers in 61% yield, but no asymmetric induction was observed in either case (Table 1, entry 1). A virtually similar result was obtained with the use of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, characterized by a bulky *tert*-butyl group (entry 2). While a significant increase in diastereoselectivity was observed with the sterically demanding *tert*-butyl diazoacetate (**2b**), we were disappointed here again to find that there was little asymmetric induction (entries 4 and 5). After several unsuccessful attempts, it was found that this goal could be achieved by the use of dirhodium(II) carboxamidate complex, dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinonate], Rh_2(*S*-PTPI)$_4$, which has proven to be the catalyst of choice for intermolecular enantioselective cyclopropanations of styrenes or 1,1-disubstituted alkenes with diazoacetates.[10] A steady increase in diastereo- and enantioselectivity was observed on increasing the steric bulk of the ester alkyl group (entries 3, 6 and 7), in which 2,4-dimethyl-3-pentyl diazoacetate (**2c**) provided the highest values (**5c**:**6c**=94:6, ee of **5c**; 53%) (entry 7).[11,12] From the fact that *erythro*/*threo* diastereoselectivities are independent of the nature of dirhodium(II) catalysts used but markedly dictated by the size of the ester group (entries 1-3 vs. 4-6), it is evident that the [2,3] sigmatropic rearrangement proceeds through free sulfonium ylides formed by metal dissociation from the dirhodium(II)-bound intermediate (**7**) as mentioned by Katsuki with chiral salen-Co(III) complex.[6] Based on the further findings that virtually similar enantioselectivities were obtained with *erythro* and *threo* products (**5** and **6**) (entries 1-6), the observed *erythro*/*threo* diastereoselectivity can be rationalized by assessing two envelope transition states (**A**) and (**B**).[6b] Clearly, the transition state (**A**) leading to *erythro* isomer (**5**) is preferred over the transition state (**B**) to give *threo* isomer (**6**) because of severe steric repulsion between the ester group and the phenyl group in **B**, which also explains a function of the size of the ester group in diazoacetates.



Provided that the [2,3] sigmatropic rearrangement occurs at a faster rate than the racemization at the sulfonium center,[13,14] the magnitude of enantioselection observed here indicates the level of differentiation between enantiotopic lone pairs on the sulfur atom by the chiral rhodium(II) carbene intermediate (**8**).[15] In this regard, it is worthy of note that the chiral rhodium(II) carbene intermediate (**8**) derived from Rh_2(*S*-PTPI)$_4$ captures selectively one of the enantiotopic sulfur lone pairs to form the configurationally stable sulfonium ylide, while that from chiral dirhodium(II) carboxylates such as Rh_2(*S*-PTPA)$_4$ or Rh_2(*S*-PTTL)$_4$ exhibits virtually no selectivity at this step.

In order to establish the efficacy of using Rh_2(*S*-PTPI)$_4$ in conjunction with 2,4-dimethyl-3-pentyl diazoacetate (**2c**), we then extended the present protocol to other allylic phenyl sulfides (**1b**-**e**) than

Table 2. Enantioselective Intermolecular Sulfonium Ylide Formation / [2,3] Sigmatropic Rearrangement Catalyzed by Rh_2(*S*-PTPI)$_4$



1a-e **2c** **5,6,9-12**

	sulfide **1**				products		
entry		R^1	R^2	R^3		% yield[a]	% ee
1	**1a**	Ph	H	H	**5**,**6**	61[b]	53[c,d]
2	**1b**	H	H	H	**9**	75	58[e]
3	**1c**[f]	Me	H	H	**10**	75[g]	45[c,h]
4	**1d**	Me	Me	H	**11**	72	27[e]
5	**1e**	H	H	Me	**12**	63	19[e]

[a] Isolated yield. [b] Yield of a 94:6 mixture of *erythro* and *threo* products. [c] Ee of *erythro* isomer. [d] Determined by HPLC (Daicel Chiralcel OJ) after $LiAlH_4$ reduction. [e] Determined by HPLC (Daicel Chiralcel OD). [f] *E*:*Z* = 93:7. [g] Yield of a 85:15 mixture of *erythro* and *threo* products. [h] Determined by HPLC (Daicel Chiralcel OD) after $LiAlH_4$ reduction.

cinnamyl phenyl sulfide (**1a**). The results are summarized in Table 2. Allyl phenyl sulfide (**1b**) used as the standard for purposes of comparison provided the highest value (58% ee) reported to date for dirhodium(II)- and copper(I)-catalyzed reactions of achiral allylic sulfides with diazoacetates (entry 2). Lower enantioselectivities were generally observed with phenyl or methyl substitution on the carbon-carbon double bond relative to **1b**, in which a dramatic drop in enantioselectivities was observed with methallyl and prenyl phenyl sulfides (**1d** and **1e**) (entries 4 and 5).

In summary, we have demonstrated the effective use of Rh_2(*S*-PTPI)$_4$ as a catalyst for enantioselective tandem allylic sulfonium ylide formation and [2,3] sigmatropic rearrangement sequence, albeit with a limited range of allylic sulfides. It has also been demonstrated that the [2,3] sigmatropic rearrangement proceeds through chiral, nonracemic free sulfonium ylides dissociated from the dirhodium(II) complex. Further extension of the present method to rearrangements *via* oxonium or ammonium ylide formation is currently in progress.

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11. It is noteworthy that a similar trend has been observed in Rh_2(*S*-PTPI)$_4$-catalyzed intermolecular cyclopropanations.
12. *Representative procedure.* A solution of 2,4-dimethyl-3-pentyl diazoacetate (**2c**) (40.0 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) was added through a syringe pump over 5 h to a refluxing CH_2Cl_2 (1 mL) solution of (*E*)-cinnamyl phenyl sulfide (**1a**) (73.7 mg, 0.33 mmol) and THF adduct of Rh_2(*S*-PTPI)$_4$ (2.6 mg, 1 mol %). After stirring at this temperature for an additional 1 h, the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel 15 g, 1:2 benzene/hexane) to give **5c** and **6c** as an inseparable mixture of *erythro* and *threo* isomers in a ratio of 94:6 (50.4 mg, 61%); white solid; mp 81-82 °C; $[\alpha]_D^{23}$ –68.6 (c=1.53, $CHCl_3$); IR νmax (film) 2969, 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.49 (d, *J* = 6.6 Hz, 3H), 0.51 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H), 1.61-1.78 (m, 2H), 3.78 (dd, *J* = 8.3, 11.2 Hz, 1H), 3.98 (d, *J* = 11.2 Hz, 1H), 4.38 (t, *J* = 5.9 Hz, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.2 Hz, 1H), 6.15 (ddd, *J* = 8.3, 10.2, 17.2 Hz, 1H), 7.15-7.55 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.7, 17.2, 19.1, 19.3, 29.1, 29.6, 51.1, 55.6, 83.8, 117.5, 127.0, 127.7, 128.2, 128.6, 128.8, 132.5,

134.1, 138.4, 141.2, 171.0; HR-EI-MS *m/z*: Calcd for $C_{24}H_{30}O_2S$ (M^+) 382.1966, found 382.1975. According to the procedure of Katsuki,[6b] a mixture of *erythro* and *threo* products (**5c** and **6c**) was submitted to reduction with $LiAlH_4$ and acetylation of the resulting alcohols. The *erythro*/*threo* ratio was determined by ^1H NMR spectroscopy [methyl signals in acetyl group: δ 1.95 (*erythro*) and 1.99 (*threo*)]. The enantiomeric excess of the *erythro* isomer (**5c**) was determined to be 53% by HPLC analysis of the corresponding alcohols, whereas that of the *threo* isomer (**6c**) could not be determined accurately owing to an exceptionally high order of diastereoselectivity: Daicel Chiralcel OJ, 9:1 hexane/2-propanol, 0.5 mL/min, t_R = 40 min (*erythro* major), t_R = 56 min (*erythro* minor), t_R = 65 min (*threo* major), t_R = 79 min (*threo* minor).

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14. For racemization of chiral sulfonium ylides, see: (a) D. Darwish and R. L. Tomilson, *J. Am. Chem. Soc.*, 1968, **90**, 5938; (b) S. J. Campbell and D. Darwish, *Can. J. Chem.*, 1974, **52**, 2953.
15. The role of the ester group in enantioselection has not yet been defined; however, it seems likely that the steric effects would give priority to the approach of one of the two enantiotopic sulfur lone pairs to the rhodium(II) carbene center.