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Enantioselective [2,3]-sigmatropic and [1,2]-Stevens rearrangements via intramolecular formation of allylic oxonium ylides catalyzed by chiral dirhodium(II) carboxylates

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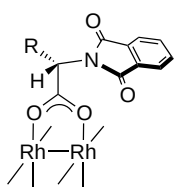
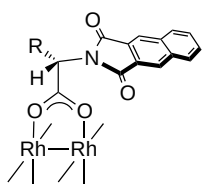
Abstract—Tandem intramolecular generation and rearrangement of allylic oxonium ylides from α-diazo β-keto esters has been effected with the aid of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] in toluene, providing benzofuran-3-ones via [2,3]-sigmatropic rearrangement in up to 76% ee. In systems with crotyl and prenyl substituents, products arising from the less common [1,2]-Stevens rearrangement as a side reaction have also been obtained in up to 66% ee. It is suggested that competitive [2,3]- and [1,2]-rearrangements proceed through a common, chiral rhodium(II)-bound oxonium ylide intermediate.

Since the first successful examples demonstrated independently by Pirrung[1] and Johnson,[2] the tandem formation and [2,3]-sigmatropic or [1,2]-Stevens rearrangement of cyclic oxonium ylides from a dirhodium(II) or copper(I) complex-catalyzed decomposition of diazocarbonyl compounds has evolved as a powerful means for the construction of substituted cyclic ethers and carbocycles.[3] Consequently, the development of a catalytic enantioselective version of this sequence would be a significant addition to the field of asymmetric synthesis.[4] A prime requirement for asymmetric induction is the use of chiral metal complex-associated oxonium ylide intermediates in the rearrangement step as it is generally believed that energy barriers to configurational inversion of chiral, non racemic, free oxonium ylides[5] detached from the chiral catalyst are very small when compared with the corresponding sulfonium ylides.[6] In 1992, McKervey and co-workers demonstrated the first example of asymmetric induction (up to 30% ee) in the [2,3]-sigmatropic rearrangement of cyclic allylic oxonium ylides derived from the diazo decomposition of α-diazo-β-keto ester in the presence of $Rh_2(HCO_3)_2[(+)\text{-Phos}]_2\cdot 5H_2O$ [(+)-PhosH=(*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate].[7] Doyle and co-workers subsequently demonstrated that this methodology could be extended to the [1,2]-Stevens rearrangement of cyclic oxonium ylides, in which high levels of asymmetric induction (up to 88% ee) were achieved with the use of $Rh_2(4S\text{-MPPIM})_4$.[8–10] In this context, we recently reported that the tandem formation and intermolecular 1,3-dipolar cycloaddition of keto- or ester-carbonyl ylides under the influence of chiral dirhodium(II) carboxylates incorporating *N*-phthaloyl- or *N*-benzene-fused phthaloyl-(*S*)-amino acids as bridging ligands gives cycloadducts with up to 93% ee.[11] These results provide conclusive evidence for the existence of chiral rhodium(II)-associated carbonyl ylide intermediates in the cycloaddition step since free carbonyl ylides are achiral. As a logical extension of our previous studies, we now address the issue of enantiocontrol in the tandem cyclic allylic oxonium ylide generation and rearrangement sequence, focusing on the mechanistic pathway for asymmetric induction as well as an assessment of our dirhodium(II) catalysts in this system.





R=Bn: Rh_2(S-PTPA)$_4$, R=Me: Rh_2(S-PTA)$_4$
R=Pr^i: Rh_2(S-PTV)$_4$, R=Bu^t: Rh_2(S-PTTL)$_4$
R=Ph: Rh_2(S-PTPG)$_4$

R=Pr^i: Rh_2(S-BPTV)$_4$
R=Bu^t: Rh_2(S-BPTTL)$_4$

Keywords: rhodium and compounds; ylides; rearrangements; enantiocontrol; diazo compounds.

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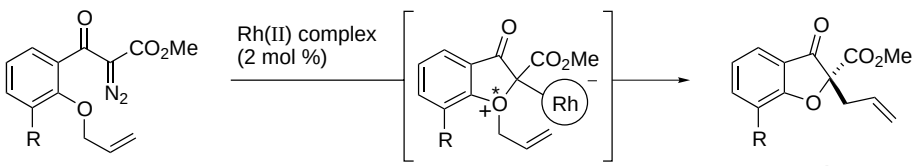
Following the pioneering work of McKervey,[7] we initially explored tandem allylic oxonium ylide formation and [2,3]-sigmatropic rearrangement from α-diazo-β-keto ester **1a** in dichloromethane at room temperature using our dirhodium(II) carboxylate catalysts (Table 1, entries 1–7). While a consistent sense of asymmetric induction was observed in all cases, ee values were found to be dependent on the catalyst. Of dirhodium(II) carboxylate catalysts, $Rh_2(S\text{-PTTL})_4$ proved to be by far the most effective catalyst, generating benzofuran-3-one derivative **2a**,[12] $[\alpha]_D^{23}$ −79.1 (*c* 1.70, $CHCl_3$), in 77% yield and with 54% ee (entry 5).[13] While our studies were in progress, McKervey and co-workers reported that the highest enantiocontrol (60% ee) with substrate **1b** devoid of the methyl group was achieved through the combinational use of $Rh_2(S\text{-PTTL})_4$ as a catalyst and hexane as a solvent where little effect of reaction temperatures of 20 and 69°C was also highlighted.[15] While the selection of $Rh_2(S\text{-PTTL})_4$ as the superior catalyst was confirmed by our work, the solvent survey revealed that toluene was the optimal solvent for this transformation, bringing about a beneficial effect on the enantioselection as well as the reaction rate (entries 5 versus 11). Thus, enhancement of up to 74% ee was possible by conducting the reaction in toluene at 0°C (entry 12), though a little variation in enantioselectivity was observed by lowering the reaction temperature to −10°C where product yield was substantially reduced (entry 13). While ether and ethyl acetate exhibited nearly the same enantioselectivities as dichloromethane (entries 9 and 10), hexane was found to be the least effective in terms of both product yield and enantioselectivity (entry 8). It is also worth noting that the reaction with **1b** required significantly longer time to reach completion compared with **1a** and produced lower enantioselectivity (58% ee, entry 14).[16] The reason for the advantage of the methyl group in **1a** is unclear at this time.

Having identified the effectiveness of the combinational use of $Rh_2(S\text{-PTTL})_4$ as a catalyst and toluene as a solvent, we then investigated the tandem reaction of α-diazo-β-keto esters **1c**–**e** containing *trans*- and *cis*-crotyl and prenyl substituents (Table 2). Somewhat surprisingly, the reactions of **1c**–**e** were found to produce a mixture of [2,3]-sigmatropic rearrangement products, **2c**–**e**,[12] and [1,2]-Stevens rearrangement products, **3c**–**e**,[12] with the former being favored.[17] While similar and reasonable degrees of enantioselectivity were observed in each series, the diastereomer ratios of **2c**,**d** were unexpectedly poor. It has been documented that cyclic allylic oxonium ylides have a virtually complete preference for symmetry-allowed [2,3]-sigmatropic rearrangements over [1,2]-Stevens rearrangements via a radical dissociation–recombination mechanism.[18] However, there are a few examples where the concerted

Table 1. Enantioselective cyclic allylic oxonium ylide formation/[2,3]-sigmatropic rearrangement catalyzed by chiral dirhodium(II) complexes[a]



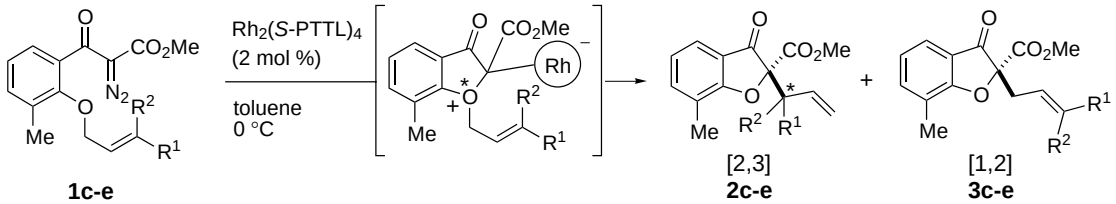
Entry	Substrate	Rh(II) complex	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**	$Rh_2(S\text{-PTPA})_4$	CH_2Cl_2	23	1	72	26
2	**1a**	$Rh_2(S\text{-PTA})_4$	CH_2Cl_2	23	1	83	33
3	**1a**	$Rh_2(S\text{-PTV})_4$	CH_2Cl_2	23	1	74	32
4	**1a**	$Rh_2(S\text{-PTPG})_4$	CH_2Cl_2	23	1	82	41
5	**1a**	$Rh_2(S\text{-PTTL})_4$	CH_2Cl_2	23	1	77	54
6	**1a**	$Rh_2(S\text{-BPTV})_4$	CH_2Cl_2	23	1	83	26
7	**1a**	$Rh_2(S\text{-BPTTL})_4$	CH_2Cl_2	23	1	68	37
8	**1a**	$Rh_2(S\text{-PTTL})_4$	Hexane	23	10	48	48
9	**1a**	$Rh_2(S\text{-PTTL})_4$	Et_2O	23	15	81	56
10	**1a**	$Rh_2(S\text{-PTTL})_4$	AcOEt	23	6	78	54
11	**1a**	$Rh_2(S\text{-PTTL})_4$	Toluene	23	0.2	73	64
12	**1a**	$Rh_2(S\text{-PTTL})_4$	Toluene	0	2	70	74
13	**1a**	$Rh_2(S\text{-PTTL})_4$	Toluene	−10	5	54	76
14	**1b**	$Rh_2(S\text{-PTTL})_4$	Toluene	0	6	79	58

[a] The following procedure is representative (entry 12): bis(ethyl acetate) adduct of $Rh_2(S\text{-PTTL})_4$ (6.2 mg, 2 mol%) was added in one portion to a solution of α-diazo-β-keto ester **1a** (60.6 mg, 0.22 mmol) in toluene (2.2 mL) at 0°C. After 2 h of stirring at this temperature, the resultant greenish solution was concentrated in vacuo and purified by column chromatography (silica gel, 10:1 hexane:ethyl acetate) to give benzofuran-3-one derivative **2a** (38.0 mg, 70%) as a colorless oil.

[b] Isolated yield.

[c] Determined by HPLC [column, Daicel Chiralpak AD; eluent, 250:1 hexane:*i*-PrOH; flow rate, 1.0 mL/min; retention time, 16.5 min (major) and 31.7 min (minor)].

Table 2. Enantioselective cyclic allylic oxonium ylide formation/rearrangement catalyzed by $Rh_2(S\text{-PTTL})_4$[a]



1c-e **2c-e** **3c-e**

Entry	Substrate	R^1	R^2	Time (h)	Yield (%)[b]	**2**:**3**[c]	dr of **2**[d]	Ee (%)[e] **2**	Ee (%)[e] **3**
1	**1c**	Me	H	2	63	92:8	60:40	70, 72[f]	64[g]
2	**1d**	H	Me	2.5	63	82:18	49:51	72, 65[f]	66[g,h]
3	**1e**	Me	Me	6	37	71:29	–	59[i]	65[i]

[a] All reactions were performed as described in Table 1.
[b] Combined yield of **2** and **3**.
[c] Determined by HPLC (column, zolbax® Sil; eluent, 50:1 hexane:ethyl acetate).
[d] Determined by 400 MHz ^1H NMR.
[e] Determined after separation of **2** and **3** with $AgNO_3$–SiO_2 TLC.
[f] Determined by HPLC (column, Daicel Chiralpak AD-H; eluent, 100:1 hexane:*i*-PrOH).
[g] Determined by HPLC (column, Daicel Chiralpak AD-H; eluent, 200:1 hexane:*i*-PrOH).
[h] Enantiomeric excess for *cis*-**3d**.
[i] Determined by HPLC (column, Daicel Chiralpak AD; eluent, 250:1 hexane:*i*-PrOH).

[2,3]-rearrangement pathway is disfavored by a severe strain so as to permit the stepwise mechanism to compete or dominate.[2,19,20] From the data, it is conceivable that the contribution of the [1,2]-Stevens rearrangement is becoming greater on increasing steric interactions (*trans*-crotyl<*cis*-crotyl<prenyl) encountered during the concerted [2,3]-sigmatropic rearrangement. It is worthy of note that the *trans* geometry of the crotyl group in **1c** was fully preserved in the [1,2]-rearrangement, and more significantly the *cis* geometry in **1d** was also retained to a considerable extent.[21] This result suggests that recombination of the radical pair intermediates is immediate. While the preferred absolute configurations of the products have not yet been determined, the uniform sense of enantioselection in both [2,3]-sigmatropic and [1,2]-Stevens rearrangements is supported by CD curve comparison. Considering that their mechanistic profiles are different, this observation, together with the foregoing similar levels of asymmetric induction observed in each series, strongly suggests that both rearrangements proceed through a common, chiral rhodium(II)-associated oxonium ylide (Fig. 1). Based on the mechanistic hypotheses proposed by Doyle[9d] and Clark,[9b] it seems likely that both rearrangements proceed with inversion of configuration at the rhodium-bound carbon. This proceeds by a mechanism in which allylic substituents extend outward to avoid intrusion into the rhodium framework and migrate in [2,3]- and [1,2]-shift modes during dissociation of the carbon–rhodium bond. Consequently, the magnitude of enantioselection indicates the level of differentiation between the two diastereotopic oxygen lone pairs by the chiral rhodium(II) carbene intermediate.

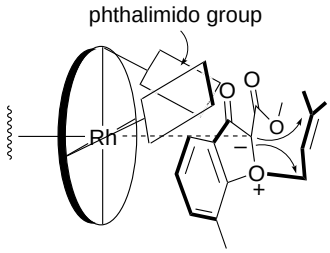
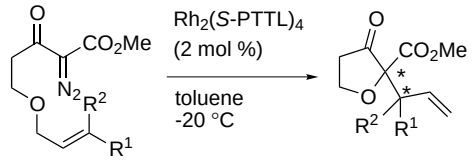


Figure 1.

Finally, we examined the enantioselective tandem reaction of the aliphatic substrate **4a**,**b** (Eq. (1)).[7,9b,15] The catalysis of **4a**,**b** with $Rh_2(S\text{-PTTL})_4$ in toluene proceeded smoothly at –20°C to give [2,3]-sigmatropic rearrangement products **5a**,**b** as the sole products in good yields. No evidence of [1,2]-rearrangement products was found. While much lower enantioselectivities than those with the corresponding aromatic substrates **1c**,**e** were observed, an exceedingly high order of diastereoselection with **4a** is worth noting. These results suggest that the presence of a phenyl ring in the tether, which might interact sterically with phthaloyl groups protruding toward the rhodium(II) carbene center,[22] is responsible for the reasonable levels of enantioselection in this methodology.



(1)

4a: R^1=Me, R^2=H
4b: R^1=R^2=Me

5a 79%, 22% ee (*dr* = 96:4)
5b 73%, 23% ee

In summary, we have demonstrated that the combinational use of $Rh_2(S\text{-PTTL})_4$ as a catalyst and toluene as a solvent is effective for enantiocontrol in tandem cyclic allylic oxonium ylide generation and rearrangement sequence from α-diazo-β-keto esters, albeit with limited substrates. In addition to the observation of the enantioselective [2,3]-sigmatropic rearrangement, the observation of the competing enantioselective [1,2]-Stevens rearrangement of cyclic allylic oxonium ylides strongly suggests that both rearrangements proceed through a common, chiral rhodium(II)-bound oxonium ylide. Further work is in progress to determine the preferred absolute stereochemistry of the products.

Acknowledgements

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12. The absolute stereochemistry of the product depicted here has not been established.
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17. Product formation via the [1,2]-Stevens rearrangement observed here was surprising as Pirrung and co-workers have demonstrated, in the key-step of their elegant total synthesis of (+)-griseofulvin, that cyclic allylic oxonium ylides generated by $Rh_2(OPiv)_4$-catalyzed decomposition of the structurally related α-diazo-β-keto ester carrying the (*S*)-(*E*)-3-penten-2-yl moiety led to the exclusive and stereocontrolled formation of a [2,3]-sigmatropic rearrangement product. The stereochemistry of this product was rationalized through a highly ordered transition state model: Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561–8562.
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