Enantioselective Construction of a 2,8-Dioxabicyclo[3.2.1]octane Ring System via [2,3]-Sigmatropic Rearrangement of Oxonium Ylide Using Chiral Dirhodium(II) Carboxylates

Naoyuki Shimada,[1] Seiichi Nakamura,[1] Masahiro Anada,[1] Motoo Shiro,[2] and Shunichi Hashimoto*[1]
[1]*Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812*
[2]*Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196-8666*

(Received March 5, 2009; CL-090226; E-mail: hsmt@pharm.hokudai.ac.jp)

Dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TFPTTL)$_4$, is an exceptionally efficient catalyst for enantioselective tandem cyclic oxonium ylide formation and [2,3]-sigmatropic rearrangement from α-diazo-β-ketoester bearing cyclic allylic acetal functionality, providing the 2,8-dioxabicyclo[3.2.1]octane core structure of zaragozic acids in up to 93% ee.

Dirhodium(II) or copper complex-catalyzed tandem intramolecular oxonium ylide formation and rearrangement sequence from diazocarbonyl precursors offers a powerful means for the rapid construction of substituted cyclic ethers[1,2] and it has found many applications in the synthesis of natural products.[3] Consequently, the development of an enantioselective version of this sequenece catalyzed by chiral metal complexes has become a challenging objective.[4,5] It has recently been suggested that a prime requirement for high levels of asymmetric induction in this process is the use of chiral catalyst-associated oxonium ylide intermediates formed through differentiation of enantiotropic ethereal oxygen lone pairs by chiral metallocarbene as it is considered unlikely that the configuration of chiral, free oxonium ylides detached from the chiral catalyst would be preserved prior to a subsequent rearrangement.[6,7] In previous studies, we demonstrated that the tandem formation and [2,3]-sigmatropic rearrangement of cyclic allylic[8] and propargylic[9] oxonium ylides from α-diazo-β-ketoesters under the influence of dirhodium(II) tetrakis[*N*-tetraphthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$ (**1a**) (Figure 1), gives rearrangement products in up to 76% ee and 79% ee, respectively.

In 1998, Calter and Sugathapala reported a novel and elegant approach to construct the 2,8-dioxabicyclo[3.2.1]octane core structure **4** of zaragozic acids (e.g., zaragozic acid C, Figure 2),[10] inhibitors of the enzyme squalene synthase, based on the generation and [2,3]-sigmatropic rearrangement of a bicyclic oxonium ylide from $Rh_2(OAc)_4$-catalyzed decomposition of α-diazo-β-ketoester **3** (eq 1).[11] They also demonstrated asymmetric induction in this reaction, wherein Rh_2(*S*-TBSP)$_4$ (**2**) afforded **4** in 47% yield and with the highest enantioselectivity

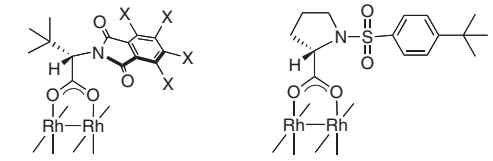


Figure 1. Chiral dirhodium(II) carboxylates.

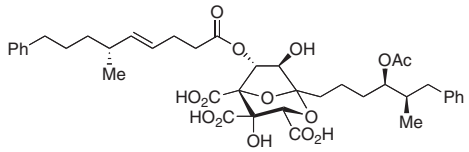
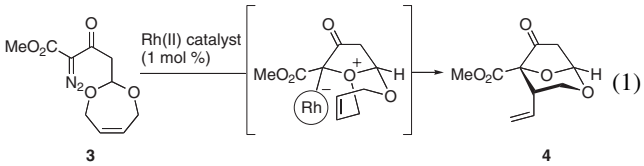


Figure 2. Structure of zaragozic acid C.

of 34% ee. As a logical extension of our studies, we directed our efforts to improving the enantioselectivity and product yield in this challenging system with a broad selection of our dirhodium(II) caraboxylate catalysts. Herein, we report that this goal can be achieved by using Rh_2(*S*-TFPTTL)$_4$ (**1b**),[12] thereby providing the zaragozic acid core structure **4** in 72% yield with 93% ee.



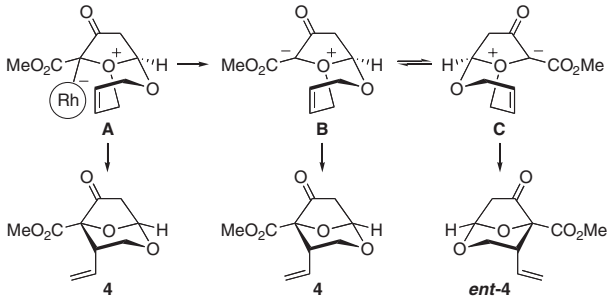
We initially explored tandem oxonium ylide formation and rearrangement from diazoketoester **3** in toluene using 1 mol % of Rh_2(*S*-PTTL)$_4$ (**1a**) (Table 1, Entry 1). The reaction proceeded at 0 °C to completion in less than 10 min, giving [2,3]-sigmatropic rearrangement product **4** in 36% yield. The enantioselectivity of this reaction was determined to be 7% ee by HPLC analysis. We next evaluated the performance of Rh_2(*S*-TFPTTL)$_4$ (**1b**) and

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

Entry	Rh^{II} catalyst	Solvent	Temp /°C	Time /min	Yield[b] /%	ee[c] /%
1	**1a**	Toluene	0	10	36	7
2	**1b**	Toluene	0	10	72	93
3	**1c**	Toluene	0	60	70	77
4	**1b**	$CF_3C_6H_5$	0	10	66	93
5	**1b**	Hexane	23	30	52	58
6	**1b**	CH_2Cl_2	0	10	40	14
7	**1b**	Toluene	30	5	76	88
8	**1b**	Toluene	60	<5	77	80

[a]All reactions were carried out as follows: To a solution of **4a** (48.0 mg, 0.2 mmol) in toluene (2 mL) was added Rh^{II} catalyst (1 mol %) at the indicated temperature. [b]Isolated yield. [c]Determined by HPLC [column: DAICEL CHIRALCEL OD-H, eluent: 19:1 hexane/*i*-PrOH, flow rate: 1.0 mL/min, detection: UV (220 nm)].

Rh_2(*S*-TCPTTL)$_4$ (**1c**),[13] fluorinated and chlorinated analogues of Rh_2(*S*-PTTL)$_4$ (**1a**), which could bring about an electron deficiency on the rhodium(II) center. Gratifyingly, the reaction under the influence of **1b** produced **4** in 72% yield with 93% ee (Entry 2). The enantioselectivity is the highest ever reported for [2,3]-sigmatropic rearrangement of a cyclic oxonium ylide. The preferred absolute stereochemistry of **4** was determined to be 1*S*, 4*S*, 5*S* by X-ray crystallographic analysis.[14] Catalysis with **1c** under the same conditions required significantly longer reaction times for full conversion due to its poor solubility in toluene and resulted in 77% ee (Entry 3). A survey of solvents with **1b** revealed that toluene was the optimal solvent for this transformation in terms of both product yield and enantioselectivity (Entries 2 and 4–6). Quite surprisingly, altering the reaction temperature was found to have only a marginal effect on the enantioselectivity of the reaction (Entries 2, 7, and 8).[6c,6f] Provided that Rh_2(*S*-TFPTTL)$_4$ functions in an asymmetric environment similar to that in which Rh_2(*S*-PTTL)$_4$ functions, the notable difference in enantioselectivity between them suggests that Rh_2(*S*-TFPTTL)$_4$ with minimal steric influence and a powerful electron-withdrawing effect of the fluorine substituent remains even more strongly associated with the oxonium ylide than does Rh_2(*S*-PTTL)$_4$.[15] Therefore, it seems likely that rearrangement with the use of Rh_2(*S*-TFPTTL)$_4$ proceeds through the relatively long-lived catalyst-bound oxonium ylide **A** to give good yield and high enantioselectivity, whereas rearrangement with the use of Rh_2(*S*-PTTL)$_4$ occurs mainly from the enantiomeric catalyst-free oxonium ylides **B** and **C** in rapid equilibrium via the free carbene[16] to give low yield and inferior level of enantiocontrol (Scheme 1).



Scheme 1.

In summary, we have demonstrated that the fluorinated catalyst Rh_2(*S*-TFPTTL)$_4$ is remarkably effective for enantioselective tandem bicyclic oxonium ylide generation and [2,3]-sigmatropic rearrangement from α-diazo-β-ketoester bearing a cyclic allylic acetal moiety, providing the zaragozic acid core structure in up to 93% ee. Further studies to expand the range of substrates are currently underway.[17]

This research was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science (JSPS).

This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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Published on the web (Advance View) April 18, 2009; doi:10.1246/cl.2009.488