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Catalytic asymmetric oxidative lactonizations of *meso*-diols using a chiral iridium complex

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Abstract—A chiral amino alcohol/Ir complex catalyzes the asymmetric oxidative lactonizations of *meso*-diols to give the corresponding lactones in up to 81% ee.

Asymmetric oxidative lactonization of *meso*-diols is one of the most important methods for the preparation of chiral lactones. Although asymmetric oxidative lactonization of *meso*-diols has been achieved by an enzymatic method[1] or by electrooxidation,[2] there is much room for improvement of selectivity and reactivity in metal-catalyzed reactions. Yoshikawa et al.[3] and Takaya et al.[4] have reported that a chiral Ru or Rh phosphine complex promotes asymmetric oxidative lactonization of prochiral or *meso*-diols in the presence of benzalacetone as a hydrogen acceptor to afford the δ- and γ-lactones in 10–29% ee in moderate to good yield.[5] Recently we have developed an efficient oxidative lactonization of diols using a novel Ir-ligand bifunctional catalyst and inexpensive acetone or 2-butanone as a hydrogen acceptor.[6] We report herein the asymmetric oxidative lactonization of *meso*-diols using a chiral iridium catalyst (Scheme 1).[7,8]

Stirring a mixture of $[Cp^*IrCl_2]_2$ (**3**) with chiral amino alcohol [(1*S*,3*R*,4*R*)-**4**][9] and *t*-C_4H_9OK (1:2:10 mol ratio) in CH_2Cl_2 at room temperature for 10 min under argon gave a dark red suspension. The soluble portion of this mixture could be used as a catalyst for asymmetric oxidative lactonization of *meso*-diols. When a mixture of *cis-endo*-2,3-bis(hydroxymethyl)bicyclo[2.2.1]-heptane (**1a**)[1c] and the in situ prepared Ir catalyst in a 2:1 acetone–CH_2Cl_2 mixed solvent (**1a**:acetone:Ir = 1:13.6:0.005 mol ratio) was stirred at room temperature for 45 h, (2*R*,3*S*)-*cis-endo*-3-(hydroxymethyl)bicyclo-[2.2.1]heptane-2-carboxylic acid lactone [(2*R*,3*S*)-**2a**] was obtained in 99% yield with 80% ee. This product is a synthetic intermediate of β-santalene.[10] Changing the ligand/Ir ratio affected the enantioselectivity. The catalyst prepared with a lower ligand/Ir ratio (**3**:**4**:*t*-C_4H_9OK = 1:1:10) gave a lower enantiomeric excess of 66%. However the catalyst prepared with a higher ratio (**3**:**4**:*t*-C_4H_9OK = 1:6:10) did not give an improved enantioselectivity (80% ee). KOH could also be used in place of *t*-C_4H_9OK. The reaction using the catalyst prepared from (*R*)-phenylglycinol [(*R*)-**5**] or (1*R*,2*R*)-diphenylethanolamine [(1*R*,2*R*)-**6**][11] in place of (1*S*,3*R*,4*R*)-**4** gave (2*S*,3*R*)-**2a** in 97% yield with 72–73% ee. Other chiral ligands gave less satisfactory results: (*R*)-valinol, 34% yield, 61% ee, (2*S*,3*R*); (1*R*,2*S*)-*cis*-1-amino-2-indanol,[12] 85% yield, 50% ee, (2*R*,3*S*); (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN),[13] 82% yield, 32% ee, (2*S*,3*R*); (*R*)-*N*-methylphenylglycinol,[14] 95% yield, 27% ee, (2*S*,3*R*).

Table 1 shows some examples of the asymmetric oxidative lactonization of diols **1** using the amino alcohol-based/Ir catalyst. The general sense of asymmetric induction with this catalytic system is schematically illustrated in Figure 1. A gram-scale reaction of **1a** was performed without special techniques (entry 2).[15] Enantiomerically pure lactone **2a** was obtained in 49% yield by recrystallization from ether–hexane. In the case of the *exo*-diol **1b**,[1c] (*R*)-**5**/Ir catalyst gave the corresponding lactone **2b** more selectively than (1*S*,3*R*,4*R*)-**4**/Ir catalyst (entries 5–7). The 7-oxa analogue **1c**[1b] was also oxidized in 73% ee to **2c** (entry 9),[16] which is convertible to SQ 28,852,[17] a potent cyclooxygenase inhibitor. The

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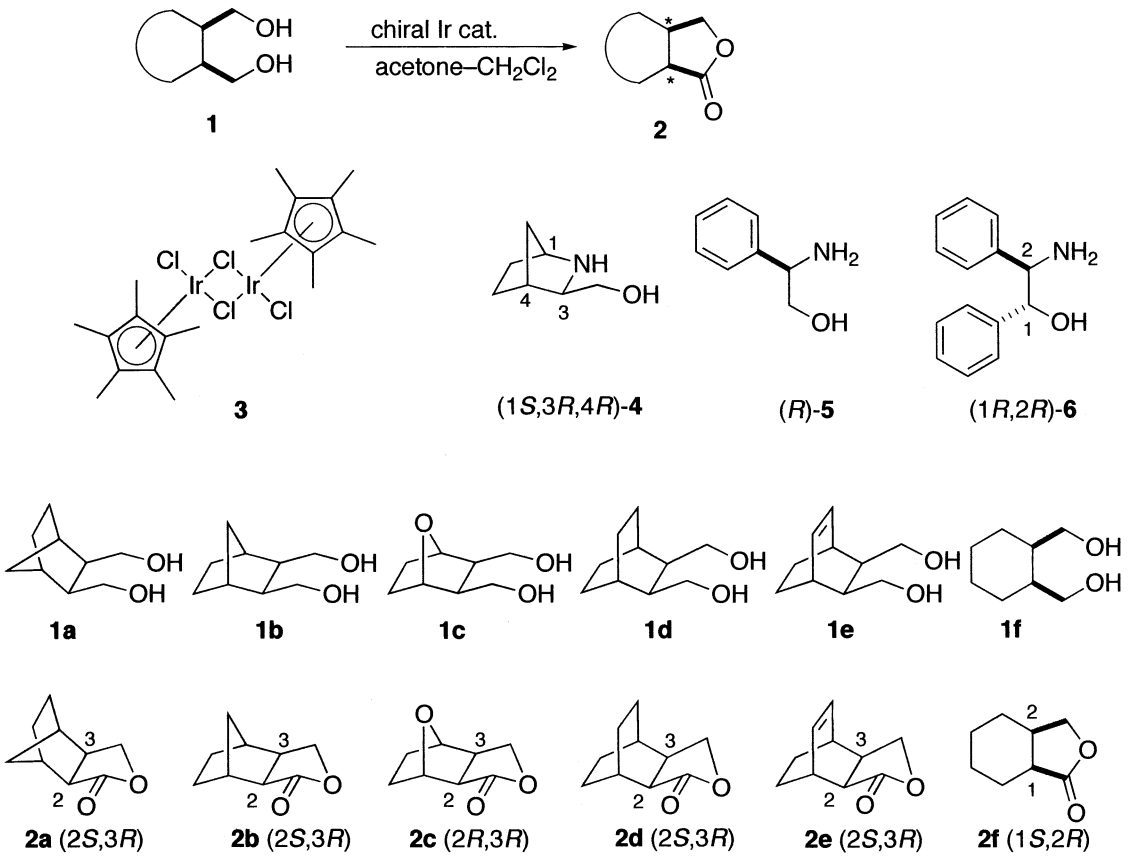

Scheme 1. Asymmetric oxidative lactonization of *meso*-diols.

reaction of *cis*-2,3-bis(hydroxymethyl)bicyclo[2.2.2]-octane **1d**[1c] gave **2d** in 68% ee and 94% yield (entry 11). Although the olefinic analogue **1e**[1c] disturbed the catalytic activity of (1*S*,3*R*,4*R*)-**4**/Ir catalyst (55% yield after 72 h, entry 14), (*R*)-**5**/Ir catalyst afforded **2e** quantitatively in 76% ee without difficulty (entry 15). Monocyclic diol **1f** gave **2f** in good yield with only moderate enantioselectivity (entry 18).[18] The product is the synthetic intermediate of NPC 12626,[19] a potent NMDA antagonist, and RU44570,[20] an ACE inhibitor.

Since transfer hydrogenation of ketone is reversible, the prolonged exposure of the chiral product to the reaction conditions decreased the product enantiomeric excess.[13,21] However the enantioselectivity of the reaction of **1a** under standard conditions using (1*S*,3*R*,4*R*)-**4**/Ir catalyst remained constant (80% ee) throughout the reaction (17%, after 1 h; >99%, after 24 h, >99% after 72 h). This result indicates the absence of the reverse process from the product lactone.[6] Moreover the corresponding lactol with the same enantiomeric excess (80%) was also obtained in 14% yield at the early stage of the reaction of **1a** (after 1 h), indicating that kinetic resolution of the lactol intermediate is not particularly significant for the enantioselectivity.

In summary, the chiral Ir complexes catalyze asymmetric oxidative lactonization. The properties of the Ir catalysts should be readily modifiable to afford more efficient catalysts, because various chiral amino alcohol derivatives are available. Although the enantioselectivity does not yet rival that of the enzymatic method, this method is attractive due to the good reactivity and simple operation. Our results should provide a basis for designing more efficient catalyst systems.

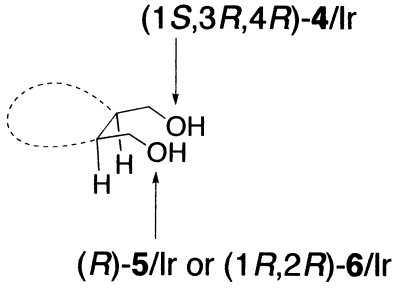

Figure 1. General sense of asymmetric oxidative lactonization catalyzed by the Ir complex.

Table 1. Asymmetric oxidative lactonization of *meso*-diols **1** catalyzed by a chiral Ir(III) complex[a]

Entry	Diol	Amino alcohol	Time (h)	Lactone			
				No.	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**1a**	(1*S*,3*R*,4*R*)-**4**	45	**2a**	99	80	(2*R*,3*S*)
2	**1a**	(1*S*,3*R*,4*R*)-**4**	48	**2a**	97[e]	81 (>99)[f]	(2*R*,3*S*)[g]
3	**1a**	(*R*)-**5**	24	**2a**	97	73	(2*S*,3*R*)
4	**1a**	(1*R*,2*R*)-**6**	48	**2a**	97	72	(2*S*,3*R*)
5	**1b**	(1*S*,3*R*,4*R*)-**4**	40	**2b**	97	32[h]	(2*R*,3*S*)
6	**1b**	(*R*)-**5**	24	**2b**	95	60[h]	(2*S*,3*R*)[i]
7	**1b**	(1*R*,2*R*)-**6**	36	**2b**	94	22[h]	(2*S*,3*R*)
8	**1c**	(1*S*,3*R*,4*R*)-**4**	45	**2c**	92	62	(2*S*,3*S*)
9	**1c**	(*R*)-**5**	24	**2c**	96	73	(2*R*,3*R*)[j]
10	**1c**	(1*R*,2*R*)-**6**	45	**2c**	98	46	(2*R*,3*R*)
11	**1d**	(1*S*,3*R*,4*R*)-**4**	50	**2d**	94	68[h]	(2*R*,3*S*)[k]
12	**1d**	(*R*)-**5**	40	**2d**	94	59[h]	(2*S*,3*R*)
13	**1d**	(1*R*,2*R*)-**6**	36	**2d**	96	48[h]	(2*S*,3*R*)
14	**1e**	(1*S*,3*R*,4*R*)-**4**	72	**2e**	55	79[h,l]	(2*R*,3*S*)[m]
15	**1e**	(*R*)-**5**	40	**2e**	99	76[h,l]	(2*S*,3*R*)
16	**1e**	(1*R*,2*R*)-**6**	36	**2e**	98	55[h,l]	(2*S*,3*R*)
17	**1f**	(1*S*,3*R*,4*R*)-**4**	40	**2f**	97	9[n]	(1*R*,2*S*)
18	**1f**	(*R*)-**5**	24	**2f**	96	42[n]	(1*S*,2*R*)[o]
19	**1f**	(1*R*,2*R*)-**6**	30	**2f**	95	18[n]	(1*S*,2*R*)

[a] Unless otherwise stated, the reaction was conducted at 30°C using 0.500 mmol of a diol in 2:1 acetone–CH_2Cl_2 mixed solvent (0.67 M) containing 0.5 mol% of the catalyst. Diol:acetone molar ratio = 1:13.6.
[b] Isolated yield.
[c] HPLC analysis using a Daicel Chiralcel OD column unless otherwise specified.
[d] Determined by the sign of rotation of the isolated product.
[e] Result of a 1 g scale reaction.
[f] After recrystallization from ether–hexane.
[g] $[\alpha]_D^{25}$ −156.4° (*c* 1.01, $CHCl_3$);[10] >99% ee.
[h] Chiralpak AS column.
[i] $[\alpha]_D^{21}$ +57.3° (*c* 0.60, $CHCl_3$);[1c] 60% ee.
[j] $[\alpha]_D^{22}$ +85.8° (*c* 1.00, $CHCl_3$);[9] 73% ee.
[k] $[\alpha]_D^{25}$ +82.0° (*c* 0.50, $CHCl_3$);[1c] 68% ee.
[l] Determined after conversion to **2d**.
[m] $[\alpha]_D^{25}$ −71.0° (*c* 1.00, $CHCl_3$);[1c] 79% ee.
[n] GC analysis using a chiral Chrompack CP-Chirasil-DEX CB column or HPLC analysis using a Daicel Chiralcel OD column.
[o] $[\alpha]_D^{21}$ +21.7° (*c* 0.50, $CHCl_3$);[1a] 42% ee.

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