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Catalytic asymmetric synthesis of 1,1′-spirobi[indan-3,3′-dione] *via* a double intramolecular C–H insertion process

Teruki Takahashi, Hideyuki Tsutsui, Masafumi Tamura, Shinji Kitagaki, Makoto Nakajima and Shunichi Hashimoto*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan. E-mail: hsmt@pharm.hokudai.ac.jp

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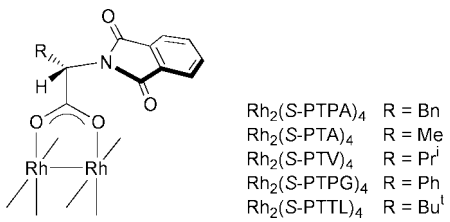
A highly efficient one-pot construction of optically active 1,1′-spirobi[indan-3,3′-dione] derivative (up to 80% ee) has been achieved by exploiting the double intramolecular C–H insertion reaction of dimethyl 2,2′-methylenebis(α-diazo-β-oxobenzenepropanoate) under the influence of dirhodium (II) tetrakis[*N*-phthaloyl-(*R* or *S*)-*tert*-leucinate] as a catalyst.

The development of efficient chiral metal complexes in the field of asymmetric synthesis has focused mainly on the design and synthesis of novel chiral ligands. BINAP, BINOL and related ligands based on the axially chiral 1,1′-binaphthyl skeleton have achieved significant success in asymmetric catalysis.[1] In this context, certain bifunctional chiral spirans with C_2-symmetry may be regarded as promising ligands, as they contain a totally rigid spiro backbone which creates an effective asymmetric environment. Although chiral *cis*,*cis*-spiro[4.4]nonane-1,6-diol has recently shown potential either as a chiral ligand itself[2] or as a precursor to other useful chiral ligands,[3] the widespread application of this class of spiran ligands has received relatively little attention.[4] Clearly, a major obstacle is the difficulty in obtaining enantiomerically pure spiran molecules, which generally involves a tedious resolution of racemates *via* fractional crystallization[5] or chromatography[6] of the diastereomeric mixtures. Thus, the development of a catalytic asymmetric synthesis of C_2-symmetrical chiral spirans would represent significant improvement over current methodologies for obtaining these ligands.[7,8]

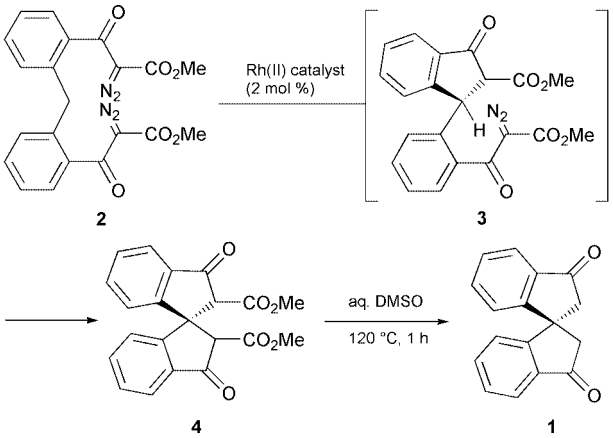
Recently, Aburel and Undheim reported a new synthetic approach to generate racemic spiro[4.4]nonane-2,7-dione derivatives from acyclic bis(α-diazoketone) using a $Rh_2(OAc)_4$-catalyzed double intramolecular C–H insertion reaction, though the product yields are found to be only 27–35%.[9] Inspired by their pioneering work, and taking advantage of our continuing research in this field,[10] we turned our attention to the feasibility of a high-yielding and enantioselective synthesis of C_2-symmetrical chiral 1,1′-spirobiindan systems. Herein we report



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

a facile path to optically pure 1,1′-spirobi[indan-3,3′-dione] **1**,[5b] a potential intermediate in the synthesis of the hitherto unknown *cis*,*cis*-1,1′-spirobi[indan-2,2′-diol], *via* an enantioselective double intramolecular C–H insertion process with up to 80% ee.

At the outset of this work, we explored the double cyclization of bis(α-diazo-β-keto ester) **2** in the presence of 2 mol % of $Rh_2(OAc)_4$.† While the use of DCM as solvent gave a complex mixture of products, the catalysis of **2** in toluene was found to proceed sluggishly at rt to produce spirobiindanone derivative



4, which, without purification, was transformed by demethoxycarbonylation to give spirobiindanone **1**. As might be expected from the results of Undheim,[9] a product yield of only 29% was found. The use of $Rh_2(O_2CC_7H_{15})_4$, $Rh_2(O_2CCPh_3)_4$[12] or $Rh_2(O_2CC_3F_7)_4$ also resulted in low yields.‡ Thus, we were gratified to find that the reaction proceeded smoothly at 0 °C with the aid of chiral dirhodium(II) carboxylates, Rh_2(*S*-PTPA)$_4$, Rh_2(*S*-PTA)$_4$, Rh_2(*S*-PTV)$_4$, Rh_2(*S*-PTPG)$_4$, and Rh_2(*S*-PTTL)$_4$, derived from *N*-phthaloyl-(*S*)-phenylalanine, -alanine, -valine, -phenylglycine, and -*tert*-leucine, respectively,[10] to give synthetically useful product yields (Table 1). Although no explanation for the striking contrast between the achiral and chiral dirhodium(II) carboxylates can be offered at present, the advantage of our catalysts extends beyond stereocontrol in this system.§ While the formation of (*R*)-1,1′-spirobi[indan-3,3′-dione] (*R*)-**1** was favored in all cases, Rh_2(*S*-PTTL)$_4$ characterized by an exceptionally bulky *tert*-butyl group proved to be the catalyst of choice for displaying a reasonable degree of enantioselectivity (68% ee, entry 5).¶ Further screening of solvents confirmed that the use of toluene was the superior choice for allowing smooth insertion at −10 °C to provide (*R*)-**1** in 78% yield with 80% ee (entry 6), which, upon a single recrystallization from ethanol, produced the optically pure sample, mp 212–213 °C, $[\alpha]_D^{25}$ −237.0 (*c* 0.69, $CHCl_3$) [lit.,[5b] $[\alpha]_D^{24}$ +238.7 (*c* 0.64, $CHCl_3$) for (*S*)-**1**], in 67% yield. The use of Rh_2(*R*-PTTL)$_4$ also generated (*S*)-**1** with 79% ee (entry 7). Thus, both enantiomers of **1** are equally available. The use of DCM provided (*R*)-**1** with 60% ee (entry 8), however, 0 °C was found to be the temperature limit for allowing smooth cyclization. It is of particular interest that the use of benzotrifluoride (α,α,α-trifluorotoluene)[14] greatly accelerated the insertion rate, though the largest ee was found to be 72% at −23 °C (entry 9).

The stereochemical outcome observed here suggests that the chiral rhodium(II) carbene intermediate generated *via* Rh_2(*S*-PTTL)$_4$-catalyzed decomposition of **2** preferentially inserts into a methylene C–H*s* bond to give (3*S*)-indan-1-one derivative **3**, which undergoes a second C–H insertion at the methine C–H bond with well-established retention of configuration[15] to

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Table 1 Enantioselective double C–H insertion reaction of **2** catalyzed by chiral dirhodium(II) complexes[a]

Entry	Catalyst	Solvent	Temp./°C	Time/h	Yield of **1** (%)[b]	Ee of **1** (%)[c]
1	Rh_2(*S*-PTPA)$_4$	Toluene	0	0.5	71	25
2	Rh_2(*S*-PTA)$_4$	Toluene	0	1	68	23
3	Rh_2(*S*-PTV)$_4$	Toluene	0	0.5	66	24
4	Rh_2(*S*-PTPG)$_4$	Toluene	0	1	67	21
5	Rh_2(*S*-PTTL)$_4$	Toluene	0	0.5	83	68
6	Rh_2(*S*-PTTL)$_4$	Toluene	−10	1	78	80
7	Rh_2(*R*-PTTL)$_4$	Toluene	−10	1	76	−79[d]
8	Rh_2(*S*-PTTL)$_4$	CH_2Cl_2	0	1	72	60
9	Rh_2(*S*-PTTL)$_4$	$CF_3C_6H_5$	−23	1	66	72

[a] Reactions were carried out as follows: 2 mol % of catalyst was added to a stirred solution of diazo compound **2** (0.20 mmol) in the indicated solvent (2 ml) at the indicated temperature under argon. After the reaction proceeded to completion, the solvent was evaporated *in vacuo* and the residue was treated with 90% aqueous DMSO (1.5 ml) at 120 °C for 1 h. Standard workup followed by chromatography provided (*R*)-**1**. [b] Overall isolated yield. [c] Determined by HPLC (column, Daicel chiralcel OD; 4.6 × 250 mm × 2; eluent, 15% propan-2-ol in hexane; flow rate, 1.0 ml min^{-1}; retention time, 31.2 min [(*R*)-**1**] and 35.1 min [(*S*)-**1**]). [d] (*S*)-**1** was preferentially formed.

provide (*R*)-**1** after demethoxycarbonylation. Thus, the sense and magnitude of enantioselection indicates the level of differentiation between methylene C–H bonds during the first C–H insertion. In accordance with the order of reactivity of the target C–H bond (methine C–H > methylene C–H),[16] we could not observe the first insertion product **3**,[9] which makes it possible to conduct this one-pot reaction under the constant conditions.

In summary, we have achieved the first catalytic, enantioselective synthesis of 1,1′-spirobi[indan-3,3′-dione] (**1**) of up to 80% ee, in which the use of Rh_2(*R* or *S*-PTTL)$_4$ as a catalyst is crucial to the success of the double C–H insertion process. The present protocol has the advantages of operational simplicity as well as a facile entry to optically pure **1** *via* a single recrystallization, thus providing great potential for large-scale preparation. Elaboration of (*R*)- or (*S*)-**1** to hitherto unexplored chiral ligands such as 1,1′-spirobi[indan-2,2′-diol] for metal catalyzed enantioselective reactions is currently in progress.

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Notes and references

† Bis(α-diazo-β-keto ester) **2** was prepared from diphenylmethane-2,2′-dicarboxylic acid[11] in 70% yield by the following three-step sequence: i, $SOCl_2$, toluene, reflux; ii, $LiCH_2CO_2Me$, THF, −78 °C; iii, MsN_3, Et_3N, MeCN.

‡ Overall isolated yield: $Rh_2(O_2CC_7H_{15})_4$, 28%; $Rh_2(O_2CCPh_3)_4$, 13%; $Rh_2(O_2CC_3F_7)_4$, 17%.

§ While reaction of the corresponding bis(α-diazoketone) with $Rh_2(OAc)_4$ in CH_2Cl_2 provided 52% yield of **1**, Rh_2(*S*-PTTL)$_4$ gave a complex mixture of products under the same conditions.

¶ Rh_2(*S*-DOSP)$_4$ developed by Davies[13] was found to be less reactive than our catalysts; catalysis of **2** with 2 mol % of Rh_2(*S*-DOSP)$_4$ in toluene proceeded at rt sluggishly to afford, after demethoxycarbonylation, (*S*)-**1** in 48% yield with 8.3% ee.

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