Practical Synthesis of Dirhodium(II) Tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate]

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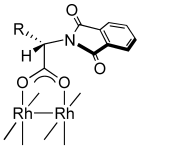
An efficient and reliable procedure for the preparation of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, a universally effective catalyst for a range of enantioselective carbene transformations, is described. The *N*-phthaloylation of (*S*)-*tert*-leucine by the method of Bose with essentially no racemization is a key to this process.

Key words *tert*-leucine; *N*-phthaloylation; dirhodium(II) carboxylate; chiral catalyst

Over the past decade, remarkable progress in dirhodium(II) complex-catalyzed, asymmetric carbene transformations of α-diazo carbonyl compounds has been achieved in a number of processes, including cyclopropanation, C–H insertion, and rearrangement or cycloaddition *via* ylide generation.[1—4] In this context, a great deal of effort continues to be devoted to the design, synthesis and evaluation of chiral dirhodium(II) catalysts. Unique in their design are chiral bridging ligands bound to the dirhodium(II) core, which constitute one of the most fundamental factors for the high level of reactivity, turnover numbers, regio-, diastereo- and enantioselectivity. Our efforts in this area have led to the development of dirhodium(II) carboxylate catalysts **1a**—**d** (Fig. 1), which incorporate *N*-phthaloyl-(*S*)-amino acids as bridging ligands.[5] The presence of phthalimido groups in the bridging ligands has proven to be crucial for a high degree of enantioselection, even though the secondary effect of the alkyl substituent of amino acids on enantioselectivities has yet to be elucidated. Of these catalysts, dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$ (**1d**), has proven to be the most universally efficient catalyst for a range of rhodium(II)-carbene transformations of α-diazo carbonyl compounds.[6—11] The effectiveness of **1d** has been particularly well demonstrated in intramolecular C–H insertions,[6] double intramolecular C–H insertions,[7] enantiotopically selective aromatic C–H insertions,[8] intermolecular 1,3-dipolar cycloadditions *via* the generation of ester-carbonyl ylides,[9] and [2,3]-sigmatropic rearrangements *via* the intramolecular formation of allylic or propargylic oxonium ylides[10,11] with high levels of enantioselectivities up to 98% ee. However, a problem associated with the original synthesis of Rh_2(*S*-PTTL)$_4$ involves product yield simply because the preparation of optically pure *N*-phthaloyl-(*S*)-*tert*-leucine (**2**) is not straightforward (*vide infra*). The purpose of this paper is to describe an improved preparation of *N*-phthaloyl-(*S*)-*tert*-leucine, bridging ligands of Rh_2(*S*-PTTL)$_4$.



R = Me: Rh_2(*S*-PTA)$_4$ (**1a**)
R = Bn: Rh_2(*S*-PTPA)$_4$ (**1b**)
R = ^{i}Pr: Rh_2(*S*-PTV)$_4$ (**1c**)
R = ^{t}Bu: Rh_2(*S*-PTTL)$_4$ (**1d**)

Fig. 1. Structure of Chiral Dirhodium(II) Carboxylates Incorporating *N*-Phthaloyl-(*S*)-amino Acid as Bridging Ligands

Dirhodium(II) carboxylate catalysts **1a**—**d** can be readily prepared from $Rh_2(OAc)_4$ by a ligand exchange reaction with the corresponding *N*-phthaloyl-(*S*)-amino acids.[12] Needless to say, the use of optically pure ligands is crucial to the facile access to extremely reliable catalysts. With respect to *N*-phthaloylation, the most widely used fusion procedure with phthalic anhydride at 145 °C is ideally suited for the preparation of *N*-phthaloyl-(*S*)-alanine, -phenylalanine, and -valine, in which optically pure products can be obtained in high yields with one recrystallization.[13] However, such is not the case for **2**. Even though the *N*-phthaloylation of (*S*)-*tert*-leucine (**3**) under the same conditions proceeded with *ca.* 10% racemization, repeated recrystallizations were required to obtain an optically pure material at the cost of product yield. The tedious operation can be attributed to the fact that small amounts of racemate (mp 190.0—190.5 °C) crystallizes out together with the optically pure material (mp 153.5—154.0 °C).

Thus, we explored the racemization-free *N*-phthaloylation of **3** by alternate procedures. Among these, the procedures of Nefkens[14] and Casimir,[15] which use *N*-ethoxycarbonylphthalimide or methyl 2-(succinimidooxycarbonyl)benzoate, respectively, have the potential advantage of allowing the *N*-phthaloylation of free amino acids under mild conditions. Indeed, the *N*-phthaloylation of **3** with *N*-ethoxycarbonylphthalimide (Na_2CO_3, H_2O, rt, 10 h) proceeded without racemization to give optically pure **2**, but the isolated yield was only 14%.[16] Furthermore, the reaction with methyl 2-(suc-

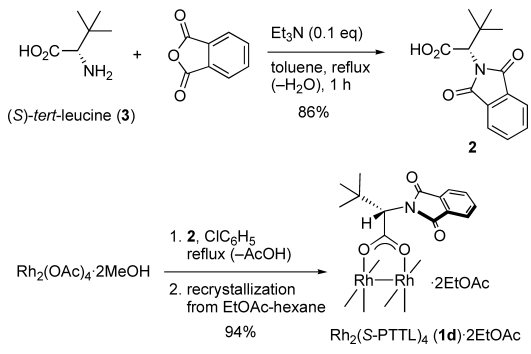


Chart 1. Preparation of Rh_2(*S*-PTTL)$_4$

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cinimidooxycarbonyl)benzoate (Na_2CO_3, aq. CH_3CN, rt, 8 h) gave none of the desired product.[17] It is clear that an exceptionally bulky *tert*-butyl group of **3** would have an effect, because of the severe steric hindrance imposed. After some experimentation, we found that this goal could be readily achieved by employing the method of Bose.[18,19] Thus, the condensation of **3** with phthalic anhydride in the presence of triethylamine was conducted in toluene at reflux for 0.5 h, while the water formed was distilled off. An aliquot of the crude product thus obtained was transformed into the methyl ester to check the extent of racemization in this process. The enantiopurity of the methyl ester was determined to be >99% ee by HPLC using a Daicel Chiralcel OJ column. This result suggests that *N*-phthaloylation of **3** under Bose's conditions proceeds with essentially no racemization, although triethylamine is present as a base. As expected, one recrystallization of the crude product from ethyl acetate-hexane provided completely optically pure **2**, mp 153.5—154.0 °C, $[\alpha]_D^{24}$ −60.6° (c=1.60, EtOH), in 86% yield.

The present *N*-phthaloylation protocol based on the method of Bose has the advantages of operational simplicity as well as reproducibility, thus providing facile and reliable access to high quality Rh_2(*S*-PTTL)$_4$.

Experimental

Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. NMR spectra were obtained with a JEOL JNM-AL400 spectrometer (^{13}C at 100 MHz), with tetramethylsilane (δ 0.0, ^{1}H) or chloroform-d_1 (δ 77.0, ^{13}C) as an internal standard. Infrared spectra were recorded on a JASCO FT/IR-5300 spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Electron impact (EI) mass spectra were obtained on a JEOL DX-303 spectrometer, operating with an ionization energy of 70 eV. FAB-MS were obtained on a JEOL JMS-HX110 spectrometer. Column chromatography was performed on Merck silica gel 60 (70—230 mesh). Analytical HPLC was performed on a JASCO PU-1580 intelligent HPLC pump with a JASCO UV-1575 intelligent UV/VIS detector. Detection was at 254 nm. A Chiralcel OJ column (0.46 cm×25 cm) from Daicel was used. Retention times (t_R) and peak ratios were determined with Shimadzu C-R6A chromatopac integrator. Reactions were carried out in flame-dried glassware under argon atmosphere. (*S*)-*tert*-Leucine was purchased from Daiichi Pure Chemicals Co., Ltd. $Rh_2(OAc)_4\cdot 2MeOH$ was purchased from Furuya Metal Co., Ltd. Reagents and solvents were purified by standard means.

***N*-Phthaloyl-(*S*)-*tert*-leucine (2)** A 100-ml round-bottom flask was equipped with a stirring bar and charged with (*S*)-*tert*-leucine (**3**, 2.50 g, 19.1 mmol), phthalic anhydride (2.82 g, 19.1 mmol) and toluene (60 ml). Triethylamine (741 mg, 1.9 mmol) was added and the mixture was heated to reflux, while the solvent was distilled off at a rate such that *ca*. 7 ml of the solvent was removed per 10 min. After heating the mixture for 0.5 h, 5% hydrochloric acid (15 ml) was added and resulting solution was extracted with EtOAc (2×30 ml). The combined organic layers were washed with brine (20 ml) and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* provided a white solid (4.73 g). Recrystallization was performed by dissolving the solid in 8 ml of hot ethyl acetate and then adding 24 ml of hexane. Colorless plates formed at room temperature after standing overnight, and were collected by suction, washed with 3 ml of hexane–EtOAc (3 : 1) and dried *in vacuo* to give **2** (4.30 g, 86%). TLC *Rf* 0.36 (10 : 1 $CHCl_3$/MeOH). mp 153.5—154.0 °C. $[\alpha]_D^{24}$ −60.6° (c=1.60, EtOH). IR (KBr) cm^{-1}: 3241, 2965, 1759, 1713, 1391. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.19 (9H, s, *t*-Bu), 4.74 (1H, s, CH), 7.73—7.78 (2H, m, ArH), 7.85—7.90 (2H, m, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.0 (CH_3), 35.7 (C), 59.8 (CH), 123.5 (CH), 131.5 (C), 134.1 (CH), 167.8 (C=O), 173.6 (C=O). FAB-MS m/z: 262 (M^++H), 216. HR-FAB-MS m/z: 262.1101 (Calcd for $C_{14}H_{16}NO_4$: 262.1079). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.18; H, 5.91; N, 5.27. The enantiopurity of **2** was determined to be >99% ee by comparison of HPLC retention time with the racemic sample after conversion to the corresponding methyl ester obtained by the treatment of **2** with diazomethane in ether [Daicel Chiralcel OJ; eluent: 9 : 1 hexane/2-propanol; flow rate: 1.0 ml/min; retention time: t_R 8.1 min (*S*), 12.4 min (*R*)].

Dirhodium(II) Tetrakis[(*S*)-*tert*-leucinate] (1d) Bis(ethyl acetate) Adduct A 100-ml round-bottom flask was equipped with a stirring bar and charged with $Rh_2(OAc)_4\cdot 2MeOH$ (1.67 g, 3.30 mmol), **1** (4.31 g, 16.5 mmol) and chlorobenzene (50 ml). The mixture was heated to reflux, while the solvent was distilled off at a rate such that *ca.* 7 ml of the solvent was removed per hour. After 3 h, the remaining solvent was removed *in vacuo*, the residue was dissolved in EtOAc (80 ml). The resulting solution was washed with saturated aqueous $NaHCO_3$ (2×20 ml) and brine (20 ml), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished a green solid (5.6 g), which was purified by column chromatography on silica gel (60 g, 1 : 1→1 : 2 hexane/EtOAc) to provide a green solid (5.0 g). This material was recrystallized by dissolving the solid in 20 ml of EtOAc and then adding 30 ml of hexane. The green needles that formed at room temperature after standing overnight, were collected by suction, washed with 3 ml of hexane/EtOAc (3 : 1) and dried *in vacuo* to yield bis(ethyl acetate) adduct of **1d** (4.42 g, 93%). TLC *Rf* 0.26 (1 : 1 hexane/EtOAc). mp >280 °C. $[\alpha]_D^{22}$ +102.2° (c=0.0481, $CHCl_3$). IR (KBr) cm^{-1}: 3476, 2963, 1777, 1717, 1611, 1383. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.07 (36H, s, *t*-Bu), 1.20 (6H, t, J=6.4 Hz, $AcOCH_2CH_3$), 2.01 (6H, s, CH_3COEt), 4.09 (4H, q, J=6.4 Hz, $AcOCH_2CH_3$), 4.87 (4H, s, CH), 7.63—7.65 (8H, m, ArH), 7.78—7.80 (8H, m, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1 (CH_3), 21.0 (CH_3), 28.0 (CH_3), 35.6 (C), 60.9 (CH_2), 61.3 (CH), 123.1 (CH), 131.8 (CH), 133.6 (C), 167.6 (C=O), 172.8 (C=O), 186.8 (C=O). FAB-MS m/z: 1246 (M^+), 986, 417. HR-FAB-MS m/z: 1246.1804 (Calcd for $C_{56}H_{56}N_4O_{16}Rh_2$: 1246.1801). *Anal.* Calcd for $C_{56}H_{56}N_4O_{16}Rh_2\cdot 2EtOAc$: C, 54.02; H, 5.10; N, 3.94. Found: C, 53.80; H, 5.03; N, 4.26. The enantiopurity of the methyl ester of **2** recovered from aqueous $NaHCO_3$ layers was determined to be >99% ee by HPLC, indicating that no racemization occurred during the ligand exchange reaction.

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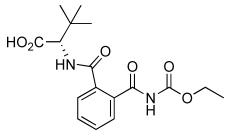
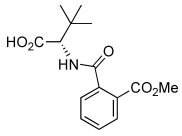
16) *N*-[2-(Ethoxycarbonyl)aminocarbonyl]benzoyl-(*S*)-*tert*-leucine was also obtained as a major product in 64% yield. Colorless viscous oil. TLC *Rf* 0.33 (4 : 1 $CHCl_3$/MeOH). $[\alpha]_D^{24}$ −4.4° (c=0.92, EtOH). IR ($CHCl_3$) cm^{-1}: 3400, 1773, 1715. ^{1}H-NMR (400 MHz, $CDCl_3$, 50 °C)

δ: 1.03 (9H, s, *t*-Bu), 1.21 (3H, m, CH_2CH_3), 4.13 (2H, m, CH_2CH_3), 4.57 (1H, d, J=8.9 Hz, CH), 6.91 (1H, d, J=8.9 Hz, NH), 7.40—7.47 (4H, m, ArH), 9.2 (1H, s, NH). ^{13}C-NMR (100 MHz, $CDCl_3$, 50 °C) δ: 14.0 (CH_3), 26.6 (CH_3), 34.6 (C), 61.1 (CH), 62.3 (CH_2), 127.3 (CH), 127.7 (CH), 130.4 (CH), 130.5 (CH), 133.7 (C), 134.6 (C), 151.6 (C=O), 168.3 (C=O), 169.0 (C=O). FAB-MS *m*/*z*: 351 (M^++H), 262. HR-FAB-MS *m*/*z*: 351.1553 (Calcd for $C_{17}H_{23}N_2O_6$: 351.1556).



17) *N*-(2-Methoxycarbonyl)benzoyl-(*S*)-*tert*-leucine was obtained as a major product in 83% yield. Colorless viscous oil. TLC *Rf* 0.57 (4 : 1 $CHCl_3$/MeOH). $[\alpha]_D^{24}$ −23.8° (c=1.38, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3426, 1725, 1671. ^{1}H-NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.11 (9H, s, *t*-Bu), 3.86 (3H, s, OCH_3), 4.69 (1H, d, J=9.0 Hz, CH), 6.40 (1H, d, J=9.0 Hz, NH), 7.49—7.55 (3H, m, ArH), 7.88 (1H, d, J=7.2 Hz, ArH). ^{13}C-NMR (100 MHz, $CDCl_3$, 50 °C) δ: 26.6 (CH_3), 34.7 (C), 60.6 (CH), 127.5 (CH), 129.1 (C), 129.8 (CH), 130.0 (CH), 131.8 (CH), 137.2 (C), 166.9 (C=O), 169.4 (C=O), 174.3 (C=O). EI-MS *m*/*z*: 294 (M^+), 262, 248, 163. HR-EI-MS *m*/*z*: 294.1342 (Calcd for $C_{15}H_{20}NO_5$: 294.1341).



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