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], Rh₂(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. 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. 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], Rh₂(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. The effectiveness of 1d has been particularly well demonstrated in intramolecular C-H insertions, double intramolecular C-H insertions, enantiotopically selective aromatic C-H insertions, intermolecular 1,3-dipolar cycloadditions via the generation of ester-carbonyl ylides, and [2,3]-sigmatropic rearrangements via the intramolecular formation of allylic or propargylic oxonium ylides with high levels of enantioselectivities up to 98% ee. However, a problem associated with the original synthesis of Rh₂(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 Rh₂(S-PTTL)₄.

Dirhodium(II) carboxylate catalysts 1a—d can be readily prepared from Rh₂(OAc)₄ by a ligand exchange reaction with the corresponding N-phthaloyl-(S)-amino acids. 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. 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 and Casimir, which use N-ethoxycarbonylphthalimide or methyl 2-succinimidoxy carbonyl)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 (Na₂CO₃, H₂O, rt, 10 h) proceeded without racemization to give optically pure 2, but the isolated yield was only 14%. Furthermore, the reaction with methyl 2-(succinimidoxy carbonyl)benzoate...
cinemidoxycarbonyl)benzoate (Na₂CO₃, aq. CH₂CN, rt, 8 h) gave none of the desired product. It is clear that an exceptionally bulky tert-buty1 group of 3 would have an effect, because of the severe steric hindrance imposed. After some experimentation, we found that this goal could be achieved by employing the method of Bose. 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 enantioselectivity of the methyl ester was determined to be >99% ee by comparison of HPLC retention time with the enantiomer. FAB-MS was measured for the crude product, while the solvent was distilled off at a rate such that 3 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 NaHCO₃ (2×20 ml) and brine (20 ml), and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo furnished a green solid (5.6 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. [α]D 102.2° (c=0.0841, CHCl₃). IR (KBr) cm⁻¹: 3476, 2963, 1777, 1717, 1611, 1383, 11.1-NMR (400 MHz, CDCl₃) δ: 1.07 (36H, s, 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 Rh₂(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-A500 spectrometer (100 MHz at 200 MHz, 300 MHz, 400 MHz, 500 MHz, 600 MHz, 700 MHz, 800 MHz for ¹H and 13C) as an internal standard. Infrared spectra were measured on a JASCO FT/IR-5300 spectrometer. Optical rotations were measured on a JASCO P-1020 polarimeter. Electron impact (EI) mass spectra were obtained with a JEOL JMS-HXII0 spectrometer. Column chromatography was performed on Merck silica gel 60 (70-230 mesh). Analytical HPLC was performed on a JASCO PU-1580 apparatus and are uncorrected. NMR spectra were obtained with a JEOL JNM-Eclipse-600 spectrometer. Reactions were carried out in flame-dried glassware under argon atmosphere. (S)-tert-Leucine was purchased from Furuya Metal Co., Ltd. Reagents and solvents were purified by distillation.

N-Phthaloyl-(S)-tert-Leucine (2) 100-ml round-bottom flask was equipped with a stirring bar and charged with (S)-tert-Leucine (3, 2.50 g, 13.7 mmol), 100 ml of hot ethyl acetate and then adding 7 ml of the solvent was removed in vacuo to yield bis(ethyl acetate) adduct of 1d (4.30 g, 86%). TLC Rf 0.12 (CHCl₃/MeOH). mp 153.5-154.0°C, [α]D 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 Rh₂(S-PTTL)₄.

References and Notes
16) [β]-Ethenediaminoic acid benzoyl-(S)-tert-leucine was also achieved by employing the method of Bose as a major product in 64% yield. Colorless viscous oil. TLC RF 0.33 (4:1 CHCl₃/MeOH). [α]D 0.84° (c=0.092, EtOH).

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δ: 1.03 (9H, s, t-Bu), 1.21 (3H, m, CH3CH2), 4.13 (2H, m, CH2CH3), 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). 13C-NMR (100 MHz, CDCl3, 50 °C) δ: 14.0 (CH3), 26.6 (CH2), 34.6 (C), 61.1 (CH), 62.3 (CH2), 127.3 (CH), 127.7 (CH), 130.4 (CH), 130.5 (CH), 133.7 (C), 134.6 (C), 151.6 (C=O), 158.8 (C=O), 169.0 (C=O). FAB-MS m/z: 351 (M^+ + H), 262. HR-FAB-MS m/z: 351.1553 (Caled for C17H23N2O6: 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 CHCl3:MeOH). [α]D^25 = -23.8° (c=1.38, CHCl3). IR (CHCl3) cm⁻¹: 3426, 1725, 1671. 1H-NMR (400 MHz, CDCl3, 50 °C) δ: 1.11 (9H, s, t-Bu), 3.86 (3H, s, OCH3), 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). 13C-NMR (100 MHz, CDCl3, 50 °C) δ: 14.0 (CH3), 26.6 (CH2), 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 (Caled for C17H20NO5: 294.1341).
