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.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 enantioselectivity, even though the secondary effect of the alkylation 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.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,9 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 ylides10,11 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.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 Nefkens14 and Casimir,15 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%.16 Furthermore, the reaction with methyl 2-(succ-

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

Chart 1. Preparation of Rh2(S-PTTL)4

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cinimidoxy carbonyl)benzoate (Na2CO3, aq. CH3CN, rt, 8 h) gave none of the desired product. It is clear that an exceptionally bulky tert-butyld 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. 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 afforded a white solid (4.31 g, 16.5 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 water formed 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 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), which was purified by column chromatography on silica gel (60 g, 1:1 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. [α]D25 +102.2° (c=0.0481, CHCl3). IR (KBr) cm−1: 3476, 2963, 1777, 1717, 1611, 1383. 1H-NMR (400 MHz, CDCl3) δ: 1.07 (36H, t, J=6.4 Hz, AcOCH2CH2), 2.01 (6H, s, CH2COOEt), 4.09 (4H, q, J=6.4 Hz, AcOCH2), 4.87 (4H, s, CH2), 7.63—7.65 (8H, m, ArH), 7.78—7.80 (8H, m, ArH). 13C-NMR (100 MHz, CDCl3) δ: 141 (CH3), 21.0 (CH2), 28.0 (CH3), 35.6 (C), 60.9 (CH2), 61.3 (CH), 123.1 (CH), 131.8 (CH3), 133.6 (C), 167.8 (C). Anal. Calcd for C56H56N4O16Rh2 · 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 NaHCO3 layers was determined to be >99% ee by HPLC, indicating that no racemization occurred during the ligand exchange reaction.

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References and Notes
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 CHCl3/MEOH). [α]D25 −4.4° (c=0.92, EtOH). IR (CHCl3) cm−1: 3400, 1773, 1715. 1H-NMR (400 MHz, CDCl3, 50°C)
δ: 1.03 (9H, s, t-Bu), 1.21 (3H, m, CH₂CH₃), 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), 9.2 (1H, s, NH). ¹³C-NMR (100 MHz, CDCl₃, 50 °C) δ: 14.0 (CH₃), 26.6 (CH₃), 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), 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 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]D¹⁰=−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: 26.6 (CH₃), 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). El-MS m/z: 294 (M⁺), 262, 248, 163. HR-El-MS m/z: 294.1342 (Calcd for C₁₅H₂₀NO₅: 294.1341).
