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

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Received July 15, 2005; accepted July 28, 2005; published online July 29, 2005

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 enantioselectivity, 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 1,3,1-di-polar 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 Netkens 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-(suc-
cinimidoxy carbonyl)benzoeate (Na₂CO₃, aq. CH₂CN, 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 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 transferred into the methyl ester to check the extent of racemization in this process. The enantiomeric excess 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, [α]D -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 R-R/S-PTTL₁

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 (400 MHz at 100 MHz), with tetramethylsilane (δ 0.00, 1H) or chloroform-d₃ (δ 77.00, 2C) as an internal standard. Infrared spectra were recorded on a JASCO FT/IR-5200 spectrometer. Optical rotations were measured on a JASCO PDU-1580 intelligent HPLC pump with a JASCO UV-1575 intelligent UVVIS detector. Detection was at 254 nm. A Chiralcel OJ column (0.46 cm x 25 cm) from Daicel was used. Retention times (tR) 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 Daisichi Pure Chemicals Co., Ltd. R₂H₂O₄ (260 mmol) was purchased from Furuya Metal Co., Ltd. Reagents and solvents were purified by standard methods.

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, 0.9 mmol) was added and the mixture was heated to reflux, while the solvent was distilled off at a rate such that ca. 6 mL of the solvent was removed per hour. After heating the mixture for 0.5 h, 5% hydrochloric acid (15 mL) was added and resulting solution was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na₂SO₄. Filtration and concentration of the residue furnished 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. Colorless plates formed at room temperature after standing overnight, and were collected by suction, washed with 3 mL of hexane/EtOAc (1:1) 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 = 0.0081, CHCl₃). IR (KBr) cm⁻¹: 3400, 2940, 1717, 1715, 1679, 1633, 1383, 1246 (M+), 986, 417. HR-FAB-MS m/z: 1246.1804 (Caled for Cs₆H₁₄O₁₆Rhz: 1246.1801).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Ms. H. Matsumoto, A. Maeda, S. Oka, and M. Kiuchi of the Center for Instrumental Analysis, Hokkaido University, for technical assistance in the MS and elemental analysis.

References and Notes

16) N-[2-(Ethoxycarbonyl)aminocarbonyl]-benzoyl-(S)-tert-leucine was also transformed into the methyl ester by HPLC, indicating that no racemization occurred during the ligand exchange reaction.
δ: 1.03 (9H, s, t-Bu), 1.21 (3H, m, CH$_2$CH$_3$), 4.13 (2H, m, CH$_2$CH$_3$), 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: 351.1555 (Caled for C$_{17}$H$_{23}$N$_2$O$_6$: 351.1556).

17) N-(2-Methoxycarbonyl)benzoyl-(S)-tert-leucine was obtained as a major product in 83% yield. Colorless viscous oil. TLC R$_f$ 0.57 (4:1 CHCl$_3$/MeOH). [α]$_D$$^23$ -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 (Caled for C$_{18}$H$_{20}$N$_2$O$_6$: 294.1341).
