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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], Rh₄(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.5–9 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], Rh₄(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,9 enantiotopically selective aromatic C–H insertions,9 intramolecular 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 ylides9,10 with high levels of enantioselectivities up to 98% ee. However, a problem associated with the original synthesis of Rh₄(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 Rh₄(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 Netkens41 and Casimir,15 which use N-ethoxycarbonylphthalimide or methyl 2-(succinimidoxyycarbonyl)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-(succinimidoxyycarbonyl)benzoate under mild conditions also failed to give optically pure 2. A better procedure (vide infra) was discovered (vide infra).

(Continued on next page)

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

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cinimidoxyccarboxyl)benzoate (Na2CO3, aq. CH3CN, rt, 8 h) gave none of the desired product. [17] It is clear that an excep-
ionally bulky tert-butyl group of 3 would have an effect, be-
cause of the severe steric hindrance imposed. After some ex-
perimentation, we found that this goal could be achieved by employing the method of Bode. [18, 19] Thus, the con-
densation 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 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 Bode'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 Bode has the advantages of operational simplicity as well as reproducibility, thus providing facile and reliable access to high quality Rθ(S-PTTL)

Experimental
Melting points were determined on a Büchi 535 digital melting point ap-
paratus and are uncorrected. NMR spectra were obtained with a JEOL JNM-
AL400 spectrometer (400 MHz at 100 MHz), with tetramethylsilane ([δ 0.0, 1H] or chloroform-d ([δ 77.0, 13C]) as an internal standard. Infrared spectra were recorded on a Jasco FT/IR-5300 spectrometer. Optical rotations were mea-
sured on a Jasco D-370 digital polarimeter. Electron impact (EI) mass spectra were obtained on a Jasco 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 detec-
or. 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 detec-
or. Detection was at 254 nm. A Chiraleel OJ column (0.46 cmX25 cm) from Daicel was used. Retention times (tR) were determined by comparison of HPLC retention time with the Caled for C14H16N04: 262.1079).

Instruments
A Varian Cary 50 spectrometer was used. Retention times (tR) were determined by comparison of HPLC retention time with the Caled for C14H16N04: 262.1079).

Analytical Data

Analytical Data

Acknowledgements
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References and Notes


3768 (2002).

16) [2-(Etioxyccarboxyl)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]D -4.4° (c = 0.92, EtOH).


3768 (2002).

26) [2-(Etioxyccarboxyl)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]D -4.4° (c = 0.92, EtOH).


\[ \delta: 1.03 (9H, s, t-Bu), 1.21 (3H, m, CH\textsubscript{2}CH\textsubscript{3}), 4.13 (2H, m, CH\textsubscript{2}CH\textsubscript{3}), 4.57 (1H, d, J=8.9 Hz, CH), 6.91 (1H, d, J=8.9 Hz, NH), 7.40-7.47 (4H, m, ArH), 9.2 (1H, s, NH). \] 

\[ \text{\textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}, 50°C) \delta: 14.0 (CH\textsubscript{3}), 26.6 (CH\textsubscript{2}), 34.6 (C), 61.1 (CH), 62.3 (CH\textsubscript{2}), 127.3 (CH), 127.7 (CH), 130.4 (CH), 130.5 (CH), 133.7 (C), 134.6 (C), 151.6 (C=O), 168.3 (C=O), 169.0 (C=O). FAB-MS m/z: 351 (M\textsuperscript{+}+H\textsuperscript{+}), 262. HR-FAB-MS m/z: 351.1553 (Caled for C\textsubscript{17}H\textsubscript{23}N\textsubscript{2}O\textsubscript{6}.)
\]

\[ \text{17) N-(2-Methoxycarbonyl)benzoyl-(S)-tert-leucine was obtained as a major product in 83% yield. Colorless viscous oil. TLC R\textsubscript{f} 0.57 (4:1 CHCl\textsubscript{3}/MeOH). [\alpha]\textsubscript{D}^20 \text{°} = -23.8° (c=1.38, CHCl\textsubscript{3}). IR (CHCl\textsubscript{3}) cm\textsuperscript{-1}: 3426, 1725, 1671. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}, 50°C) \delta: 1.11 (9H, s, t-Bu), 3.86 (3H, s, OCH\textsubscript{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). \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}, 50°C) \delta: 26.6 (CH\textsubscript{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\textsuperscript{+}), 262, 248, 163. HR-EI-MS m/z: 294.1342 (Caled for C\textsubscript{17}H\textsubscript{20}N\textsubscript{2}O\textsubscript{6}).
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