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Asymmetric Dipolar Cycloaddition Reactions of Diazocompounds Mediated by a Binaphtholphosphate Rhodium Catalyst

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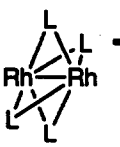
Key Words: binapthol; cycloaddition; furo[2,3-*b*]furan; dirhodium catalysts.

Abstract: *A new class of chiral rhodium catalysts derived from binapthol promotes the dipolar cycloaddition of diazocompounds to heterocycles with good asymmetric induction.*

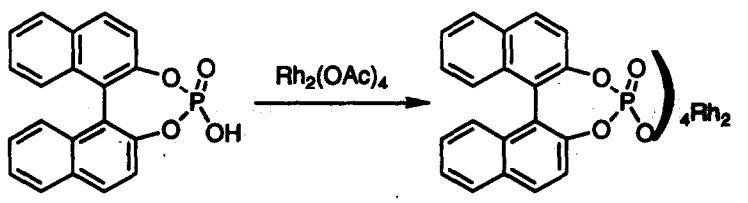
The synthetic utility of rhodium (II) salts in the catalytic decomposition of diazocompounds has become apparent over the last decade.[1] By comparison to classical synthetic methodology involving copper or its complexes,[2] rhodium-mediated carbenoid reactions generally proceed under much milder conditions. Undoubtedly one of the most practical carbene reactions in organic synthesis is the rhodium carboxylate-promoted intramolecular N-H insertion reaction that is the key step in the Merck synthesis of thienamycin. This is a transformation that proceeds in yields far exceeding 90% and that is conducted on a scale of tens of thousands of kilograms annually.[3]

The opportunities for carbenoid transformations catalyzed asymmmetrically have been apparent for some time. Many reports have been made of copper complexes[4] of, *inter alia*, C_2-symmetric dinitrogen ligands[5] that give high enantiomeric excess in cyclopropanation reactions with ethyl diazoacetate. Chiral rhodium complexes, including amide and carboxylate derivatives, have also been investigated for these purposes.[6]



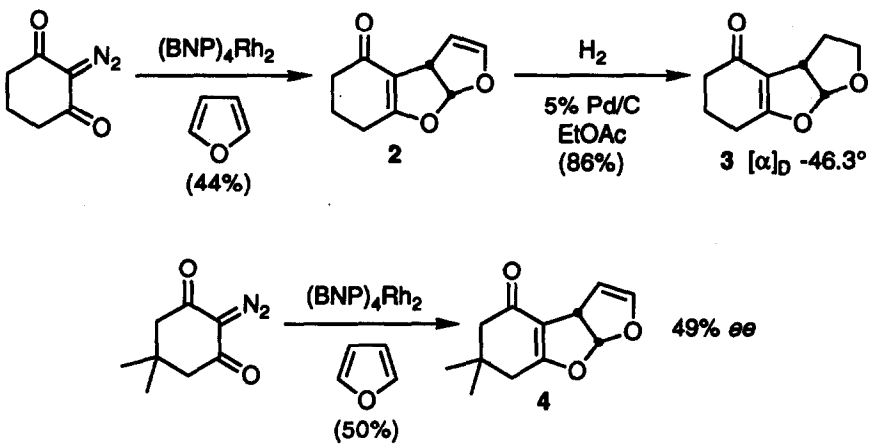
Rh_2L_4	(r_{Rh-Rh})					
t-$BuCO_2$	HCO_2	AcO	CF_3CO_2	H_2PO_4	AcS
2.37	2.38	2.39	2.41	2.49	2.55

Despite the rich coordination chemistry of the dirhodium(II) core of the rhodium carboxylates,[7] little correlation of structure with catalytic activity has been made. We were intrigued by the observation that rhodium phosphate has a rhodium-rhodium bond length *ca.* 0.1 Å longer than the corresponding carboxylates[8] and wondered what effect this structural difference would have on the catalytic properties of such complexes. To impart organic solubility and eliminate acidic protons, a phosphodiester appeared to be a more advantageous choice for a ligand. The cyclic phosphate of binapthol meets these needs with the added benefit of providing a C_2-symmetric chiral ligand commercially-available in both enantiomeric series. We describe in this Letter the preparation of the tetrakisbinaptholphosphate dirhodium {$(BNP)_4Rh_2$, **1**} catalyst and its value in a diazocarbonyl reaction currently under study in our laboratory, dipolar cycloaddition with heterocycles.[9]

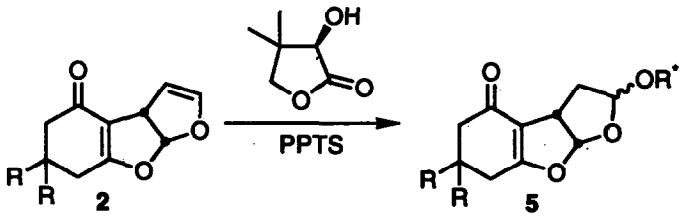


(1)

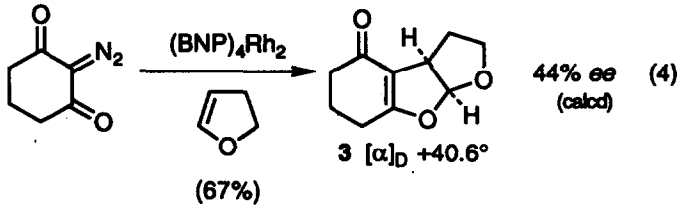
$(BNP)_4Rh_2$, prepared by exchange with rhodium acetate (eq 1), promotes the room temperature addition of diazocyclohexane-1,3-dione to furan as solvent (eq 2, absolute configuration not determined). The product is isolated in 44% yield after 12h. Enantiomeric excess in the cycloadduct **2** (50% *ee*) is determined by derivatization with (*R*)-pantolactone under catalysis by PPTS (eq 3). The acetal **5** is obtained as a 3/1 mixture of isomers differing on the basis of addition from the *exo* or *endo* face, respectively, of the dihydrofuro[2,3-*b*]furan ring system. The ^1H NMR signals for the bridgehead H's show doubling in each diastereomer of the racemic derivative and permit ready determination of the optical purity of cycloadduct **2** by integration. The enantiomeric excess can also be determined by GC analysis of the acetal products. Dilution of the reaction with inert solvent leads to lower yield and only marginal enhancement of *ee*. Likewise, cycloaddition of diazodimedone to furan catalyzed by **1** provides **4** in 50% yield and with 49% ee (eq 2). Substances such as **2** and **4**, now available in scalemic form in 2 steps and 40% yield from commercially-available materials, are key intermediates in projected syntheses of *Aspergillus* metabolites.[10]



(2)



The working hypothesis for the dipolar cycloaddition reaction involves initial cyclopropanation,[9] and this model was used to try to rationalize the asymmetric induction observed. However, this hypothesis is difficult to reconcile with further observations. An unusual reversal in the sense but not the degree of asymmetric induction as engendered by **1** occurs when dihydrofuran is used as the cycloadding partner (eq 4, absolute configuration not determined). This point was established by hydrogenation of **2** to a sample of **3** and comparison of the sign of the optical rotation. Also, examination of several of the well-known catalysts for asymmetric cyclopropanation gave negative results. They were either unsuccessful in decomposing the diazocompound ($Cu(N)_2$ complexes) or provided material of inferior *ee* ($Rh_2(MEPY)_4$).[6]



An experimental description of the preparation of $(BNP)_4Rh_2$ follows. To a 100 mL flask fitted with a Soxhlet extractor containing a 1:1 sand:Na_2CO_3 mixture was added (*R*)-binaptholhydrogen phosphate (5.0 g, 14.4 mmol), $Rh_2(OAc)_4$ (0.441 g, 1.0 mmol), and chlorobenzene (50 mL). The reaction mixture was refluxed for 48 h as the original green color was replaced by a greenish-yellow. Evaporation of the solvent afforded a residue to which was added 50 mL CH_2Cl_2 to dissolve the product. Filtration provided recovered excess binapthol phosphate, and concentration of the filtrate gave a green-yellow solid. Recrystalization from CH_2Cl_2 /hexane afforded a yellowish solid, mp >300 °C (1.37 g, 95%).[11]

Future challenges include the development of new cyclic phosphate derivatives that can afford holemic products.

Samples of this catalyst are available on request by FAX to (919) 660-1591.

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11. ^{1}H NMR for $Rh_2(BNP)_4$ ($CDCl_3$): δ 7.89 (d, J = 8.1, 2H); 7.85 (d, J = 9.2, 2H); 7.59 (d, J = 8.8, 2H); 7.46 (m, 4H); 7.32 (m, 2H). ^{13}C NMR (CDCl3): d 147.9, 132.3, 131.8, 131.1 128.5, 127.2, 126.5, 125.5, 121.6,121.3.

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