ORGANIC LETTERS

2003
Vol. 5, No. 21
3863−3866

Highly Efficient Asymmetric Lewis Acid Catalysis with Platinum Group Complexes of Conformationally Flexible 1,3-Butadiene-Bridged Diphosphines, NUPHOS

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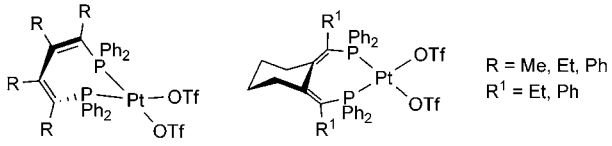
Received July 28, 2003

ABSTRACT



δ-**4a-c** δ-**4d-e**

Palladium and platinum complexes of conformationally flexible 1,3-butadiene-bridged diphosphines NUPHOS can be resolved with (*S*)-BINOL at elevated temperatures to afford diastereopure *δ*-[(NUPHOS)M{(*S*)-BINOL}] (M = Pd, Pt). The homochiral Lewis acid complexes *δ*-[(NUPHOS)M][OTf]$_2$, generated by protonation of *δ*-[(NUPHOS)M{(*S*)-BINOL}] with trifluoromethanesulfonic acid, catalyze the Diels–Alder reaction between acryloyl-*N*-oxazolidinones and cyclopentadiene to give ee values up to 96%. The corresponding enantiopure dichlorides *δ*-[(NUPHOS)PtCl$_2$] react with AgClO$_4$ to form highly efficient catalysts that give good endo/exo selectivities and high endo enantioselectivity.

For decades, the design of ligands for asymmetric catalysis has been guided by the concept that high enantioselectivities require a conformationally restricted ligand.[1] Recently though, alternative strategies that do not rely on the screening of resolved ligands have been investigated, including (i) chiral poisoning,[2] (ii) asymmetric activation,[3] and (iii) the use of flexible achiral ligands that can adopt chiral conformations.[4] In the last of these, a chiral activator interacts with an achiral ligand and causes the latter to preferentially exist in one of its asymmetric conformations, which acts to define the chiral environment of the catalyst.[5] Mikami and Noyori have applied this strategy to the highly enantioselective ruthenium-catalyzed asymmetric reduction of ketones by exploiting the

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10.1021/ol035409i CCC: $25.00
Published on Web 09/25/2003

conformational flexibility of the *tropos* diphosphine 2,2′-bis(3,5-dimethylphenylphosphino)biphenyl (DM-BIPHEP).[6,7] Addition of (*S*,*S*)-dpeda [(*S*,*S*)-1,2-diphenylethylenediamine] to [$RuCl_2$(BIPHEP)$(dmf)_n$] gave [$RuCl_2$(BIPHEP){(*S*,*S*)-dpeda}], which formed as a 1:1 mixture of diastereoisomers as a result of the axial chirality of coordinated BIPHEP. Slow atropinterconversion of the enantiomeric conformations of BIPHEP gave a 3:1 thermodynamic mixture of diastereoisomers that exhibited a large difference in relative rates for the hydrogenation of 1-acetonaphthone, to give *R*-1-(1-naphthyl)ethanol with an ee of 84%; an improvement on the performance of the corresponding catalyst generated from *rac*-BINAP which gave an ee of 80%. Gagné has demonstrated that coordination of BIPHEP to a substitutionally inert metal such as platinum(II) significantly slows atropinversion such that the diastereoisomeric complexes λ/δ-[Pt(BIPHEP)-{(*S*)-BINOL}] can be separated, the chiral resolving ligand removed, and the resulting homochiral Lewis acid platinum complexes λ- and δ-[(BIPHEP)Pt$(OTf)_2$] used to catalyze asymmetric Diels−Alder cycloaddition reactions and the glyoxylate-ene reaction.[8] The high ee's obtained in both reactions clearly demonstrate that conformationally flexible diphosphines can be used as effective chiral ligands to achieve high enantioselectivities in asymmetric catalysis. This is the first example of the use of a conformationally flexible diphosphine as the sole source of stereocontrol for catalysis. Following this, Mikami resolved racemic palladium complexes of BIPHEP with (*R*)-2,2′-diaminobinaphthyl [(*R*)-DABN], by complexation followed by tropointerconversion at 80 °C to give a single diastereoisomer of [Pd{(*R*)-BIPHEP}{(*R*)-DABN}].[9] Enantiopure [Pd{(*R*)-BIPHEP}-$(MeCN)_2$][SbF_6]$_2$ acts as a highly effective catalyst for the hetero Diels−Alder reaction between cyclohexadiene and ethyl glyoxylate to give ee values up to 82%. Moreover, diastereopure [Pd{(*R*)-BIPHEP}{(*R*)-DABN}] can be used as an activated asymmetric catalyst directly without liberating the chiral activator, the ee value of 94% being a significant improvement on that obtained with enantiopure [Pd{(*R*)-BIPHEP}$(MeCN)_2$][SbF_6]$_2$.

There is a clear similarity between BIPHEP and the NUPHOS-type diphosphines **1a**−**e** (Figure 1) recently developed in our laboratory[10] in that both are based on two diphenylphosphino groups linked by a four-carbon sp^2-hybridized tether and exhibit atropisomerism when coordinated to a transition metal. With this in mind, we have

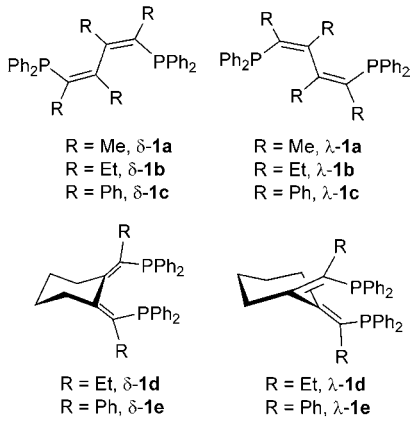

Figure 1. Acyclic 1,2,3,4-R_4-NUPHOS (**1a**−**c**) and monocyclic 1,4-R_2-*cyclo*-C_6H_8-NUPHOS (**1d**−**e**)-type diphosphines.

recently initiated a program to explore the applications of NUPHOS-type diphosphines in asymmetric catalysis, with an emphasis on using their modular construction to optimize catalyst performance. Herein, we report that palladium and platinum complexes of conformationally flexible NUPHOS diphosphines form highly efficient Lewis acid catalysts for the Diels−Alder reaction between acryloyl-*N*-oxazolidinones and cyclopentadiene.

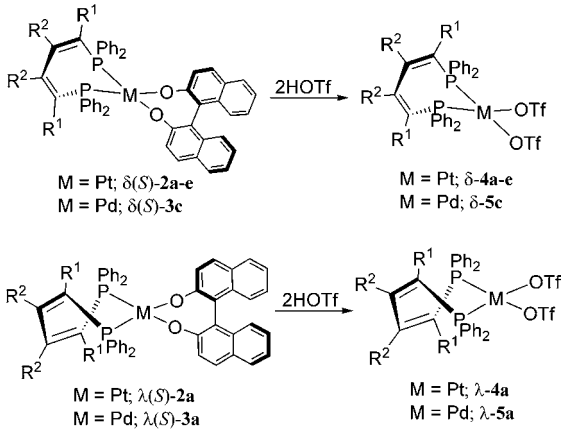

Figure 2. Formation of homochiral Lewis acid catalysts δ- and λ-[(NUPHOS)M$(OTf)_2$] (NUPHOS = **1a**−**e**).

We have recently demonstrated that (*S*)-BINOL can be used as an effective resolving agent for platinum complexes of NUPHOS-type diphosphines.[11] A 1:1 diastereoisomeric mixture of [(NUPHOS)Pt{(*S*)-BINOL}], obtained by reaction of Na_2-(*S*)-BINOL with *rac*-[(NUPHOS)$PtCl_2$], undergoes atropinversion at high temperatures to afford a diastereoenriched mixture that can be crystallized to give a diastereopure

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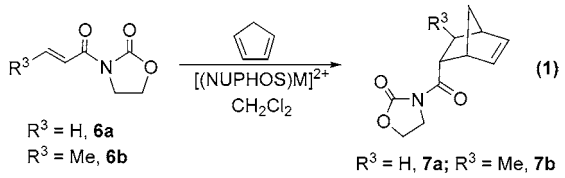
sample of the thermodynamically favored δ-[(NUPHOS)Pt{(*S*)-BINOL}] (δ-**2a**−**e**). Similarly, we have now shown that (*S*)-BINOL can be used to resolve *rac*-[(NUPHOS)$PdCl_2$], although the resulting BINOLate complexes are less stable than their platinum counterparts and cannot be heated to effect diastereointerconversion. Fortuitously though, diastereopure samples of λ-[(1,2,3,4-Me_4-NUPHOS)Pd{(*S*)-BINOL}] (**3a**) and δ-[(1,2,3,4-Ph_4-NUPHOS)Pd{(*S*)-BINOL}] (**3c**) have been isolated by crystallization from a 1:1 mixture of diastereoisomers at room temperature. A single-crystal X-ray study of **3a** has shown that the diphosphine adopts a λ-skew conformation in the same manner as that in [(1,2,3,4-Me_4-NUPHOS)Pt{(*S*)-BINOL}].[11] A variable-temperature ^{31}P NMR study of a representative sample of crystals confirmed that the crystal chosen corresponds to the thermodynamically less favored diastereoisomer.

The homochiral Lewis acids δ-[(NUPHOS)Pt$(OTf)_2$] (δ-**4a**−**e**), generated by protonation of δ-[(NUPHOS)Pt{(*S*)-BINOL}] with trifluoromethanesulfonic acid, are remarkably effective catalysts for the benchmark Diels−Alder reaction between acryloyl-*N*-oxazolidinone **6a** and cyclopentadiene (eq 1). In a typical experiment, a dichloromethane solution of δ-[(NUPHOS)Pt{(*S*)-BINOL} (δ-**2a**−**e**) and acryloyl-*N*-oxazolidinone was treated with trifluoromethanesulfonic acid at room temperature to form δ-**4a**−**e**, after which the solution was cooled, cyclopentadiene added, and the mixture stirred at the appropriate temperature. After 20 h, the reaction mixture was quenched and the corresponding Diels−Alder adduct **7a** purified by column chromatography. In each case, analysis of the product by ^{1}H NMR spectroscopy and chiral HPLC revealed that catalysts **4a**−**e** afford cycloadduct **7a** with high endo selectivity and good to excellent endo enantioselectivity (65−96%, (2*R*)-configuration). The absolute configuration of the cycloadduct was determined by comparison with samples generated from catalysts based on (*R*)-BINAP[12] and λ-BIPHEP.[8a] Reaction mixtures were routinely quenched by addition of 1 equiv of (*S*,*S*)-dpeda to establish the extent of atropinversion during activation and reaction. In all cases, the ^{31}P NMR spectrum showed the presence of only a single diastereoisomer, confirming that the stereochemistry of NUPHOS is stable under the reaction conditions.

The results listed in Table 1 clearly show that the performance of catalysts based on acyclic NUPHOS diphosphines **1a**−**c** (Figure 1) depends markedly on R such that enantioselectivity increases with increasing size in the order Me < Et < Ph (entries 1−4). In contrast, catalysts **2d** and **2e**, based on monocyclic NUPHOS diphosphines, gave the cycloadduct with ee values of 96 and 95%, respectively (entries 5 and 6). As expected, λ-[(1,2,3,4-Me_4-NUPHOS)Pt$(OTf)_2$] (λ-**4a**) catalyzes the Diels−Alder reaction with acryloyl-*N*-oxazolidinone **6a** to give cycloadduct **7a** of opposite absolute stereochemistry and with an enantioselectivity similar to that obtained with its enantiomeric counterpart δ-**4a** (entry 2). In this regard, NUPHOS-type diphosphines behave in much the same manner as BIPHEP, the first conformationally flexible nonresolvable diphosphine to be used in asymmetric Lewis acid catalysis (entry 14).[8]

Table 1. Asymmetric Diels−Alder Reaction Between Acryloyl-*N*-oxazolidinone and Cyclopentadiene



entry	dienophile	catalyst (mol %)	temp,°C (time, h)	yield, %[a]	endo:exo ratio[b]	endo ee (configuration)[c]
1	**6a**	**4a** (10)	−60 (20)	74	85:15	65 (2*R*)
2	**6a**	**4a** (10)[e]	−60 (20)	71	81:19	69 (2*S*)
3	**6a**	**4b** (10)	−60 (20)	73	83:7	86 (2*R*)
4	**6a**	**4c** (10)	−60 (20)	76	82:18	94 (2*R*)
5	**6a**	**4d** (10)	−60 (20)	82	92:8	96 (2*R*)
6	**6a**	**4e** (10)	−60 (20)	85	93:7	95 (2*R*)
7	**6a**	**5a** (10)	−60 (24)	72	88:12	94 (2*S*)
8	**6a**	**5c** (10)	−60 (24)	70	84:16	91 (2*R*)
9	**6a**	**8a** (20)[d]	−60 (20)	66	92:8	95 (2*S*)
10	**6a**	**8c** (20)	−60 (20)	55	84:16	88 (2*R*)
11	**6b**	**8a** (20)[d]	−20 (40)	68	93:7	90 (2*S*)
12	**6b**	**8c** (20)	−20 (40)	73	90:10	87 (2*R*)
13	**6a**	**10** (20)	−20 (40)	64	82:12	82 (2*R*)
14	**6a**	BIPHEP[e]	−60 (20)	84	95:5	95 (2*S*)

[a] Isolated yield after column chromatography. [b] Endo/exo ratio determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess (ee) was determined by chiral HPLC (Daicel Chiralcel OD-H). Average of three runs. [d] λ-Stereoisomer used. [e] λ-[(BIPHEP)Pt$(OTf)_2$] generated from diastereopure λ-[(BIPHEP)Pt{(*S*)-BINOL}] according to ref 8a.

While the stereochemistry of [(NUPHOS)Pt$(OTf)_2$] is stable, quenching experiments revealed that the corresponding palladium complexes are conformationally less stable and readily undergo atropinversion at room temperature. The extent of atropinversion was measured by addition of (*S*,*S*)-dpeda to a sample of δ-[(1,2,3,4-Ph_4-NUPHOS)Pd$(OTf)_2$], generated by addition of trifluoromethanesulfonic acid to a dichloromethane solution of δ-[(1,2,3,4-Ph_4-NUPHOS)Pd-{(*S*)BINOL}] at room temperature. The ^{31}P NMR spectrum of a reaction mixture quenched after 15 min showed a 70:30 mixture of the diastereoisomeric amine complexes δ/λ-[(1,2,3,4-Ph_4-NUPHOS)Pt{(*S*,*S*)-dpeda}], confirming a significant level of atropinversion. Although these compounds are kinetically unstable, atropinversion can be avoided by generating the Lewis acid at −40 °C prior to addition of cyclopentadiene. Under these conditions, **5a** and **5c** are highly selective catalysts for the reaction between dienophile **6a** and cyclopentadiene, giving cycloadduct **7a** with endo enantioselectivities of 94 and 91%, respectively (entries 7 and 8).

Since catalyst precursors would be more versatile in the form of their dichlorides, λ-[(1,2,3,4-Me_4-NUPHOS)Pt{(*S*)-BINOL}] and δ-[(1,2,3,4-Ph_4-NUPHOS)Pt{(*S*)-BINOL}] have been converted into the corresponding enantiopure λ-[(1,2,3,4-Me_4-NUPHOS)$PtCl_2$] λ-**8a** and δ-[(1,2,3,4-Ph_4-

(12) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157.

NUPHOS)$PtCl_2$] δ-**8c**, respectively, by treatment of a dichloromethane solution of the BINOLate complex with HCl. Addition of (*S*,*S*)-dpeda to the resulting dichlorides gave a single diastereoisomer of δ/λ-[(NUPHOS)Pt{(*S*,*S*)-dpeda}], confirming that protonation occurs with retention of stereochemistry. Catalyst mixtures generated by activation of δ-**8c** with $AgClO_4$ afford cycloadduct **7a** with high endo/exo selectivity and an endo enantioselectivity comparable to that obtained with catalyst generated from the BINOLate precursor (entry 10). Similarly, the performance of catalyst generated from λ-**8a** (entry 9) compares favorably with that of λ-**4a**, giving cycloadduct **7a** in comparable yields with a slight improvement in the endo enantioselectivity (95% ee, (2*S*)-configuration). Lewis acids generated from λ-**8a** and δ-**8c** also catalyze the Diels−Alder reaction between cyclopentadiene and crotonoyl oxazolidinone **6b** with high endo/exo selectivity and excellent endo enantioselectivity (entries 11 and 12). As expected, methyl-substituted oxazolidinone **6b** reacts more slowly than **6a** and these reactions must be conducted at higher temperatures (−20 °C). Interestingly, attempts to perform this reaction with catalyst mixtures generated from δ-[(NUPHOS)Pt{(*S*)-BINOL}] and trifluoromethanesulfonic acid proved to be unsuccessful and in each case gave less than 5% conversion. The ^{31}P NMR spectrum of the reaction mixture contains a single resonance at δ −5.7, which we tentatively suggest corresponds to the deactivated complex [(NUPHOS)Pt(η^5-Cp)]$^+$ on the basis that the large $^1J_{Pt-P}$ of 4542 Hz is similar to that of 4528 Hz recently reported for [(BIPHEP)Pt(η^5-Cp)]$^+$. At this stage, it is unclear why [(NUPHOS)Pt(η^5-Cp)]$^+$ forms so readily in catalyst solutions prepared from the BINOLate precursor while those prepared from the dichloride form less than 10% of the deactivated complex at the same temperatures.

The absolute stereochemistry of cycloadducts **7a** and **7b** ((2*R*)-configuration) is consistent with the transition state model recently proposed by Ghosh and used to account for the high level of enantiofacial selection obtained in the [M{(*R*)-BINAP}$(OTf)_2$] (M = Pd, Pt) catalyzed Diels−Alder reaction between acryloyl-*N*-oxazolidinones and cyclopentadiene.[12] By analogy, the δ-conformation of acyclic and monocyclic NUPHOS diphosphines behave in much the same manner as (*S*)-BINAP in that the pseudoequatorial phenyl ring orientated below the MP_2 plane prevents attack of the incoming diene at the *Re*-face and endo-*Si*-face attack to give cycloadduct with (2*R*)-absolute configuration is favored. The modular construction of NUPHOS-type diphosphines offers immense scope for structural modification since the basic building blocks are either alkynes or diynes and an electrophilic chlorophosphine. In a preliminary comparative study, we have examined the performance of the chiral NUPHOS diphosphine **9** in the palladium-catalyzed reaction between cyclopentadiene and dienophile **6a**. A single resonance in the ^{31}P NMR spectrum of the palladium dichloride derivative **10** is consistent with one diastereoisomer corresponding to either a δ- or λ-conformation of the C_4-tether. A dichloromethane solution of **10** activated with 2 equiv of silver hexafluoroantimonate gave cycloadduct **7a** with good endo/exo selectivity and high enantioselectivity (82%, (2*R*)-configuration), consistent with a δ-skew conformation of the diphosphine.

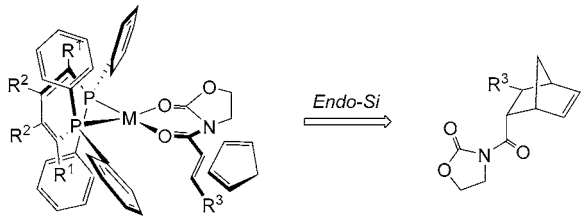


Figure 3. Stereochemical model showing favored *Si*-face attack of cyclopentadiene to give cycloadduct with (2*R*)- absolute configuration (M = Pd, Pt).

In conclusion, platinum group complexes of conformationally flexible NUPHOS-type diphosphines can be resolved and are stable with respect to atropinversion in the absence of a chiral activator. The corresponding Lewis acid fragments δ- or λ-[(NUPHOS)M]$^{2+}$ are highly efficient catalysts for the Diels−Alder reaction between acryloyl-*N*-oxazolidinones and cyclopentadiene, giving ee values as high as 96%. Results of preliminary catalyst testing are encouraging, and further studies are underway to prepare chiral versions of NUPHOS, exploit their modular construction to optimize catalyst performance, and explore their applications in a wide range of asymmetric reactions.

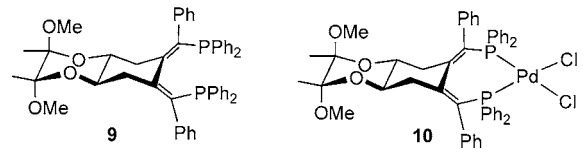


Figure 4. Chiral NUPHOS diphosphine **9** and corresponding palladium dichloride complex **10**.

Acknowledgment. We gratefully acknowledge the EPSRC (R.K.R.) and the McClay Trust (C.R.N.) for funding and Johnson Matthey for loans of palladium salts. Thanks are also extended to Professor Michael Gagné for his valued assistance.

Supporting Information Available: Experimental procedures, spectroscopic and analytical data for **4a** and **4c**, crystallographic data collection parameters, a full listing of bond lengths and angles, anisotropic displacement parameters, and hydrogen atomic coordinates for compound **3a**, as well as an ORTEP view. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035409I