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Asymmetric Catalysis with the Normally Unresolvable, Conformationally Dynamic 2,2′-Bis(diphenylphosphino)-1,1′-biphenyl (Biphep)

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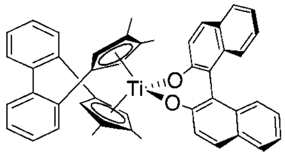
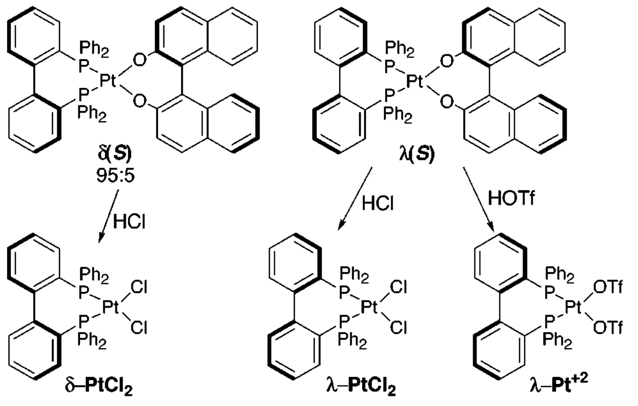
Achieving high enantioselectivites in asymmetric catalysis usually requires rigid, conformationally restricted chiral ligands (e.g., BINAP, DuPhos).[1] Recently a new approach has emerged where conformationally flexible ligands are intentionally used to magnify the effect of other chiral ligands.[2] For example, Et_2Zn addition to aldehydes can be made enantioselective with titanium catalysts containing flexible bis(sulfonamide) ligands in combination with a normally ineffective chiral alkoxide ligand.[2a] The chiral alkoxide is proposed to magnify its chirality by inducing a selective conformation in the sulfonamide ligand. Similarly, chiral amine or amine *N*-oxide additives induce chiral conformations in otherwise achiral (salen)manganese(II) complexes and lead to enantioselective alkene epoxidation catalysis.[2b−d] 1,1′-Bis(diphenylphosphino)biphenyl (biphep) interconverts between two atrop forms, one of which is favored (3:1) when coordinated to the chiral ruthenium fragment, Cl_2Ru(*S*,*S*-dpeda), (*S*,*S*-dpeda = (*S*,*S*)-1,2-diphenylethylenediamine).[2e−f] This 3:1 mixture selectively hydrogenates ketones in up to 92% ee.

Each of the above cases utilizes a flexible ligand to magnify the stereochemical induction of a chiral catalyst. More rare is the utilization of a flexible ligand that is locked into a metastable state to provide the only source of asymmetry for catalysis. Brintzinger's biphenyl-bridged bisCp titanium catalyst functions in this manner.[3] In this unique case, thermolysis of a mixture of diastereomers leads to a single complex where BINOL's preference for one atrop form of the ansa ligand provides an enantio- and diastereopure titanocene precatalyst, which after BINOL removal hydrogenates 1-phenylpyrroline in up to 98% ee. The sole source of stereocontrol in this catalyst comes from the biphenyl-bridged ligand. Expanding this strategy to chiral ligands with broad utility in catalysis (e.g., diphosphines) promises to expand the chiral ligand base beyond those normally considered resolvable.



We recently demonstrated that, even though the enantiomers of biphep rapidly interconvert at room temperature, coordination to a substitution-inert metal such as platinum(II) significantly slows atropinversion.[4] Since P_2PtBINOL complexes react with triflic acid (TfOH, 2 equiv) to generate[5] $P_2Pt(OTf)_2$ Lewis acids,[6] we reasoned that diastereopure (biphep)Pt(*S*-BINOL) complexes could be a source of the enantiopure (biphep)Pt^{2+} Lewis acid fragment, a potential catalyst whose chirality was solely engendered in the coordinated biphep ligand (Scheme 1).

Scheme 1



The availability of pure λ(***S***) and 95:5 δ(***S***) (biphep)Pt(*S*-BINOL)[4,7] provides the means to test this hypothesis. To also generate the dicationic catalysts by traditional AgOTf treatments, the BINOLate complexes were converted to the dichlorides by treatment with HCl, a process that occurs with retention of configuration. Fortunately, the 95:5 mixture of δ-$\mathbf{PtCl_2}$ and λ-$\mathbf{PtCl_2}$ obtained from the mixture of diastereomers in δ(***S***) recrystallized to enantiopure δ-$\mathbf{PtCl_2}$ (Scheme 1).[8] The three obtainable enantio- and diastereopure catalyst precursors were utilized to test if biphep was viable for use in asymmetric catalysis.

To first confirm that the stereochemistry of (biphep)Pt^{2+} was indeed stable in the absence of the BINOL's bias, we carried out quenching experiments on the dication (λ-$\mathbf{Pt^{+2}}$) derived from triflic acid treatment of λ(***S***). The in situ generated ditriflate, was quenched after variable periods of time with *S*,*S*-dpeda to form diamine complexes (eq 1).[9] Analysis of the diastereomeric ratio of the diamine complexes by ^{31}P NMR conveniently probes for unintended atrop inversion during catalyst activation. The data in Table 1 show that while slight erosion does occur, the ditriflate is kinetically stable for at least 8 h (rt) without the BINOL.

To assess the viability of the putative homochiral catalyst formulations, the benchmark Lewis acid-catalyzed Diels−Alder reaction in eq 2 was chosen. The catalyst λ-$\mathbf{Pt^{2+}}$ was generated in two ways, by the addition of 1.7 equiv of HOTf to λ(***S***) and

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[1] Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Catlalysis*; Wiley: New York, 1995.

[2] (a) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc*. **2000**, *122*, 1802−1803. (b) Miurra, K.; Katsuki, T. *Synlett* **1999**, 783−785. (c) Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541−9552. (d) Hashihayata, T.; Ito, Y.; Katsuki, T. *Synlett* **1996**, 1079−1081. (e) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuna, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed*. **1999**, *38*, 495−497. (f) Korenaga, T.; Aikawa, K.; Terada, M.; Kawauchi, S.; Mikami, K. *Adv. Synth. Catal.* **2001**, *343*, 284−288.

[3] Ringwald, M.; Stürmer, R.; Brintzinger, H. H. *J. Am. Chem. So*c. **1999**, *121*, 1524−1527.

[4] Tudor, M. D.; Becker, J. J.; White, P. S.; Gagné, M. R. *Organometallics* **2000**, *19*, 4376−4484.

[5] Brunkan, N. M.; Gagné, M. R. Unpublished results.

[6] For several recent references describing P_2M^{+2} (M = Pd, Pt) Lewis acid catalysis, see: (a) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157−2159. (b) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160−5167. (c) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059−4062. (d) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233−1236. (e) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, T. *J. Org. Chem.* **1999**, *64*, 8660−8662. (f) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (g) Hattori, T.; Suzuki, Y.; Uesugi, O.; Oi, S.; Miyana, S. *Chem. Commun.* **2000**, 73−74. (h) Hori, K.; Kodana, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017−5023. (i) Hori, K.; Ohta, T.; Furukawa, I. *Tetrahedron* **1998**, *54*, 12737−12744.

[7] To distinguish biphep and BINOL stereochemistry we arbitrarily label the biphep stereochemistry in terms of its skew conformation (λ/δ), and BINOL by its axial designation (*R/S*).

[8] Assayed by halide displacement with *S,S*-dpeda and diastereopurity analysis by ^{31}P NMR, see ref 9.

[9] δ-$\mathbf{PtN_2}$ and λ-$\mathbf{PtN_2}$ were independently synthesized from (biphep)$PtCl_2$ and completely characterized. (δ-$\mathbf{PtN_2}$: δ −0.92, J_{P-Pt} = 3325 Hz, λ-$\mathbf{PtN_2}$: δ 0.62, J_{P-Pt} = 3366 Hz). δ-$\mathbf{PtN_2}$ was characterized by X-ray crystallography, see Supporting Information.

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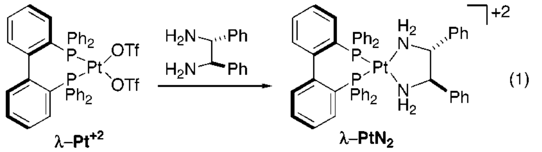
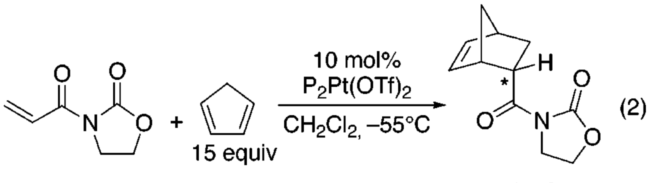
Table 1. Diamine Diastereomer Ratios (dr) (λ-**PtN$_2$**:δ-**PtN$_2$**) after HOTf Treatment of λ(*S*) and *S,S*-dpeda Quenching[a]



time (min)[b]	dr	time (min)[b]	dr
30	99:1	240	98:2
60	99:1	480	98:2

[a] Protonation at ambient temperature. ^{31}P NMR analysis with a 2 s delay time.[9] [b] Time from addition of HOTf to quench.

by treatment of λ-**PtCl$_2$** with AgOTf, both in the presence of dienophile (CH$_2$Cl$_2$, Scheme 1).[10] After 15 min of stirring, the solutions were cooled to −78 °C, 15 equiv of cyclopentadiene (CpH) was added, and the reactions were warmed to −55 °C. In both cases, the Diels−Alder adduct 2*S*-**1** was obtained in 92−94% ee (93:7 endo:exo), and the absolute stereochemistry was that expected from a λ, *R*-BINAP-like, diphosphine ligand as predicted by the stereochemical model of Ghosh for (*R*-BINAP)-Pt(OTf)$_2$.[6a] Moreover, as hoped, the catalyst derived from δ-**PtCl$_2$** yielded the opposite enantiomer of product, 2*R*-**1**, with an equally high enantioselectivity 92−94% ee (94:6 endo:exo).[11] These results confirmed that an otherwise nonresolvable diphosphine ligand can in fact be utilized in asymmetric catalysis.



2*R* - **1** for δ-biphep
2*S* - **1** for λ-biphep

During the course of experiments aimed at determining the enantio-composition of the (biphep)Pt^{2+} catalyst under catalytic conditions,[12] we detected an unidentified species in the ^{31}P NMR (5−10%). This material was characterized by unusually sharp ^{195}Pt satellites in the ^{31}P NMR, a large $J_{\mathrm{Pt-P}}$ (4528 Hz), and a triplet at 5.46 ppm in the ^{1}H NMR, also with Pt-satellites ($^{3}J_{\mathrm{P-H}}$ = 1.6 Hz and $^{2}J_{\mathrm{Pt-H}}$ = 8.4 Hz). By independent synthesis,[13] this complex was determined to be the unusual 18-electron (biphep)Pt(η^5-Cp)$^+$OTf$^-$ complex (**2**, Figure 1), which results from the reaction of the dication with excess CpH.[5,14] Consistent with its formulation as an 18-electron complex, isolated **2** does not catalyze the Diels−Alder reaction and is air- and water-stable.

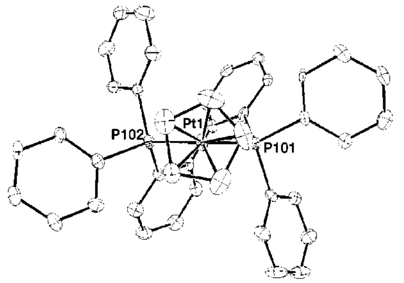
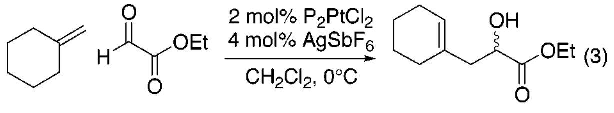


Figure 1. ORTEP representation of the δ-cation of **2** (thermal ellipsoids at the 50% probability level). Average Pt−C bonds are 2.26 Å, average P−Pt bonds are 2.24 Å, and average P−Pt−P angles are 94.5°.

To determine if the rigidified (biphep)Pt^{2+} catalyst was applicable to other asymmetric transformations, we examined the glyoxylate-ene reaction in eq 3.[6c,d] At 0 °C in CH$_2$Cl$_2$, 2 mol % of the dication generated from δ-**PtCl$_2$** and AgSbF$_6$ (2 equiv) converts the starting materials to *R*-**3** with 72% ee (50% conv, 5 h; 70% ee, 90% conv at rt), while the catalyst derived from λ-**PtCl$_2$** produces *S*-**3** with 70% ee (62% conv, 5 h; 71% ee, 99% conv at rt).[15]



R - **3** for δ-biphep
S - **3** for λ-biphep

In summary, we have demonstrated that normally unresolvable biphenyl-based diphosphines can adopt conformationally robust enantiopure atrop forms in inert coordination spheres.[16] Coordinating this ligand to substitution-inert metals such as Pt(II) provides the balance of conformational mobility and stereochemical stability to enable enantioselective catalysis. Since chelating diphosphines are ubiquitous ligands in catalysis, this strategy should find use in additional asymmetric applications.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for δ-**PtN$_2$**, λ-**PtN$_2$**, and **2**, and tables of crystallographic data collection parameters and metrical parameters for δ-**PtN$_2$** and **2** (PDF).

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[10] Activation of the catalysts in the presence of dienophile provided the most reproducible results.

[11] Protonation of the 95:5 δ(***S***) mixture provides a catalyst that is significantly less selective than that from δ-**PtCl$_2$**. Preliminary data point to an unusual nonlinear effect that is currently under investigation.

[12] Quenching with *S,S*-dpeda reveals that, at >90% conversion, biphep racemization is consistent with the data in Table 1.

[13] Fallis, S.; Rodriguez, L.; Anderson, G. K.; Rath, N. P. *Organometallics* **1993**, *12*, 3851−3855.

[14] The byproduct from the reaction of P$_2$Pt(OTf)$_2$ and 2 equiv of CpH is a CpH/HOTf species that we have not identified.[5] Since the product derived from a mixture of HOTf/CpH provides racemic Diels−Alder product (96:4 endo:exo) at −55 °C, this byproduct does not compete with the Pt catalyst for product formation.

[15] As in the Diels−Alder reaction, the λ-biphep provides the same absolute configuration of product as *R*-BINAP and *R*-MeOBiphep, see refs 6c,d.

[16] For a recent example of a crystallization-induced spontaneous resolution of an atrop-labile diphosphine (BIPHOS), kinetic stabilization by coordination to PdCl$_2$, and its utility in asymmetric catalysis, see: Tissot, O.; Gouygou, M.; Dallemer, F.; Daran, J.-C.; Balavoine, G. G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1076−1078.