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Asymmetric Activation of the Pd Catalyst Bearing the *Tropos* Biphenylphosphine (BIPHEP) Ligand with the Chiral Diaminobinaphthyl (DABN) Activator[1]

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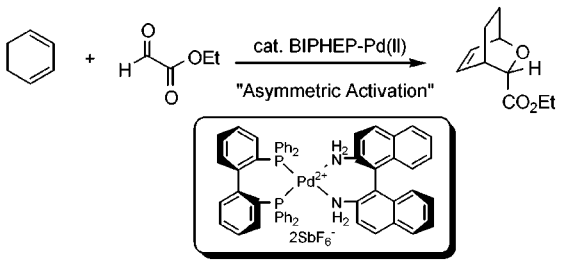
ABSTRACT



The enantio- and diastereomerically pure Pd complex of the *tropos* biphenylphosphine (BIPHEP) ligand is obtained through complexation of the enantiopure (*R*)-diaminobinaphthyl (DABN) with either enantiomer of the BIPHEP−Pd catalyst, followed by *tropo*-inversion of the less favorable (*S*)-BIPHEP−Pd/(*R*)-DABN diastereomer to the more favorable (*R*)-BIPHEP−Pd/(*R*)-DABN diastereomer. The enantiopure BIPHEP−Pd catalyst with DABN affords higher enantioselectivity and catalytic efficiency as an activated Lewis acid catalyst than the enantiopure BIPHEP−Pd catalyst without DABN.

In an asymmetric catalysis,[2] the design of a chirally rigid ligand has been the key to establish high enantioselectivity and to increase the catalytic activity from an achiral pre-catalyst ("ligand accelerated catalysis"[3]). A chiral metal catalyst is formed from an achiral pre-catalyst via ligand exchange with an often atropisomeric (*atropos*) ligand such as binaphthylphosphines (BINAP). The asymmetric catalysts thus prepared can be further transformed into highly activated catalysts with association of chiral activators ("asymmetric activation"[4]). This asymmetric activation process is particularly useful in in situ racemic catalysis; A "chiral activator" selectively activates one enantiomer of a racemic catalyst to attain higher enantioselectivity than that achieved with the enantiopure catalyst, in addition to a higher level of catalytic efficiency. We report here a further advanced strategy for "asymmetric activation" of a racemic Pd catalyst bearing the *tropos* biphenylphosphine (BIPHEP) ligand that achieves

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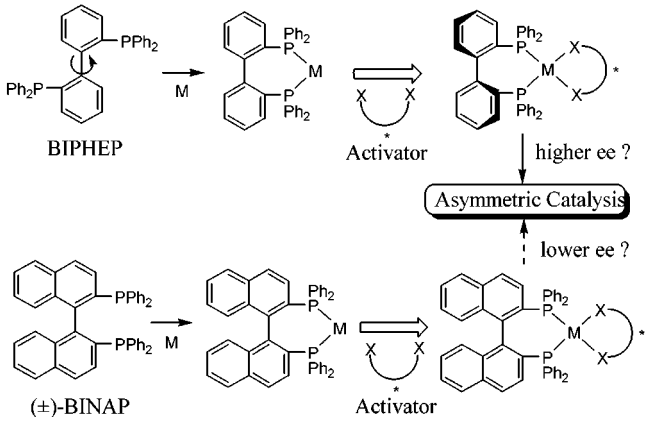
higher enantioselectivity and catalytic efficiency than those attained by *atropos* and racemic BINAP ligands in carbon−carbon bond-forming reactions. Combination of racemic BINAPs−$RuCl_2$[5] or BINAPs−PdX_2 (X = SbF_6)[6] even with a 0.5 molar amount of an enantiopure diamine, diphenylethylenediamine (DPEN) gives a 1:1 mixture of BINAPs−M (M = Ru or Pd)/DPEN diastereomers. However, when *atropos* BINAPs are replaced by *tropos* BIPHEPs, the single diastereomer can be formed after *tropo*-inversion, where a chiral activator (1) completely controls the BIPHEP−M chirality and (2) significantly increases the catalyst activity of BIPHEP−M in in situ asymmetric catalysis of carbon−carbon bond-forming reactions (Scheme 1).

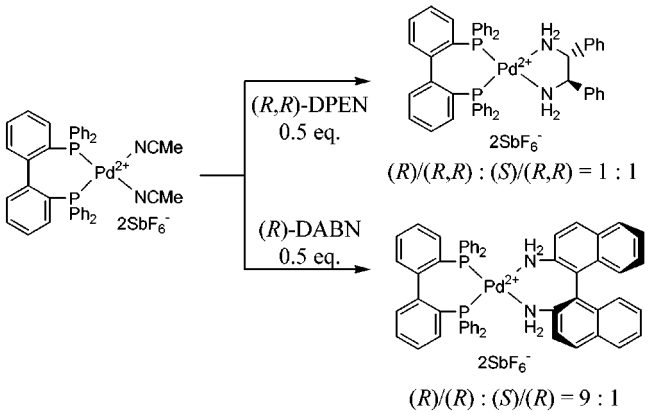
Scheme 1



First, the selectivity in the complexation stage of the BIPHEP−Pd(SbF_6)$_2$ catalyst was examined with a variety of diols, amino alcohols, and diamines. Unfortunately, however, diols such as binaphthols (BINOLs) and their ethers did not complex with BIPHEP−Pd(SbF_6)$_2$. With the diamine DPEN, as expected, complexation of the BIPHEP−Pd enantiomers was observed in a nonselective manner even with a 0.5 molar amount of enantiopure (*R*,*R*)-DPEN. With 0.5 equiv of (*R*)-diaminobinaphthyl (DABN), by contrast, highly selective (9:1) complexation of one enantiomer of the BIPHEP−Pd(SbF_6)$_2$ complex was observed with (*R*)-BIPHEP−Pd/(*R*)-DABN as the major diastereomer (Scheme 2). With 1.0 equiv of (*R*)-DABN, however, complexation of either enantiomer of the BIPHEP−Pd complex resulted in the formation of a diastereomeric mixture of (*R*)-BIPHEP−Pd/(*R*)-DABN and (*S*)-BIPHEP−Pd/(*R*)-DABN (1:1).

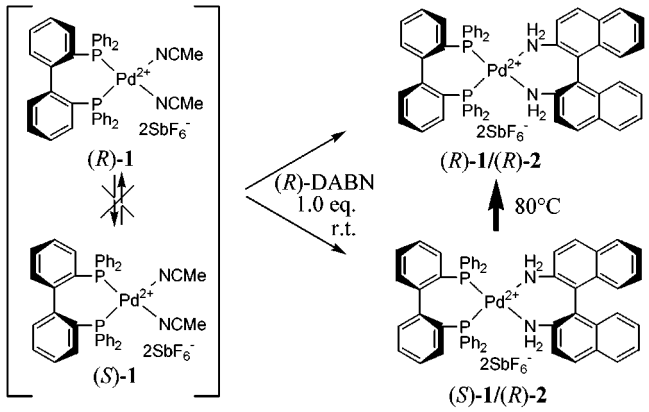
Next, *tropo*-inversion was examined to convert the diastereomeric mixture of (*R*)-BIPHEP−Pd/diamine and (*S*)-BIPHEP−Pd/diamine (1:1) into the single BIPHEP−Pd/

Scheme 2



diamine diastereomer. With respect to the 1:1 DPEN diastereomers, no change in the diastereomeric ratio was observed even at 80 °C. The 1:1 mixture of DABN diastereomers did not isomerize at room temperature over 3 days, but exhibited *tropo*-inversion at 80 °C after 12 h to the favorable (*R*)-BIPHEP−Pd/(*R*)-DABN diastereomer exclusively (Scheme 3). The (*R*)/(*R*)-configuration of the

Scheme 3



BIPHEP−Pd/DABN diastereomer was determined by the X-ray analysis of the single crystal obtained from a hexane−chloroform solution (Figure 1).[7]

The single diastereomer, (*R*)-BIPHEP−Pd/(*R*)-DABN, thus obtained, even bearing the *tropos* BIPHEP ligand, can be used as an activated asymmetric catalyst for carbon−carbon bond-forming reactions such as the hetero Diels−Alder (HDA) reactions[8] at room temperature (Table 1).[9] This is exemplified by the higher chemical yields and enantioselectivity (62% yield, 94% ee) in the HDA reaction of ethyl glyoxylate with 1,3-cyclohexadiene attained by 0.5 mol % of the (*R*)-BIPHEP−Pd/(*R*)-DABN complex than those (11% yield, 75% ee) attained by the enantiopure (*R*)-BIPHEP−Pd without DABN, obtained by protonation of (*R*)-BIPHEP−Pd/(*R*)-DABN (entries 1 vs 2). In 2.0 mol % of catalyst

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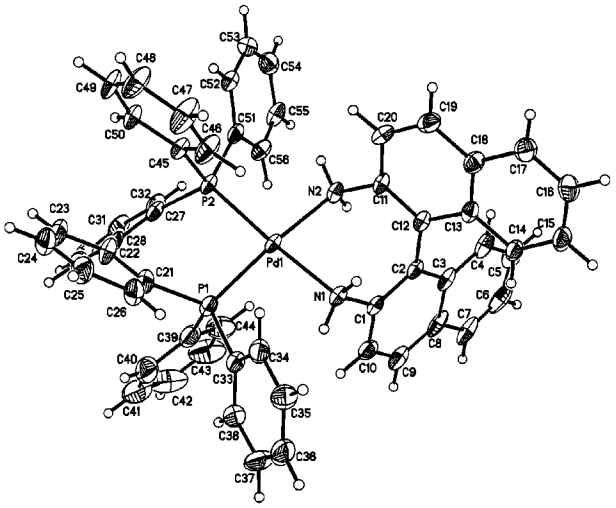

Figure 1. ORTEP drawing of (*R*)-BIPHEP−Pd/(*R*)-DABN complex.

loading, the (*R*)-BIPHEP−Pd/(*R*)-DABN complex gave a higher chemical yield and enantioselectivity (75% yield, 92% ee) than those attained by the *atropos* and racemic BINAP counterpart with DABN activator (61% yield, 7% ee) and racemic BIPHEP−Pd with DABN (64% yield, 9% ee) (entries 3 vs 4 and 5).

In summary, asymmetric activation thus provides a general and powerful strategy even for the use of *tropos* ligands without enantiomeric resolution or asymmetric synthesis. Furthermore, the metal complex with the *tropos* BIPHEP ligand and DABN activator can establish, in in situ asymmetric catalysis of carbon−carbon bond-forming reactions, higher enantioselectivity and catalytic efficiency than those attained by the BIPHEP complex without DABN or the *atropos* and racemic BINAP complex with DABN. The mechanism of asymmetric activation is now under investigation.

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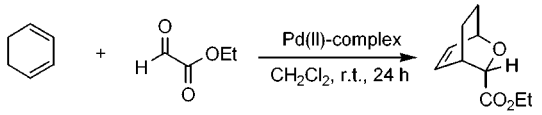
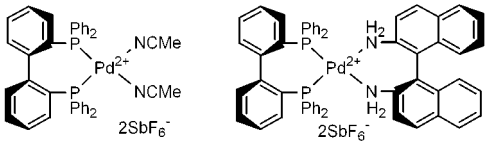
Table 1. Asymmetric Hetero Diels−Alder Reaction of Ethyl Glyoxylate and 1,3-Cyclohexadiene

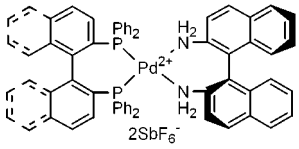


entry	catalyst	mol (%)	yield (%)[a]	% ee[b]
1	(*R*)-**1**	0.5	11	75 (1*R*,3*S*,4*S*)
2	(*R*)-**1**/(*R*)-**2**	0.5	62	94 (1*R*,3*S*,4*S*)
3	(*R*)-**1**/(*R*)-**2**	2	75	92 (1*R*,3*S*,4*S*)
4	(±)-**3**/(*R*)-**2**	2	61	7 (1*S*,3*R*,4*R*)
5	(±)-**1**/(*R*)-**2**	2	64	9 (1*S*,3*R*,4*R*)

[a] Isolated yield. [b] Determined by GC analysis using CP−Chirasil-Dex CB. Exo product was not observed.



(*R*)-**1** (*R*)-**1**/(*R*)-**2**



(±)-BINAP : (±)-**3**/(*R*)-**2**
(±)-BIPHEP : (±)-**1**/(*R*)-**2**

(7) The single-crystal growth was carried out in a hexane/chloroform mixed solvent at room temperature. X-ray crystallographic analysis was performed with a Bruker SMART 1000 diffractometer (graphite monochromator, Mo Kα radiation, $\lambda = 0.7107(3)$ Å. Crystal data for [Pd{(*R*)-biphep}{(*R*)-dabn}]$(SbF_6)_2$·4$CHCl_3$: $C_{60}H_{48}Cl_{12}F_{12}N_2P_2PdSb_2$, pale yellow, crystal dimension 0.4 × 0.3 × 0.3 mm, orthorhombic, space group $P2_1$, $a = 10.0024(5)$ Å, $b = 26.7485(14)$ Å, $c = 12.6505(7)$ Å, $V = 3382.2(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.829$ g/cm^3, μ(Mo Kα) = 1.65 cm^{-1}, $T = 100$ K, 16134 reflections were independent and unique, and 1050 with $I > 2\sigma(I)$ ($2\theta_{max} = 31.4°$) were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. $R = 0.0650$, $wR_2 = 0.1644$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-173070. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Selective bond lengths (Å) and bond and torsion angles (deg): Pd1−P1 2.283(17), Pd1−P2 2.288(15), Pd1−N1 2.16(5), Pd1−N2 2.17(5): P1−Pd1−P2 89.6(6), N1−Pd1−N2 84.2(19): C1−C2−C12−C11 63.88, C21−C22−C28−C27 67.06.

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(9) **Typical Experimental Procedure (Table 1).** To a solution of [Pd{(*R*)-biphep}{(*R*)-dabn}]$(SbF_6)_2$ (0.01 mmol, 2 mol % of ethyl glyoxylate) in CH_2Cl_2 (1 mL) was added ethyl glyoxylate (0.5 mmol) and 1,3-cyclohexadiene (0.75 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 h, directly loaded onto a silica gel column, and eluted with hexane/ether (3:2) to give HDA product as a colorless oil.