

# Electron-Poor Benzonitriles as Labile, Stabilizing Ligands in Asymmetric Catalysis

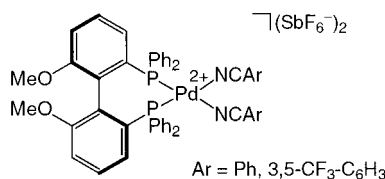
Jennifer J. Becker, Lori J. Van Orden, Peter S. White, and Michel R. Gagné\*

Department of Chemistry CB #3290, University of North Carolina,  
Chapel Hill, North Carolina 27599-3290

mgagne@unc.edu

Received December 12, 2001

## ABSTRACT



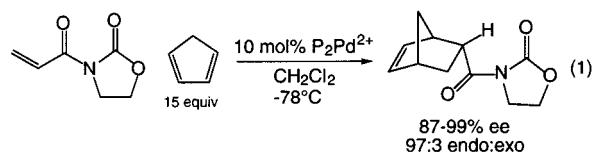
A chiral palladium catalyst [(*S*)-MeObiphep]Pd(NCAr)<sub>2</sub>(SbF<sub>6</sub>)<sub>2</sub>, (*S*)-4c], has been developed for a variety of asymmetric transformations. (*S*)-4c is bench-stable and has activity comparable to that of the nitrile free Lewis acid catalyst for Diels–Alder, hetero-Diels–Alder, and glyoxylate-ene reactions.

Dicationic platinum(II) and palladium(II) complexes are well-known Lewis acid catalysts for a variety of asymmetric transformations;<sup>1</sup> however, the free dications tend to be extremely hygroscopic and often form a  $\mu$ -OH dimer upon exposure to water.<sup>2</sup> In the case of platinum dications, these Lewis acids are often sufficiently electrophilic to also abstract chloride from halogenated solvents such as dichloromethane. As a result, we and others have typically generated the active catalyst in situ by AgX or HX treatment of suitable precursors. To increase the stability and/or isolability of these dicationic catalysts, acetonitrile or benzonitrile ligands have been added to bind the open coordination sites, which results in a bench-stable catalyst that requires no further activation.<sup>3</sup>

Although we have found no direct comparisons between catalysts with and without nitrile ligands, we postulated that

these nitrile ligands, while stabilizing the dication, were also acting as competitive inhibitors for substrates and compromising the potential activity of the catalysts. To obtain catalyst precursors that were more reactive than the CH<sub>3</sub>CN- or PhCN-stabilized dications but still maintained the desirable properties of air/water stability, we chose to investigate the effect of benzonitrile ligands with electron withdrawing groups on Lewis acid catalysis.

We began by investigating the Diels–Alder reaction in eq 1. The Lewis acid catalysts were generated in situ by



addition of 2.5 equiv of AgSbF<sub>6</sub> and 2.0 equiv of various

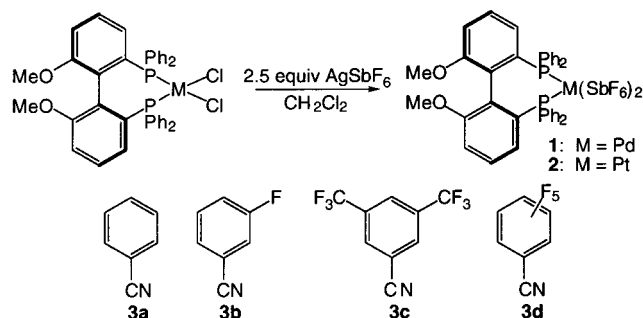
(1) (a) Becker, J. J.; White, P. S.; Gagné, M. R. *J. Am. Chem. Soc.* **2001**, *122*, 9478–9479. (b) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157–2159. (c) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233–1236. (d) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160–5167. (e) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549. (f) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947–5950.

(2) For example, see: (a) Gavagnin, R.; Cataldo, M.; Pinna, F.; Strukul, G. *Organometallics* **1998**, *17*, 661–667. (b) Bandini, A. L.; Banditelli, G.; Demartin, F.; Manassero, M.; Minghetti, G. *Gazz. Chim. Ital.* **1993**, *123*, 417–423. (c) Longato, B.; Pilloni, G.; Valle, G.; Corain, B. *Inorg. Chem.* **1988**, *27*, 956–958. (d) Bushnell, G. W.; Dixon, K. R.; Hunter, R. G.; McFarland, J. J. *Can. J. Chem.* **1972**, *50*, 3694–3699.

(3) (a) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059–4062. (b) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, T. *J. Org. Chem.* **1999**, *64*, 8660–8662. (c) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017–5023. (d) Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett.* **1998**, *39*, 6253–6256. (e) Oi, S.; Kashiwagi, K.; Terada, E.; Ohuchi, K.; Inoue, Y. *Tetrahedron Lett.* **1996**, *37*, 6351–6354. (f) Hori, K.; Ito, J.; Ohta, T.; Furukawa, I. *Tetrahedron* **1998**, *54*, 12737–12744.

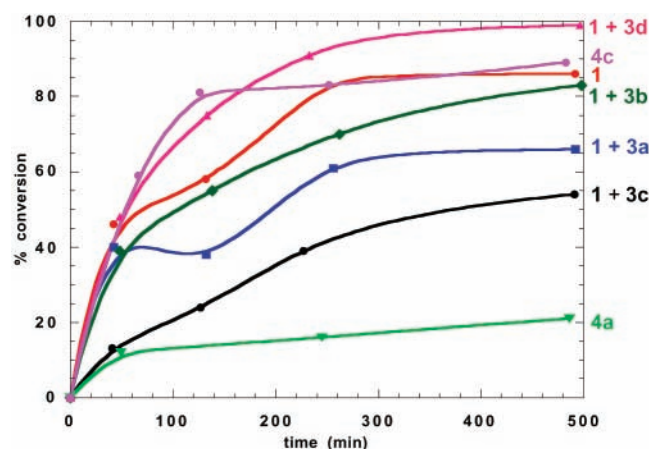
nitriles to ((*S*)-MeObiphep)PdCl<sub>2</sub> in dichloromethane (Scheme 1). After 30 min of stirring at ambient temperature, the

**Scheme 1.** In Situ Generated Catalysts



solutions were filtered from the silver salts under N<sub>2</sub> atmosphere and dienophile was added. After the mixture was cooled to  $-78^{\circ}\text{C}$ , 15 equiv of cyclopentadiene (CpH) was added, and the reactions periodically monitored by GC.<sup>4</sup>

Consistent with our original hypothesis, the rate of conversion to Diels–Alder product was dependent on the added nitrile,<sup>5</sup> with the most active catalyst being generated with the least coordinating pentafluorobenzonitrile ligand (99% conv, 8 h, Figure 1). The catalyst generated in the



**Figure 1.** Conversion to Diels–Alder product vs time for eq 1.

presence of benzonitrile was considerably less active with only 66% conversion after 8 h. Surprisingly, on the basis of the trends in the data, the catalyst generated from 3,5-bis(trifluoromethyl)benzonitrile **3c** was the least reactive of those tested (54% conv), a phenomenon that was ultimately traced to the catalyst/nitrile adduct's lower solubility, which

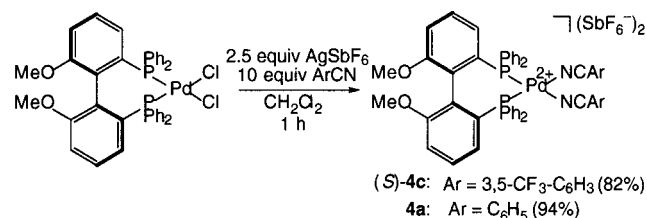
(4) Catalysis experiments with 10 equiv of CpH showed nearly identical reactivity profiles as with 15 equiv; slightly diminished activities were observed with 5 equiv of CpH (70% conv (8 h), cf. 90%).

(5) The enantioselectivities were invariant for each nitrile (98–99% ee) except for the combination of **1** + **3d**, which provided Diels–Alder product with only 87% ee. The cause of this decreased selectivity is unknown.

caused it to be prematurely removed at the point the AgCl was filtered away. Nevertheless, the rate data clearly established a kinetic inhibitory role for the stabilizing nitrile ligand.

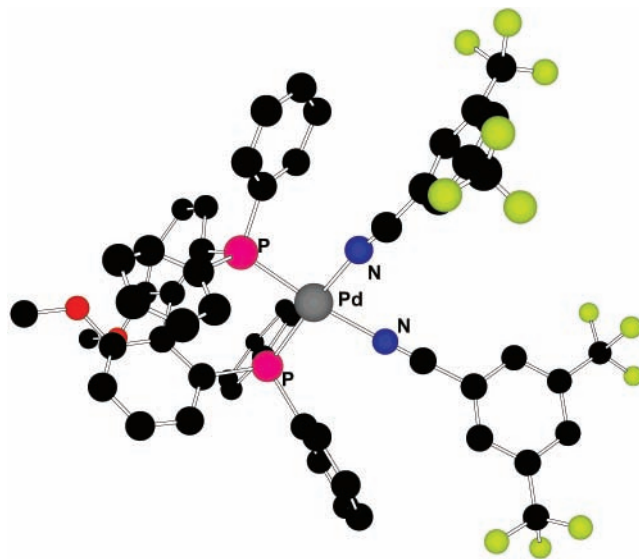
On the basis of solubility and reactivity considerations, we chose to isolate the Lewis acid catalyst (*S*)-**4c** (Scheme 2). Treating ((*S*)-MeObiphep)PdCl<sub>2</sub> with 2.5 equiv of AgSbF<sub>6</sub>

**Scheme 2.** Synthesis of Bench-Stable Lewis Acid Catalysts



under N<sub>2</sub> generated the bright orange dication, which quickly turned yellow upon addition of 10 equiv of 3,5-bis(trifluoromethyl)benzonitrile. After stirring for 1 h, the reaction mixture was opened to the atmosphere, and the silver salts were filtered. The yellow solid was washed with hexanes to remove excess nitrile, and (*S*)-**4c** was isolated in 82% yield. To directly compare the activity of (*S*)-**4c** with a more common stabilizing ligand, **4a** was also synthesized.<sup>6</sup> Both (*S*)-**4c** and **4a** are air- and water-stable for months and are routinely stored on the benchtop.<sup>7</sup>

An X-ray structure of (*R*)-**4c** was obtained (Figure 2) by



**Figure 2.** CHEM-3D representation of the P<sub>2</sub>Pd<sup>2+</sup> fragment of (*R*)-**4c**, obtained from the X-ray structure (see Supporting Information).

evaporation of solvent from a CH<sub>2</sub>Cl<sub>2</sub> solution. Pd–P and Pd–N bond lengths and P–Pd–P and N–Pd–N bond angles are similar to those of previously reported P<sub>2</sub>Pd(NCPh)<sub>2</sub><sup>2+</sup> and P<sub>2</sub>Pd(NCCH<sub>3</sub>)<sub>2</sub><sup>2+</sup> structures.<sup>3b,8</sup>

Isolated catalysts **4a** and (*S*)-**4c** were used for the Lewis acid catalyzed Diels–Alder reaction. Whereas **4a** showed a significant decrease in activity compared to that of the same catalyst generated in situ (20% conv, 8 h), (*S*)-**4c** displayed activity comparable to that of the nitrile free catalyst (89% conv) (Figure 1).<sup>9</sup> Complete conversion to Diels–Alder product was obtained using 2 mol % (*S*)-**4c** at –78 °C after 12 h. The product was isolated in 94% yield (97:3 *endo*/*exo*) and 98% ee. The major enantiomer of Diels–Alder product (2*R*) is that expected from a (*S*)-MeObiphepPd<sup>2+</sup> fragment.<sup>1b</sup>

To gain more insight into the relative binding abilities of the different nitrile ligands to P<sub>2</sub>Pd<sup>2+</sup> the analogous P<sub>2</sub>Pt-(NCAr)<sub>2</sub>(SbF<sub>6</sub>)<sub>2</sub> complexes were generated in situ and the Pt–P coupling constants measured. In a series of ligands, a larger *J*<sub>P–Pt</sub> is typically associated with a weaker bond trans to phosphorus,<sup>10</sup> and thus a more weakly coordinated nitrile ligand. Consistent with our original hypothesis, the more electron-withdrawing nitriles led to larger Pt–P coupling constants.

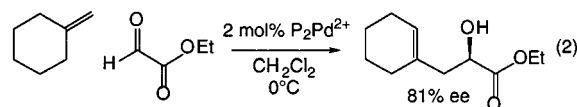
**Table 1.** Comparison of Nitrile Ligand and *J*<sub>P–Pt</sub> Coupling

| entry <sup>a</sup> | catalyst                     | <i>J</i> <sub>P–Pt</sub> (Hz) |
|--------------------|------------------------------|-------------------------------|
| 1                  | <b>2</b> + NCCH <sub>3</sub> | 3635                          |
| 2                  | <b>2</b> + <b>3a</b>         | 3631                          |
| 3                  | <b>2</b> + <b>3b</b>         | 3640                          |
| 4                  | <b>2</b> + <b>3c</b>         | 3646                          |
| 5                  | <b>2</b> + <b>3d</b>         | 3684                          |

<sup>a</sup> NMR experiment; 10 μmol of **2**, 25 μmol of AgSbF<sub>6</sub>, and 20 μmol of **3** in CD<sub>2</sub>Cl<sub>2</sub>.

To expand the scope and utility of these catalysts and to study the effect of nitrile on rate of reaction, we investigated several other asymmetric transformations known to be catalyzed by P<sub>2</sub>Pd<sup>2+</sup> Lewis acids such as the glyoxylate-ene<sup>1c,3a</sup> and hetero-Diels–Alder reactions.<sup>3b</sup>

The glyoxylate-ene reaction in eq 2 was investigated using



conditions similar to those developed by Mikami,<sup>3a</sup> but with only 2 mol % catalyst. As seen in Table 2, the effect of nitrile on the rate of reaction for in situ generated catalysts was

(6) Compound **4a** could only be isolated as a crystalline solid when (*rac*)-MeObiphepPdCl<sub>2</sub> was used; a pure powder was used for the reported catalysis experiments.

(7) Diels–Alder reactivity and selectivity profiles for (*S*)-**4c** after 2 months of benchtop storage were identical to those of freshly prepared catalyst.

(8) Lindner, E.; Schmid, M.; Wald, J.; Queisser, J. A.; Geprägs, M.; Wegner, P.; Nachtigal, C. *J. Organomet. Chem.* **2000**, 602, 173–187.

(9) The solubility of (*S*)-**4c** is significantly enhanced by the presence of coordinating substrates.

(10) (a) Pidcock, A.; Richards, R. E.; Venanzi, L. M. *J. Chem. Soc. A* **1966**, 1707–1710. (b) Appleton, T. G.; Bennett, M. A. *Inorg. Chem.* **1978**, 17, 738–747.

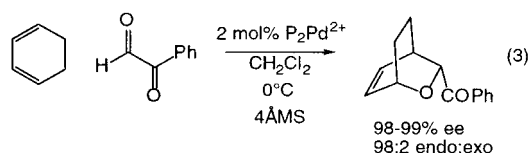
**Table 2.** Comparison of Activity and Enantioselectivity for Equation 2 as a Function of Catalyst

| entry <sup>a</sup> | catalyst                | conv (%) <sup>b</sup> | % ee |
|--------------------|-------------------------|-----------------------|------|
| 1                  | <b>1</b>                | 55 <sup>c</sup>       | 81   |
| 2                  | <b>1</b> + <b>3a</b>    | 43 <sup>c</sup>       | 81   |
| 3                  | <b>1</b> + <b>3c</b>    | 46 <sup>c</sup>       | 81   |
| 4                  | <b>1</b> + <b>3d</b>    | 48 <sup>c</sup>       | 81   |
| 5                  | <b>4a</b>               | 50 ± 10 <sup>d</sup>  |      |
| 6                  | ( <i>S</i> )- <b>4c</b> | 70 ± 10 <sup>d</sup>  | 81   |

<sup>a</sup> 2 mol % of catalyst, methylene cyclohexane (0.5 mmol) and ethyl glyoxylate (1.5 mmol) in 1.5 mL of CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. <sup>b</sup> Conversion for a 5 h run, measured by GC. <sup>c</sup> Single experiment. <sup>d</sup> Average of multiple runs (3+).

less sensitive than that for the Diels–Alder reaction, with the more electron-withdrawing benzonitriles being only slightly more active. Isolated catalysts (*S*)-**4c** and **4a** displayed higher reactivity after 5 h ((*S*)-**4c**, 70% conv; **4a**, 50% conv) compared to the in situ generated catalysts, though some variability in conversion was observed (entries 5 and 6). On a preparative scale (1 mmol) the ene product was obtained in 93% isolated yield using 2 mol % (*S*)-**4c** at room temperature. Ambient temperature was optimal for achieving >98% conversion to product, though % ee suffered slightly (80% ee).

The hetero Diels–Alder reaction of phenyl glyoxal and 1,3-cyclohexadiene shown in eq 3 was also investigated.



Conditions developed by Oi<sup>3b</sup> were employed using 2 mol % catalyst, at 0 °C, in the presence of 4 Å MS. As can be seen in Table 3, reaction conversion was insensitive to the

**Table 3.** Comparison of Activity and Enantioselectivity for Equation 3 as a Function of Catalyst

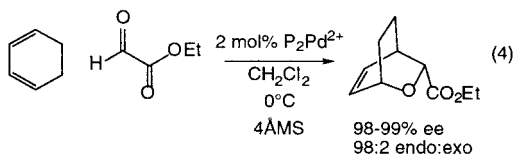
| entry <sup>a</sup> | catalyst                | conv (%) <sup>b</sup> | % ee <sup>c</sup> |
|--------------------|-------------------------|-----------------------|-------------------|
| 1                  | <b>1</b>                | 76 <sup>d</sup>       | 99                |
| 2                  | <b>1</b> + <b>3a</b>    | 76 <sup>d</sup>       | 99                |
| 3                  | <b>1</b> + <b>3b</b>    | 80 <sup>d</sup>       | 99                |
| 4                  | <b>1</b> + <b>3c</b>    | 72 <sup>d</sup>       | 98                |
| 5                  | <b>1</b> + <b>3d</b>    | 78 <sup>d</sup>       | 99                |
| 6                  | <b>4a</b>               | 56 ± 2 <sup>e</sup>   |                   |
| 7                  | ( <i>S</i> )- <b>4c</b> | 55 ± 3 <sup>e</sup>   | 99                |

<sup>a</sup> 2 mol % of catalyst, 1,3-cyclohexadiene (1.0 mmol), and phenyl glyoxal (0.67 mmol) in 1.0 mL of CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. <sup>b</sup> Conversion for a 5 h run, measured by GC. <sup>c</sup> Determined by HPLC. By comparison of the sign of the rotation<sup>3b</sup> (*S*)-**4c** gives the (+) product, as expected from a (*S*)-MeObiphep fragment. <sup>d</sup> Single experiment. <sup>e</sup> Average of multiple runs.

added nitrile after 5 h. Cycloaddition products were consistently obtained with 98–99% ee and a 98:2 diastereomeric

ratio. Isolated catalysts **4a** and (*S*)-**4c** were also used for this transformation. After 5 h with (*S*)-**4c**,  $55 \pm 3\%$  conversion was observed, with excellent enantioselectivity and diastereoselectivity, and  $56 \pm 2\%$  conversion was observed with **4a**. On a preparative scale, after 48 h using 2 mol % (*S*)-**4c**, 88% conversion was achieved. Pure product could be isolated after column chromatography in 85% yield with 99% ee and a 98:2 diastereomeric ratio.

The hetero-Diels–Alder reaction of ethyl glyoxylate and 1,3-cyclohexadiene was also investigated, eq 4. Conditions



developed by Oi,<sup>3b</sup> employing 2 mol % catalyst were used. In situ generated catalysts showed 56–69% conversion after 5 h with no apparent correlation to nitrile, Table 4. In situ and isolated catalysts produced cycloadducts with 98–99% ee and a 98:2 diastereomeric ratio. After 5 h, only  $55 \pm 3\%$  conversion to products was observed. Similarly, **4a** provided only  $56 \pm 2\%$  conversion after 5 h. On a preparative scale, after 24 h, complete conversion was obtained and pure product could be isolated in 83% yield and 99% ee (99:1 *endo/exo*).

In summary, we have successfully developed a new bench-stable Lewis acid catalyst that demonstrates a reactivity profile similar to unstabilized  $P_2Pd^{2+}$  catalysts, and in some

**Table 4.** Comparison of Activity and Enantioselectivity for Equation 4 as a Function of Catalyst

| entry <sup>a</sup> | catalyst                | conv (%) <sup>b</sup>    | % ee <sup>c</sup> |
|--------------------|-------------------------|--------------------------|-------------------|
| 1                  | <b>1</b>                | 54 <sup>d</sup>          | 99                |
| 2                  | <b>1</b> + <b>3a</b>    | 68 <sup>d</sup>          | 99                |
| 3                  | <b>1</b> + <b>3b</b>    | 61 <sup>d</sup>          | 98                |
| 4                  | <b>1</b> + <b>3c</b>    | 66 <sup>d</sup>          | 99                |
| 5                  | <b>1</b> + <b>3d</b>    | 64 <sup>d</sup>          | 98                |
| 6                  | <b>4a</b>               | 63 $\pm$ 11 <sup>e</sup> |                   |
| 7                  | ( <i>S</i> )- <b>4c</b> | 54 $\pm$ 2 <sup>e</sup>  | 99                |

<sup>a</sup> 2 mol % of catalyst, 1,3-cyclohexadiene (0.68 mmol), and ethyl glyoxylate (2.93 mmol) in 1.0 mL of  $CH_2Cl_2$ , 0 °C. <sup>b</sup> Conversion for a 5 h run, measured by GC. <sup>c</sup> Determined by GC. By comparison of the sign of the rotation,<sup>3b</sup> (*S*)-**4c** gives the (3*R*) product. <sup>d</sup> Single experiment. <sup>e</sup> Average of multiple runs.

cases shows enhanced activity compared to traditional benzonitrile- and acetonitrile-stabilized dications.

**Acknowledgment.** This work was partially supported by NIGMS (RO1 GM60758-01), the Petroleum Research Fund, DuPont, and Union Carbide. M.R.G. is a Camille Dreyfus Teacher Scholar (2000).

**Supporting Information Available:** Experimental procedures, spectroscopic and analytical data for **4a** and (*S*)-**4c**, and crystallographic data collection parameters and metrical parameters for (*R*)-**4c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL017218Q