

# Palladium Catalysts for Aerobic Oxidative Kinetic Resolution of Secondary Alcohols Based on Mechanistic Insight

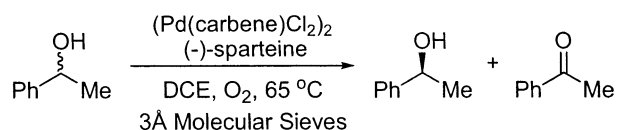
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## ABSTRACT



The oxidative kinetic resolution of secondary alcohols has been accomplished using 1:1 complexes of PdCl<sub>2</sub> and N-heterocyclic carbenes. In these reactions, both achiral and chiral carbene ligands are used in conjunction with the chiral base (–)-sparteine. A general synthesis of 1:1 PdCl<sub>2</sub>–carbene complexes has been developed and is amenable to a wide range of carbene ligands. The potential of these complexes in aerobic oxidations is highlighted by the use of a chiral Pd(II) complex and the chiral base (–)-sparteine to enhance the kinetic resolution of a racemic alcohol.

Oxidations utilizing molecular oxygen as a terminal oxidant represent an important challenge for catalysis.<sup>1</sup> Of particular interest to our research efforts are catalytic asymmetric aerobic oxidations. In this framework, we reported an aerobic oxidative kinetic resolution of secondary alcohols using (–)-sparteine, Pd(II), and O<sub>2</sub>.<sup>2,3</sup> A significant limitation of this system is the requirement of (–)-sparteine, which is only readily available as a single antipode and is a difficult template to optimize through systematic structural variations. However, mechanistic studies from our laboratory have provided a foundation for a new approach to catalyst development.<sup>4</sup> It was found that (–)-sparteine has a dual capacity as both a ligand on Pd(II) and an exogenous chiral base to deprotonate the Pd(II)-bound alcohol.

(1) Barton, D. H. R.; Martell, A. E.; Sawyer, D. T. *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Plenum Press: New York, 1993.

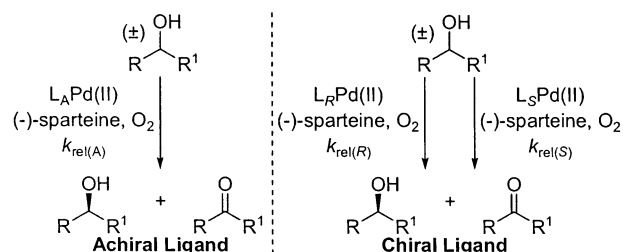
(2) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475.

(3) Simultaneously and independently, a closely related aerobic oxidative kinetic resolution of secondary alcohols was reported; see: Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.

(4) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202.

Since interactions between the base and ligand influence the Pd-catalyzed oxidative kinetic resolution, we chose to examine two approaches that exploit this interplay (Scheme 1). In the first approach, a Pd complex with an achiral ligand

**Scheme 1.** Approaches to New Oxidative Kinetic Resolution Catalysts



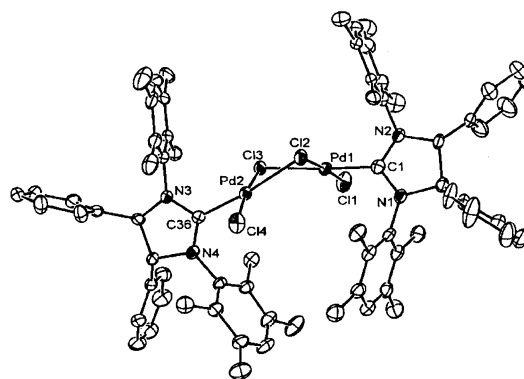
is used in combination with exogenous (–)-sparteine. The enantiodiscrimination,  $k_{rel}(A)$ , in this scenario would arise from interactions of the chiral base, (–)-sparteine, with an achiral Pd complex.<sup>5</sup> In the second approach, a chiral ligand on Pd is used in combination with exogenous (–)-sparteine

to introduce two elements of chirality. Due to the potential diastereomeric interactions between (–)-sparteine and a chiral ligand, antipodes of a chiral ligand should afford different  $k_{rel}$  values,  $k_{rel}(S) \neq k_{rel}(R)$ . This scenario provides the ability to enhance the kinetic resolution through “matched” ligand diastereomeric interactions with (–)-sparteine. Herein we provide confirmation of these approaches by using achiral and chiral palladium N-heterocyclic carbene complexes with exogenous (–)-sparteine as an effective catalyst system for the aerobic oxidative kinetic resolution of secondary alcohols.

The challenge in applying this strategy is identifying a ligand class that meets two criteria: (1) the ligand must form a Pd(II) complex that is competent for the oxidation of alcohols and (2) the ligand must not be displaced by (–)-sparteine over the course of the reaction. After a variety of common amine and phosphine ligands were screened, none were found to satisfy both criteria.<sup>6</sup>

N-heterocyclic carbenes were then selected as a possible ligand class due to the inertness of the derived metal complexes toward ligand substitution.<sup>7</sup> Pd(II)–carbene complexes have been synthesized by simple ligand substitution using 1:1 mixtures of soluble PdCl<sub>2</sub> salts and the free carbene.<sup>8</sup> Unfortunately, this method was rather unreliable in the preparation of pure material and difficult to extend to structurally diverse carbene complexes. Accordingly, a new route, amenable to diverse N-aryl-substituted carbenes, was developed (Table 1). Reaction of (Pd(allyl)Cl)<sub>2</sub> with the carbene, either isolated or generated in situ, gives the corresponding Pd(allyl)Cl–carbene complex in excellent

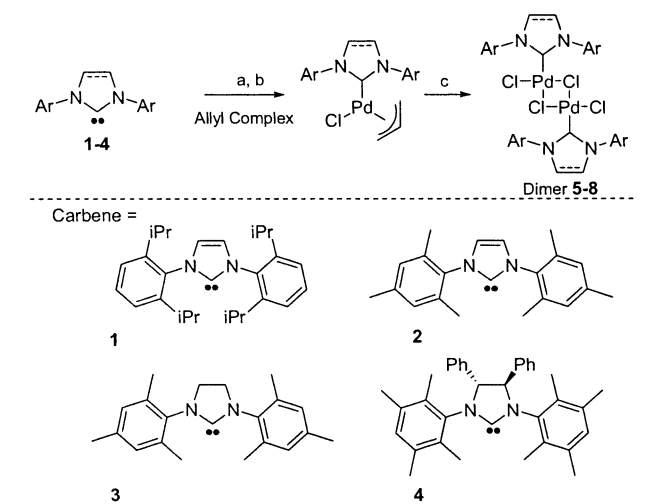
yield.<sup>9</sup> A key feature of the allyl complexes is their ability to be purified by flash chromatography.<sup>10,11</sup> Protonolysis of the allyl group with HCl in ether proceeds smoothly to liberate propene and deliver the PdCl<sub>2</sub>–carbene complexes in quantitative yield and excellent purity.<sup>12,13</sup> Two of the PdCl<sub>2</sub>–carbene complexes, **6** and (*R,R*)-**8**, were analyzed by X-ray crystallography and found to exist as ground-state dimers (Figure 1, (*R,R*)-**8** is pictured).



**Figure 1.** ORTEP of Pd(II) dimer (*R,R*)-**8**.

With a reliable synthesis of 1:1 PdCl<sub>2</sub>–carbene complexes, it was possible to clearly demonstrate that these complexes were competent for aerobic oxidative kinetic resolution when the chiral base (–)-sparteine was added (Table 2, entries 1–5).<sup>14,15</sup> With the use of Pd(II) dimers derived from carbenes with unsaturated backbones, dimer **5** gave faster rates and higher  $k_{rel}$  values than dimer **6**. The carbene with a simple saturated backbone, **7**, also gives a competent catalyst. Remarkably, since these three carbene ligands are achiral, the enantiomeric discrimination must arise from diastereomeric interactions with the chiral base (–)-sparteine.<sup>16</sup> This is a novel application of an achiral ligand and a chiral additive for asymmetric catalysis.<sup>17–20</sup>

**Table 1.** Synthesis of Pd(II)–Carbene Dimers<sup>a</sup>



entry	carbene	product	overall yield
1	<b>1</b>	<b>5</b>	99
2	<b>2</b>	<b>6</b>	>99
3	<b>3</b>	<b>7</b>	81
4	( <i>S,S</i> )- <b>4</b>	( <i>S,S</i> )- <b>8</b>	92
5	( <i>R,R</i> )- <b>4</b>	( <i>R,R</i> )- <b>8</b>	95

<sup>a</sup> Reagents and conditions: (a) carbene, (Pd(allyl)Cl)<sub>2</sub>, THF (see Supporting Information for details); (b) flash chromatography; (c) HCl–ether (quantitative yield).

(5)  $k_{rel}$  is calculated using  $k_{rel} = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$ , where  $C$  = conversion and  $ee$  = enantiomeric excess. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(6) Several nitrogen- and phosphorus-based ligands were tested, e.g., Troger's base, P(*t*Bu)<sub>3</sub>, P(*m*Tol)<sub>3</sub>, P(*n*Bu)<sub>3</sub>, xantphos, and BINAP.

(7) For a recent review, see: Hermann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

(8) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229.

(9) After our paper was submitted, the preparation of Pd(allyl)Cl–carbene complexes was independently reported; see: Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053.

(10) Caddick, S.; Cloke, F. G. N.; Clentsmith, G. K. B.; Hitchcock, P. B.; McKerrecher, D.; Titcomb, L. R.; Williams, M. R. V. *J. Organomet. Chem.* **2001**, *617–618*, 635.

(11) For the use of chromatography to purify Pd(II)–carbene complexes, see: Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348.

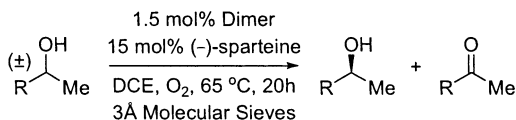
(12) For protonolysis of allyl groups from Pd, see: Jolly, P. W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 283.

(13) Protonolysis proceeds smoothly for *N*-aryl carbene complexes; however, protonolysis of *N*-alkyl carbene complexes leads to a mixture of products.

(14) PdCl<sub>2</sub>–carbene dimers are inert towards alcohol oxidation without added base.

(15) NMR experiments indicate that (–)-sparteine does not substitute for the carbene ligand.

**Table 2.** Use of Achiral Pd(II) Dimers in Oxidative Kinetic Resolution

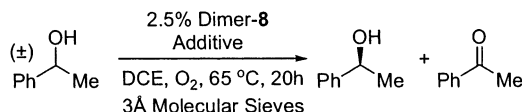


entry	dimer	R	% conversion (% ee) <sup>a</sup>	k <sub>rel</sub> <sup>a</sup>
1	<b>5</b>	C <sub>6</sub> H <sub>5</sub>	64.7 (96.0)	11.6
2	<b>5</b>	2-naphthyl	52.7 (65.9)	7.8
3	<b>5</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	42.8 (58.2)	14.3
4 <sup>b</sup>	<b>6</b>	C <sub>6</sub> H <sub>5</sub>	36.2 (34.9)	6.1
5 <sup>b</sup>	<b>7</b>	C <sub>6</sub> H <sub>5</sub>	45.0 (54.1)	6.4

<sup>a</sup> Average of multiple experiments. <sup>b</sup> Conditions: 2.5 mol % dimer, 20 mol % (-)-sparteine.

Both enantiomers of **8** were evaluated in the oxidative kinetic resolution of an alcohol using (-)-sparteine as the base (Table 3).<sup>21</sup> Use of enantiomeric complexes allowed

**Table 3.** Use of Chiral Pd(II) Dimers in Oxidative Kinetic Resolution



entry	dimer	additive	% conversion (% ee) <sup>a</sup>	k <sub>rel</sub> <sup>a</sup>
1	( <i>R,R</i> )- <b>8</b>	(-)-sparteine <sup>c</sup>	39.7 (36.4)	4.5
2	( <i>S,S</i> )- <b>8</b>	(-)-sparteine <sup>c</sup>	34.6 (42.0)	11.8
3 <sup>b</sup>	( <i>S,S</i> )- <b>8</b>	AgOAc <sup>d</sup>	34.5 (10.2)	1.6

<sup>a</sup> Average of multiple experiments. <sup>b</sup> Toluene used as a solvent. <sup>c</sup> Sparteine (20 mol %). <sup>d</sup> AgOAc (10.5 mol %).

the exploration of “matched” and “mismatched” diastereomeric interactions between the chiral ligand and (-)-sparteine. A significantly higher *k*<sub>rel</sub> value of 11.8 was observed for catalyst (*S,S*)-**8** versus (*R,R*)-**8**. This observation of a matched interaction showcases the approach outlined in Scheme 1 in which the chiral ligand and chiral base can act in concert to enhance the kinetic resolution.

To further highlight the contribution of the ligand in the matched oxidative kinetic resolution, a Pd complex with the

(16) (-)-Sparteine could act as a transient ligand, a base, or both.

(17) Asymmetric catalysis has been accomplished with a racemic catalyst and an enantiopure activator; for an example, see: Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angéloud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532.

chiral carbene ligand, (*S,S*)-**4**, was evaluated with acetate as the base. Pretreatment of dimer (*S,S*)-**8** with silver acetate led to replacement of the chlorides and gave a competent catalyst. As expected, the complex with the (*S,S*)-ligand preferentially oxidized the same enantiomer of alcohol as oxidations using (-)-sparteine.

In conclusion, both achiral and chiral N-heterocyclic carbene ligands in conjunction with a chiral base, (-)-sparteine, are effective for the Pd(II)-catalyzed aerobic oxidative kinetic resolution of secondary alcohols. A general synthesis of 1:1 PdCl<sub>2</sub>-carbene complexes has been developed that is amenable to an array of carbene ligands and has potential applications in a variety of Pd(II)-catalyzed processes.<sup>22</sup> The potential of these complexes in aerobic oxidations is highlighted by the use of a chiral Pd(II) complex and the chiral base (-)-sparteine to enhance the kinetic resolution of a racemic alcohol. Continued investigation into the nature of ligand/base interactions toward an improved oxidative kinetic resolution catalyst system as well as application of this approach to new reaction types will be reported in due course.

**Acknowledgment.** This work was supported by the National Institutes of Health (NIGMS #RO1 GM63540) and supported by a Research Innovation Award sponsored by Research Corporation. D.R.J. is supported by an ACS Division of Organic Chemistry Graduate Fellowship sponsored by Schering-Plough Research Institute. The crystal structure analysis was performed by Atta Arif. We thank Professor Steven Nolan for helpful discussions and initial supplies of various carbene salts.

**Supporting Information Available:** Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) Achiral and meso additives have been used with an enantiopure ligand; for an example, see: Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 6929.

(19) For the use of achiral ligands with chiral conformations, see: (a) Hashihayata, T.; Ito, Y.; Katsuki, T. *Synlett* **1996**, 1079–1081. (b) Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541–9552. (c) Miura, K.; Katsuki, T. *Synlett* **1999**, 783–785. (d) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495–497. (e) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802–1803.

(20) For a review of achiral additives in asymmetric catalysis, see: (a) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570. (b) For a specific example where a reversal in enantiofacial selectivity was observed by addition of an achiral additive, see: Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083.

(21) For the use of similar chiral carbene ligands, see: Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225.

(22) For examples of the use of 1:1 Pd-carbene complexes in catalysis, see: (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.