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

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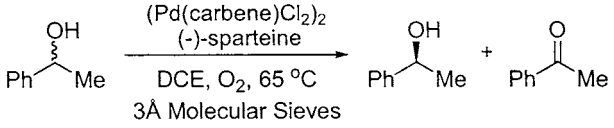
ABSTRACT

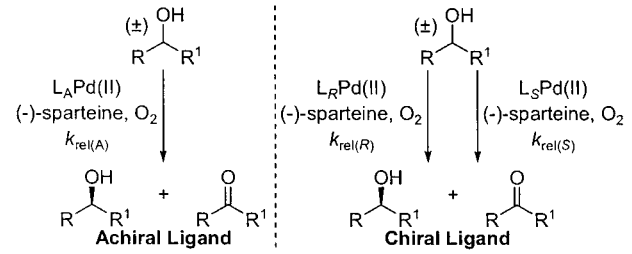


The oxidative kinetic resolution of secondary alcohols has been accomplished using 1:1 complexes of $PdCl_2$ and N-heterocyclic carbenes. In these reactions, both achiral and chiral carbene ligands are used in conjunction with the chiral base (–)-sparteine. A general synthesis of 1:1 $PdCl_2$–carbene 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.[1] 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_2.[2,3] 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.[4] 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.

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 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.[5] In the second approach, a chiral ligand on Pd is used in combination with exogenous (−)-sparteine

Scheme 1. Approaches to New Oxidative Kinetic Resolution Catalysts



(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.

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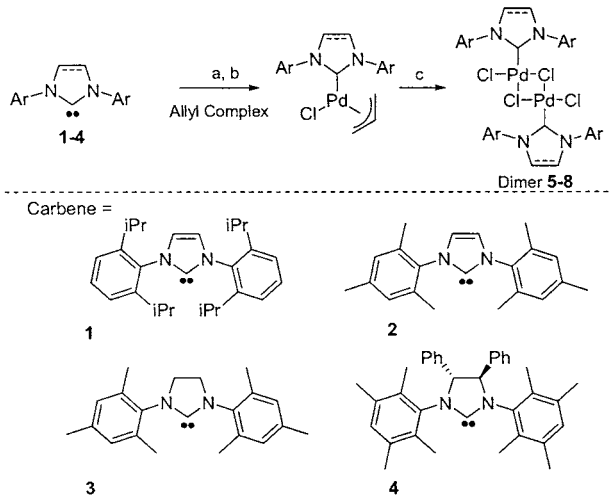
to introduce two elements of chirality. Due to the potential diastereomeric interactions between (−)-sparteine and a chiral ligand, antipodes of a chiral ligand should afford different k_{rel} values, $k_{rel}(S) \neq k_{rel}(R)$. This scenario provides the ability to enhance the kinetic resolution through "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.[6]

N-heterocyclic carbenes were then selected as a possible ligand class due to the inertness of the derived metal complexes toward ligand substitution.[7] Pd(II)−carbene complexes have been synthesized by simple ligand substitution using 1:1 mixtures of soluble $PdCl_2$ salts and the free carbene.[8] 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 $(Pd(allyl)Cl)_2$ with the carbene, either isolated or generated in situ, gives the corresponding Pd(allyl)Cl−carbene complex in excellent yield.[9] A key feature of the allyl complexes is their ability to be purified by flash chromatography.[10,11] Protonolysis of the allyl group with HCl in ether proceeds smoothly to liberate propene and deliver the $PdCl_2$−carbene complexes in quantitative yield and excellent purity.[12,13] Two of the $PdCl_2$−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).

Table 1. Synthesis of Pd(II)−Carbene Dimers[a]



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

[a] Reagents and conditions: (a) carbene, $(Pd(allyl)Cl)_2$, THF (see Supporting Information for details); (b) flash chromatography; (c) HCl−ether (quantitative yield).

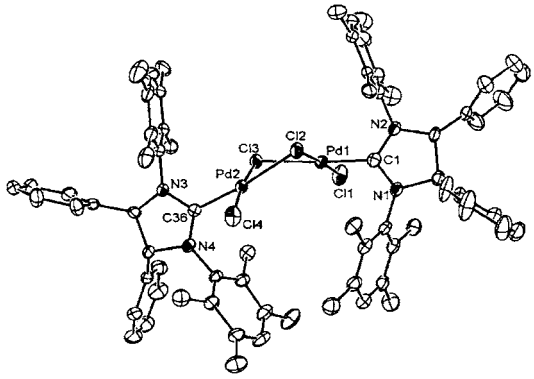


Figure 1. ORTEP of Pd(II) dimer (*R*,*R*)-**8**.

With a reliable synthesis of 1:1 $PdCl_2$−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).[14,15] 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.[16] This is a novel application of an achiral ligand and a chiral additive for asymmetric catalysis.[17−20]

(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)$_3$, P(*m*Tol)$_3$, P(*n*Bu)$_3$, 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.

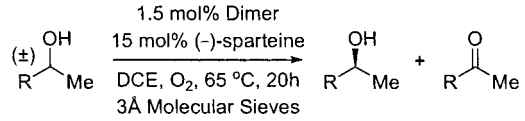
(12) For protonolysis of allyl groups from Pd, see: Jolly, P. W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 283.

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

(14) $PdCl_2$−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

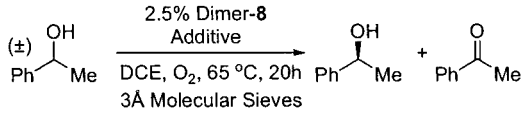


entry	dimer	R	% conversion (% ee)[a]	k_{rel}[a]
1	**5**	C_6H_5	64.7 (96.0)	11.6
2	**5**	2-naphthyl	52.7 (65.9)	7.8
3	**5**	*p*-$MeOC_6H_4$	42.8 (58.2)	14.3
4[b]	**6**	C_6H_5	36.2 (34.9)	6.1
5[b]	**7**	C_6H_5	45.0 (54.1)	6.4

[a] Average of multiple experiments. [b] 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).[21] Use of enantiomeric complexes allowed

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



entry	dimer	additive	% conversion (% ee)[a]	k_{rel}[a]
1	(*R*,*R*)-**8**	(−)-sparteine[c]	39.7 (36.4)	4.5
2	(*S*,*S*)-**8**	(−)-sparteine[c]	34.6 (42.0)	11.8
3[b]	(*S*,*S*)-**8**	AgOAc[d]	34.5 (10.2)	1.6

[a] Average of multiple experiments. [b] Toluene used as a solvent. [c] Sparteine (20 mol %). [d] AgOAc (10.5 mol %).

the exploration of "matched" and "mismatched" diastereomeric interactions between the chiral ligand and (−)-sparteine. A significantly higher k_{rel} 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 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 $PdCl_2$−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.[22] 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.

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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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(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.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532.

(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.