Kinetic Resolution

DOI: 10.1002/anie.200801865

Palladium-Catalyzed Enantioselective Oxidation of Chiral Secondary Alcohols: Access to Both Enantiomeric Series**

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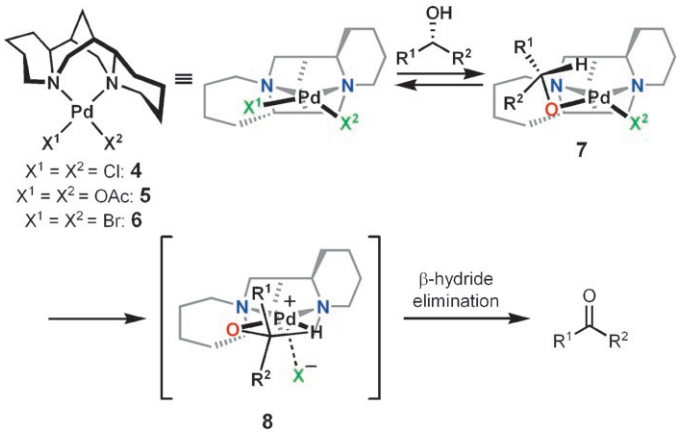
Enantioenriched alcohols are ubiquitous in the structures and syntheses of natural products and pharmaceuticals. Catalytic, asymmetric alcohol oxidation can be a useful method to access these molecules.[1] Previously, we reported the development of an aerobic kinetic resolution of alcohols by catalytic [Pd(nbd)Cl_2] (**1**, nbd = norbornadiene) and the naturally occurring alkaloid (−)-sparteine ((−)-**2**) in the presence of molecular oxygen.[2–6] Although this system successfully resolves a wide range of secondary alcohols to high enantiomeric excess, the rates of oxidation for certain substrates are prohibitively slow. Furthermore, the use of **2** as a ligand, which is only commercially available as the (−)-antipode, restricts access to alcohols in one enantiomeric series.[7] Herein, we disclose the development of a catalyst based on an understanding of the reaction mechanism that effects dramatic rate increases, thereby permitting resolution of a broader range of substrates. This more active catalyst allows the use of an alternative chiral diamine ligand in the resolution, making either enantiomer of the secondary alcohols easily obtainable. The utility of the system is demonstrated in the formal total synthesis of naturally occurring (−)-amurensinine ((−)-**3**).

Our initial screens of various Pd sources revealed the dichloride complexes to be superior to the acetate and trifluoroacetate species.[2] X-ray crystallographic analyses of a series of crystalline palladium(II) complexes[8] and computational studies of mechanistic pathways[9] led to a better understanding of the role of the halide counterion in the resolution. The sterically crowded, C_1 symmetric (−)-sparteine ligand induces a significant distortion of the square planar geometry in many palladium complexes (Scheme 1).[8] Specifically, for the solid-state structure of [Pd(sp)Cl_2] (**4**), the sum of the six angles around the metal center is 705.99°,[8] compared to 720° for an ideal square planar geometry.[10] The



Scheme 1. Model of the alcohol oxidation with [Pd(sp)X_2].

majority of this distortion is because of the deflection of X^2 away from the projecting piperidine ring of (−)-**2**. For dichloride complex **4**, X^2 is 9.9° out of the plane. This deformation is even more pronounced in the structure of a palladium alkoxide that mimics a proposed alcohol oxidation intermediate (**7**, R^1 = Ph, R^2 = CF_3, X^2 = Cl, sum of six palladium–ligand angles: 701.58°, X^2 deflection: 15.4°).[8] The less active [Pd(sp)$(OAc)_2$] catalyst (**5**) for the kinetic resolution[11] has a smaller deviation from the ideal square planar geometry (sum of six palladium–ligand angles: 711.40°, X^2 deflection: 5.3°).[12] This (−)-sparteine induced distortion of X^2 results in a geometry that is more like the transition state (**8**),[9] potentially lowering the energy barrier to β-hydride elimination. Thus, we predicted that palladium complexes with coordinated counterions that display a greater X^2 deflection would serve as more active oxidation catalysts.

This hypothesis inspired us to investigate bromide as a larger, but still coordinating counteranion. X-ray crystallographic analysis of a single crystal of [Pd(sp)Br_2] (**6**)[13] revealed a greater deviation of one of the bromides from the Pd square plane (sum of six palladium–ligand angles: 699.22°, X^2 deflection: 14.0°) compared to that of complex **4**, suggesting the potential for superior reactivity.

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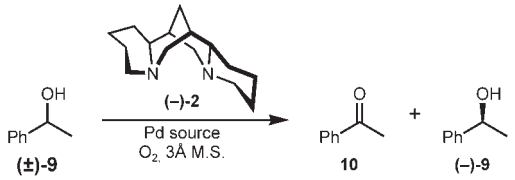
[**] We are grateful to the NIH-NIGMS (R01 GM65961-01), NSF (predoctoral fellowship to D.C.E.), NDSEG (predoctoral fellowship to D.C.E.), Bristol-Myers Squibb and the American Chemical Society (predoctoral fellowship to R.M.T.), EPSRC, and EU.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801865.

Previously, $PdBr_2$ had been examined as a palladium source in this transformation, but rapid formation of a black mixture and low conversion indicated catalyst decomposition at 80 °C. Use of preformed complex **6** is only slightly more successful (Table 1, entry 1). However, in reactions performed at 60 °C or below, dibromide complex **6** is quite stable and catalyzes facile oxidation of secondary alcohols (Table 1, entry 2) relative to dichloride complex **4** (Table 1, entry 3).[14] Importantly, high selectivity (*s*) is maintained in the reactions with dibromide **6**.[15] Analogous to our experiments with dichloride complex **4** (Table 1, entry 4),[3] chloroform proved to be an excellent solvent, affording product ketone at good rates at 23 °C (Table 1, entry 5).[16]

Table 1: Optimization of conditions with $[Pd(sp)X_2]$.[a]



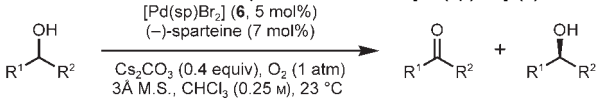
Entry	Solvent	*T* [°C]	Pd source	*t* [h]	Conv. [%][b]	Alcohol *ee* [%][c]	*s*
1[d,e]	$PhCH_3$	80	$[Pd(sp)Br_2]$ (**6**)	76	32	27	5
2	$PhCH_3$	60	$[Pd(sp)Br_2]$ (**6**)	9	58	99	29
3	$PhCH_3$	60	$[Pd(sp)Cl_2]$ (**4**)	24	54	90	21
4[f]	$CHCl_3$	23	$[Pd(sp)Cl_2]$ (**4**)	48	60	99	31
5[f]	$CHCl_3$	23	$[Pd(sp)Br_2]$ (**6**)	4	56	96	28

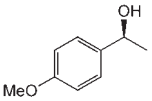
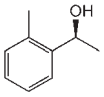
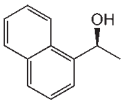
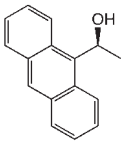
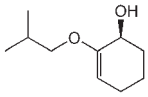
[a] Pd source (5 mol%), (−)-sparteine (15 mol%), O_2 (1 atm), 0.25 M in solvent, unless otherwise noted. [b] Determined by GC analysis. [c] Determined by chiral HPLC methods.[10] [d] 0.1 M in $PhCH_3$. [e] Pd black observed. [f] (−)-Sparteine (7 mol%), Cs_2CO_3 (40 mol%). 3 Å M.S. = 3 Å molecular sieves; sp = (-)-sparteine.

Oxidative kinetic resolution of a number of secondary alcohols was facile with this $PdBr_2$ system (Table 2). Alcohols previously resolved with dichloride **4**[3] are oxidized much more rapidly with dibromide **6** (Table 2, entries 1, 3, and 5), and the selectivity factors increase at lower temperatures (Table 2, entries 4 and 5). To our delight, a variety of secondary alcohols that displayed very poor reactivity with **4** are readily oxidized by using catalyst **6**. Sterically hindered benzylic alcohols (Table 2, entries 6–10), allylic alcohols (Table 2, entry 11), and even less activated saturated alcohols (Table 2, entries 12 and 13) are resolved to high enantiomeric excesses. Furthermore, the use of ambient air instead of pure oxygen as the stoichiometric oxidant is sufficient for a successful resolution (Table 2, entries 2, 7, 9, and 13).

Encouraged by our success in promoting rapid oxidation with a palladium bromide complex, we began to explore other diamines in the kinetic resolution. Although the availability of (−)-**2** made it an attractive chiral ligand for the process, the scarcity of its enantiomer (i.e. (+)-**2**) was a major limitation to the broad utility of the method.[17] The insights gained from the investigation of complexes of (−)-**2**, specifically: A) the importance of an electron-rich, rigid ligand and B) the need for an aerobically stable chiral ligand able to induce halide counterion distortion in its corresponding palladium complex,

Table 2: Resolution of a variety of alcohols with $[Pd(sp)Br_2]$ (**6**).

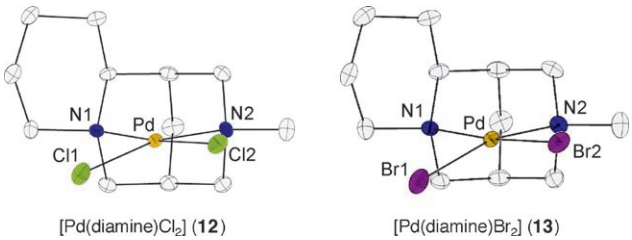


Entry	Alcohol[a]	*t* [h]	Conv. [%][b] (yield [%])[c]	Alcohol *ee* [%][d]	*s*
1		4	56 (43)	96	28
2[e]		5	55	95	27
3		4	59 (41)	95	17
4[f]		8	59	97	20
5[g]		24	60	98	20
6		41	64 (35)	97	14
7[e]		30	63	96	13
8		24	60 (40)	93	14
9[e]		21	65	99	15
10		15	60	91	12
11		48	62	97	16
12		49	58 (40)	91	15
13[e]		45	58	91	15

[a] Major enantiomer shown. [b] Determined by GC or ^1H NMR methods. [c] Yield of the isolated enantioenriched alcohol. [d] Determined by chiral HPLC or GC methods.[10] [e] Performed under ambient air. [f] Performed at 10 °C. [g] Performed at 4 °C.

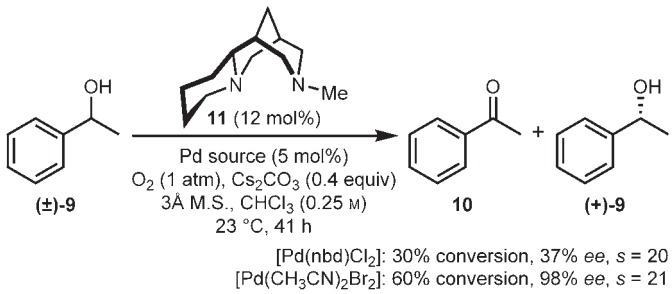
led us to diamine **11**.[18] Prepared in a three-step sequence from the easily accessible alkaloid (−)-cytisine, **11** was shown to act as a (+)-sparteine mimic in a variety of processes.[19,20]

As in the case of palladium complexes with (−)-**2**, X-ray crystallographic analyses of $[Pd(diamine)X_2]$ reveal a greater counterion distortion for Br compared to Cl with diamine **11** (Figure 1, sums of six palladium–ligand angles and X^1 deflection for **12**: 704.67° and 11.9°, respectively, and for **13**: 701.69° and 14.2°, respectively).[13] Indeed, reactions performed with the two catalysts led to disparate results favoring dibromide **13** (Scheme 2).



[Pd(diamine)Cl_2] (**12**) [Pd(diamine)Br_2] (**13**)

Figure 1. X-ray crystallographic structures of $[Pd(diamine)X_2]$.

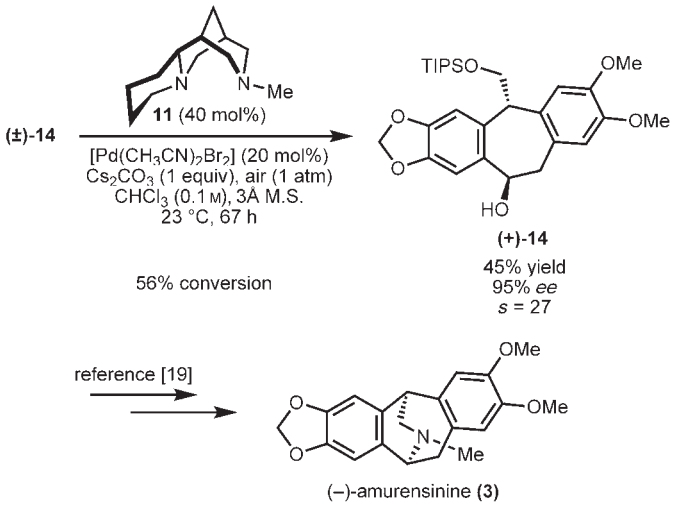


Scheme 2. Kinetic resolution of (±)-**9** with PdX_2 and diamine **11**.

Gratifyingly, complex **13** could be generated in situ and resulted in greatly improved reactivity (Table 3). Thus, a variety of benzylic (Table 3, entries 1–5), allylic (Table 3, entries 6–10), and cyclopropylcarbinyl (Table 3, entries 11 and 12) alcohols can be resolved with high selectivity. Ambient air is also a suitable oxidant (Table 3, entries 2 and 4). Importantly, this protocol yields alcohols in the opposite enantiomeric series to that obtained with (−)-**2**.

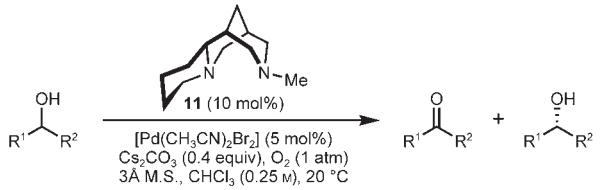
To additionally test these results, we investigated a synthetically interesting substrate that had proven challenging for our $PdCl_2$ system. Recently, we reported an enantioselective total synthesis of (+)-amurensinine ((+)-**3**) which employed an oxidative kinetic resolution as the key step to produce an enantioenriched intermediate ((−)-**14**) en route to the antipode of the natural product.[21] To access the naturally occurring enantiomer ((−)-**3**), we applied diamine **11** to the resolution of (±)-**14**. The use of the dibromide complex provided enantioenriched alcohol (+)-**14** in high yield and excellent enantiomeric excess ($s = 27$, Scheme 3). This application constitutes a formal total synthesis of natural (−)-amurensinine ((−)-**3**).

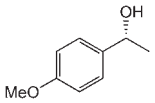
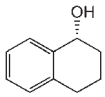
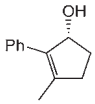
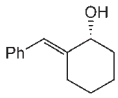
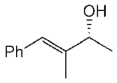
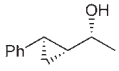
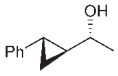
In conclusion, we have developed a greatly improved oxidative kinetic resolution of secondary alcohols based on an understanding of the factors that contribute to the reactivity and the selectivity in this process. Furthermore, these improvements have allowed us to employ alternative diamine



Scheme 3. Preparation of (+)-**14**. TIPS = triisopropylsilyl.

Table 3: Resolution of alcohols with $[Pd(CH_3CN)_2Br_2]$ and diamine **11**.



Entry	Alcohol[a]	t [h]	Conv. [%][b] (Yield [%])[c]	Alcohol ee [%][d]	s
1		30	58 (40)	97	25
2[e]		34	58	96	22
3		30	60	98	19
4[e]		34	61	98	19
5		24	61 (38)	90	11
6		46	57 (43)	91	17
7		12	55	94	27
8		18	63	94	12
9		46	59 (39)	91	13
10		35	63	92	11
11		32	59 (40)	90	13
12		35	62	90	10

[a] Major enantiomer shown. [b] Determined by GC or ^1H NMR methods. [c] Yield of isolated enantioenriched alcohol. [d] Determined by chiral HPLC or GC methods.[10] [e] Performed under ambient air.

ligand **11** in the oxidation to afford alcohols in the enantiomeric series opposite to that obtained with (−)-sparteine. Importantly, solid-state X-ray crystallographic analysis was used extensively as a guide in these studies and they provided invaluable insights. Finally, this methodology was applied to the kinetic resolution of alcohol (±)-**14**, allowing access to the natural enantiomer of the isopavine alkaloid (−)-amurensinine. Efforts to additionally enhance reactivity and selectivity in these oxidations, to use this method in complex molecule synthesis, and to apply these findings to other palladium-catalyzed oxidations are ongoing.

Received: April 22, 2008
Published online: ■■ ■■, 2008

Keywords: alcohols · asymmetric catalysis · oxidation · palladium · synthetic methods

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[10] See the Supporting Information for details.

[11] Oxidations of (+)-**9** conducted with $[Pd(sp)X_2]$ as the catalyst displayed the following trend in reactivity: $Br > Cl > O_2CCF_3 > I > OAc$, see the Supporting Information for details.

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[14] Poor reactivity and selectivity were observed in the oxidative kinetic resolution with $[Pd(sp)I_2]$ as the catalyst, see the Supporting Information for details.

[15] The selectivity factor s was determined by using the equation $s = k_{fast}/k_{slow} = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where C is conversion, see: reference [6a].

[16] The reactivity of **6** in chloroform was comparable to complexes prepared in situ from a variety of $PdBr_2$ sources, see the Supporting Information for details.

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Communications

Kinetic Resolution

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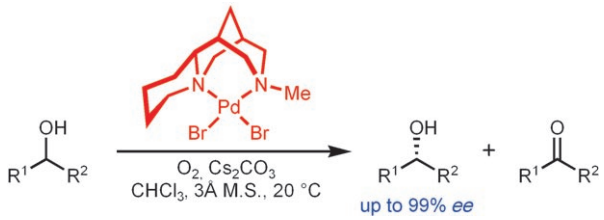
Palladium-Catalyzed Enantioselective Oxidation of Chiral Secondary Alcohols: Access to Both Enantiomeric Series



Rapid resolution: A new catalyst system for the oxidative kinetic resolution of secondary alcohols leads to dramatic rate increases. This system allows the use of a diamine to provide access to either enantiomer of a range of alcohols with good selectivity factors (see scheme). This method has been applied to the formal total synthesis of (−)-amurensinine.