Kinetic Resolution

Palladium-Catalyzed Oxidative Kinetic Resolution with Ambient Air as the Stoichiometric Oxidation Gas**

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As part of a general program aimed toward developing enantioselective oxidation reactions in the presence of catalytic palladium, we recently reported the oxidative kinetic

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Communications

resolution of secondary alcohols.[1–3] Our system employed a simple protocol involving a commercially available palladium complex, sparteine, and molecular oxygen. Although our original conditions promoted effective resolutions, several issues restricted the practicality of the method, namely long reaction times and high operating temperatures in flammable mixtures of organic solvents and oxygen. Herein we report a new palladium-catalyzed oxidative kinetic resolution that employs nonflammable solvents, proceeds with excellent levels of enantioselectivity, and for the first time uses ambient air as the stoichiometric oxidation gas.[4]

In the course of our studies, it was determined that the addition of an inorganic exogenous base such as Cs_2CO_3 could accelerate the asymmetric oxidation of secondary alcohols.[1b] Further investigations into the effect of additives on the resolution revealed that the presence of the spectator alcohol tBuOH further enhanced reaction rates. The combined effect of these independent additives greatly enhanced the overall reaction rate of the oxidative kinetic resolution of secondary alcohols while preserving the selectivity of the process (Scheme 1).[5,6]

While the purpose of the carbonate base fit well with our initial mechanistic model for resolution, the effect of tBuOH was more subtle. We hypothesized that the exogenous alcohol was affecting reaction rates by forming hydrogen bonds to a number of plausible intermediates along the reaction pathway and/or by aiding in the solvation of halide anions. A number of possibilities are outlined in Scheme 2 and include: A) hydrogen bonding to, or solvation of one chlorine substituent of the [Pd(sparteine)Cl$_2$] complex to activate the compound toward alcoholysis, B) subsequently aiding in the solvation of another chloride to open a coordination site needed for the β-hydride elimination event, C) assisting in the product exchange, D) facilitating conversion of an [L$_n$Pd(H)Cl] species into a palladium(0) species, E) aiding in the proposed opening of a peroxopalladium species to the corresponding hydroperoxide, and F) participating in the turnover exchange of the palladium hydroperoxide to the bound alcohol complex.[5]

With these hypotheses in mind, we initiated a solvent screen to explore the effect of hydrogen-bond-donating solvents as well as solvents capable of effective chloride anion solvation. Importantly, as part of our screen, we examined solvents that have the capacity to do
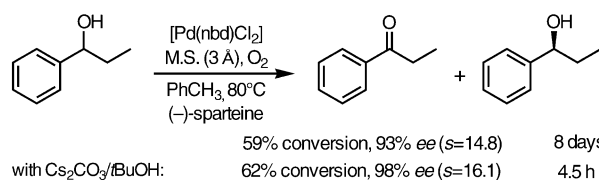
Scheme 1. Cs_2CO_3/tBuOH-modified oxidative kinetic resolution.

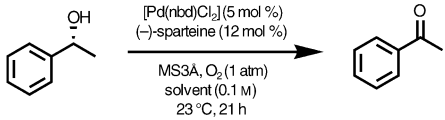|		
	59% conversion, 93% ee (s=14.8)	8 days
with Cs_2CO_3/tBuOH:	62% conversion, 98% ee (s=16.1)	4.5 h

both, that is, less traditional H-bond-donating halohydrocarbon solvents such as $CHCl_3$ (Table 1). For simplicity, enantiopure (R)-(+)-1-phenylethanol was used as the substrate.

The nonflammable solvent chloroform quickly emerged as a superior solvent for the reaction, supporting rapid reaction rates even at room temperature (Table 1, entry 1).[7] Dichloromethane is also an effective solvent (Table 1, entry 3); however, when applied to the resolution, inferior selectivities are observed. Comparison of the trihalomethanes (Table 1, entries 1 and 2) and dihalomethanes (Table 1, entries 3 and 4) reveals a tendency for more electron-deficient, thus better hydrogen-bonding, halocarbons to accelerate conversion. Furthermore, when CCl_4 is substituted for a protic member of the halogenated hydrocarbon series, conversion is severely impacted (Table 1, entry 6). In accord with our mechanistic hypothesis (Scheme 2), this trend suggests the importance of weak but potential hydrogen-
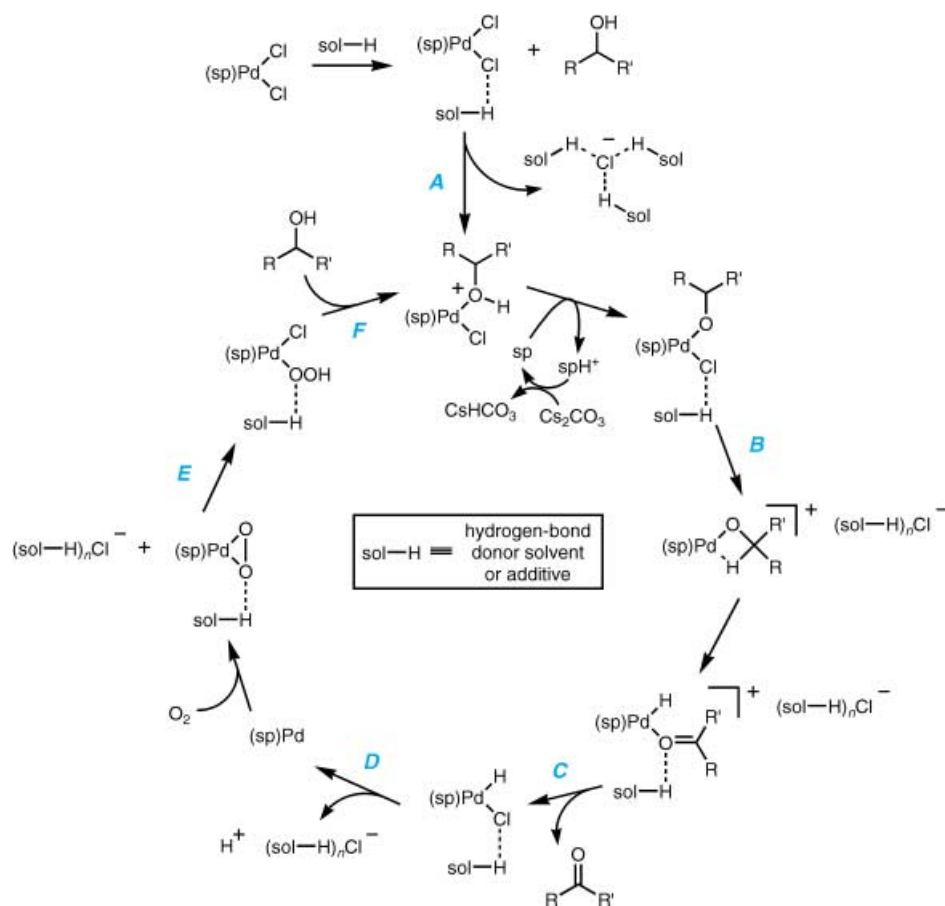
Scheme 2. Plausible mechanism involving H-bonding species.

Table 1: Screen with various solvents.

Entry	Solvent	Conversion [%]
1	CHCl$_3$	74
2	CHBr$_3$	68
3	CH$_2$Cl$_2$	83
4	CH$_2$Br$_2$	73
5	ClCH$_2$CH$_2$Cl	46
6	CCl$_4$	2
7	PhCH$_3$	23
8	PhCH$_3$/1 equiv *t*BuOH	39
9	THF	14
10	CH$_3$CN	3
11	2-propanol	7
12	PhCH$_3$/*t*BuOH (1:1)	29
13	*tert*-amyl alcohol	21
14	H$_2$O/2-propanol	0
15	pinacolone	21

bond donors as a parameter for efficient resolution.[8a] Having identified chloroform as the most effective solvent for kinetic resolution, we determined that additional *t*BuOH no longer imparted any benefit to the reaction. We reconciled this observation by reasoning that the H-bond-donating solvents may have supplanted the donating effect of the *t*BuOH additive. The carbonate base, however, still enhanced the reaction rate.[8b]

After observing such a dramatic impact on conversion rates and disparate additive effects by simply changing the solvent from toluene to chloroform, it became clear that all other parameters would require reinvestigation. A study of the loading of the sparteine ligand revealed that 12 mol% of sparteine was an optimal concentration for the reaction, in contrast to the 20 mol% previously reported in both toluene and dichloroethane.[1, 2] A decrease in the excess sparteine represents a further improvement to the system by conserving our source of chirality in the catalytic system. Evaluation of Cs$_2$CO$_3$ stoichiometry revealed that no further benefit to conversion rate was observed beyond 40 mol%.

With the essential parameters optimized, we explored the generality of our modified catalyst system (Scheme 3). Importantly, all previously reported alcohol substrates[1, 2] were resolved to high enantiomeric excess when subjected to the new conditions. These resolutions were performed at mild operating temperatures (usually room temperature) and the selectivities for the process also increased, often by a factor of 2.[9]

Particularly striking is the enhancement in selectivity of the non-benzylic alcohol **G**. Previously, this substrate proved to be difficult to resolve to high *ee* values, displaying a low selectivity in the oxidative kinetic resolution process ($s = 6.6$). Under our conditions in chloroform, the resolution proceeds at room temperature to provide the resolved alcohol in 99.0% *ee* with a selectivity factor of 18. The allylic alcohol depicted in **G** may be readily converted into more useful functionality and represents a facile method for the highly enantioselective resolution of less activated secondary alcohols.
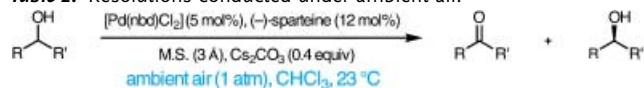
Encouraged by the success of our modified reaction conditions and curious to test whether the solvent could influence the post-resolution portion of the proposed mechanism (Scheme 2, C–F), we attempted to resolve secondary alcohols in the presence of the most abundant and inexpensive stoichiometric oxidant conceivable: ambient air.[10] By simply performing the experiments in a reaction vessel equipped with a drying tube open to the air, effective oxidations proceeded to resolve secondary alcohols to high *ee* values, and with high associated selectivity factors (Table 2). Curiously, the time required to conduct the highly selective resolutions was often significantly lower. The subtleties of this effect are currently under investigation.[11]

Prompted by concerns over the reproducibility of our results under variable atmospheric concentrations of molecular oxygen, we sought to ascertain the lower limit required for effective resolution. After preparing mixed volumes of nitrogen and oxygen, we found that robust oxidation was consistently supported by as little as 5% O$_2$. In experiments conducted on enantiopure (*R*)-(+)-1-phenylethanol, it was observed that variable oxygen concentrations in the range of 5–100% had little impact on the conversion (Table 3). For this reason, it is expected that local environmental variability in
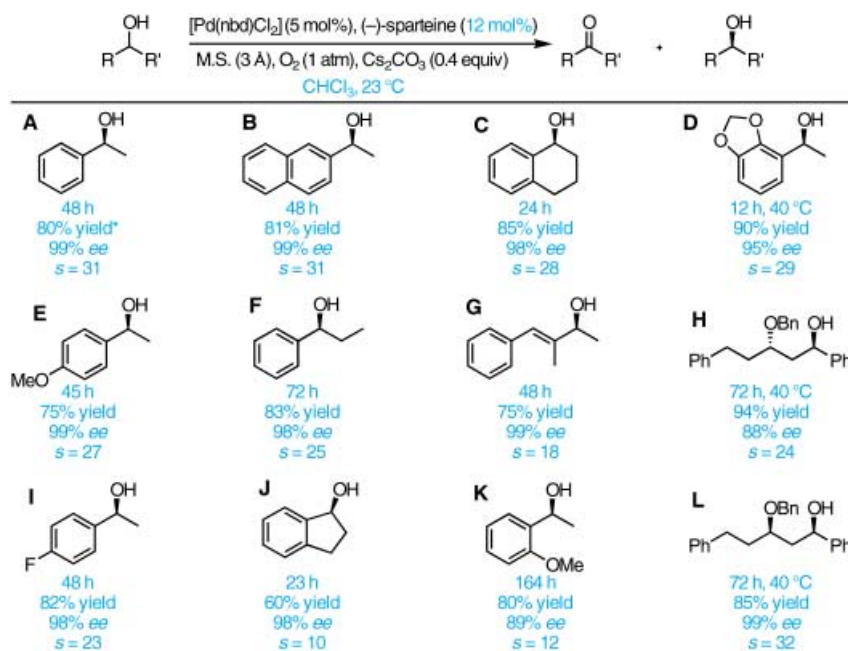
Scheme 3. Modified oxidative kinetic resolution in chloroform. [*] Yields are based on a theoretical maximum of 50%. The total yield was greater than 95% in all cases.

Table 2: Resolutions conducted under ambient air.

Entry	Unreacted alcohol, major enantiomer	t [h]	Conv. [%][a]	ee (ROH) [%]	s
			Black = O₂, Blue = air		
1	[structure: MeO-phenyl-CH(OH)-CH₃]	48	62.6	99.9	27.1
		24	62.3	99.8	25.4
2	[structure: F-phenyl-CH(OH)-CH₃]	48	59.3	98.0	23.0
		24	56.7	93.0	19.5
3	[structure: naphthyl-CH(OH)-CH₃]	48	59.3	99.6	31.1
		24	55.5	98.0	37.3
4	[structure: tetrahydronaphthalenol]	24	57.5	98.0	27.6
		16	60.2	99.6	28.0
5	[structure: Ph-CH=C(CH₃)-CH(OH)-CH₃]	48	62.6	98.7	17.9
		44	64.7	98.9	15.7
6	[structure: phenyl-CH(OH)-CH₂-CH₃]	72	62.6	98.2	24.4
		48	56.8	94.9	21.7

[a] Conversion was measured by GC on a DB-wax column (see Supporting Information for details)

Table 3: Effect of the concentration of oxygen on the oxidation of secondary alcohols.
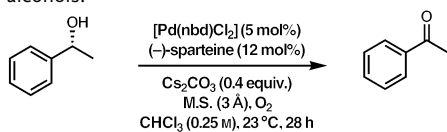
Entry	O₂/N₂ [vol %]	Conv. [%]
1	100	75.4
2	25	77.5
3	20	80.3
4	15	76.4
5	10	78.9
6	5	76.9
7	2.5	54.3
8	0	5.3

ambient oxygen concentration will not adversely affect the oxidative kinetic resolution under these conditions.[12] That no decrease in reaction efficiency is observed down to 5% oxygen underscores the power of molecular oxygen to reoxidize palladium(0).

In conclusion, by investigating the role of solvents capable of H-bond donation and chloride ion solvation, we have discovered the most mild and selective conditions for the oxidative kinetic resolution of secondary alcohols by catalytic palladium to date. The features of this catalyst system suggest some interesting mechanistic variations involving H-bonded intermediates: specifically, the activation of the [Pd(sparteine)Cl₂] salt toward attack by an alcohol, and activation of

intermediates along the reoxidation pathway. The practical implications of this system include room temperature reactivity in nonflammable solvents and a significant increase in the resolution selectivity. This improvement brings previously poorly resolving, yet synthetically important substrates, namely allylic alcohols, into the synthetically useful range. Furthermore, we have demonstrated the first efficient palladium-catalyzed oxidative kinetic resolution process employing ambient air as the stoichiometric oxidant. Efforts to extend these results to other types of asymmetric dehydrogenation reactions are currently ongoing.[13]

[1] a) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2001**, *123*, 7725; b) J. T. Bagdanoff, E. M. Ferreira, B. M. Stoltz, *Org. Lett.* **2003**, *5*, 835.

[2] Simultaneous to our publication of reference [1a], a related system was reported: D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Am. Chem. Soc.* **2001**, *123*, 7475.

[3] The kinetic resolutions in references [1] and [2] were based on a non-asymmetric oxidation of alcohols employing Pd(OAc)₂, pyridine, and O₂: T. Nishimura, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, *64*, 6750.

[4] For examples of related enzymatic oxidative kinetic resolutions, see: a) K. Faber, *Biotransformations in Organic Chemistry*, 3rd ed., Springer, Berlin, **1997**, pp. 201–205; b) I. J. Jackovac, H. B. Goodbrand, K. P. Lok, J. B. Jones, *J. Am. Chem. Soc.* **1982**, *104*, 4659–4665.

[5] Recently, mechanistic details of related non-asymmetric systems were studied: a) B. A. Steinhoff, S. S. Stahl, *Org. Lett.* **2002**, *4*, 4179; b) B. A. Steinhoff, S. S. Stahl, *J. Am. Chem. Soc.* **2002**, *124*, 766; c) S. S. Stahl, J. L. Thorman, R. C. Nelson, M. A. Kozee, *J. Am. Chem. Soc.* **2001**, *123*, 7188.

[6] For discussions on kinetic resolution, see: a) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237; b) C.-S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, *104*, 7294; c) H. B. Kagan, J. C. Fiaud in *Topics in Stereochemistry, Vol. 18* (Ed.: E. L. Eliel), Wiley, New York, **1988**, pp. 249–330.

[7] a) The solubility of O₂ is not a likely factor in disparate reactivities, particularly between toluene and chloroform, in which O₂ is equally soluble. For relevant tables, see: F. Fischer, G. Pfleiderer, *Z. Anorg. Allg. Chem.* **1922**, *124*, 61; b) No correlation between solvent dielectric constant (an estimate of polarity) and conversion is apparent; for relevant tables, see: E. W. Flick in *Industrial Solvents Handbook*, 3rd ed. (Ed.: E. W. Flick), Noyes Data Corp., New Jersey, **1985**, pp. 637–647.

[8] a) No dichlorocarbene was detected under the reaction conditions; b) Exposure of [Pd(sparteine)Cl₂] to Cs₂CO₃ in CHCl₃ leads to the production of an interesting [Pd(sparteine)CO₃] complex (see Supporting Information for the solid-state structure). This complex is inactive as a catalyst for kinetic resolution under a variety of conditions.

[9] The selectivity factor (s) was determined from the equation: $s = k_{rel}(\text{fast/slow}) = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$ (C = conversion).

[10] For an example of a non-asymmetric oxidation of alcohols catalyzed by palladium in the presence of air as the stoichiometric oxidant, see: K. Hallman, C. Moberg, *Adv. Synth. Catal.* **2001**, *343*, 260.

[11] Spectroscopic grade chloroform (Aldrich) or chloroform stabilized by amylenes was used without further purification. While a drying tube was employed in the reaction setup, no marked effect was observed when wet air was used. Addition of trace amounts of concentrated HCl during the resolution had little effect. Additionally, freshly distilled $CHCl_3$ (washed with H_2O, dried over $CaCl_2$, and distillation from $CaCl_2$) gives identical results. Chloroform stabilized by EtOH must be distilled prior to use.

[12] Oxygen-uptake experiments confirm a 2:1 stoichiometry for substrate/O_2, indicating that $CHCl_3$ is not involved as an oxidant.

[13] We recently reported a number of palladium-catalyzed oxidative hetero- and carbocyclization reactions with molecular oxygen: a) R. M. Trend, Y. K. Ramtohul, E. M. Ferreira, B. M. Stoltz, *Angew. Chem.* **2003**, *115*, 2998–3001; *Angew. Chem. Int. Ed.* **2003**, *42*, 2892–2895; b) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579.