The Resolution of Important Pharmaceutical Building Blocks by Palladium-Catalyzed Aerobic Oxidation of Secondary Alcohols

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Abstract: The palladium-catalyzed aerobic oxidative kinetic resolution of key pharmaceutical building blocks is described. Substrates investigated are relevant to the enantioselective preparation of Prozac®, Singulair®, and the promising hNK-1 receptor antagonist from Merck. The latter provides the most selective aerobic oxidative kinetic resolution yet described.

Keywords: asymmetric catalysis; kinetic resolution; oxidation; oxygen; palladium; pharmaceutical substance

As part of a general program initiated in the area of asymmetric dehydrogenation chemistry, we recently reported the oxidative kinetic resolution of secondary alcohols using a simple palladium dichloride catalyst precursor [Pd(nbd)Cl_2] in conjunction with (−)-sparteine serving as both ligand and base and molecular oxygen as the stoichiometric oxidant.[1–3] We have made a number of conceptual improvements to this system that allow a range of alcohols to be resolved under a variety of experimental procedures depending on the substrate.[1b,1c] Additionally, this catalysis has been extended to oxidative cyclizations including both heterocyclizations and carbocyclizations (Figure 1).[4,5] Herein, we report the resolution of a number of key building blocks for the synthesis of biologically relevant drug substances. The versatility of this resolution is further demonstrated by the diversity associated with the substrates chosen for this study, and for the first time extends the utility of the resolution to include amino alcohol derivatives, cyclic allylic alcohols, and highly functionalized benzylic alcohols.

To demonstrate the potential utility of our palladium-catalyzed enantioselective alcohol oxidation, we investigated the aerobic oxidative kinetic resolution of a diverse set of small molecules representing key building blocks of bioactive pharmaceutically relevant materials

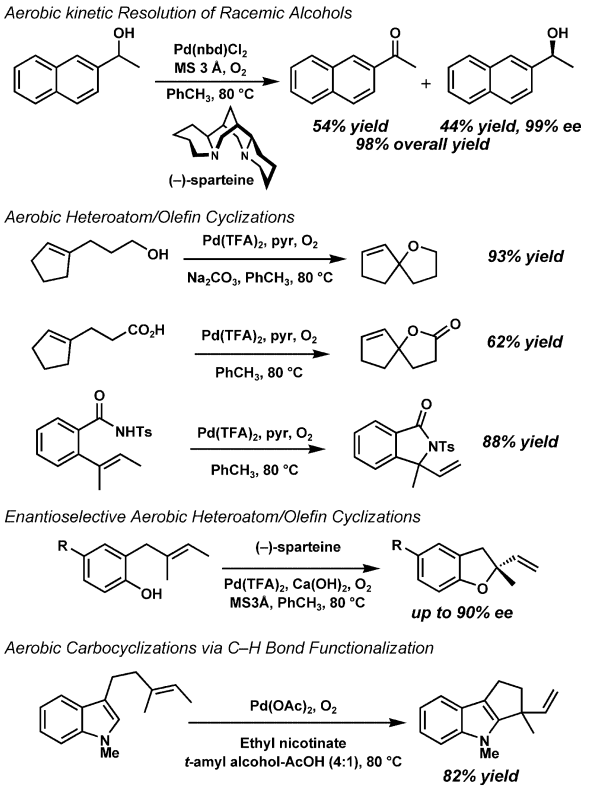

Figure 1. Palladium-catalyzed aerobic oxidation chemistry.

(Figure 2). The pharmaceutical substances included A) the antidepressants fluoxetine hydrochloride (Prozac®, **1a**), norfluoxetine (**1b**), tomoxetine (**2**), and nisoxetine (**3**),[6] B) the orally active leukotriene receptor antagonist monteleukast sodium (Singulair®, **4**),[7] and C) Merck's promising human neurokinin-1 (hNK-1) receptor antagonist (**5**).[8] These compounds were specifically chosen due to the inclusion of a key benzylic or allylic alcohol in the known synthetic routes (i.e., **6**–**8**). We believed that such intermediates would represent an ideal testing ground for our new asymmetric methodology.

To this end, we prepared a number of key intermediates by the literature procedures and subjected them to

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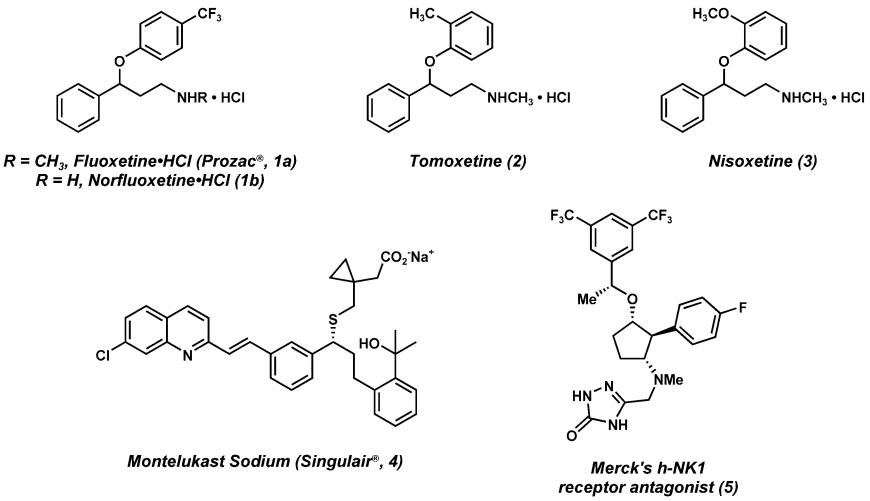
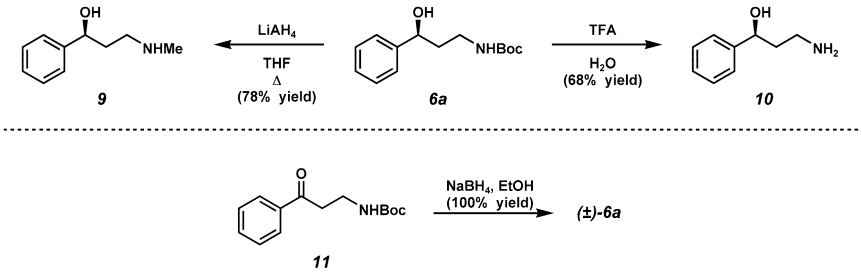


Figure 2. Pharmaceutical substances.



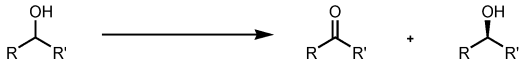
Scheme 1. Functionalization of **6a** and recycling of **11**.

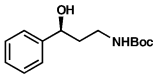
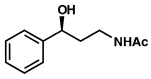
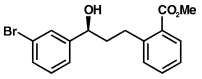
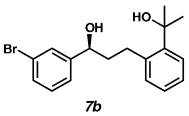
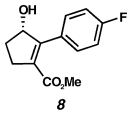
kinetic resolution using a variety of our palladium-catalyzed aerobic conditions. To our delight, all of the intermediates were resolved to high enantiomeric excess and with good to excellent selectivity(ies) between the *R* and *S* enantiomers (s = 9–82).[9] As shown in Table 1, the amino alcohol derivatives **6a** and **6b**, relevant to the antidepressants **1**–**3**, could be resolved under our original conditions, employing $Pd(nbd)Cl_2$, (−)-sparteine, and O_2.[1a] While acetamide **6b** was reasonably selective (s = 9), the more synthetically versatile BOC derivative **6a** could be resolved with a selectivity factor of nearly 18. Notably, the carbamate **6a** could be easily converted to the *N*-methyl derivative **9** by reduction with $LiAlH_4$ (78% yield) or to the primary amine **10** by treatment with TFA (68% yield), and the ketone **11** could be recycled to (±)-**6a** by quantitative reduction with $NaBH_4$ (Scheme 1).[10]

The molecules relevant to the Singulair® system also resolved quite efficiently (Table 1, entries 3 and 4). In order to minimize the experimental time involved for the resolution of compounds **7a** and **7b**, we chose to employ our recently described base-accelerated conditions.[1b] Smooth and rapid kinetic resolution was observed for both substrates (4.5 h) leading to production of the relevant enantiomer for use in Singulair®. Importantly, these resolutions provide a guide to the functional group compatibility of the rate-accelerated system, as aryl bromides and benzoate esters are tolerated in the oxidation. Again, the corresponding ketones **12a** and **12b** could be easily recycled *via* borohydride reduction. Furthermore, elaboration of both **7a** and **7b** to intermediates used in the production of monteleukast sodium proceeded by intermolecular Heck reactions to provide the quinoline derivatives **13a** and **13b** (Scheme 2).

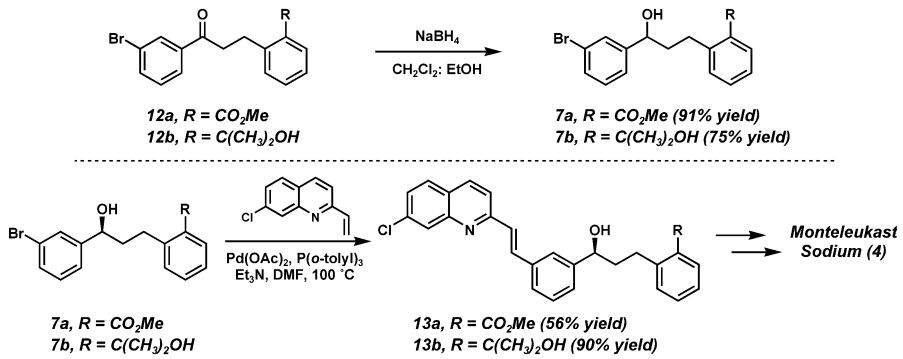
To our delight, the cyclopentenol structure **8** responded to all of our kinetic resolution conditions with exceptional selectivity and enhanced reactivity (Table 1, entry 5). Under all three of our reaction conditions (original,[1a] rate-accelerated,[1b] and room temperature chloroform[1c]) this substrate performed exceedingly well. It is noteworthy that these resolutions represent the most selective reactions observed to date for a palladium-catalyzed aerobic oxidation, with relative rates greater than 50:1. Gratifyingly, again the ketone by-product (i.e., **14**) could be trivially recycled to the racemic alcohol (±)-**8** (Scheme 3). We are currently investigating the generality of these important substrates (2-arylcycloalk-2-en-1-ols) toward oxidative kinetic resolution and planning their use in the synthesis of complex natural products.

Table 1. Oxidative kinetic resolution of pharmaceutical building blocks.



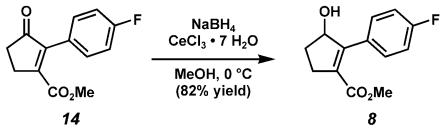
Entry	Unreacted alcohol, major enantiomer	Method[a]	Time	Conversion [%]	ee ROH [%][f]	s
1	 **6a**	A	24 h	57.5[c]	93.1	17.9
2	 **6b**	A	14.5 h	70.0[c]	97.0	9.0
3	 **7a**	B[b]	4.5 h	62.5[d]	92.9	11.2
4	 **7b**	B[b]	4.5 h	70.6[c]	99.9	15.3
5	 **8**	A	4 h	55.6[e]	99.5	50.2
		B	1 h	55.5[e]	99.5	51.1
		C	9 h	50.8[e]	94.7	82.7

[a] Method A: 5 mol % $Pd(nbd)Cl_2$, 20 mol % (−)-sparteine, MS 3 Å, O_2 (1 atm), 0.1 M in $PhCH_3$, 80 °C. Method B: 5 mol % $Pd(nbd)Cl_2$, 20 mol % (−)-sparteine, 0.5 equiv. Cs_2CO_3, 1.5 equivs. *t*-BuOH, MS 3 Å, O_2 (1 atm), 0.25 M in $PhCH_3$, 60 °C. Method C: 5 mol % $Pd(nbd)Cl_2$, 12 mol % (−)-sparteine, 0.4 equiv Cs_2CO_3, MS 3 Å, O_2 (1 atm), 0.25 M in $CHCl_3$, 23 °C.
[b] Performed at 80 °C.
[c] Conversion determined by isolated yield.
[d] Conversion determined by ^1H NMR.
[e] Conversion determined by GC using a DB-wax column.
[f] Enantiomeric excess (ee) determined by chiral HPLC (see Supporting Information for details). Total mass recovery in all cases is greater than 85%.



Scheme 2. Recycling and functionalization in the Singulair® series.

In conclusion, we have employed the palladium-catalyzed aerobic oxidative kinetic resolution for the enantioselective preparation of a variety of pharmaceutical substances including Prozac®(**1a**), Singulair®(**4**), and Merck's hNK-1 receptor antagonist (**5**). These examples demonstrate the power and utility of the methods that we have developed to overcome many subtleties of substrate functionality. In this regard we have resolved amino alcohol derivatives and multi-functionalized aromatic molecules. We have also discovered the novel resolution capacity of 2-arylcyclopentenol derivatives (i.e., **8**), which is the most selective



Scheme 3. Recycling in the hNK-1 series.

substrate yet investigated for aerobic oxidative kinetic resolution. Efforts to develop new catalyst systems and expand the utility and generality of asymmetric aerobic dehydrogenations continue.

Experimental Section

Kinetic Resolution Conditions A[1a]

To an oven-dried reaction tube with stir bar was added oven-dried powdered 3 Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol) followed by toluene (2.5 mL) and then (−)-sparteine (23.4 mg, 23 μL, 0.10 mmol) were added. The reaction mixture was vacuum evacuated, purged with O_2 (3 ×), and heated to 80 °C with vigorous stirring under an O_2 atmosphere (1 atm) for 20 min. A solution of allylic alcohol **8** (118.1 mg, 0.50 mmol) in toluene (2.5 mL) was added, and the reaction was allowed to proceed under O_2 atmosphere (1 atm) at 80 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed for conversion and ee. Purification of ketone **14** and enantioenriched alcohol **8** was accomplished by direct chromatography of the crude reaction mixture.

Kinetic Resolution Conditions B[1b]

To an oven-dried reaction tube with stir bar was added oven-dried powdered 3 Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by toluene (2 mL) and then (−)-sparteine (46.9 mg, 46 μL, 0.20 mmol) were added. The reaction vessel was then vacuum evacuated, purged with O_2 (3 ×), and was heated (60 °C) with vigorous stirring under an O_2 atmosphere (1 atm) for 20 min. Finely powdered anhydrous Cs_2CO_3 (162.9 mg, 0.50 mmol) was added, followed by a solution of allylic alcohol **8** (236.3 mg, 1.0 mmol), *t*-butanol (111.2 mg, 143 μL, 1.5 mmol) and toluene (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 60 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **14** and enantioenriched alcohol **8** was accomplished by direct chromatography of the crude reaction mixture.

Kinetic Resolution Conditions C[1c]

To an oven-dried reaction tube with stir bar was added oven-dried powdered 3 Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by chloroform (2 mL, stabilized with amylenes) and then (−)-sparteine (28.1 mg, 27.6 μL, 0.12 mmol) were added. The reaction mixture was then vacuum evacuated, purged with O_2 (3 ×), and stirred vigorously at 23 °C under an O_2 atmosphere (1 atm) for 15 min. Finely powdered anhydrous Cs_2CO_3 (130.3 mg, 0.40 mmol) was added, followed by a solution of allylic alcohol **8** (236.3 mg, 1.0 mmol) in chloroform (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **14** and enantioenriched alcohol **8** was accomplished by direct chromatography of the crude reaction mixture.

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

[10] See Supporting Information for details.

