Palladium-based Kinetic Resolution of Racemic Tosylaziridines

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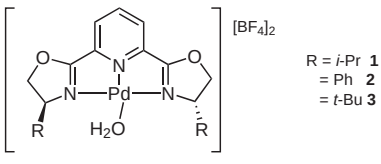
Abstract: Dicationic Pd(II) complexes with chiral pyridine bis(oxazoline) ligands are catalysts for kinetic resolution of racemic styrene tosylazirdines. Treatment of styrene tosylaziridine with 0.5 equivalents of alcohol in the presence of the chiral Pd catalyst affords β-alkoxy tosylamide with ee up to 71%.

Key words: palladium, kinetic resolution, aziridine, asymmetric, alcoholysis

Aziridines are versatile building blocks for nitrogen-containing compounds.[1] Of synthetic significance is nucleophilic ring opening of aziridines by alcohols to give β-alkoxy amides.[2] Recently, Jacobsen and coworkers demonstrated that Co(salen) complexes can catalyze highly enantioselective ring opening of epoxides by water and alcohols.[3] Significantly, the Co(salen)-based ring opening reactions have been successfully used for kinetic resolution of racemic terminal epoxides with excellent stereoselectivity and efficiency.[4,5] This prompted us to investigate into a similar approach to kinetic resolution of racemic aziridines via their enantioselective alcoholysis. Although metal-catalyzed asymmetric cleavage of aziridines by thiols,[6] azide[7] and Grignard reagents[8] has been well developed, there are no reports on catalytic asymmetric alcoholysis of aziridines. We are particularly interested in Pd-based alcoholysis due to the recent findings that Pd(II) complexes are capable of catalyzing C–O bond forming reactions,[9] apparently via Pd alkoxide intermediates. We herein report on our preliminary results of kinetic resolution racemic tosylaziridines with chiral dicationic Pd(II) complexes [Pd(*S*-Rpybox)(H_2O)][BF_4]$_2$ (*S*-Rpybox = 2,6-bis[(4*S*)-(+)-alkyl-2-oxazolin-2-yl]pyridine)[10] (Figure 1).



[Pd(*S*-Rpybox)(H_2O)][BF_4]$_2$

Figure 1

Treatment of racemic substituted styrene tosylaziridine (X-STA) with 0.5 equivalents of alcohol in the presence of 10 mol% of *S*-**1** at 0 °C resulted in isolation of 2-alkoxy tosylamide **4** in 22–41% yield along with the minor product 2-hydroxy tosylamide **5** (Table 1).[11] The formation of **4** with high regioselectivity is in contrast with the Co(salen)-catalyzed alcoholysis of styrene oxide, in which a mixture of regioisomeric products were produced.[5] Thus, methanolysis of STA with *S*-**1** led to isolation of **4** (34% yield, 46% ee) and **5** (8% yield, 26% ee), and recovery of STA (58% yield, 50% ee) (entry 1). Similar yields and ee's were obtained for the reaction with the Phpybox complex *S*-**2**. When 0.8 equiv of MeOH was used, STA was recovered in lower yield (34%) but higher ee (76%) (entry 2). Aliphatic aziridines such as cyclohexene aziridine did not react under these conditions. It seems likely that the hydroxy group in **5** was derived from the moisture of solvent and substrate rather than the aquo ligand in *S*-**1** because similar amounts of **5** were obtained when different loadings of *S*-**1** were used. An attempt to eliminate **5** by addition of molecular sieves (4 Å) to the reaction mixture was unsuccessful. The Pd catalyst appeared to be deactivated by molecular sieves and no alcoholysis was observed. Methanolysis with non-aqua complexes such as [Pd(*S*-Prpybox)(MeCN)]$^{2+}$ and [Pd(Prpybox)(CF_3SO_3)$_2$] was found to be less stereoselective (ee of **4** < 20%) than that with **1**. Other [M(*S*-Rpybox)]$^{2+}$ complexes (e.g. M = Cu, Pt) are not active in aziridine ring opening.

Using water as nucleophile, ring opening of STA afforded **5** as the sole product in 16% ee (entry 5). It appears that the stereoselectivity for aziridine alcoholysis increases as the steric demand of alcohol increases. For example, the k_{rel} value[12] increases from ca. 3.4 for MeOH to 7.7 for *i*-PrOH. However, the reaction was very slow when either *t*-BuOH or [Pd(*S*-Bupybox)(H_2O)][BF_4]$_2$ was used. Similar to the acid-catalyzed alcoholysis of styrene oxides,[13] the substituent X on the phenyl ring has a profound influence on both the rate and selectivity of the alcoholysis of X-STA. Thus, methanolysis of electron-rich 4-MeSTA was fast and non-selective (entry 8) whereas that of 4-ClSTA was slower but more selective (k_{rel} ≈ 7.2) (entry 10). The rate of alcoholysis was found to decrease in the order 4-FSTA > STA > 3-FSTA > 4-CF_3STA, indicating that the reactive intermediate may carry partial positive

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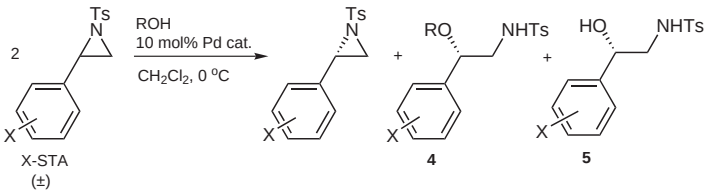
Table 1 Pd-Catalyzed Asymmetric Alcoholysis of Styrene Tosylaziridines[a]

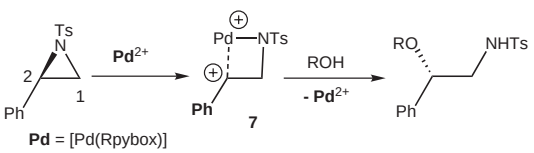


Entry	X	ROH	Catalyst	Time/ h	% Yield[b] (% ee[c])		
					Recovered X-STA	**4** [k_{rel}[d]]	**5**
1	H	MeOH	*S*-**1**	3	58 (50, *S*)	34 (46, *S*) [3.4]	8 (26, *S*)
2	H	MeOH[e]	*S*-**1**	5	34 (76, *S*)	57 (31, *S*) [2.7]	9 (17, *S*)
3	H	MeOH	*S*-**2**	5	49 (33, *S*)	41 (43, *S*) [3.3]	10 (33, *S*)
4	H	MeOH	R-**1**	5	52 (33, R)	34 (42, R) [3.0]	13 (8, R)
5	H	H_2O	*S*-**1**	5	56 (27, *S*)	–	41 (16, *S*)
6	H	EtOH	*S*-**1**	2	48 (47, *S*)	39 (55, *S*) [4.8]	11 (13, *S*)
7	H	*i*-PrOH	*S*-**1**	2	63 (35, *S*)	28 (71, *S*) [7.7]	9 (36, *S*)
8[f]	4-Me	MeOH	*S*-**1**	1	43 (0)	33 (0) [1]	10 (0)
9	4-F	MeOH	*S*-**1**	1	58 (30, *S*)	31 (43, *S*) [3.0]	10 (19, *S*)
10	4-Cl	MeOH	*S*-**1**	3	69 (29, *S*)	22 (71, *S*) [7.2]	5 (32, *S*)
11	4-Cl	MeOH	*S*-**1**[g]	3	51 (14, *S*)	43 (66, *S*) [7.9]	6 (25, *S*)
12	4-Br	MeOH	*S*-**1**	2	62 (48, *S*)	29 (69, *S*) [7.2]	4 (2, *S*)
13	4-CF_3	MeOH	*S*-**1**	5	95 (3, *S*)	5 (N.D.[h])	N.D.
14	3-F	MeOH	*S*-**1**	5	90 (7, *S*)	9 (58, *S*) [4.0]	N.D.

[a] Aziridine (0.27 mmol), Pd catalyst (0.027 mmol) and ROH (0.14 mmol) in CH_2Cl_2 (1 mL) at 0 °C.
[b] Isolated yield (based on starting aziridine).
[c] Determined by chiral HPLC analysis using a (*S*,*S*) WHELK-O column. Absolute configuration determined by optical rotation.
[d] See ref.[12]
[e] 0.8 equiv of MeOH used.
[f] Run at –10 °C.
[g] 20 mol% catalyst used.
[h] Not determined.

charge at the benzylic position, which also accounts for the observed C2-selectivity for the aziridine ring opening. Furthermore, given the stereoselectivitiy of the alcoholysis it is reasonable to assume that the intermediate is a Pd-bound cationic species (*vide infra*) instead of free benzylic carbocation. Recently, β-aryl amides were prepared by the reaction of tosylaziridines with electron-rich arenes in the presence of $In(OTf)_3$,[14] which presumably also involves similar cationic intermediates. Non-labile [Pd(*S*-Prpybox)Cl][BF_4] is not an active catalyst, suggesting that a vacant coordination site on Pd for binding to aziridine or alcohol is an important step for the catalysis. However, we rule out the possibility of nucleophilic attack on aziridine by Pd(II) alkoxide because no reaction was found between *S*-**1** and ROH in the absence of STA under the experimental conditions, although refluxing *S*-**1** in MeOH yielded a Pd(I) dimer [Pd_2(*S*-Prpybox)$_2$][BF_4]$_2$ **6**,[15] presumably via reductive elimination of a Pd–OMe intermediate. We believe that the first step of the catalytic cycle involves the binding of STA to Pd and ring opening of aziridine to give a Pd-bound cationic intermediate **7** that possibly has a metallacycle-like structure with substantial Pd-C2 interaction (Scheme 1). A similar metallacycle intermediate has previously been proposed for Rh-catalyzed carbonylation of aziridines.[16] Concerted nucleophilic attack at C2 by alcohol gives the 2-alkoxy ring-opening product with inversion of configuration.

Proposed mechanism



Scheme 1

A preliminary kinetic study[17] showed that the Pd-catalyzed alcoholysis is first order in the Pd catalyst and zero order in alcohol, suggesting that the rate-determining step is Pd-mediated ring opening of aziridine instead of nucleophilic attack by alcohol. This is in contrast with the Jacobsen's Cr(salen)-catalyzed ring opening of epoxides, which is second order in the Cr catalyst.[3]

In summary, we have developed a new method for kinetic resolution of racemic styrene tosylaziridines based on chiral Pd catalysts. To our knowledge, this is the first report on Pd-catalyzed ring opening of aziridines. This reaction has potential applications to the synthesis of chiral β-alkoxy amides. Efforts are being made to improve the stereoselectivity factor for the kinetic resolution by tuning the metal and/or ligand of catalyst.

Acknowledgement

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(10) Asymmetric aldol reaction of methyl isocyanate with benzaldehyde catalysed by $[Pd(S\text{-Prpybox})(MeCN)][BF_4]_2$ has been reported: Nesper, R.; Pregosin, P. S.; Puentener, K.; Woerle, M. *Helv. Chim. Acta* **1993**, *76*, 2239.
(11) *Typical procedure for Pd-catalyzed alcoholysis of styrene tosylaziridine*: To a mixture of aziridine (50 mg, 0.18 mmol) and *S*-**1** (12 mg, 0.018 mmol) in CH_2Cl_2 (1 mL) was added dried MeOH (4 μL, 0.09 mmol) under nitrogen at 0 °C. The mixture was stirred at that temperature for 1–5 h and purified by flash chromatography (silica gel, 50% ether–hexane). Spectroscopic data for $PhCH(OMe)CH_2NHTs$: ^1H NMR (400 MHz, acetone-d_6): δ 7.90 (d, J = 8.0 Hz, 2 H), 7.53 (d, J = 8.0 Hz, 2 H), 7.45 (m, 5 H), 6.65 (s, br, 1 H), 4.35 (dd, J = 8.8, 4.4 Hz, 1 H), 3.20 (m, 2 H), 3.25 (s, 3 H), 2.56 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6): δ 143.5, 140.0, 139.0, 130.1, 129.1, 128.7, 127.6, 127.3, 83.0, 56.8, 50.2, 21.3; MS (+CI) *m/z* (relative intensity): 306 ($M + H^+$, 18), 274 ($M - OMe^+$, 100). Anal. Calc. for $C_{16}H_{19}NOS_3$ (305.39): C, 62.93; H, 6.27; N, 4.59. Found: C, 62.91; H, 6.35; N, 4.54.
(12) The k_{rel} values were calculated using the equation $k_{rel} = \ln[1 - c(1+ee)]/\ln[1 - c(1 - ee)]$ where ee and c are the enantiomeric excess and conversion of the product, respectively. See for example: Eliel, E. L.; Wilen, S. H.; Mander, L. M. *Stereochemistry of Organic Compounds*; Wiley: New York, **1994**, 395.
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(17) Initial rates of reactions were estimated by monitoring the concentration of aziridine using GLC.