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Palladium-Mediated Regiodivergent Kinetic Resolution

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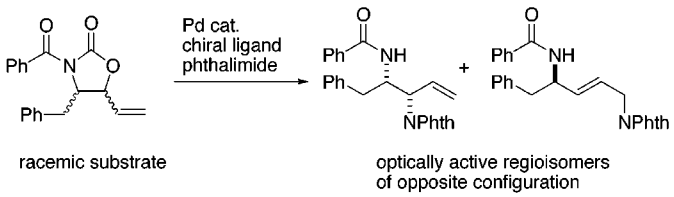
ABSTRACT



The allylic substitution of racemic 5-vinyloxazolidinones with phthalimide and a chiral palladium catalyst afforded optically enriched regioisomeric products. Optimal divergence was found by employing chiral DIOP ligands in toluene. These results demonstrate the influence of chiral ligand/chiral substrate matching on the regioselectivity in a novel resolution strategy.

Since the first report of the kinetic resolution of enantiomers by Pasteur nearly 150 years ago,[1] many novel and interesting resolution processes have been developed.[2] In a traditional resolution, enantiomers are separated by the selective reaction of one enantiomer with a chiral reagent leading to a maximum 50% yield of an enantioenriched product or recovered starting material. Recently, processes in which both enantiomers react in a divergent sense to form two different optically enriched products have been investigated. Parallel kinetic resolution (PKR), where two different chiral reagents react with a racemic substrate to form two different products, has been examined.[3]

Conceptually similar to PKR is a process wherein a single chiral catalyst or reagent may react with a racemic substrate to form regioisomers of opposite configuration (Figure 1). The theoretical aspects of regiodivergent resolution were recently described by Kagan.[4] In practice, there are only a few examples to demonstrate the concept. The enzymatic or copper-catalyzed asymmetric Bayer−Villiger oxidation of racemic cycloalkanones led to the formation of regioisomeric lactones of opposite configuration with high enantiomeric excess.[5] Asymmetric copper-catalyzed alkylation of

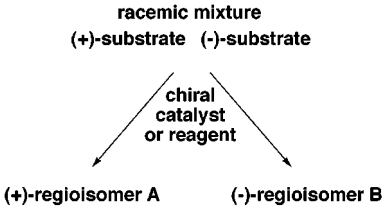


Figure 1. Divergent kinetic resolution of enantiomers by the formation of regiosomeric products of opposite configuration.

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(3) (a) For a recent review, see: Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885−888. See also: (b) Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123*, 2428−2429. (c) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584−2585. (d) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535−538. (e) Cardona, F.; Valenza, S.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1999**, 1319−1323. (f) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021−11022.
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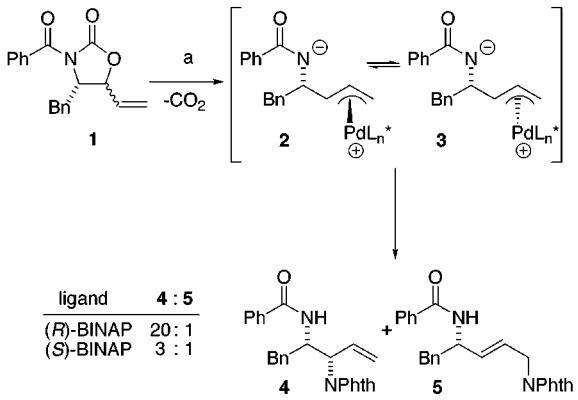
Scheme 1. Chiral Ligand Dependent Regioselectivity in the Pd-Catalyzed Allylic Substitution of 5-Vinyloxazolidinones[a]



[a] (a) cat. $[C_3H_5PdCl]_2$/chiral ligand, phthalimide, cat. K-phthalimide, THF, rt.

racemic vinylepoxides with dialkyl zinc reagents afforded optically enriched regioisomeric alcohols via a S_N2 or S_N2' mechanism.[6] Also, Pfaltz has recently demonstrated a variant of this concept in the Pd-catalyzed allylic substitution reaction where the regiodivergent products stemmed from the configuration of starting substrates.[7]

As part of our program to develop new methods for the stereoselective preparation of vicinal diamines, we have investigated the Pd-catalyzed allylic substitution of 5-vinyloxazolidinones with phthalimide nucleophile (Scheme 1).[8] Reaction of diastereomeric mixtures of **1** with a Pd(0) catalyst resulted in the formation of equilibrating diastereomeric complexes **2** and **3**. Addition of phthalimide to the allyl complexes led to the stereoselective formation of vicinal diamine **4** and 1,4-diamine **5**. When chiral ligands were employed in this reaction, the regioselectivity was found to be highly dependent on the matching of the ligand chirality and the substrate chirality. (*R*)-BINAP afforded a 20:1 regioselectivity, whereas (*S*)-BINAP gave a reduced 3:1 regioselectivity. Interestingly, diastereoselectivity was completely controlled by the substrate and the chiral ligand did not exert any influence.

As the regioselectivity of the allylic substitution of **1** was dependent on the asymmetric matching of the ligand and substrate, we anticipated that reaction of *rac*-**1** with phthalimide in the presence of a chiral catalyst would afford optically active regiodivergent products. Herein we present the results of our investigation of the regiodivergent kinetic resolution of *rac*-**1**.

As shown in Scheme 2, the allylic substitution of *rac*-**1** is complicated by the presence of equilibrating diastereomers. Reaction of enantiomer (*S*)-**1** will lead to diastereomeric complexes (*S*)-**2** and (*S*)-**3**, while reaction of (*R*)-**1** will give (*R*)-**2** and (*R*)-**3**. The vicinal diamine products (*S,S*)- and (*R,R*)-**4** can only be derived from (*S*)-**2** and (*R*)-**2**, respectively. However, the 1,4-diamine products (*S*)-**5** could arise from either (*S*)-**2** or (*S*)-**3**. Likewise, either (*R*)-**2** or (*R*)-**3** could give (*R*)-**5**. Fortunately, as we have previously shown,[8] the chiral ligand matching with the substrate has no influence on the diastereoselectivity and the *syn*-isomers of **4** should be produced from either set of equilibrating intermediates. Thus, this system would not be complicated by the presence of *anti*-**4**.

The results of the enantioselective regiodivergent kinetic resolution[9] are summarized in Table 1. Ideally, for optimal regiodivergence, the chirality match and mismatch should be opposite (e.g., 100:0 vs 0:100). As the reaction of (*S*)-**1** with (*R*)- or (*S*)-BINAP was found to afford the same major

Scheme 2. Regiodivergent Kinetic Resolution

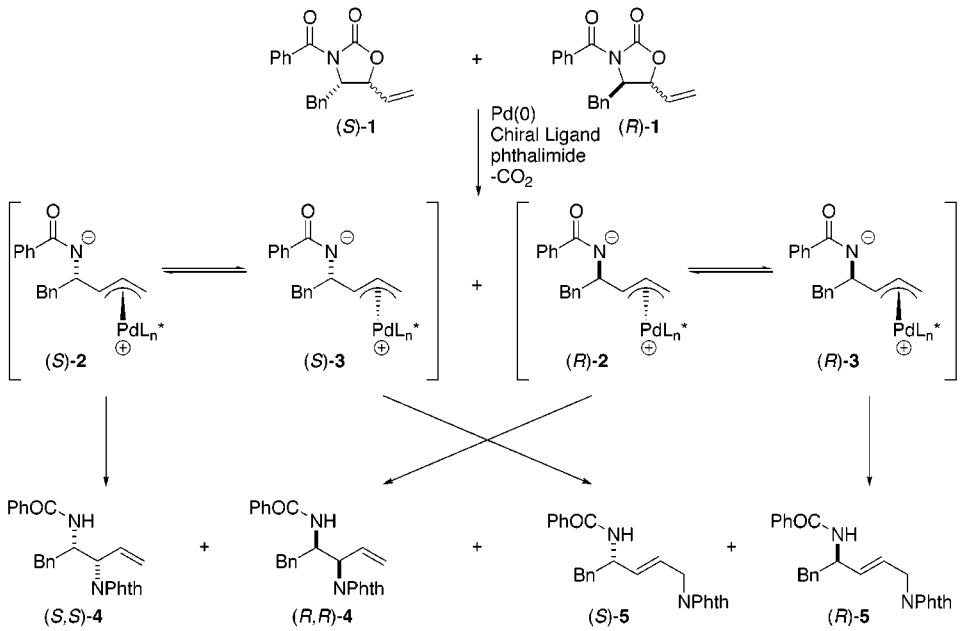


Table 1. Regiodivergent Kinetic Resolution of 5-Vinyloxazolidinones[a]

				% ee[d] (config)		yield[e]	
entry	ligand[b]	solvent	regioselectivity[c] (**4**:**5**)	**4**	**5**[f]	**4**	**5**
1	(*R*)-BINAP	THF	5:1	14 (*S*,*S*)	62 (*R*)	73	11
2	(*S*)-BINAP	THF	5:1	9 (*R*,*R*)	57 (*S*)	69	16
3	(*R*)-BINAP	CH_2Cl_2	1:1	33 (*S*,*S*)	29 (*R*)	35	37
4	(*S*)-BINAP	CH_2Cl_2	1:1	35 (*R*,*R*)	36 (*S*)	34	36
5	(*R*)-BINAP	CH_3CN	1:2.4	36 (*S*,*S*)	17 (*R*)	24	47
6	(*S*)-BINAP	CH_3CN	1:2.4	37 (*R*,*R*)	13 (*S*)	24	47
7	(*R*,*S*)-JOSIPHOS	THF	2:1	11 (*R*,*R*)	22 (*S*)	53	25
8	(*S*,*R*)-JOSIPHOS	THF	2:1	11 (*S*,*S*)	22 (*R*)	54	25
9	(*R*,*R*)-DIOP	THF	1:1.8	45 (*R*,*R*)	38 (*S*)	26	44
10	(*S*,*S*)-DIOP	THF	1:1.8	44 (*S*,*S*)	37 (*R*)	23	47
11	(*R*,*R*)-DIOP	toluene	1:1.2	52 (*R*,*R*)	48 (*S*)	33	39
12	(*S*,*S*)-DIOP	toluene	1:1.2	50 (*S*,*S*)	46 (*R*)	35	41

[a] 1 mol % $[(C_3H_5)PdCl]_2$, 4 mol % ligand, 10 mol % potassium phthalimide, 1.1 equiv phthalimide. [b] (*R*)-BINAP = (*R*)-2,2′-bis(dihpenylphosphino)-1,1′-binaphthyl, (*R*,*S*)-JOSIPHOS = (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine, (*R*,*R*)-DIOP = (4*R*,5*R*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. [c] Regioselectivity was determined by 1H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by chiral HPLC (Chiracel OD or Chiralpak AS) analysis after chromatographic separation of the regioisomers. [e] Isolated yield. [f] The ee of **5** was measured after hydrogenation of the double bond.

regioisomer but with different levels of selectivity (20:1 vs 3:1, respectively), it is not surprising that BINAP ligands employed under our original conditions with *rac*-**1** would not provide very high selectivity. Indeed, this was the case, as shown in entries 1 and 2. The vicinal diamine was formed as the major regioisomer (5:1) with a low 10% ee. The minor regioisomer was, however, significantly enhanced in optical purity (~60% ee). The use of other solvents that provide a more equal mixture of regiosomers provided proof of concept for regiodivergent resolution (entries 3 and 4). Although optical purity was not high, both regioisomers were obtained with nearly the same level and opposite configurations. The use of acetonitrile as the solvent led to an increased amount of **5**. Again, the major regioisomer was obtained with lower ee than the minor (entries 5 and 6). Other commercially available bisphosphine ligands were briefly investigated. JOSIPHOS provided low levels of enantiomeric excess (entries 7 and 8), whereas DIOP ligands afforded the highest ee for both regioisomers in a single reaction (entries 9−12).

In conclusion, we have established the asymmetric regiodivergent kinetic resolution of 5-vinyloxazolidinones by a Pd-catalyzed allylic substitution with phthalimide. Optimal divergence was found by employing chiral DIOP ligands in toluene. While the ee's are only modest, these results demonstrate the influence of chiral ligand/chiral substrate matching to command, not stereochemistry, but regioselectivity in a novel resolution strategy. Currently we are investigating the utility of chiral nucleophiles in this regiodivergent kinetic resolution and our results will be reported in due course.

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Supporting Information Available: Characterization data and NMR spectra for **4**, **5** and hydrogenated **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **General Procedure.** A 10-mL Schlenk flask was charged with 5-vinyloxazolidinone **1** (77 mg, 0.25 mmol), phthalimide (41 mg, 0.27 mmol), potassium phthalimide (9.3 mg, 0.05 mmol), $[(\pi\text{-}C_3H_5)PdCl]_2$ (0.9 mg, 1 mol %), and ligand (4 mol %) and sealed with a rubber septum. The flask was evacuated and flushed with nitrogen three times. Solvent (2 mL) was added, and the reaction was stirred at ambient temperature until TLC indicated complete consumption of starting material. The regioisomers were separated on silica gel (200−400 mesh) using 10−35% v/v ethyl acetate/hexane as eluent to afford pure **4** and **5**. The 1,4-products **5** were hydrogenated under 1 atm H_2 with 5% Pd/C in ethyl acetate for 2 h prior to HPLC analysis.