Enhanced Enantioselectivity in the Desymmetrization of Meso-Biscarbamates

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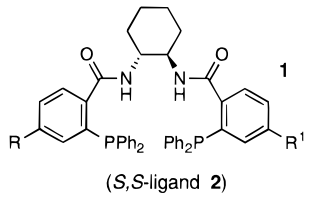
The palladium-catalyzed desymmetrization of meso-2-ene-1,4-diol diesters has proven to give the monosubstitution products in high ee (Scheme 1, path a).[1] On the other hand, our "standard" ligand **1** gave the oxazolidin-2-ones from the bis-carbamates (R = NHTs) in significantly lower ee's.[1a] Since the leaving group is involved in the enantiodiscriminating step, we believed the differences derived from a leaving group effect on the chiral discrimination, which we also observed in comparing acetate to benzoate as the leaving group.[1b] As a result, considering the utility of this asymmetric oxazolidin-2-one synthesis, we have been designing new ligands in an effort to enhance the ee of this cyclization.[2] In the course of these studies, we discovered a very simple solution to this problem whereby the "standard" ligands suffice and which has significant mechanistic implications.

Molecular modeling studies suggested that there may exist a conformation wherein one of the carbonyl oxygens of the ligand comes within van der Waals contact with palladium, suggesting an electronic effect superimposed on any steric effect that is responsible for the chiral recognition.[3] To strengthen such an interaction, we synthesized the symmetrical (**1a**) and unsymmetrical (**1b**) *p*-methoxy ligands and examined the cyclization of



1

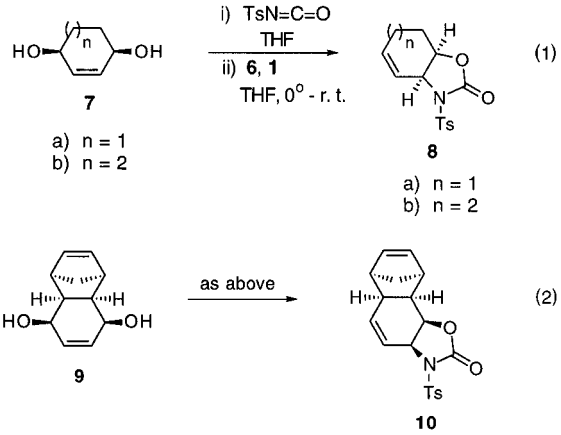
(*S,S*-ligand **2**)

a) R = R^1 = OCH$_3$
b) R = OCH$_3$, R^1 = H
c) R = R^1 = H

3d generated normally in situ by reaction of the diol with 2 equiv of *p*-tosyl isocyanate. The urethane was treated with 2.5 mol % of palladium catalyst precursor and 7.5 mol % of ligand in THF at 0 °C to room temperature. Surprisingly, both the yield and the ee were somewhat low using π-allylpalladium chloride dimer (**5**) as the catalyst precursor with ligands **1a** or **1b**. Switching to $(dba)_3Pd_2{\cdot}CHCl_3$ (**6**) saw the ee return to the same level as with ligand **1c** (or **2c**) (i.e. 79% ee for **1a** versus 78% ee for **1c**), but the yield was still low (40% for **1a** versus 97% for **1c**).

Since cyclization requires the nonionized urethane to be deprotonated, we envisioned that the low yield may arise from sluggish deprotonation of the pronucleophile in the case of the new ligands compared to **1c**. Adding 1 equiv of triethylamine did increase the yield to 53% but dramatically increased the ee to 96%! To establish whether the effect of triethylamine was ligand related, we reexamined the reaction with ligand **1c**. Adding 1 equiv of triethylamine to an otherwise standard protocol as previously described, oxazolidinone **4** was formed in 84% yield and with an ee of >99%!

To determine the generality of the effect, we studied the series of desymmetrizations previously explored and summarized in eqs 1 and 2 and Table 1. The data shows two trends. First, the ee increased in every case to ≥94%. Thus, the standard ligand **1c** now provides a convenient synthetic entry to oxazolidin-2-ones and, by deblocking, to vicinal cis-hydroxy-amines with excellent enantioselectivity. Second, the yield and ee had some dependence on the quantity of triethylamine. The yields appear to improve with lower amounts of base, but there may be a tradeoff in terms of ee. The lack of a consistent trend suggests that for optimum results in any specific case, some variation should be explored. The lower yield with increasing base may stem from base-catalyzed elimination competing with cyclization.



The significance of the base effect provides insight into the mechanism of the asymmetric induction. The simplest rationale recognizes that the ionization event, which determines the ee, may not be the rate-limiting event (see Scheme 2). In the absence of base, the ionization event produces either π-allylpalladium intermediate A or B. However, effective cyclization requires formation of the zwitterion C or D to give product. Since the base present is the carboxylate generated upon ionization, which means a weak base is present in very low concentration,[4] the rate of formation of C or D may become the rate-limiting step or, at least, competitive with the ionization

(1) (a) Trost, B. M.; van Vranken; D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (b) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745. (c) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143. (d) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3039. (e) Trost, B. M.; Madsen, R.; Guile, S. D. *Tetrahedron Lett.* **1997**, *38*, 1707.

(2) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.

(3) Hagelin, H., unpublished results in these laboratories.

(4) It is possible to envision loss of CO_2 from the carbamic anion to form the anion of tosylamide which then serves as base. However, the large difference in pK_a between a carbamic acid and tosylamide suggests that such decarboxylation would not be spontaneous and would require protonation.

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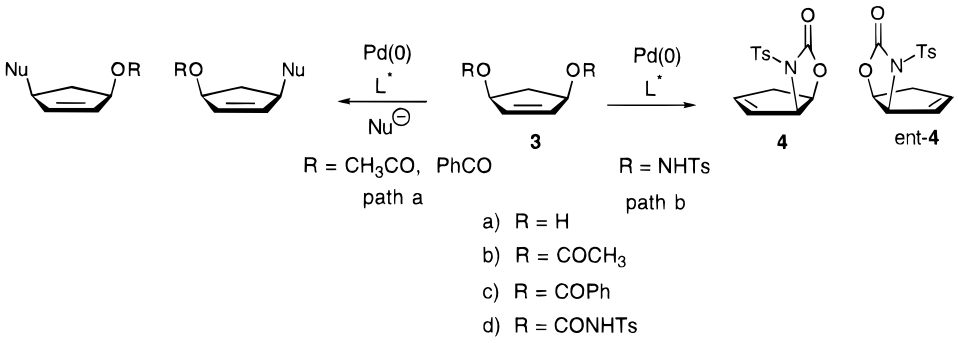
Scheme 1



Scheme 2. Mechanistic Rationale for Base Effect

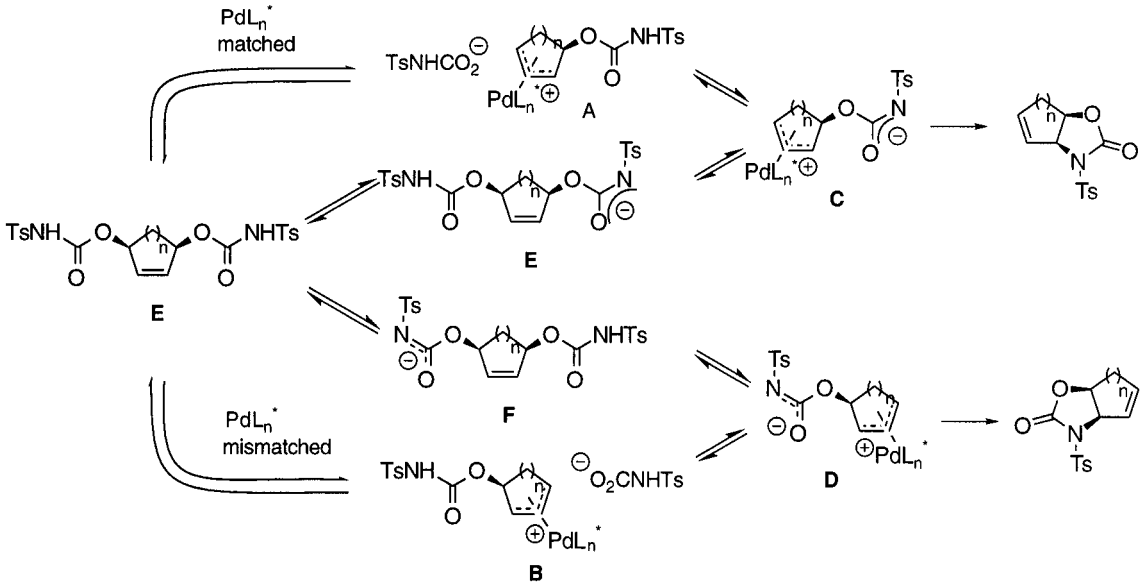


Table 1

entry	diol	oxazolidin-2-one	without $(C_2H_5)_3N$, % yield	without $(C_2H_5)_3N$, % ee	with $(C_2H_5)_3N$, % yield	with $(C_2H_5)_3N$, % ee
1	**3a**	**4**	97	78	1 eq. 84	>99
					0.5 eq. 79	>99
2	**7a**	**8a**	92	85	1 eq. 85	99
					0.5 equiv, 88	93
3	**7b**	**8b**	85	90	1 eq. 70	99
					0.5 eq. 92	97
4	**9**	**10**	66	81	1 eq. 60	94
					0.5 eq. 89	89

event. In this circumstance, significant return to starting material competes with cyclization. Under such conditions, more significant competition between the matched and mismatched pathways would ensue leading to an erosion of the ee. If the return of the initial π-allyl intermediate to starting material could be eliminated, the intrinsic enantiodiscrimination in the ionization step could be observed. Addition of external base could affect the process in two ways. First, it would speed the conversion of A to C (and B to D) and thereby decrease the competitive return of A to starting material (and B to starting material). Second, the first step may involve deprotonation to E or F fast and reversibly. Ionization of these anions directly to C or D, which constitutes the enantiodiscriminating event, then becomes the rate-limiting event. The net result again becomes one in which the kinetic chiral recognition is reflected in the enantiomeric purity of the product. Of course, both phenomena can be operating synergistically.

This work has significant broader implications for palladium-catalyzed desymmetrization of meso substrates. To the extent that the initial ionization is reversible, a deterioration of the ee will be seen. For maximum chiral recognition, the kinetically preferred π-allylpalladium intermediate must be captured by nucleophile faster than capture by the departed leaving group. These observations also suggest an explanation for the higher enantioselectivity we observed with meso-dibenzoates and meso-dicarbonates compared to meso-diacetates despite being better leaving groups. The poorer nucleophilicity of benzoate or carbonate compared to acetate makes their return less competitive with capture by nucleophile. Consideration of the competition between return of leaving group and capture of nucleophile becomes another factor in maximizing enantiodiscrimination. At the same time, the results imply that this family of ligands exhibits extraordinary levels of molecular recognition in the ionization step with a broad array of leaving groups.

As previously indicated, this simplifies access to these valuable building blocks. For example, many glycosidase inhibitors can derive from these intermediates. We previously demonstrated racemic syntheses of mannostatin and allosamizoline which can now be made completely enantioselective using this chemistry.[5]

(5) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.

Table 2. Experimental Details for Desymmetrization of Meso Biscarbamates

starting material	TosNCO	ligand **1**	dba_3Pd_2/ $CHCl_3$	TEA	THF	product[b]
1c,[a] 60 mg, 0.122 mmol		6.9 mg, 0.01 mmol	3.1 mg, 0.003 mmol	0.017 mL, 0.122 mmol	0.45 mL	**4**, 28.5 mg, 0.102 mmol, 84%, (>99% ee)
1c,[a] 60 mg, 0.122 mmol		6.9 mg, 0.01 mmol	3.1 mg, 0.003 mmol	0.008 mL, 0.06 mmol	0.45 mL	**4**, 27.0 mg, 0.097 mmol, 79%, (>99% ee)
7a, 25 mg, 0.219 mmol	101 mg, 0.513 mmol	12.5 mg, 0.018 mmol	5.7 mg, 0.0055 mmol	0.0305 mL, 0.219 mmol	0.8 mL	**8a**, 54.5 mg, 0.185 mmol, 85%, (99% ee)
7a, 25 mg, 0.219 mmol	101 mg, 0.513 mmol	12.5 mg, 0.018 mmol	5.7 mg, 0.0055 mmol	0.015 mL, 0.109 mmol	0.8 mL	**8a**, 56.3 mg, 0.193 mmol, 88%, (93% ee)
7a, 25 mg, 0.219 mmol	101 mg, 0.513 mmol	12.5 mg, 0.018 mmol	5.7 mg, 0.0055 mmol	none	0.8 mL	**8a**, 58.9 mg, 0.20 mmol, 92%, (85% ee)
7b, 25.6 mg, 0.2 mmol	92.9 mg, 0.468 mmol	11.4 mg, 0.0165 mmol	5.3 mg, 0.005 mmol	0.028 mL, 0.2 mmol	0.7 mL	**8b**, 42.6 mg, 0.14 mmol, 70%, (99% ee)
7b, 25.6 mg, 0.2 mmol	92.9 mg, 0.468 mmol	11.4 mg, 0.0165 mmol	5.3 mg, 0.005 mmol	0.014 mL, 0.1 mmol	0.7 mL	**8b**, 56.3 mg, 0.184 mmol, 92%, (97% ee)
7b, 25.6 mg, 0.2 mmol	92.2 mg, 0.468 mmol	11.4 mg, 0.0165 mmol	5.3 mg, 0.005 mmol	none	0.7 mL	**8b**, 53.5 mg, 0.175 mmol, 87%, (90% ee)
9, 39 mg, 0.219 mmol	101 mg, 0.513 mmol	12.5 mg, 0.018 mmol	5.7 mg, 0.0055 mmol	0.0305 mL, 0.219 mmol	0.8 mL	**10**, 46.8 mg, 0.131 mmol, 60%, (94% ee)
9, 39 mg, 0.219 mmol	101 mg, 0.513 mmol	12.5 mg, 0.018 mmol	5.7 mg, 0.0055 mmol	0.015 mL, 0.109 mmol	0.8 mL	**10**, 69.2 mg, 0.193 mmol, 89%, (89% ee)
9, 39 mg, 0.219 mmol	101 mg, 0.513 mmol	12.5 mg, 0.018 mmol	5.7 mg, 0.0055 mmol	none	0.8 mL	**10**, 51.5 mg, 0.104 mmol, 66%, (81% ee)

[a] In this case, the starting material was preformed bis-urethane. [b] All enantiomeric excesses were determined by chiral HPLC: Chiralpak AD column, 85:15 heptane:2-propanol, 1 mL/min, 254 nm, **4**: (+) 23.22 min, (−) 28.42 min. **8a**: (+) 24.03 min, (−) 30.98 min. **8b**: (−) 26.60 min, (+) 43.72 min. Chiralcel OD column, 85:15 heptane:2-propanol, 1 mL/min, 254 nm, **10**: (−) 12.29 min, (+) 14.51 min.

Experimental Section

General. All reagents were obtained commerically and were used without further purification. All reactions were carried out under an inert atmosphere (N_2) unless otherwise indicated. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Triethylamine was distilled from calcium hydride. Column chromatography was carried out on E. Merck silica gel 60 (60−75 mesh) using the solvent system listed under the individual experiments. All enantiomeric excesses were determined by chiral HPLC on a solid stationary phase Chiralpak AD or Chiralcel OD column using heptane/2-propanol mixtures as eluents. Melting point were taken in open end capillary tubes and are uncorrected.

General Procedure for Oxazolidin-2-one Formation. To a solution of the meso diol (0.2 mmol) in 0.35 mL of THF was added tosyl isocyanate (101 mg, 0.47 mmol). This colorless solution was stirred at room temperature for 15 min and at 60 °C for 30 min. The reaction was allowed to cool to room temperature, and triethylamine (0.028 mL, 0.2 mmol) was added. The resulting white slurry was cooled to 0 °C, and an orange solution of tris(dibenzylidineacetone)dipalladium(0) chloroform complex (5.2 mg, 0.005 mmol) and ligand **1** (11.4 mg, 0.017 mmol) in 0.35 mL of THF was added. The orange reaction solution was stirred at 0 °C for 2 h and at room-temperature overnight. Solvent was removed in vacuo, and column chromatography on silica (15% EtOAc/pet ether) gave the desired product as a white solid. **4**: mp 121−5 °C (lit.[1a] mp 131 °C); $[\alpha]^{25}_D$ 114.8 (c = 2.15, CH_2Cl_2) (lit.[1a] $[\alpha]^{25}_D$ (99% ee) 114 (c = 2.52, CH_2Cl_2)). **8a**: mp 127−9 °C; (99% ee) 95.5 (c = 1.38, CH_2Cl_2), (93% ee) 91.4 (c = 1.85, CH_2Cl_2), (85% ee) 80.0 (c = 1.77, CH_2Cl_2) (lit.[2] $[\alpha]^{25}_D$ (97% ee) 87.5 (c = 2.27, CH_2Cl_2)). **8b**: mp 171−2 °C; $[\alpha]^{25}_D$ (99% ee) 96.6 (c = 3.40, CH_2Cl_2), (97% ee) 94.6 (c = 1.43, CH_2Cl_2), (90% ee) 95.6 (c = 1.37, CH_2Cl_2) (lit.[2] $[\alpha]^{25}_D$ (70.2 (c = 2.68, CH_2Cl_2)). **10**: mp 164−5 °C (lit.[1a] mp 160−1 °C); $[\alpha]^{25}_D$ (94% ee) 62.0 (c = 4.44, CH_2Cl_2), (89% ee) 68.2 (c = 1.77, CH_2Cl_2), (82% ee) 55.1 (c = 4.44, CH_2Cl_2) (lit.[1a] $[\alpha]^{25}_D$ (87%) 69.4° (c = 2.08, CH_2Cl_2)). The details for each of the individual runs are summarized in Table 2.

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