On Asymmetric Induction in Allylic Alkylation via Enantiotopic Facial Discrimination

Barry M. Trost,* Michael J. Krische, Rumen Radinov, and Giuseppe Zanoni

Department of Chemistry, Stanford University Stanford, California 94305

Received February 28, 1996

Metal catalyzed allylic alkylations differentiate themselves from most transition metal catalyzed reactions in that many different phenomena may lead to asymmetric induction.[1−3] One of the lesser explored phenomena involving discrimination in complexing enantiotopic faces followed by ionization to lead to asymmetric induction has not been very successful in Pd-catalyzed processes.[4,5] Scheme 1 outlines some of the issues that complicate such studies. A major obstacle in Pd-catalyzed reactions stems from the propensity of nucleophiles to attack at the sterically more accessible terminal position (path b) which leads to an achiral product.[6] While changing the metal to Mo[7] or W[8] may overcome this issue, the greater scope of Pd-catalyzed reactions makes them the method of choice when possible. Nevertheless, within a limited range of allylic substrates, some promising results with W involving enantiotopic discrimination have been obtained.[9] A second obstacle is the facility of migration of Pd from one enantiotopic face to the other (path c) via a $\eta^3-\eta^1-\eta^3$ mechanism.[1,6a] Indeed, such a phenomenon, if fast relative to nucleophilic attack, can lead to asymmetric induction if the difference in activation energies for path a and ent-path a is sufficiently large in the presence of chiral ligands. In such an event, the nucleophilic addition step determines the asymmetric induction.[10] A third obstacle derives from the fact that the preferred motions with chiral scalemic ligands during the ionization and alkylation steps must be opposite. Thus, if the former is a matched event, the latter must become a mismatched one and vice versa. Such stereochemical mismatching would tend to favor paths b and c competing with path a or ent-path a. We wish to report that asymmetric Pd-catalyzed allylic alkylations, which differentiate enantiotopic faces of the substrate, can be synthetically useful with the modular asymmetric ligands under development in these laboratories.[3]

Scheme 1. Asymmetric Induction via Enantiotopic Facial Discrimination

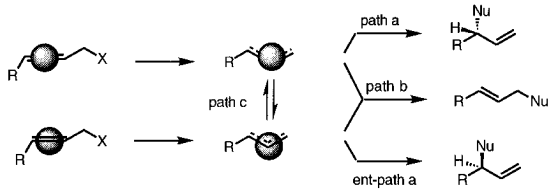
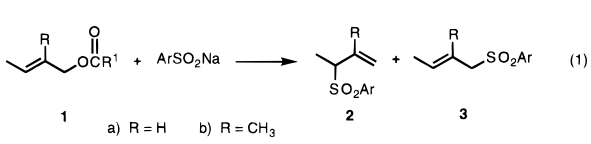


Table 1. Asymmetric Sulfone Formation with Crotyl Carbonate[a]

entry	substrate	ligand	temp (°C)	time (h)	isolated yield	ratio[b] **2**:**3**	%ee **2**[c]	config
1	**E-1a**	**4**	0	1	97%	83:17	90 (92)	***R***
2	**E-1a**	**4**	20	2	91%	76:24	80	***R***
3	**E-1a**	**5**	0	3	84%	70:30	80	***S***
4	**E-1a**	**6**	0	2	92%	69:31	28	***R***
5	**Z-1a**	**4**	0	2	92%	79:21	29	***R***
6	**Z-1a**	**4**	20	0.33	99%	82:18	16	***R***
7[d]	**E-1a**	**4**	0	2	92%	79:21	(92)	***R***

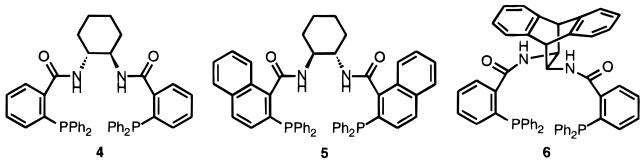
[a] Reaction performed with 0.25 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 0.6 mol % L*, 6% $(n\text{-}C_6H_{13})_4NBr$, 1.5 equiv $PhSO_2Na$, 3:1 CH_2Cl_2:H_2O unless otherwise stated. [b] Determined by GC or HPLC analysis. [c] Determined by chiral HPLC (Chiralpak AD column) using 90:10 heptane−isopropanol as eluting solvent; values in parentheses were determined by NMR spectroscopy with a chiral shift reagent. [d] *p*-Toluenesulfinate rather than benzenesulfinate was employed as the nucleophile.

Our initial efforts focused on the concept of rapidly interconverting π-allyl intermediates thereby requiring chiral recognition in the nucleophilic addition step.[10a] We examined the reaction of eq 1 because prior studies with a tartrate-derived



(1)

bis-phosphine ligand (DIOP) and chiral 2-(2-diphenylphosphino)oxazolines have suggested that such equilibration was rapid.[5,11] Table 1 summarizes the results we obtained for the reaction of crotylmethyl carbonate (**1a**, $R^1 = OCH_3$) using our modular ligands **4**,[3] **5**,[10a] and **6**[2g] under phase transfer conditions



4 **5** **6**

(see footnote *a* of Table 1). The absolute configuration was established by chemical correlation[12] with *S*-2-butylphenyl sulfone and comparison to the literature.[5a]

The reaction with ligand **4** gives the highest ee recorded, 92%. In addition, the regioselectivity favoring **2** improves from 3:1 with other chiral ligands[5a,11] to 5:1 with **4**. However, inspection of the table reveals that it does not arise by rapid equilibration of the π-allyl intermediates with enantiodiscrimination occurring in the subsequent alkylation step. Notably, the racemic regioisomeric substrate 1-buten-3-yl methyl carbonate gives a 94% yield of an 87:13 mixture of **2**:**3** in which **2** is racemic in contrast to the high ee with the achiral **E** substrate. Thus, in contrast to other chiral ligands,[5] the source of the enantiodiscrimination

(1) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* 1996, in press.
(2) For a few examples with the most successful ligands, see: (a) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. (b) Hayashi, T.; Yamamoto, A.; Hagihara, I.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. (d) Springz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (e) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (f) Trost, B. M.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.
(3) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745. Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.
(4) For a creation of axial chirality, see: Legros, J. Y.; Fiaud, J. C. *Tetrahedron* **1994**, *50*, 465. Gil, R.; Fiaud, J. C. *Bull. Soc. Chim. Fr.* **1994**, 584.
(5) Complete or partial equilibration has normally been observed. See: (a) Hiroi, K.; Makino, K. *Chem. Pharm. Bull.* **1988**, *36*, 1744. (b) Hayashi, T.; Kishi, K.; Yamamoto, H.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743. (c) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 669. (d) Hayashi, T.; Ohno, A.; Lu, S.; Matsumoto, Y.; Uozumi, Y.; Miki, M.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 775. (e) Takemoto, T.; Nishikimi, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 3572, 3531. (f) Yamamoto, K.; Deguchi, R.; Ogimura, Y.; Tsuji, J. *Chem. Lett.* **1984**, 1657. (g) Genét, J. P.; Grisone, S. *Tetrahedron Lett.* **1988**, *29*, 4543.
(6) (a) Godleski, S. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford: Vol. 4, Chapter 3.3, pp 585−662. (b) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837.
(7) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469; *Tetrahedron* **1987**, *43*, 4817.
(8) Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176. Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757.
(9) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462.
(10) (a) Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99. (b) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 461. (c) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.
(11) Eichelmann, H.; Gais, H.-J. *Tetrahedron: Asymm.* **1995**, *6*, 643.
(12) cf.: Hiroi, K.; Kitayama, R.; Sato, S. *Chem. Pharm. Bull.* **1984**, *32*, 2628.

S0002-7863(96)00649-X CCC: $12.00

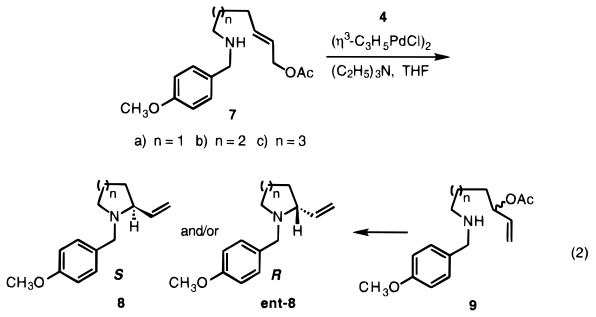
Table 2. Asymmetric Induction in Cyclization to *N*-Heterocycles[a]

entry	substrate	$(\eta^3\text{-}C_3H_5PdCl)_2$ mol %	temp (°C)	time (h)	isolated yield	%ee (er ***S*:*R***)
1	**7a**	5	−25	6	90	80 (90:10)
2	**7a**	5	−50	48	92	81 (90.5:9.5)
3	**7a**	1	−45	2.5	97	91 (95.5:4.5)
4	**7b**	2.5	−30	16	82	88 (94:6)
5	**7c**	1	0	7	(30)[c]	51 (24.5:75.5)
6	**7c**	4	20	1.5	48	41 (29.5:70.5)
7	**9a**	2.5	−78	16	70	4 (48:52)
8	**9b**	5	−50	16	83	6 (53:47)
9	**9c**	1	−35 to 0	2.5	84	92 (96:4)

[a] All reactions were performed with a ligand to $(\eta^3\text{-}C_3H_5PdCl)_2$ ratio of 2.5−3 in THF. [b] Determined by HPLC using a Chiralcel OD column using 99.5:0.5 heptane−isopropanol containing 0.1% diethylamine as eluting solvent. [c] Percent conversion determined by GC.

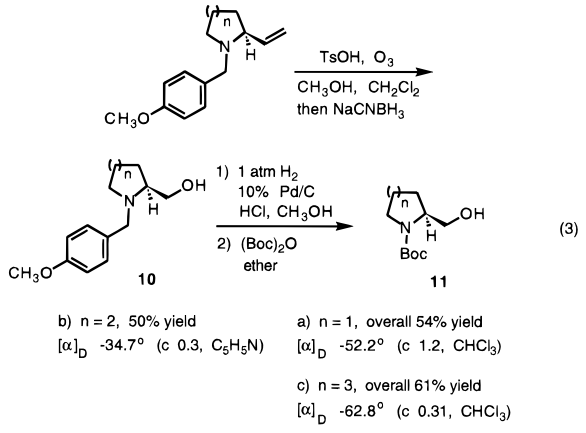
occurs in the alkene complexation, the first example of such chiral recognition with this family of ligands. Similar results were obtained using tiglyl methyl carbonate **1b** whereby **2b** of 94% ee was obtained.

Attempts to extend this asymmetric induction to amine nucleophiles were thwarted by an unfavorable regioselectivity. Resolution of this problem lay in tethering the nucleophile. Alkylation in the presence of the chiral scalemic ligand **4** only gives internal alkylation regardless of the tether length for n = 1, 2, or 3 (see eq 2 and Table 2). The enantioselectivities were



(2)

established by chiral stationary phase HPLC. The absolute configurations were determined as shown in eq 3, all of which



(3)

were synthesized independently as either *S* or *R* enantiomers from commercially available *S* or *R* amino acids.[13]

Several aspects revealed by the data are quite interesting. For the five- and seven-membered rings, lowering the amount of palladium precursor had a more beneficial effect on ee (entries 2 and 3) than lowering temperature (entries 1 and 2). For five- and six-membered ring formation, the achiral substrates **7a** and **7b** gave good enantioselectivities with the *R*,*R*-ligand **4** giving the (*S*)-2-vinylpyrrolidine and piperidine, respectively. On the other hand, starting with the chiral racemic precursors **9a** and **9b**, only low enantioselectivities have been observed. These results are quite consistent with the enantioselectivity being determined by asymmetric recognition in the complexation step.

A completely different picture emerges in going from the six- to seven-membered ring substrate. With the achiral substrate **7c**, the reaction was very slow, gave low yields even at ambient temperature, and gave a maximum ee of 51% (entry 5). Furthermore, the major enantiomer produced was *R* (ent-**8c**). On the other hand, the reaction using the chiral racemic precursor **9c** (entry 9) went to completion with 1% catalyst between −35 and 0 °C in 2.5 h to give both high yield and high ee of the *S* enantiomer **8c**. This remarkable behavior of **7c** and **9c** in contrast to the other ring sizes can be rationalized by the notion of the need to dock the substrate in a chiral pocket.[14] Such a pocket should have steric constraints wherein a limit will be reached as to what can sterically be accommodated. Apparently that limit is reached between **7b** and **7c**. On the other hand, fitting the regioisomeric starting material **9c** into the pocket orients the sterically bulky portion of the molecule toward a less sterically demanding region thereby permitting more facile ionization, although not as rapidly as either **7a** or **7b**. The high enantioconvergency observed with the racemic substrate requires that pseudoracemization (i.e., a mechanistic pathway which would constitute racemization in the presence of achiral ligands) be faster than cyclization. Apparently, the slower rate of formation of a seven-membered ring compared to a five- or six-membered ring allows the equilibration to dominate. Interestingly, the formation of the same enantiomeric product with high ee for **7a**, **7b**, and **9c** means that the sense of chiral recognition for the two mechanisms for enantiodiscrimination must be the same. Thus, the product determining intermediate is the kinetically accessible one from **7a** and **7b** (but not **7c**) but becomes accessible only by thermodynamic equilibration from **9c** (but not **9a** nor **9b**).

The results reported herein demonstrate the utility of enantiofacial discrimination for asymmetric induction in Pd-catalyzed reactions. The intramolecular version would have particular utility in order to control unambiguously the regioselectivity of the process, a phenomenon that may result from both the effect of the ligand and the nature of the nucleophile. Combining the concept of a cleavable tether with the current reaction should extend the utility of this asymmetric process to noncyclic products. Choice of regioisomeric substrate may be important. A delicate balance can exist between enantiodiscrimination by complexation in the ionization event and by alkylation of rapidly equilibrating diastereomeric intermediates as a function of steric bulk of the substrate and ring size. By properly choosing the mechanism for chiral recognition, high ee can be achieved in formation of five-, six-, and seven-membered heterocyclic rings in which the stereochemistry of the product is dictated by the "chiral space" regardless of the mechanism. The products obtained herein are useful building blocks as in a synthesis of indolizidines and quinolizidines[13b,15] and in ring expansions to medium-sized rings.[16]

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were generously provided by the Mass Spectrometry Facility, University of California-San Francisco, supported by the NIH Division of Research Resources. Palladium salts were loaned by Johnson Matthey Alfa Aesar.

Supporting Information Available: Characterization data for **2a** (R = H, Ar = Ph), **2b** (R = CH_3, Ar = Ph), **8a** (n = 1), **8b** (n = 2), and **8c** (n = 3) and typical experimental procedures for an inter- and intramolecular reaction (3 pages). Ordering information is given on any current masthead page.

JA960649X

(13) (a) Cf., for 5 ring: Pettit, G. R.; Singh, S. B.; Herald, D. L.; Lloyd-Williams, P.; Kantoci, D.; Burkett, D. D.; Barkóczy, J.; Hogan, F.; Wardlaw, T. R. *J. Org. Chem.* **1994**, *59*, 6287. For 6 ring and 7 ring: Pauly, R.; Sasaki, N. A.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 237. (b) For racemic **8**, n = 1 and 2, see: Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6690.

(14) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817.

(15) Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W. H. *J. Org. Chem.* **1991**, *56*, 2775.

(16) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *J. Org. Chem.* **1978**, *43*, 1185. Vedejs, E.; Arco, M. S.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831.