Asymmetric Induction in Allylic Alkylations of 3-(Acyloxy)cycloalkenes

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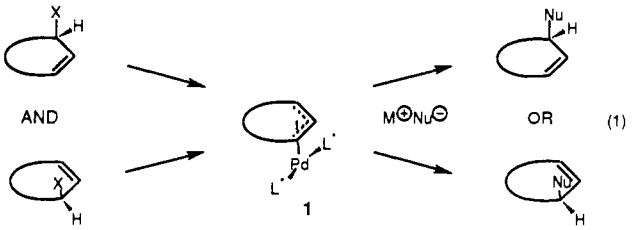
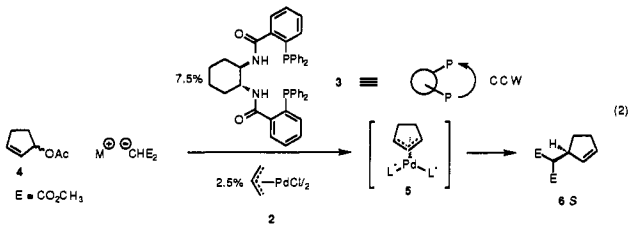
While great strides in asymmetric induction have been made in many types of transition metal catalyzed reactions exemplified by hydrogenation,[1] epoxidation,[2] dihydroxylation,[3] cyclopropanation,[4] and aziridination,[5] progress in allylic alkylations with stabilized nucleophiles has been sporadic.[6-11] The reason stems from the nature of the processes. Whereas in all of the areas first mentioned bond formation occurs within the coordination sphere of the metal and therefore within the asymmetric environment created by the chiral fragments, in allylic alkylation the crucial bond-making (or bond-breaking) event occurs on the face of the allyl fragment distal to the metal and therefore remote from the asymmetric environment created by the chiral ligands. Furthermore, for the case in which asymmetric induction involves nucleophilic attack on a prochiral (π-allyl)palladium intermediate **1** as the enantiodiscriminating step as illustrated in eq 1, the nature of the nucleophile may have a profound effect. Early



(1)

work in our laboratories established that excellent enantioselectivity was possible with 1,3-diphenylallyl acetate[7] (L* = BINAP, 92% ee, 73% yield at 60 °C with acetylacetone and BSA as base[12]). Replacing the phenyl groups by sterically less demanding substituents decreased the enantioselectivity. Other ligands, most notably the oxazolines derived from 2-(diphenylphosphino)benzoic acid, showed similar trends with superb enantioselectivity for the "standard" diphenyl substrate.[11] Nevertheless, the maximum enantioselectivity recorded for a cyclic substrate is ~70%.[7c,9b] In this communication, we report the critical role the nature of the ion pair as nucleophile plays in determining the enantioselectivity in allylic alkylations and the first examples of excellent enantioselectivities with 3-(acyloxy)cycloalkenes.

We employed the reaction of racemic 3-acetoxycyclopentene (**4**) with the anion of dimethyl malonate as our test. Utilizing our recently developed chiral ligand **3**[13] and extrapolating our mnemonic for determining the sense of chirality (vide infra), we predict that **6***S* should be the product. Our observations were



(2)

both gratifying and disappointing. Using the sodium salt of malonic ester in THF at 0 °C gave the predicted enantiomer but only in 38% ee. The sense of chirality was established by hydrolysis and decarboxylation to the known 3-cyclopentenylacetic acid.[14] The % ee was established by a combination of ^{1}H NMR shift experiments and this correlation.

The limited solubility of the sodium salt of dimethyl malonate led to the use of tetraalkylammonium salts. As the data in Table 1 shows, such salts had a dramatic effect, with the ee increasing with increasing size of the alkyl group and reaching a maximum of approximately 70% using tetra-*n*-hexylammonium bromide (THAB). Upon decreasing the amount of dimethyl malonate and sodium hydride to nearly stoichiometric quantities, the ee varied from 68% to 86%. This variability was removed by adding the solution of the nucleophile to that of the allylic acetate over a 1-h period, an operation which increased the ee to 82% (Table 1, entry 5). Since all of these salts should exist as ion pairs in THF, these results support a strong dependence of the ee on the nature of the ion pair of the attacking nucleophile.[15] The recent independent work of Reetz, Hütte, and Goddard showing that the tetra-*n*-butylammonium salt of dimethyl ethylmalonate exists not only as an ion pair but also as a dimer even in DMSO provides strong support for our conclusion.[16] Since the nature of the ion pair should vary with solvent, we examined an even poorer cation-solvating solvent, methylene chloride. *In this case, the ee jumped to 98%!*

With conditions established to give excellent ee's, we explored the effect of ring size. The lower reactivity of the larger rings led to using the better leaving-group ability of the methyl carbonate

(1) Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 3.2.
(2) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, Chapter 3.2.
(3) Crispino, G. A.; Jeong, K .S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785 and earlier references cited therein.
(4) For some recent examples, see: Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
(5) For a recent example, see: Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
(6) For reviews, see: Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, Chapter 3.3. Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257. Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.
(7) (a) Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200. (b) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649. (c) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(8) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron Lett.* **1990**, *31*, 5049; *Tetrahedron: Asymmetry* **1991**, *2*, 663.
(9) (a) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7 and references cited therein. (b) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191.
(10) Luetenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.
(11) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
(12) Singleton, D. A. Unpublished observations in these laboratories, 1985–1987.
(13) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(14) Mislow, K.; Steinberg, I. V. *J. Am. Chem. Soc.* **1955**, *77*, 3807.
(15) For recent overviews, see: Willard, P. G. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 1–48. Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 1–64. Also, see: Arnett, E. M.; Harrelson, J. A. *Gazz. Chim. Ital.* **1987**, *117*, 237. Ellington, J. C., Jr.; Arnett, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 7778.
(16) Reetz, M. T.; Hütte, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339.

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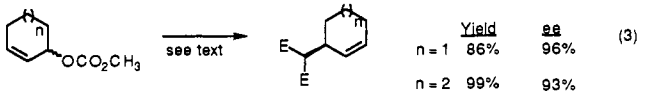
Table 1. Dependence of Enantiomeric Excess on Ion Pair[a]

entry	added salt	solvent	$[\alpha]_D$, deg	% ee	% yield
1	none	THF	−28.0	38	77
2	$(CH_3)_4NCl$	THF	−29.9	41	88
3	$(n\text{-}C_4H_9)_4NCl$	THF	−41.7	57	74
4	$(n\text{-}C_6H_{13})_4NBr$ (THAB)	THF	−49.8	68	92
5[b]	$(n\text{-}C_6H_{13})_4NBr$ (THAB)	THF	−59.7	82	73
6	$(n\text{-}C_8H_{17})_4NBr$	THF	−48.0	66	74
7	Adogen 464	THF	−43.8	59	59
8[b]	*$(n\text{-}C_6H_{13})_4NBr$*	*CH_2Cl_2*	*−71.7*	*98*	*81*

[a] All reactions were run at 0 °C; isolated yields have not been optimized. [b] A solution of the nucleophile generated from dimethyl malonate, sodium hydride, and tetra-*n*-hexylammonium bromide (THAB) was added over 1 h to the reaction mixture containing palladium complex **2**, ligand **3**, and allylic acetate **4**. In all other cases, this solution of nucleophile was added all at once.

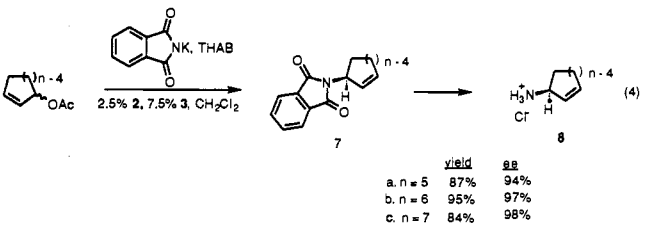
and to performing the alkylations at room temperature. As shown in eq 3, excellent results were obtained independent of ring size.



(3)

In the case of the six-membered-ring substrate, the same result was obtained whether the nucleophile was added over 1 h or all at once. The results cited in eq 3 involve addition all at once. The seven-membered ring behaved similarly to the five-membered ring in that slow addition of the nucleophile was required to achieve the best ee.

Replacing the anion of malonate with that of phthalimide as nucleophile under otherwise analogous reaction conditions except that slow addition of the nucleophile was unnecessary also gave excellent results as outlined in eq 4. The insolubility of potassium

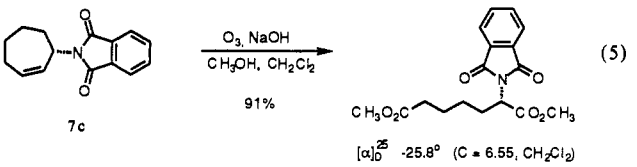


(4)

phthalimide required a short initial period of sonication in the presence of THAB to facilitate reaction. Standard removal of the phthalic acid moiety (NH_2NH_2, C_2H_5OH, reflux, followed by 6 N aqueous HCl at reflux)[17] gave the known amines **8a–c**,[18] thereby establishing the absolute configuration as *S* as depicted. NMR methods were employed to establish the % ee.

The results herein dramatically illustrate the surprising importance of the counterion of the nucleophile in allylic alkylations with tetrahexylammonium giving the optimum results to date. Given this cation, excellent enantioselectivities (93–98%) have been routinely obtained with both a carbon and a nitrogen nucleophile and with varying ring sizes to a degree not previously achieved. The absolute stereochemistry is independent of both the nucleophile and the ring size. Adopting the mnemonic we established for asymmetric induction in allylic alkylations with our modular ligands for desymmetrization of ene dicarboxylates[13] to the current case allows prediction of absolute stereochemistry in which a counterclockwise or "*S*" type ligand as **3** (see eq 2) induces attack at the *pro-S* terminus.[19]

The utility of the products that result makes their availability in high enantiomeric purity of special significance. Juxtaposition of the functionality allows easy regio- and diastereoselectivity in further elaborations. Access to either enantiomer of the alkylation product **6** constitutes asymmetric syntheses of a wide range of biologically important compounds represented by the leprostatic agent chaulmoogric acid,[14] the antimycobacterial agent hydnocarpic acid,[20] the sedative cyclopentobarbital,[21] and synthetic insect pheromones of the European corn borer and the red banded leaf roller.[22] The reported inability to obtain one of the enantiomeric series by resolution[22] highlights the importance of this catalytic method which gives equivalent access to either enantiomeric series. The allylic amines serve as convenient precursors to amino acids, natural and unnatural.[23] For example, dipeptides of (*S*)-2-aminopimelic acid, a protected form of the latter available by ozonolysis of **7c** (eq 5),[24] have shown antibiotic activity against Gram-negative bacteria by inhibiting the biosynthesis of an essential component of the bacterial cell wall peptidoglycan.[24b]



(5)

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Supplementary Material Available: Typical experimental procedures for asymmetric alkylation and characterization data for alkylation products (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) Ing, H. R.; Manske, R. F. H. *J. Am. Chem. Soc.* **1926**, 2348.
(18) Braun, H.; Felber, H.; Kresse, G.; Ritter, A.; Schmidtchen, F. P.; Schneider, A. *Tetrahedron* **1991**, *47*, 3313.
(19) Because of the effect of substituents on priorities as given by the Cahn–Ingold–Prelog rules, this latter mnemonic must be utilized cautiously with substrates whose designation as *S* or *R* would differ from the designation of the unsubstituted ring system as the result of substitution.
(20) Diaper, D. G. M.; Smith, J. C. *Biochem. J.* **1948**, *42*, 581. Bokil, K. V.; Nargund, K. S. *Proc.—Indian Acad. Sci., Sect. A* **1941**, *13*, 233. For biological activity, see: Jacobsen, P. L.; Ng, H.; Levy, L. *Am. Rev. Respir. Dis.* **1973**, 1022. Jacobsen, P. L.; Levy, L. *Antimicrob. Agents Chemother.* **1973**, *3*, 373.
(21) Centolella, A. P.; Nelson, J. W.; Kolloff, H. G. *J. Am. Chem. Soc.* **1943**, *65*, 2091.
(22) Chapman, O. L.; Mattes, K. C.; Sheridan, R. S.; Klun, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 4878.
(23) Marshall, J. A.; Garafalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675. Jumnah, R.; Williams, J. M. J.; Williams A. C. *Tetrahedron Lett.* **1993**, *34*, 6619.
(24) (a) For a previous synthesis, see: Barton, D. H. R.; Herve, Y.; Potier, P.; Thierry, J. *Tetrahedron Lett.* **1987**, *43*, 4297. (b) Berges, P. A.; DeWolf, W. E., Jr.; Dunn, G. L.; Grappel, S. F.; Newman, D. J.; Taggart, J. J.; Gilvarg, C. *J. Med. Chem.* **1986**, *29*, 89.