Palladium-Catalyzed Asymmetric Alkylation of Ketone Enolates

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Received April 12, 1999

The asymmetric alkylation of ketone enolates to generate quaternary centers has been the subject of investigation in recent years.[1] Initial attempts took advantage of stoichiometric chiral auxiliaries or self-replicating chirality to induce asymmetry.[2] The alkylation of enolates using catalytic amounts of a chirality inducing agent has proven more difficult; however, recent advances have been made in this area.[3,4] We[5] and others[6] have been interested in developing the palladium-catalyzed asymmetric allylic alkylation (AAA reaction) of prochiral nucleophiles.[7] In order for chiral ligands to effect stereochemical control in this reaction, they must influence bond making and bond breaking events occurring outside the coordination sphere of the metal; thus, they must transmit their stereochemical information through space. Discrimination of enantiotopic faces of the nucleophile is especially difficult as the nucleophile is segregated from the chiral environment by the π-allyl moiety. The success with stabilized nucleophiles such as β-ketoesters[5] emboldened us to inquire whether simple ketone enolates, perhaps the most important class of nucleophiles, would function, let alone give good enantioselectivity. Nonstabilized enolates have generally proven to be unsatisfactory in palladium-catalyzed allylic alkylations although some success has been achieved with their tin[8] and boron[9] derivatives. With the family of chiral ligands being developed in these laboratories, the presence of the secondary amides would seem to limit the operable pH range. Due to increased basicity of simple enolates, will the nucleophile deprotonate the amide hydrogens on the ligand? If so, will the reaction still proceed and with what ee? Herein we wish to report the successful application of the palladium-catalyzed AAA reaction to nonstabilized ketone enolates.

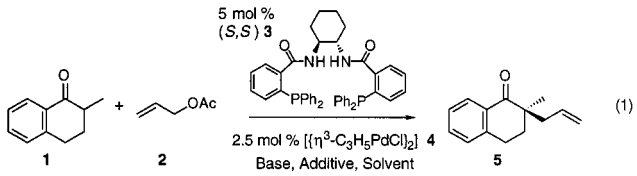
Initial studies examined the reaction of 2-methyl-1-tetralone (**1**) with allyl acetate (**2**) using chiral ligand **3** and palladium complex **4** (eq 1). Gratifyingly, formation of the tin derivative by in situ treatment of the lithium enolate with tri-*n*-butyltin chloride led to alkylated product **5a** in 53% yield and 63% ee.

Table 1. Selected Optimization Studies[a]

entry	base (eq no.)	additive[b]	time (h)	% yield[c]	% ee[d]
1	LDA (1)	$(C_4H_9)_3SnOSO_2CF_3$	3	21	32
2	LDA (1)	$(C_4H_9)_3SnCl$	2	53	65
3	LDA (1)	$(CH_3)_3SnCl$	3	65	69
4	LDA (1.25)	$(CH_3)_3SnCl$	2.5	78	78
5	LDA (1.5)	$(CH_3)_3SnCl$	2.5	99	80
6	LDA (2)	$(CH_3)_3SnCl$	0.5	99	88
7	LDA (3)	$(CH_3)_3SnCl$	1.75	61	84
8	LiHMDS (2)	$(CH_3)_3SnCl$	2	94	71
9	LiTMP (2)	$(CH_3)_3SnCl$	0.5	99	86
10	LDA (2)	none	1	96	85

[a] All reactions were performed in DME (0.15 M in nucleophile) at room temperature using 1.1 equiv of allyl acetate using the catalyst system of eq 1. [b] Use of 1.0 equiv of the additive. [c] Isolated yields. [d] The ee was determined by chiral HPLC using a Chiracel OD column with 99.9:0.1 heptane/2-propanol, t_R = 17.95 (*R*), 19.14 (*S*) min.

The reaction was optimized by varying the solvent, base, and the addition of various Lewis acids. The choice of solvent had a



(1)

moderate effect on the yield and enantioselectivity of the reaction. DME, THF, methylene chloride, toluene, dioxane, and 10% HMPA/THF were all examined with DME giving the best results. The effect of solvent on the state of aggregation of the enolate may be the source of this selectivity.

The presence of additives and choice of base conditions had a much more significant effect. A variety of Lewis acids were screened and, in general, stannanes gave far superior results than did boranes and borates. The yield and enantioselectivity of the reaction was found to correlate with the leaving group ability on the tin (Table 1, entry 1 vs 2). Lewis acids with poor leaving groups gave better results than those with good leaving groups. This suggests that an ate complex rather than a simple trialkylstannyl ether may be the nucleophile. Also, the size of the Lewis acid and the enantioselectivity correlated as smaller Lewis acids gave higher yields and slightly higher ee's than did more sterically demanding Lewis acids (entry 2 vs 3). Given these observations, trimethyltin chloride became the Lewis acid of choice.

The choice of base had a dramatic effect on the reaction. Only lithium bases gave the desired reaction whereas sodium and potassium bases gave recovery of the starting material. The reaction was found to be dependent on the amount of base used in the reaction with 2 equiv of base giving the best results (entries 3−7). Changing the amide to hexamethyldisilazide (entry 8) decreased the ee but changing to the piperidide (entry 9) had little effect. To summarize, the optimum reaction conditions were found to consist of using DME as the solvent, 2 equiv of LDA as the base, and trimethyltin chloride as the Lewis acid. With these conditions, the allylated product **5a** could be isolated in 99% yield and 88% ee. It should be noted that the use of tin is not absolutely necessary as the reaction could be performed in the absence of any Lewis acid (entry 10). Thus, upon generation of the lithium enolate of **1** with 2 equiv of LDA, **5a** could be obtained in 96% yield and in slightly lower ee (85%). A similar observation occurred in the alkylations of 2-ethyltetralone in the presence (vide infra) or absence of tin. While the lowering of the ee, in the absence of tin, was small in both cases, it was very reproducible. As a result, we chose to include the tin in our general protocol. These results emphasize the robust nature of the catalyst as the

(1) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1998**, 388. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(2) J. Seyden-Penne *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

(3) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

(4) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476. Conn, R. S. E.; Lowell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710. Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *104*, 446. Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745.

(5) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879.

(6) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113.

(7) For reviews of the palladium-catalyzed allylic alkylation reaction, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975. Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. Fiaud, J. C. In *Metal-Promoted Selectivity in Organic Synthesis*; Graziani, M., Hubert, A. J., Noels, A. F., Eds.; Kluwer Academic Publishers: Dordrecht, 1991. Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

(8) Trost, B. M.; Self, C. R. *J. Org. Chem.* **1984**, *49*, 468. Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591.

(9) Negishi, E.-I.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188.

10.1021/ja991135b CCC: $18.00
Published on Web 07/02/1999

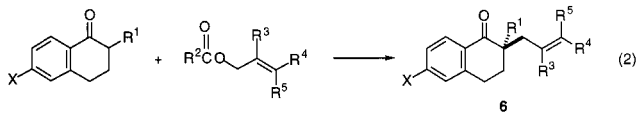
Table 2. AAA Reaction of 1-Tetralones[a]

entry	R^1	R^2	R^3	R^4	R^5	X	time (h)	product, yield	% ee[d]
1	CH_3	CH_3	H	H	H	H	0.5	**5**, 99%	88%
2	CH_3	CH_3	H	H	H	OCH_3	1	**6a**, 83%	85%
3	CH_2CH_3	CH_3	H	H	H	H	0.5	**6b**, 96%	80%
4	CH_2Ph	CH_3	H	H	H	H	1	**6c**, 71%	85%
5	CH_3	OCH_3	H	CH_3	H	H	3	**6d**,[d] 84%	90%
6	CH_3	OCH_3	H	H	$TBDMSO(CH_2)_2$	H	5	**6e**,[d] 72%	82%
7	CH_3	OCH_3	CH_3	H	H	H	4	**6f**, 82%	47%
8	$CH_2CH{=}CH_2$	OCH_3	H	CH_3	H	H	4	**6g**,[d] 71%	85%

[a] All reactions were performed in DME (0.15 M in nucleophile) at room temperature using 1.1 equivalents of electrophile, 2 equivalent of LDA, and 1 equivalent of $(CH_3)_3SnCl$. [b] Isolated yields. [c] The ee was determined by chiral hplc. [d] The alkene geometry in the product was *E*.

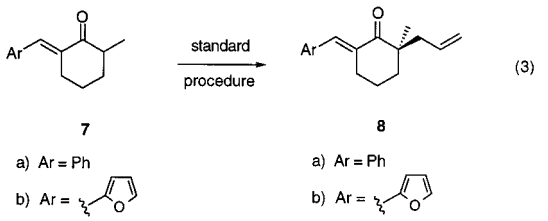
reaction proceeds even in the presence of a second equivalent of LDA. The absolute configuration of **5**, generated with the *S,S* ligand, has been established as *R* using the *O*-methylmandelate esters of an alcohol derivative.[10] No asymmetric alkylation occurs in the absence of palladium.

Using the optimized conditions, we explored a range of tetralones and allylating agents as summarized in eq 2 and Table 2.

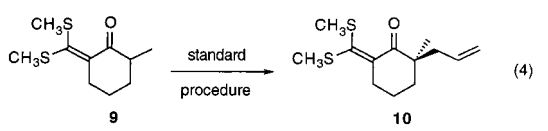


The reaction shows little sensitivity to the substituent in the 2-position since methyl (entries 1, 2, 5−7), ethyl (entry 3), allyl (entry 8), and benzyl (entry 4) all gave comparable results. Linearly substituted allyl systems starting from either *E* (entries 5 and 8) or *Z* (entry 6) isomers gave products of only *E* geometry with good ee. On the other hand, a branched allyl system (entry 7) gave good yields but lower ee's. Changing ring sizes to either indanone or benzosuberone also led to alkylations with rather low ee's.

Other cyclohexanones participate equally well in these alkylations. The benzylidene[11] **7a** gave the allylated product **8a**[12] nearly quantitatively (98% yield of 82% ee (eq 3). In the case of



the furanylidene derivative **7b**,[13] we explored a temperature effect. At room temperature (normal optimized conditions) the product was produced in 79% ee (89% yield), whereas at 0 °C the enantioselectivity increased to 92% (95% yield). A similar effect was observed with the ketene thioacetal derivative **9**[14] (eq 4). In



this case, the reaction at room temperature gave **10** of 70% ee (64% yield) which increased to 82% ee (67% yield) at −10 °C.[15]

The allylated products generated in this reaction are versatile substrates for further transformations. For example, 1,3-carbonyl

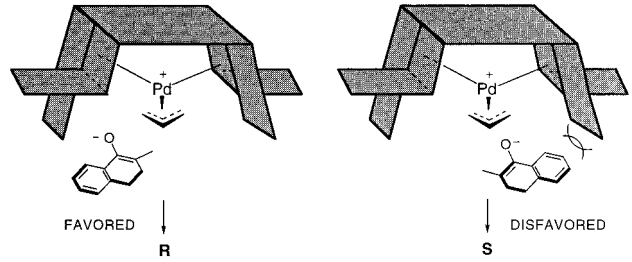
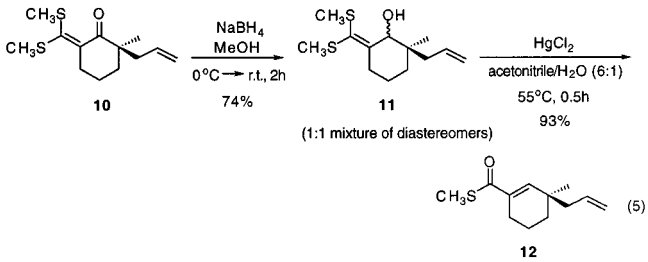


Figure 1. Rational for chiral recognition.

transposition[16] of keto ketene dithioacetal **10** gives α,β-unsaturated thiol ester **12**, a useful substrate for annulation protocols (eq 5).[17]



These results indicate that allylations of simple ketone enolates of six-membered rings can now be achieved asymmetrically in a catalytic fashion. The importance of the cations associated with the enolate is illustrated by their effect (on both reactivity and ee). This strongly suggests that the actual structure of the nucleophile is not simple and likely an aggregate. Quaternary centers are being formed with a high degree of absolute stereochemical control. The mnemonic that we developed depicted in Figure 1 provides a rationale for the observed stereochemistry. The success of less stabilized nucleophiles such as simple enolates provides impetus for exploring a much broader range of nucleophiles. The compatibility of the types of ligands employed herein, which contain secondary amides, to such strong bases raises questions about whether these amides are deprotonated under the reaction conditions. The allylated products available by this method are quite versatile for further elaboration including annulation protocols.[18]

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences for the generous support of our programs. G.M.S. is supported by a NSF Predoctoral Fellowship. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California−San Francisco supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991135B

(10) This assignment required hydroboration−oxidation of the alkene and ketone reduction to produce diastereomeric diols whose relative and absolute stereochemistry were established by NMR methods. Details appear in the Supporting Information.

(11) Johnson, W. S. *J. Am. Chem. Soc.* **1943**, *65*, 1317.

(12) Cornubert, C. *Ann. Chim. (Paris)* **1921**, *16*, 172.

(13) Islam, A. M.; Zemaity, M. T. *J. Am. Chem. Soc.* **1957**, *79*, 6023.

(14) Dieter, R. K. *J. Org. Chem.* **1981**, *46*, 5031.

(15) Two equivalents of allyl acetate were used in the experiment performed at −10 °C.

(16) Dieter, R. K.; Lin, Y. J.; Dieter, J. W. *J. Org. Chem.* **1984**, *49*, 3183. Trost, B. M.; Stanton, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 4018.

(17) Aggarwal, V. K.; Thomas, A.; Schade, S. *Tetrahedron* **1997**, *53*, 16213.

(18) After submission of this manuscript, the report of the alkylation of the lithium enolate of 2-substituted tetralones generated from enol silyl ethers using chiral amine inducers appeared, see: Yamashita, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1999**, *40*, 2803.