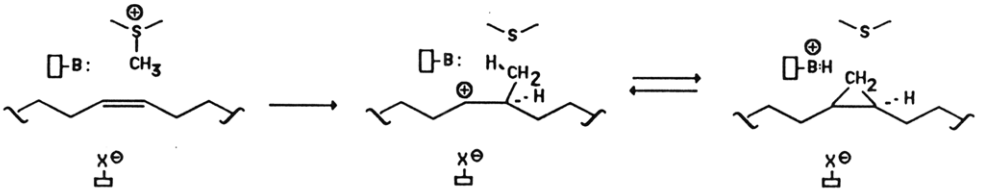
Scheme I



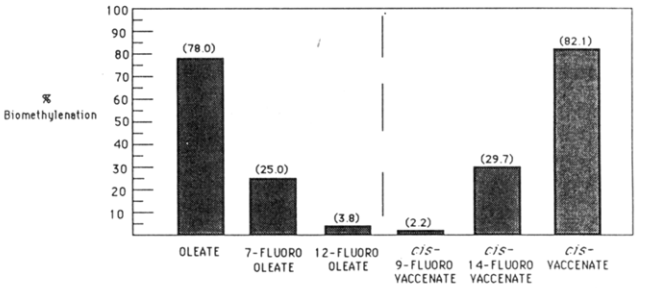


Figure 1. Percent biomethylenation of fluorinated olefinic fatty acids as a function of double bond position. The cyclopropyl product was identified in each case by comparison of its GC capillary retention time and MS (obtained by GC/MS) with authentic synthetic standards as previously described.[5]

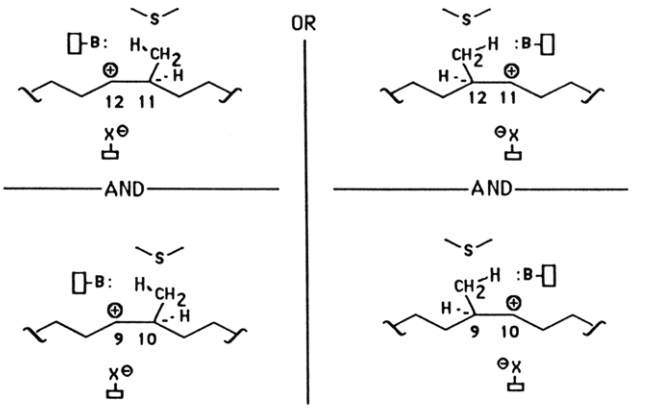


Figure 2. Relationship between the possible carbocationic intermediates derived from methylation of *cis*-9-octadecenoic acid and *cis*-11-octadecenoic acid.

methylating agent as shown in Figure 2.[7] Thus if the carbocation is generated at carbon 12 during methylation of vaccenic acid, then the carbocation must be formed at carbon 9 during methylation of oleic acid. Alternatively, if the carbocation is generated at carbon 11 during methylation of vaccenic acid, then it must be formed at carbon 10 during methylation of oleic acid. At this time we cannot distinguish between these two alternatives since we do not know precisely at what point(s) in the catalytic cycle the fluorine substituent effect is acting. The situation is complicated by the fact that we and others have produced evidence that the deprotonation step may be reversible.[8,9]

Our probe for the regiochemistry of carbocation formation has borne an important stereochemical consequence: namely that the absolute configurations of the cyclopropyl products derived from our fluorinated *cis*-vaccenates and oleates should turn out to be opposite in sense. We are currently preparing these fluorinated compounds in enantiomerically pure form in order to address this intriguing question. An important clue has already been obtained in collaboration with D. Arigoni and coworkers who have determined that the absolute configuration of the cyclopropyl product produced by *L. plantarum* from **1** is 11*R*,12*S*, while the absolute configuration of the cyclopropyl product biosynthesized from **2** by the same bacterium is 9*S*,10*R*.[10] These findings rule out any mode of binding in which the same olefinic face of the two positional isomers is engaged.

In conclusion, we would like to point out that what began as a mechanistic study has serendipitously led us to raise an entirely unexpected issue: namely can a single enzyme or enzymic active site handle both positional isomers or are two isozymes involved? We anticipate being able to solve this problem using appropriate competition experiments with our fluorinated substrates. Should it turn out that a single active site is involved, important questions of fatty acid conformation will have been raised.

Acknowledgment. The financial support of NSERC and Carleton University is gratefully acknowledged. Gabe Leger and Judy Findlay were of invaluable assistance. We wish to thank Professor D. Arigoni (ETH, Zürich) for catalytic discussions.

(7) We wish to thank Professor D. Arigoni (ETH, Zürich) for helpful discussions on this point.
(8) Buist, P. H.; Maclean D. B. *Can. J. Chem.* **1982**, *60*, 371.
(9) Arigoni, D. *Chimia* **1987**, *41*, 9.
(10) Manuscript in preparation.

Enantioselective Route to γ-Butyrolactones: Chiral Auxiliary Mediated Amide Alkylation and Iodolactonization

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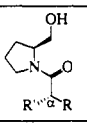
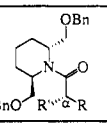
Summary: A number of chiral, γ,δ-unsaturated amides (**1** and **2**) have been prepared and their subsequent alkylation and iodolactonization to γ-butyrolactones (**3**) investigated.

Earlier work in our laboratories has established that resident stereochemistry can profoundly influence the course of electrophilic cyclization reactions. For example, *d,l*-3,5-dimethylhepta-1,6-diene-4-carboxylic acid cyclizes[2]

(1) Recipient of an Alfred P. Sloan Research Fellowship, 1987–1991, and an NIH Research Career Development Award (ES00182), 1989–1994.
(2) Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844.

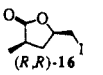
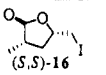
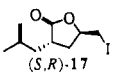
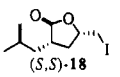
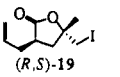
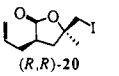
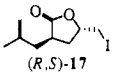
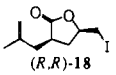
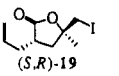
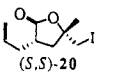
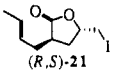
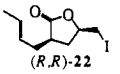
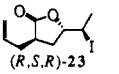
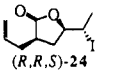
0022-3263/90/1955-6241$02.50/0

Table I. Cα-Alkylation of (*S*)-(+)-2-Pyrrolidinemethanol and (2*R*,6*R*)-(+)-2,6-Bis((benzyloxy)methyl)piperidine Derived Amides

AUX-C(O)-CH$_2$R	R′X		
R = CH_3	CH_2=$CHCH_2Br$	81:19 (**4**)	94:6 (**9**)
R = CH_2CH=CH_2	CH_3I	73:27 (**5**)	>99:<1 (**10**)
R = CH_2CH=CH_2	CH_2=$C(CH_3)CH_2Cl$	75:25 (**6**)	>99:<1 (**11**)
R = $CH_2C(CH_3)$=CH_2	CH_2=$CHCH_2Br$	75:25 (**7**)	99:1 (**12**)
R = (*E*)-CH_2CH=$CHCH_3$	CH_2=$CHCH_2Br$	82:18 (**8**)	95:5 (**13**)
R = CH_2CH=CH_2	(*E*)-CH_3CH=$CHCH_2Br$	-	(**14**)[d]

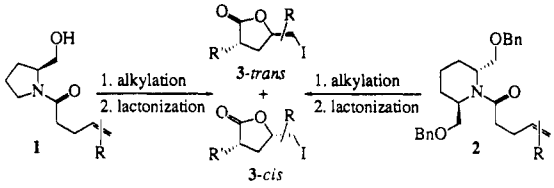
[a] The major product in each alkylation is the diastereomer depicted with the minor product being epimeric at Cα. The number in parentheses is the compound number. [b] Diastereomer product ratios were determined by integration of diastereomeric signals in the 300-MHz ^{1}H NMR. [c] Diastereomer product ratios were determined by analytical HPLC (25 cm SiO_2 column, hexane–EtOAc 95:5, 1 mL/min). [d] A complex, inseparable mixture of S_N2 and S_N2' alkylation products was obtained.

Table II. Enantioselective Iodolactonization of (*S*)-(+)-2-Pyrrolidinemethanol and (2*R*,6*R*)-(+)-2,6-Bis((benzyloxy)methyl)piperidine Derived Amides

entry	cyclization method[a]	amide	 (*R*,*S*)-**15**	 (*S*,*R*)-**15**	 (*R*,*R*)-**16**	 (*S*,*S*)-**16**
i	A	4	75	17	6	2
ii	A	5	24	68	3	5
iii	B	9	79	11	8	2
iv	B	10	11	83	1	5
			 (*S*,*R*)-**17**	 (*S*,*S*)-**18**	 (*R*,*S*)-**19**	 (*R*,*R*)-**20**
v	A	6	49	4	27	20
vi	B	11	49	1	23	27
			 (*R*,*S*)-**17**	 (*R*,*R*)-**18**	 (*S*,*R*)-**19**	 (*S*,*S*)-**20**
vii	C	7	40	2	36	22
viii	B	12	4	0	38	58
			 (*R*,*S*)-**21**	 (*R*,*R*)-**22**	 (*R*,*S*,*R*)-**23**	 (*R*,*R*,*S*)-**24**
ix	A	8	78	8	12	2
x	C	13	8	0	10	82

[a] Cyclization methods: A = 3 equiv of I_2, DME–H_2O, 1:1, room temperature, ≈3 days, B = 3 equiv of I_2, THF–H_2O, 1:1, 0 °C, ≈3 days; C = 3 equiv of I_2, THF–H_2O, room temperature, ≈3 days.

with remarkable olefin and face selectivity, while the various diastereomers of 3-hydroxy-2-(2′-methylenecyclohexan-1′-yl)butyric acid cyclize[3] with complete nucleophile (i.e., OH vs CO_2R) and face selectivity. These observations, coupled with numerous reports of excellent diastereoselectivity in both the C-alkylation of chiral amides[4] and the electrophilic cyclization of α-branched γ,δ-unsaturated *N*,*N*-dialkylamides,[5] led us to develop a versatile synthesis of chiral γ-butyrolactones by a three-step route consisting of N-acylation of chiral amines, Cα-alkylation, and iodolactonization. Chiral auxiliaries employed in the this study were (*S*)-(+)-2-pyrrolidinemethanol[6] as in amide **1** and (2*R*,6*R*)-(+)-2,6-bis((benzyloxy)methyl)piperidine [(+)-BBMP][6b] as in amide **2**. As evidenced by the much greater diastereoselectivity obtained with amide **2** (→ **3** vs **1** → **3**), the "C_2 symmetry axis"[7] of (+)-BBMP plays a pivotal role, both in the alkylation and iodolactonization steps.



Our starting chiral amides (i.e., AUX-C(O)CH_2R in Table I) were prepared from the chiral amine and the

(3) Kurth, M. J.; Beard, R. L.; Macmillan, J. G.; Olmstead, M. *J. Am. Chem. Soc.* **1989**, *111*, 3712.

(4) (a) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137. (b) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (c) Mori, K.; Ito, T. *Tetrahedron* **1983**, *39*, 2303. (d) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857. (e) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1984**, *25*, 6015. (f) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1985**, *26*, 1343. (g) Schultz, A.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. *Ibid.* **1985**, *26*, 4575. (h) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1985**, *26*, 4643. (i) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1986**, *27*, 2463. (j) Uchikawa, M.; Hanomoto, T.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1986**, *27*, 4577. (k) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

(5) (a) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (b) Hart, D. J.; Huang, H. C.; Krishnamurthy, R.; Schwartz, T. *Ibid.* **1989**, *111*, 7507. (c) Fuji, K.; Node, M.; Naniwa, Y. Kawabata, T. *Tetrahedron Lett.* **1990**, *31*, 3175.

(6) (a) (*S*)-(+)-2-Pyrrolidinemethanol (≈100% ee) is commercially available from the Aldrich Chemical Company, Inc. [18,651-1]. (b) (2*R*,6*R*)-(+)-2,6-Bis((benzyloxy)methyl)piperidine (≈76% ee) was prepared from (*S*)-(+)-2-((benzyloxy)methyl)oxirane (≈76% ee; Aldrich Chemical Company, Inc. [36-353-7]). See: Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279. Consequently, the major iodolactone product in entries iii/iv/vi/viii/x of Table II was obtained in ≈75% ee.

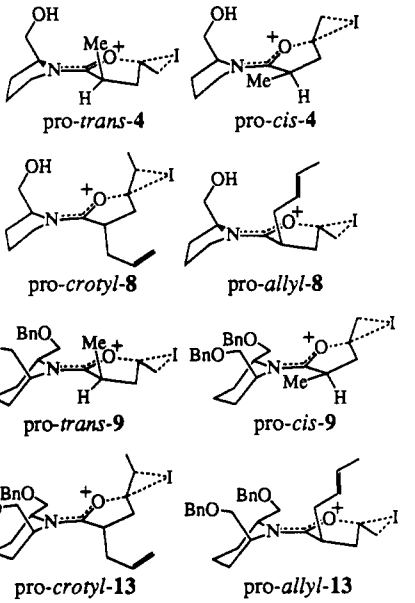
(7) (a) A strict application of the C_2 symmetry element does not apply in the ground-state arrangement of (2*R*,6*R*)-(+)-2,6-bis((benzyloxy)-methyl)piperidine. However, this substrate possess functional C_2 symmetry[7b] since the nitrogen atom, which lies on the pseudo-C_2 axis, is chirotopic but nonstereogenic. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–90.

corresponding anhydride (or the trimethylacetic–mixed anhydride) by treatment with triethylamine (1.2 eqiv) and 4-(dimethylamino)pyridine (0.05 equiv) at room temperature in dichloromethane. Subsequent enolate formation (THF, −78 °C, 2.1 equiv of LDA with amide 1 or 1.1 equiv of LDA with amide 2) and alkylation produced the Cα-alkylated amides in Table I. As a point of clarification, these alkylation conditions are optimized for the piperidine series (≥94% ds and 60–93% yield) but not the pyrrolidine series,[8] and the relative stereochemistry at Cα in amides **4–14** was assigned by analogy with previous examples of chiral amide alkylations.[6]

Iodolactonization of **4–13** was anticipated to (i) liberate the chiral auxiliary for recovery and recycle, (ii) exploit amide resident stereochemistry as the critical control element in establishing new stereogenic center(s) as the olefinic carbons undergo $sp^2 \rightarrow sp^3$ rehybridization, and (iii), in the case of dienamides **7/8/12/13**, differentiate and selectively cyclize one of the two olefinic moieties. Furthermore, entries i–iv in Table II illustrate three unique features of this iodolactonization reaction. First, these *N*-pyrrolidino (**4** and **5**) and *N*-piperidino (**9** and **10**) 2-methylpent-4-enamides are moderately more trans selective than Yoshida's *N,N*-dimethyl-2-methylpent-4-enamide (≥9:1 *trans*-**15**:*cis*-**16**). Second, since the amide C-alkylation reaction proceeds with moderate to excellent diastereoselectivity on a nonracemic substrate (see Table I), the *trans*-iodolactone is formed enantioselectively. Third, either antipode of the *trans*-iodolactone can be prepared by simply controlling the Cα relative stereochemistry in the amide alkylation step [i.e., **4/9** → (*R,S*)-**15** and **5/10** → (*S,R*)-**15**). The degree of overall enantioselectivity in the preparation of **15–24** is a consequence of both the degree of diastereoselectivity in the amide C-alkylation step[9] and the optical purity of the starting chiral auxiliary.[6b]

In parallel with Yoshida's *N,N*-dimethylamide,[7a] amides **4–13** undergo trans-selective iodolactonization because A(1,3) strain[10] disfavors the pro-cis transition state (cf., *pro-cis*-**4** or *pro-cis*-**9**), forcing the α-alkyl substituent to adopt a quasi-axial orientation as in *pro-trans*-**4** and *pro-trans*-**9**. Thus, while the pyrrolidino and piperidino chiral auxiliaries differentiate the *re* and *si* faces of the amide enolate in the C-alkylation step, they afford no advantage over the *N,N*-dimethyl moiety in the iodolactonization step *for substrates with only one site of γ,δ-unsaturation. Entries viii and x (Table II) demonstrate that the (+)-BBMP auxiliary profoundly influences the iodolactonization of dienamides*!

The critical role played by the chiral auxiliary in the heterocyclization reaction is most apparent in iodolactonizations of (*E*)-1,6-octadiene-4-carboxylic acid derivatives. Kinetic iodolactonization of the lithium carboxylate (THF, −78 °C) gives a 15:27:22:36 (42:58 allyl–crotyl selectivity) mixture of (±)-lactones **21**, **22**, **23**, and **24**, respectively, whereas the corresponding pyrrolidine amide gives the same lactones as a 61:4:30:5 (65:35, allyl-*N*-crotyl selectivity) mixture. The (*S*)-(+)-2-pyrrolidinemethanol derivative (amide **8**, Table II/entry ix) is marginally more allyl selective (86:14; 78:8:12:2 mixture of the four lactones). This progression from crotyl to allyl selectivity reflects the amide's kinetic preference for the least hindered olefin, a bias which intensifies as the amide becomes more hindered, and the dramatic switch from ≈3:2 cis selectivity with the acid to ≈10:1 trans selectivity with chiral amide **8** reflects the significance of A(1,3) strain.



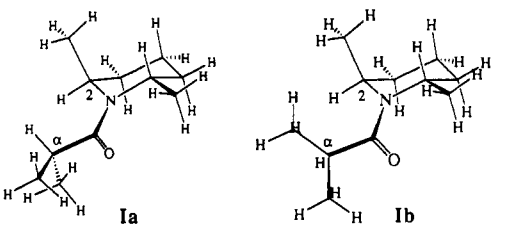
Remarkably, *the derivative **13** is crotyl selective* (8:92, 8:0:10:82 mixture of the four lactones)! This changeover in olefin selectivity can be understood as follows. Olefin selectivity in the iodolactonization of **8** (*pro-crotyl*-**8** vs *pro-allyl*-**8**) reflects a kinetic preference of the amide moiety for the least hindered olefin; the stereogenic center in the chiral amine has little additional influence on the reaction. In contrast, **13** experiences significant destabilization of the pro-allyl transition state by a benzyloxymethyl·crotyl interaction[11] and the pro-crotyl transition state is preferred over the least hindered olefin (i.e., **8** → *trans*-**21**)! The significance of this (benzyloxy)methyl interaction is further underscored with amides **6/7** and **11/12** (Table II entries vi and viii). While amides **6**, **7** (Table II entries v and vii), and **11** (entry vi) give approximately equal allyl and methallyl cyclization, (+)-BBMP amide **12** (entry viii) is 96:4 methallyl selective because both conformation (i.e., a destabilizing benzyloxymethyl·methallyl interaction in its pro-allyl transition state) and electronics[12]

(8) For a detailed experimental procedure and optimal alkylation conditions for alkylation of (*S*)-(+)-2-pyrrolidinemethanol derived amides, see ref 4k.

(9) For iodolactones **15** and **16**, enantiomeric excesses were determined by HPLC (SiO_2/hexane–EtOAc, 19:1) separation of the cis and trans mixture and then enantiomer resolution by capillary GC [β-cyclodextrin on OV-1701 (30-m) column, 100 °C isothermal, H_2 at 6 psi: R_f (*R,S*)-**15** = 157.8 min, R_f (*S,R*)-**15** = 160.2 min].

(10) (a) See ref 7a. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (c) Overman, L. E.; Yokomatsu, T. *J. Org. Chem.* **1980**, *45*, 5229. (d) Wilson, S. R.; Misra, R. N. *Ibid.* **1980**, *45*, 5079.

(11) (a) This 92:8 crotyl selectivity reflects destabilization (by a benzyloxy·crotyl interaction) of the *pro-allyl*-**13** transition state relative to the *pro-crotyl*-**13** transition state. Indeed, MM2 modeling[11b] of simplified analog I indicates that the C_2-methyl/Cα-methyl "eclipsed" conformation Ib (i.e., a ground-state analogue of *pro-allyl*-**13**) is destabilized by 0.65 kcal/mol relative to the C_2-methyl/Cα-hydrogen "eclipsed" conformation Ia (i.e., a ground-state analogue of *pro-crotyl*-**13**).



(b) MM2 77 Allinger-QCEP395 and MMP1 Pi Allinger-QCEP318 which includes model parameters by Still and atom and trial constants by K. E. Gilbert and J. J. Gajewski, Indiana University.

favor the pro-methallyl transition state.

The preceding examples establish that (+)-BBMP affords unique advantages as a chiral auxiliary in a two-step, enantioselective process consisting of amide C-alkylation and iodocyclization. This chemistry provides an effective means for the enantioselective preparation of *trans*-γ-butyrolactones.

(12) The iodolactonization of racemic 2-methyl-1,6-heptadien-4-oic acid is ≈97:3 methallyl versus allyl selective. See: Kurth, M. J.; Brown, E. G.; Lewis, E. J.; McKew, J. C. *Tetrahedron Lett.* **1988**, *29*, 1517.

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Supplementary Material Available: Experimental details for the preparation of and spectral data for (2*R*,6*R*)-2,6-bis-((benzyloxy)methyl)-1-(4′-pentenoyl)piperidine, (2*R*,6*R*,2′*S*)-2,6-bis((benzyloxy)methyl)-1-(2′-methyl-4′-pentenoyl)piperidine (**10**), and (3*S*,5*R*)-dihydro-5-(iodomethyl)-3-methyl-2(3*H*)-furanone [(*S*,*R*)-**15**] (3 pages). Ordering information is given on any current masthead page.

Palladium-Catalyzed Cross-Coupling of Aryl Halides and Olefinic Epoxides via Palladium Migration

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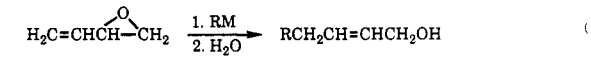
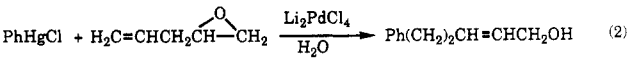
Summary: The palladium-catalyzed cross-coupling of aryl halides and olefinic epoxides bearing one to ten carbons between the two functional groups affords good yields of arylated allylic alcohols by a palladium migration process.

The cross-coupling of 3,4-epoxy-1-alkenes and stoichiometric amounts of organolithium, -boron, -copper, -mercury, -nickel, and -palladium compounds provides an important route to allylic alcohols (eq 1).[1] We have re-



(1)

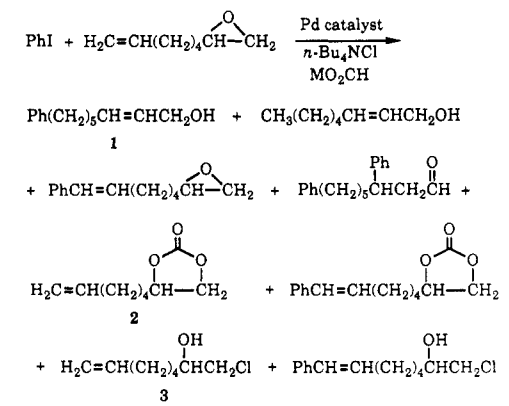
cently reported one example of the analogous arylation of 4,5-epoxy-1-pentene employing stoichiometric amounts of an arylmercurial and either stoichiometric or catalytic amounts of palladium salts (eq 2).[2] We now report a



(2)

valuable, very general, new process for the synthesis of aryl allylic alcohols which employs catalytic amounts of palladium, a variety of olefinic epoxides, and organic halides rather than organometallic reagents.

The cross-coupling of iodobenzene and 7,8-epoxy-1-octene was selected as a model system. In the presence of catalytic amounts of palladium and a reducing agent, the desired allylic alcohol **1** was obtained, alongside a variety of side products which were dependent upon the precise reaction conditions employed (eq 3). By a careful,



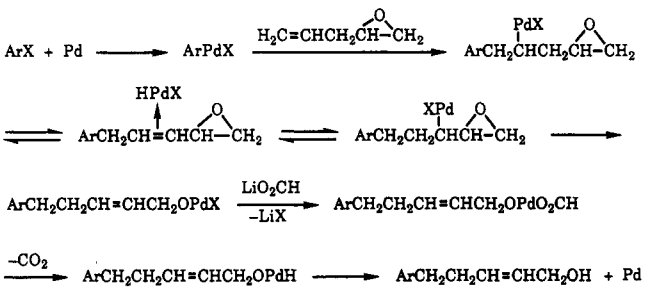
(3)

1

2

3

Scheme I



systematic examination of the influence of a variety of palladium catalysts [3–10% $Pd(OAc)_2$ or $Pd(dba)_2$], reducing agents [1–3 equiv of MO_2CH (M = Li, Na, K, Et_3NH); Et_3N; Et_3SiH; *n*-Bu_3SnH], solvents [2–4 mL/mmol of PhI; DMF, 9:1 DMF/MeOH, DMSO, CH_3CN, THF, CH_2Cl_2], in the presence or absence of *n*-Bu_4NCl (1 equiv), H_2O (10 equiv), alkali metal halides [LiCl (1–2 equiv), NaI (1 equiv)], and bases [$NaHCO_3$, Na_2CO_3, Et_3N, *i*-Pr_2NEt, (c-C_6H_{11})$_2$NEt], we have been able to arrive at optimal conditions for the formation of the desired allylic alcohol **1**. By employing 1 equiv of PhI, 3 equiv of the olefinic epoxide, 10% $Pd(OAc)_2$, 1 equiv of *n*-Bu_4NCl, 3 equiv of LiO_2CH, 3 equivs of *i*-Pr_2NEt, and 1 equiv of LiCl at 50 °C in DMF (4 mL/mmol of ArI), we have been able to eliminate the majority of side products and obtain the desired alcohol **1** in 62% isolated yield. Only minor amounts of the products **2** and **3** arising from ring opening of the excess starting olefinic epoxide are observed, and they can usually be easily separated from the desired alcohol.

A variety of olefinic epoxides have been arylated in a similar fashion in good to excellent yields (Table I). Unlike the analogous arylation of long-chain olefinic alcohols,[3] the yields and regioselectivity here are observed to drop off as the distance between the C–C double bond and the epoxide increases. With 4,5-epoxy-1-alkenes, only aryl allylic alcohols arising from aryl addition to the terminal alkene carbon are observed. With longer chain olefinic epoxides, small amounts of aryl allylic alcohols arising from aryl addition to the internal carbon are also observed. The stereoselectivity of C–C double bond formation is similar to that observed with organoboron, or-

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers, Inc.: New York, 1989; pp 123–124. (b) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.
(2) Larock, R. C.; Ilkka, S. J. *Tetrahedron Lett.* **1986**, *27*, 2211.
(3) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. K. *Tetrahedron Lett.* **1989**, *30*, 6629.

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