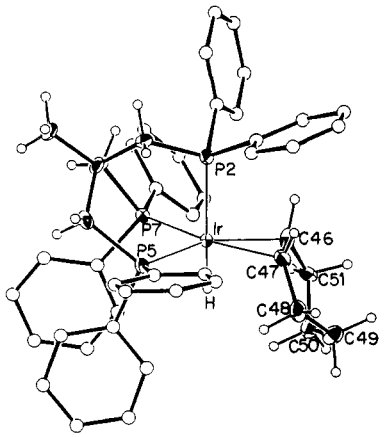


Figure 1. ORTEP drawing of $[CH_3C(CH_2PPh_2)_3]IrH(C_6H_{10})$, showing selected atom labeling. For clarity, phenyl hydrogens have been omitted and their carbons are shown as spheres. The coplanarity of five of the six cyclohexene hydrogens is evident. Selected structural parameters: Ir-C46, 2.168 (7) Å; Ir-C47, 2.171 (7); Ir-P2, 2.301 (2); Ir-P5, 2.278 (2); Ir-P7, 2.291 (2); C46-C47, 1.463 (10).

critical spectral features include a static $^{31}P\{^1H\}$ AM_2 pattern and a hydride trans (J(HP) = 149 Hz) to one phosphorus and cis (J(HP) = 13 Hz) to two others. This compound is acid sensitive, regenerating **5** (with elimination of H_2) on treatment with $HBF_4{\cdot}OEt_2$. The 1,3-diyl product **6** is the kinetic product, and it isomerizes in THF solution (2 days, 20 °C) to the cyclohexene isomer, **7**.[13] Since this isomerization also occurs in the solid state (80% conversion in 10 days), we suggest that the isomerization is intramolecular. The ^{31}P, ^1H, and ^{13}C NMR spectra of **7** are consistent with a static (^{31}P NMR) molecule based on a trigonal bipyramid. This was confirmed by X-ray diffraction[14] (Figure 1).

Protonation (i.e., oxidation) of **7** with equimolar $HBF_4{\cdot}OEt_2$ in THF yields $(triphos)Ir(H_2)(THF)^+$ (**9**)[15] as the only metal-containing product and completes the stepwise conversion of three molecules of acetylene to cyclohexene (GC and ^1H NMR evidence). A detectable intermediate in this process is the Ir^{III} dihydrido cyclohexene complex **8**.[16]

Certain of these results deserve comment: (1) The hydride nucleophiles in steps c and e (Scheme I) are delivered to the internal carbon of the coordinated olefin, consistent with certain previous literature reports.[17] It is noteworthy that the hydride in step e does not deprotonate this cationic hydride, but instead acts as a nucleophile at carbon. (2) The "central carbon attack" product **6** in reaction e is not thermodynamically stable, consistent with literature reports.[18] (3) Deuterium labeling studies will be required to establish whether all reactions occur by direct attack on carbon or whether, in certain cases, the kinetic site of attack is at the metal.

Acknowledgment. We thank the Indiana University Institute for Advanced Study for supporting C.B. in Bloomington and the U.S. NSF (Grant No. CHE-9103915) and Progetti Finalizzati "Chimica Fine II", CNR, Rome, Italy, for operating expenses.

Supplementary Material Available: Listings of full synthetic, spectroscopic, and analytical details, (for **7**) atomic positional parameters, and bond lengths and angles (12 pages). Ordering information is given on any current masthead page.

(12) Selected spectral data (20 °C, CD_2Cl_2): $^{31}P\{^1H\}$ NMR AM_2 with δ_A = -28.06, δ_M = -23.42, J_{AM} = 12; ^1H NMR δ_{IrH} = -8.85 (dt, J = 149 and 13); IR (Nujol) 2052 cm^{-1} (Ir-H).

(13) Selected spectroscopic data (all at 20 °C in CD_2Cl_2): $^{31}P\{^1H\}$ NMR YX_2 spin system δ_Y = -18.55, δ_X = -18.03, J_{XY} = 20 Hz; $^{13}C\{^1H\}$ NMR 30.89 (vinyl, AXX'Y spin system), 35.6 (CH_2, d, J_{CP} = 5), 24.81 (CH_2, s); ^1H NMR of hydride nucleus δ_M = -11.52 (MXX'Y) spin system with J_{MX} = 14, J_{MY} = -141; IR (Nujol) 2063 cm^{-1} (Ir-H).

(14) Crystallographic data for $(triphos)IrH(C_6H_{10})$ at -170 °C: a = 10.102 (1) Å, b = 14.994 (2), c = 25.674 (3), β = 90.56 (0)° with Z = 4 in space group $P2_1/c$. Using anisotropic thermal parameters on all non-hydrogen atoms and isotropic thermal parameters on all hydrogen atoms, $R(F)$ = 0.0351 and $R_w(F)$ = 0.0317 for 4310 reflections with $F > 3\sigma(F)$.

(15) Selected spectral data: $^{31}P\{^1H\}$ NMR (THF-d_8, 20 °C) AM_2, δ_A = -1.53, δ_M = -6.26 (J = 12 Hz); ^1H NMR (THF-d_8, 20 °C) AA'XX'Y, δ(H) = -6.68 ($J_{AX} + J_{AX'}$ = 127 Hz, J_{AY} = 15 Hz); IR (Nujol) 2050 cm^{-1} (Ir-H).

(16) Selected spectral data: $^{31}P\{^1H\}$ NMR (THF-d_8, 20 °C) AM_2, δ_A = -3.04, δ_M = -21.20 (J = 20 Hz); ^1H NMR (THF-d_8, 20 °C) AA'XX'Y, δ_M = -10.86 ($J_{AX} + J_{AX'}$ = 111 Hz, J_{AY} = 12 Hz).

(17) (a) Sautet, P.; Eisenstein, O.; Nicholas, K. M. *Organometallics* **1987**, *6*, 1845. (b) Semmelhack, M. F.; Herndon, J. W.; Springer, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 2497.

(18) (a) Wakefield, J. B.; Stryker, J. M. *J. Am. Chem. Soc.* **1991**, *113*, 7057 and references therein. (b) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 7346. (c) McGhee, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 3388. (d) Tjaden, E. B.; Stryker, J. M. *Organometallics* **1992**, *11*, 16.

A Protecting Group Strategy for Desymmetrization

Thomas R. Hoye* and Nancy E. Witowski

Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455
Received February 14, 1992

Desymmetrization issues in synthesis are important.[1-3] Through our interest in epoxide cascade reactions,[4] the need arose to regioselectively convert the symmetrical diepoxide diol **1** into

(1) Examples from the last decade involving enzymatic approaches include the following: (a) Ohno, M. In *Organic Syntheses, An Interdisciplinary Challenge*, Proceedings of the 5th IUPAC Symposium Organic Synthesis; Streith, J., Prinzbach, H., Schill, H., Eds.; Blackwells: Oxford, 1984; pp 189-204. (b) Wang, Y.; Chen, C.; Girdaukas, G.; Sih, C. J. *Ciba Found. Symp. Enzymes Org. Synth.* **1985**, *111*, 128. (c) Ohno, M. *Ciba Found. Symp. Enzymes Org. Synth.* **1985**, *111*, 175. (d) Jones, J. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 9. (e) Schneider, M.; Engel, N.; Hönicke, P.; Heinemann, G.; Görisch, A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 67. (f) Jones, J. B.; Francis, C. J. *Can. J. Chem.* **1984**, *34*, 4087 (and earlier refs). (g) Gais, H.-J.; Lukas, K. L.; Ball, W. A.; Braun, S.; Lindner, H. J. *Liebigs Ann. Chem.* **1986**, 687 (and earlier refs). (h) Guo, Z.; Wu, S.; Chen, C.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942 (and earlier refs). (i) Kurihara, M.; Kamiyama, K.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1985**, *26*, 5831. (j) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255. (k) Kazlauskas, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953. (l) Estermann, H.; Prasad, K.; Shapiro, M. J.; Repic, O.; Hardtmann, M. J.; Bolsterli, J. J.; Walkinshaw, M. D. *Tetrahedron Lett.* **1990**, *31*, 445. (m) Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546. (n) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1990**, *31*, 6421. (o) Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 2597 (and earlier refs).

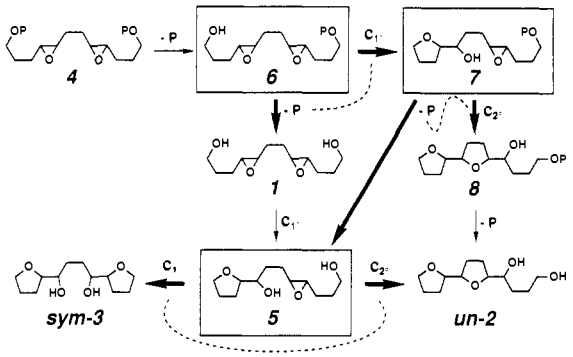
(2) Examples involving various chemical approaches: (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563 (and earlier refs). (b) Hajos, Z. G.; Parrish, D. R. *Organic Syntheses*; Saucy, G., Ed.; Wiley: New York, 1985; Vol. 63, p 26 (and earlier refs). (c) Hoye, T. R.; Peck, D. P.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618. (d) Bartlett, P. A.; Johnson, W. S.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (e) Bertz, S. H. *Tetrahedron Lett.* **1983**, *24*, 5576. (f) Whitesell, J. K.; Allen, D. E. *J. Org. Chem.* **1985**, *50*, 3025. (g) Hatakeyama, S.; Sakurai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759. (h) Häfle, B.; Schröter, D.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 87. (i) Dokuzovic, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034. (j) Oshima, M.; Mukaiyama, T. *Chem. Lett.* **1987**, 377 (and earlier refs). (k) Aubé, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 150. (l) Naruse, Y.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 6021 (and earlier refs). (m) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793 (and earlier refs). (n) Tamao, K.; Topma, T.,; Inui, N.; Nakayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333. (o) Harada, T.; Wada, I.; Uchimura, J.; Inoue, A.; Tanaka, S.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1219. (p) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090.

(3) Examples involving lactonization reactions: (a) Nagao, Y.; Ikeda, T.; Yagi, M.; Fujita, E.; Shiro, M. *J. Am. Chem. Soc.* **1982**, *104*, 2079. (b) Hoye, T. R.; Peck, D. P.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738. (c) Fuji, K.; Node, M.; Terada, S.; Murata, M.; Nagasawa, H.; Taga, T.; Machida, K. *J. Am. Chem. Soc.* **1985**, *107*, 6404. (d) Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844. (e) Sakamoto, A.; Yamamoto, Y.; Oda, J. *J. Am. Chem. Soc.* **1987**, *109*, 7188 (and earlier refs). (f) Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 277. (g) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 12. (h) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 16. (i) Fuji, K.; Node, M.; Naniwa, Y.; Kawabata, T. *Tetrahedron Lett.* **1990**, *31*, 3175.

(4) (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312. (b) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855. (c) Hoye, T. R.; Jenkins, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 6196. (d) Hoye, T. R.; Hanson, P. A.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369.

0002-7863/92/1514-7291$03.00/0

Scheme I[a]



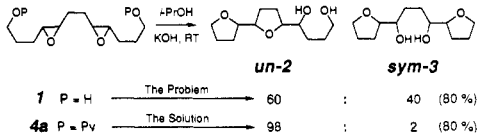
[a] Intermediates which lie at crucial branch points are boxed. Heavy arrows are the competitive partitioning events. C and -P denote cyclization and protecting group loss, respectively.

Table I. Results of Cyclization (at ~25 °C) of Diol **1** and the Bis-Acetate and Bis-Pivalate Derivatives **4b** and **4a** to the Desired and Undesired Bis-THFs *un*-**2** and *sym*-**3**

entry	substrate	P (in **4**)	catalyst	solvent	product ratio[a] *un*-**2**:*sym*-**3**
1	**1**	H	KOH	*i*-PrOH	60:40
2	**1**	H	CSA	CH_2Cl_2	55:45
3	**4b**	Ac	KOH	MeOH	61:39
4	**4b**	Ac	KOH	EtOH	60:40
5	**4b**	Ac	KOH	*i*-PrOH	56:44
6	**4a**	Pv	KOH	MeOH	83:17
7	**4a**	Pv	KOH	EtOH	96:4
8	**4a**	Pv	KOH	*i*-PrOH	98:2

[a] Determined by acetylation of crude reaction product mixtures and subsequent capillary GC analysis; in several instances this was further substantiated by preparative-scale SiO_2 separation of the diols. Controls to ensure nonselective partitioning during aqueous workup were also performed.

the desired, *un*symmetrical, bis-THF diol *un*-**2** while minimizing concurrent production of the *sym*metrical counterpart, *sym*-**3**. It was not surprising[5] to learn that base-catalyzed cyclization of a ~1:1 diastereomeric mixture[6] of the *d,l* and meso forms of diol **1** was relatively nonselective, giving a 60:40 ratio of *un*-**2**:*sym*-**3**. This problem of end-differentiation was solved simply by using as substrate the bis-pivalate ester derivative **4a**. Under the same reaction conditions, a 98:2 ratio favoring the desired product *un*-**2** was realized. Why?



The important neutral intermediates for these reactions are gathered in Scheme I. Starting from the diol **1** a single branch point is encountered. The obligatory monoepoxide **5** partitions by competitive intramolecular attack on the remaining epoxide ring by secondary vs primary hydroxyl groups to give **un-2** vs **sym-3**, respectively. The 60:40 product ratio confirms that the rates of these two events are comparable under base (or acid) catalysis (see entries 1 and 2 in Table I).[7]

Use of **4**, a doubly protected derivative of diol **1**, demands that at least one of the protecting groups P be removed before even the first epoxide can cyclize. Two additional branch points are then encountered. The relative rates of deprotection vs cyclization clearly dictate the **6** → **1** vs **7** and the **7** → **5** vs **8** partitionings.

Under circumstances where protecting group loss is considerably faster than cyclization, the intermediate monoprotected diepoxide **6** will be drained essentially entirely to **1** (vs **7**), as will the minor amount of **7** to **5** (vs **8**). The resulting ratio of bis-THFs *un*-**2**:*sym*-**3** should be nearly identical to that observed starting with **1** itself. However, if the loss of protecting group is tailored to be significantly slower than the cyclization, then intermediate **6** should be effectively shunted to **8** via **7**. A second, leisurely deprotection would then afford *un*-**2**.

Underlying the development of this strategy was the presumption that we could dictate the rate of deprotection. For example, for the subset of protecting groups P comprising esters removable under base-induced transesterification/saponification conditions, two obvious parameters likely to *differentially* affect the deprotection vs cyclization events are the nature of the protecting group itself and the steric hindrance of the nucleophilic solvent molecules. These could be readily and independently adjusted to influence the rate of loss of P.

The bis-acetate derivative **4b** (P = Ac) gave essentially the same ratio of *un*-**2**:*sym*-**3** as did diol **1** itself, regardless of the degree of steric hindrance of the solvent used for the deprotection/cyclization reaction (entries 3-5, Table I). Apparently the rate of transesterification of the acetate **6** to give **1** was faster than the rate of cyclization of **6** to generate **7**.

In contrast, alcoholysis of the more hindered bis-pivalate derivative **4a** (P = Me_3CCO) proceeded as hypothesized (entries 6-8, Table I). In methanol a modest enhancement of product ratio was realized. Changing to the more hindered solvents ethanol and isopropyl alcohol provided substantial improvement in the *un*-**2**:*sym*-**3** ratio. Loss of the pivalate group in isopropyl alcohol was sufficiently slow to allow intermediate **6** to be efficiently siphoned to *un*-**2** (98:2) via **8**, thereby exemplifying this protecting group strategy for desymmetrization.

Acknowledgment. This investigation was supported by Grant GM-34492 awarded by the DHHS.

Registry No. DL-**1**, 142395-88-8; *meso*-**1**, 142436-23-5; **2**, 142395-91-3; **3**, 142421-10-1; DL-**4a**, 142395-89-9; *meso*-**4a**, 142436-24-6; DL-**4b**, 142395-90-2; *meso*-**4b**, 142436-25-7; **5**, 142421-10-1; DL-**6** (P = $COC(CH_3)_3$), 142395-93-5; *meso*-**6** (P = $COC(CH_3)_3$), 142436-26-8; DL-**6** (P = Ac), 142395-95-7; *meso*-**6** (P = Ac), 142436-27-9; **7** (P = $COC(CH_3)_3$), 142395-94-6; **7** (P = Ac), 142395-96-8.

(5) Cf. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(6) These and related diastereomeric 1,4-bisepoxides have always proven inseparable by standard liquid or gas chromatographic techniques in our hands, but ratios are discernible from ^1H and ^{13}C NMR data.[4a-c]

(7) Perhaps the slight preference (≤1.5) for regioselective attack by the secondary hydroxyl group is a manifestation of the Thorpe-Ingold or reactive rotamer effect; for example: Jung, M. E. *Synlett* **1990**, 186.

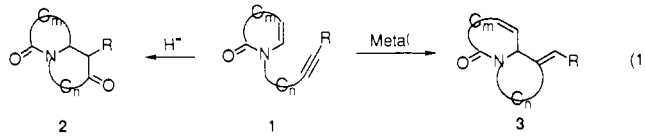
Palladium-Catalyzed Cycloisomerizations of Alkynyl *N*-Acyl Enamines

Barry M. Trost* and Conchi Pedregal

Department of Chemistry
Stanford University
Stanford, California 94305-5080

Received May 15, 1992

The vast importance of nitrogen heterocycles has stimulated the development of new methodology for their construction. Among the most useful recently developed methods are iminium ion initiated cyclizations[1-3] as illustrated in eq 1 (**1** → **2**).[1]



(1)

(1) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. For a leading reference on the question of regioselectivity in the acid-catalyzed cyclization, see: Hiemstra, H.; Ino, M. H. A. M.; Vijin, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.

(2) Also see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

0002-7863/92/1514-7292$03.00/0