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CsOH-promoted epoxide ring-opening with phosphines: mild and efficient synthesis of monohydroxyphosphines

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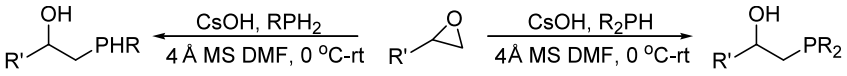
Abstract—A mild and convenient synthesis of monohydroxyphosphines has been achieved by epoxide ring-opening using primary or secondary phosphines in the presence of cesium hydroxide, 4 Å molecular sieves and DMF at room temperature. These reaction conditions were found to be highly regio- and stereoselective producing various monohydroxyphosphines exclusively in moderate to high yields.

Epoxides are versatile intermediates that serve as pre-eminent building blocks in organic synthesis.[1] Epoxides can be opened under a variety of conditions, although, the most practical and widely employed strategy for the synthesis of 1,2-bifunctional compounds is via nucleophilic ring-opening using a Lewis acid promoter or a strong base.[2] Epoxide ring-opening reactions with carbanions[3], alcohols,[4] amines,[5] and thiols[6] have been extensively studied, since they provide a suitable route for the formation of C–C, C–O, C–N, and C–S σ-bonds, respectively. However, ring-opening reactions with phosphorus nucleophiles (e.g. phosphines) have received little attention. In conjunction with the ongoing work in our laboratory toward the synthesis of bidentate ligands as transition-metal-based catalysts, monodenate hydroxyphosphines are of particular interest.[7] We found that pre-existing ring-opening protocols using phosphines are hampered by the use of harsh reagents,[8] low reaction temperature,[9] and result in unsatisfactory yields.[10] In this context, we herein disclose our results regarding a mild and convenient epoxide to monohydroxyphosphine ring-opening procedure using primary and secondary phosphines.

In the presence of cesium hydroxide, activated powdered 4 Å molecular sieves, and anhydrous *N*,*N*-dimethylformamide (DMF) in an inert nitrogen atmosphere, various epoxides underwent facile ring-opening using primary and secondary phosphines (Scheme 1). The reaction was begun at 0°C and gradually allowed to warm to room temperature. We propose that the reaction proceeds via the phosphide anion weakly coordinated with the cesium cation (e.g. 'naked anions'), thereby exhibiting enhanced nucleophilicity without the aid of a Lewis-acid promoter as a trigger for the reaction.[11] Moreover, these conditions were found to be highly regio- and stereoselective, affording various structurally diverse β-hydroxyphosphines in moderate to high yields.

Initially, structurally diverse epoxides were probed to test the feasibility of ring-opening reactions using a secondary phosphine. Several examples illustrating this simple and practical methodology are summarized in Table 1. As a typical procedure, the preparation of *trans*-2-$PPh_2(C_6H_{10}OH)$ was performed at 0°C by dropwise addition of cyclohexene oxide (**1**) (1.2 equiv.) to a stirred solution of diphenylphosphine (1 equiv.), CsOH (1 equiv.), in the presence of molecular sieves and DMF. After the addition of **1** was complete, the dark red-orange color immediately disappeared and turned yellow. The reaction was quenched with water



Scheme 1.

Keywords: epoxides; phosphines; monohydroxyphosphine; cesium hydroxide; bidentate ligands.
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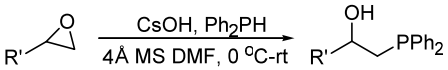
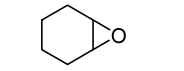
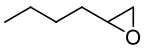
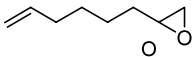
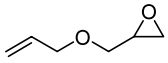
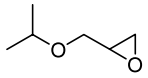
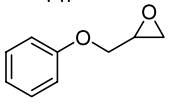
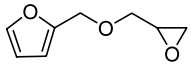
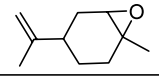
Table 1. CsOH-promoted epoxide ring-opening of various epoxides using Ph_2PH

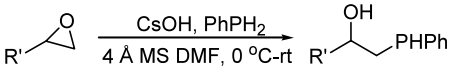


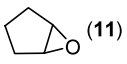
entry	epoxide		time (h)	yield
1		(**1**)	24	50%
2		(**2**)	52	65%
3		(**3**)	24	42%
4		(**4**)	96	62%
5		(**5**)	69	50%
6		(**6**)	72	76%
7		(**7**)	44	66%
8		(**8**)	24	69%
9		(**9**)	50	69%
10		(**10**)	24	50%

(degassed with nitrogen), extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was subsequently purified by recrystallization (THF/hexane), affording *trans*-2-(diphenylphosphino)cyclohexanol as the sole reaction product in moderate yield (Table 1, entry 1).[12] To our delight, *cis*-2-(diphenylphosphino)cyclohexanol was not detected, demonstrating the high stereoselectivity embedded in this protocol. To test issues of regioselectivity, several epoxides were studied. In each case, as expected, nucleophilic ring-opening occurred at the less substituted carbon (entries 2–3). With this data in hand, epoxides with additional functionality were next investigated in order to provide a more complete picture of the substrate versatility of the epoxide partner. Similarly, reaction of diphenylphosphine with both 1,2-epoxy-7-octene (**4**) and allyl glycidal ether (**5**) generated the coupled products in yields of 62 and 50%, respectively (entries 4–5). In each example, the terminal alkene was left intact. Furthermore, no side products stemming from elimination, rearrangements, or oxidation of phosphorus were detected in any example.[13] Next, several epoxides containing the ether moiety were examined to further probe the limits of the proposed conditions. Isopropyl glycidal ether (**6**) underwent facile ring-opening with Ph_2PH to afford the desired product in high yield after 72 h (entry 6). Reaction with styrene oxide (**7**) produced the β-monohydroxyphosphine as the major product in shorter reaction time (entry 7). Likewise, phenyl glycidal ether (**8**) reacted efficiently offering similar yield (entry 8). Epoxides containing heterocyclic groups also proved successful. For example, furfuryl glycidal ether (**9**) was subjected to ring-opening in the presence of diphenylphosphine generating the appropriate β-phosphino-alcohol smoothly in good yield (entry 9). Whereas the reaction of the in situ generated diphenylphosphide anion with commercially available (+)-limonene oxide (**10**), which is a mixture of *cis*- and *trans*-epoxides, delivered only one (+)-*trans*-isomer as an air-sensitive white solid after 24 h (entry 10).[14] Interestingly, (−) α-pinene oxide, a crowded epoxide, was subjected to this methodology, however, failed to react with the phosphide anion, even under heating conditions.

With acceptable results in hand for ring-opening reactions using a secondary phosphine, we next turned our focus to performing similar reactions with a primary phosphine, phenylphosphine. Due to the tendency of primary phosphorus compounds to rapidly oxidize, we were pleased to find that our protocol described for secondary phosphines was viable for the primary as well. Therefore, several epoxides were reacted with phenylphosphine to determine the synthetic utility of the conditions. As delineated in Table 2, reaction of phenylphosphine with numerous epoxides gave the desired monohydroxyphosphine in moderate to excellent yields. In the case of cyclopentene oxide (**11**), a *meso*-epoxide, ring-opened products were completely *anti*-stereoselective giving only the *trans* isomers after 23 h (Table 2, entry 1). Comparatively, cyclohexene oxide (**1**) reacted efficiently to generate products which were obtained as a single diastereomer also possessing *trans*-stereochemistry (entry 2). An epoxide containing an aliphatic chain, 1,2-epoxyhexane (**2**), likewise underwent ring-opening producing the preferred result in a high yield (entry 3). Coming full circle, epoxides containing different functionality and steric constraints were again examined to observe whether the existing protocol was effective. Isopropyl glycidal ether (**5**) was reacted with phenyl phosphine to give rise to the corresponding monohydroxyphosphine in moderate yield (entry 4). Similarly, **6** underwent the desired ring-open-

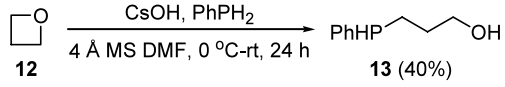
Table 2. CsOH-promoted epoxide ring-opening of various epoxides using $PhPH_2$



entry	epoxide	time (h)	yield
1	 (**11**)	23	46%
2	**1**	96	43%
3	**2**	5 d	92%
4	**5**	44	52%
5	**6**	43	42%
6	**7**	36	43%
7	**10**	24	50%

ing to afford the product in a 42% yield after 43 h (entry 5). Styrene oxide (**7**) also opened to produce the coupled product in a moderate yield (entry 6). Finally, (+)-limonene oxide (**10**) reacted with $PhPH_2$ generating the (+)-*trans*-isomer of $PhPH(C_6H_{10}OH)$ in a 50% yield after hydrolysis and purification (entry 7). All of the compounds were fully characterized by IR, ^1H, ^{13}C, ^{31}P NMR, mass, and elemental analysis or otherwise compared with the known compounds.[15]

As an application of our methodology, we applied our conditions to the ring-opening of oxetanes. These four-membered rings have traditionally proven more resistant to opening than epoxides. Thus, the established conditions for the opening of epoxides also proved applicable in opening the less-strained trimethylene oxide (**12**) to the γ-monohydroxyphosphine **13** using phenylphosphine in good yield by employing a similar strategy (Scheme 2).



Scheme 2.

In conclusion, we report a mild and efficient method for the preparation of monohydroxyphosphines using cesium hydroxide monohydrate as the base of choice. These improved procedures not only offer a novel synthetic route to monohydroxyphosphines, but do so regio- and stereospecifically. Furthermore, the mild, near neutral reaction environment is an improvement over the use of Lewis acid or strong base typically needed to perform these ring-openings. Additionally, the experimental conditions set forth herein show a broad scope, as they proved equally useful for both primary and secondary phosphines. Furthermore, the ring-opening of oxetanes also proved successful using the aforementioned experimental conditions. Applications of this methodology toward the preparation of additional monohydroxyphosphines via use of chiral epoxides are underway and their direct use in the synthesis of coordination compounds are currently in progress and will be reported in due course. Furthermore, ring-opening of azirdines with phosphines for the synthesis of P,N-ligands will next be explored.

Acknowledgements

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10. Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000.
11. It is plausible the reaction proceeds via the diphenylphosphide anion, which is prepared in situ by reaction of Ph_2PH and CsOH. The anion, presumably is weakly coordinated to the cesium cation, hence, a 'naked anion' demonstrating enhanced nucleophilicity, as defined by the 'cesium effect'. Preliminary observations during the course of the reaction are consistent with previously reported examples using other alkali metal counterparts. However, since the cesium cation is weakly coordinated to the phosphide anion, we cannot discount the role the cesium cation may play in the ring-opening. Currently, the mechanism is under investigation and these results will be reported in due course. For formation of 'naked

anions' by solvation of cesium ions which has been previously postulated and studied extensively in other systems, see: (a) Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230. (b) For reviews on the 'cesium effect', see: Ostrowicki, A.; Vogtle, F. *Topics in Current Chemistry*; 1991; Vol. 161. For formation of alkyl metal diphenylphosphides, see: (c) Aguiar, A. M.; Greenberg, H. J.; Rubenstein, K. E. *J. Org. Chem.* **1963**, *28*, 2091; (d) Fisher, C.; Mosher H. S. *Tetrahedron Lett.* **1977**, *18*, 2487; (e) Chatt, J.; Hart, F. A. *J. Chem. Soc.* **1960**, 1378. (f) For Ph_2PCs, see: Fluck, E.; Issleib, K. *Z. Naturforsch. B* **1965**, *20*, 1123.

12. For *trans-2-(diphenylphosphino)cyclohexanol* (Table 1, entry 1): Air-sensitive white solid; mp: 144–146°C; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (m, 1H), 1.20 (m, 2H), 1.40 (m, 1H), 1.62 (m, 1H), 1.71 (m, 2H), 2.08 (m, 1H), 2.34 (m, 1H), 2.68 (br s, 1H, OH), 3.47 (m, 1H), 7.32–7.37 (m, 6H), 7.52 (m, 2H), 7.45 (m, 2H). ^{13}C NMR (70 MHz, $CDCl_3$) δ 24.2, 25.8, 27.0, 35.1, 43.5, 71.9, 127.6, 127.9, 128.0, 132.5, 134.0, 137.3, 138.4. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ −7.6. MS (m/z): 284 (M^+), 267, 229, 186, 183, 108. Anal. calcd for $C_{18}H_{21}OP$: C, 77.08; H, 7.39. Found: C, 76.61; H, 7.44.
13. ^{31}P NMR spectra were obtained for both crude and purified products substantiating the claim for complete specificity and purity of each monohydroxyphosphine product. Side products stemming from elimination and oxidation of the phosphine were not detected in an example.
14. Commercially available (+)-limonene oxide is assumed to be a 1:1 mixture of (+)-*cis*- and (+) *trans*-isomers, but ^1H NMR suggests a greater proportion of the *trans*-isomer. For a similar result using $LiPPh_2$, see: Newhall, W. F. *J. Org. Chem.* **1964**, *29*, 185 and Ref. 9a.
15. All the reported ring-opened products gave analytical and spectroscopic data in agreement with the proposed structures. ^1H, ^{13}C, ^{31}P NMR, GC/MS and IR spectra were taken and compared with the known compounds. Elemental analyses were obtained by the Materials Characterization Center at WKU. The stereochemistry of the products have been assigned *trans* configuration by comparison with the known compounds. See Ref. 9a.