Reinvestigation of a Catalytic, Enantioselective Alkene Dibromination and Chlorohydroxylation

Scott E. Denmark* and Nessa Carson

Roger Adams Laboratory, Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801, United States

Supporting Information

ABSTRACT: Attempts to reproduce eight, putative, enantioselective dibromination and chlorohydroxylation reactions from oft-cited literature studies are described. The reactions were performed with full fidelity to the original report wherever possible. Analysis of the enantiomeric composition was performed by chiral stationary phase HPLC or SFC (CSP-HPLC or CSP-SFC), as opposed to the original report, which used chiral shift reagent NMR spectroscopy. After careful study, the reported levels of enantioselectivity were found to be incorrect. Possible explanations for the false positive results are discussed.

The halofunctionalization of alkenes with electrophilic halogenating agents has long been a staple of stereoselective synthesis, prized for its predictable constitutional selectivity and relative stereochemical course. However, catalytic dihalogenation methods, in which the absolute configuration of the products is controlled from an achiral starting material, have proved elusive until recently. Enantioselective bromination is of particular interest due to the ability of bromide to act as a leaving group in stereospecific substitution reactions. Additionally, over 3500 organobromine compounds are known in nature, the majority isolated from marine organisms.

Despite the extensive history of dihalogenation and other halofunctionalization reactions of alkenes, methods to form stereodefined dihalogenated products from olefins are rare. In the reactions of olefins with Br2, vicinal dibromides are formed via bromide ion attack on either an alkene−Br2 π-complex or a bromiranium ion, resulting in anti-stereospecific addition of Br2 across the double bond. However, strategies for enantioselectivity may be thwarted in a number of ways: (1) Racemic background reaction may occur from the formation of molecular bromine (or its equivalent) when both electrophilic and nucleophilic bromine sources are present; (2) Facial selectivity must also be controlled to produce an enantioenriched alkene−Br2 π-complex or bromiranium ion intermediate; (3) Bromiranium ions are configurationally unstable in the presence of excess olefin, via an alkene-to-alkene transfer pathway; and (4) The regioselectivity of bromide addition must also be controlled, since attack on either carbon atom of a non-C2-symmetric bromiranium ion intermediate yields enantioselective products.

In 2011, Nicolaou et al. reported a dichlorination reaction of allylic alcohols using (DHQ)2-PHAL as the catalyst and 4-Pr(C6H4)ICl2 as the chlorinating agent. Dichloride products were formed in a wide range of selectivities (50:50 to 90.5:9.5 er). More recently, Burns et al. developed an enantioselective dibromination of allylic alcohols using dibromomalonate as an electrophilic bromine source and BrTi(Oi-Pr)3 as a nucleophilic bromine source, with a TADDOL-derived catalyst. The dibromide products were formed with good enantioselectivities (85.5:14.5−92.5:7.5 er). This work has been extended to enantioselective bromochlorination with constitutional site selectivities of 6:1→20:1 and enantioselectivities of 89:11−98.5:1.5 er.

The Wacker oxidation has also been modified for halofunctionalization of alkenes. The use of high chloride ion concentrations under Wacker-type conditions results in the conversion of ethylene to ethylene chlorohydrin, instead of the expected acetaldehyde product. An enantioselective variant of this reaction was subsequently reported by Henry and co-workers, using chiral, nonracemic palladium(II) bisphosphine catalysts to achieve the enantioselective generation of chlorohydrins from terminal alkenes. The possibility of a facile background reaction stemming from dihalogen formation was reduced by the use of chloride as the sole halogen source. A limited number of chlorohydrins were produced, with constitutional site selectivities of 5.5:1→95:1, and reported enantioselectivities of 64:36−91:9 er (Scheme 1a). In all cases, yields were reported based solely on O2 uptake.

Enantioselectivity was improved in later work by Henry and co-workers, by the use of dinuclear palladium(II) complexes with bridging triketone ligands, although no direct comparisons to the mononuclear catalysts were made. Terminal olefins were oxidized to chlorohydrins with constitutional site selectivities of 2.3:1→95:1 and enantioselectivities of 57.5:42.5−97:3 er (Scheme 1b). Henry and co-workers later reported an extension of this work to the enantioselective dibromination of olefins, using similar Wacker-type conditions with 2.5−17.7 mol % (per Pd atom) palladium(II) catalyst or 4 (Scheme 2). The
dibromides rather than bromohydrins as the major products. Although the yields of dibromides reported were highly variable (59:41 er), with the exception of methyl camphorate, although neither spectra nor details of concentrations were given. Optical rotation data were provided for only two of the nine dibromide products.

We have attempted to replicate four reactions in the original report from Henry and co-workers (Table 1, entries 1–7). The allylic ether dibromination procedures were repeated as rigorously as the described procedures allow, albeit on a smaller scale (0.25 mmol versus 2.8–3.7 mmol allylic ether in the original work). To confirm that scale was not a critical factor, one trial, Table 1, entry 3, was performed on the original 3.0 mmol scale and was allowed to run for the original reaction time of 6 days. Although dibromides 6 revert back to the corresponding allylic ethers 5a–d over several weeks in light, running reactions and isolating products in the dark affected neither the yields nor enantioenrichment of products. Workup and chromatographic isolation of products was performed immediately and identically to the original protocol so as to obviate any possibility of epimerization over time.

The catalyst used in Table 1, entry 1 was produced by replication of Henry’s described method with as complete fidelity as possible. This procedure afforded a mixture of compounds, as determined by 31P NMR spectroscopy. The dinuclear palladium complexes used in Table 1, entries 2, 5, and 6 were synthesized by a modification of Henry’s method, in which NaH rather than Et3N was used as a Brønsted base. The complex used in Table 1, entry 1 was produced by in situ generation of a dinuclear palladium complex from Pd(MeCN)4(BF4)2 and the requisite chiral bisphosphate. This procedure afforded compounds that appeared to be pure by 31P NMR spectroscopy and circumvented the laborious separation of triethylammonium tetrafluoroborate from the complex. The pure complexes were stored in a moisture- and oxygen-free environment and were found to decompose over time in solution, and under vacuum, with decomposition observable by NMR spectroscopy after just a few minutes under vacuum. The complexes were therefore characterized and used immediately after purification. The decomposition product (readily visible as a multiplet exhibiting P–P coupling by 31P NMR spectroscopy) could be removed by extensive washing of the solid with anhydrous, degassed toluene under an argon atmosphere. Nonetheless, the method of preparation of the dinuclear complex had no impact on the reaction outcome (Table 1, entries 1–2). For operational simplicity, the mononuclear Pd(II) bisphosphine complexes 3 used in entries 3–4 were generated in situ from Pd(MeCN)4(BF4)2 and the corresponding allylic ether dibromination procedures were repeated as in the original work). To confirm that scale was not a critical factor, one trial, Table 1, entry 3, was performed on the original 3.0 mmol scale and was allowed to run for the original reaction time of 6 days. Although dibromides 6 revert back to the corresponding allylic ethers 5a–d over several weeks in light, running reactions and isolating products in the dark affected neither the yields nor enantioenrichment of products. Workup and chromatographic isolation of products was performed immediately and identically to the original protocol so as to obviate any possibility of epimerization over time.

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Moderate to high yields of dibrominated products 6 were obtained, with small amounts of side products observable in the 1H NMR spectra. Both the crude product mixtures and the chromatographically pure dibromides were analyzed by CSP-HPLC or CSP-SFC to assess enantioenrichment. In every case examined, the vicinal dibromides were racemic (Table 1, entries 1, 2, 3). Enantiomeric ratios were determined by 1H NMR spectroscopic analysis using Eu(hfc)3 (europium tris[3-(heptafluoropropyl-hydroxymethylene)-d-
In light of these results, four chlorohydroxylation reactions from Henry and co-workers’ earlier reports were also investigated (Table 1, entries 8–11). These experiments were performed on a 0.5–1.0 mmol scale (original scale: 3.7–6.5 mmol where reported). However, analysis by CSP-SFC and chiral stationary phase gas chromatography (CSP-GC) again revealed that all chlorohydrin products were racemic.

In their original report, Henry et al. proposed a mechanism that bypasses a bromiranium ion intermediate (Scheme 3), instead suggesting that the palladium complex (shown as mononuclear with a chiral ligand abbreviated as L) coordinates olefin S. Free bromide then attacks the activated olefin I from the opposite face, yielding an alkylpalladium(II) complex II. Cu(II) may stereoretentively oxidize the C–Pd(II) bond to form the alkyl bromide without an overall oxidation state change at Pd. It is unknown whether this bromide is derived from the coordination sphere of Pd or that of Cu in complex II.

Henry et al. claimed the rate does not decrease during the course of the reaction, i.e. overall zeroth order. Qaseer later reported a similar system using Wacker-type conditions and a racemic dinuclear Pd(II) catalyst 4 to generate vicinal dibromides and reported a zeroth order rate of O2 uptake. However, measurement of O2 uptake is insufficient to substantiate claims related to the rate of product formation. For example, the yield for the dibromination of methyl cinnamate (catalyzed by a mononuclear palladium(II) bisoxazoline complex) is reported as 80% (Table S1, entry 6) based on O2 uptake. However, the amount of recovered starting material is 30% by mass. This inconsistency exemplifies that O2 uptake is not a reliable method for monitoring product formation.

The ability to reproduce the formation of the dibromides and chlorohydrins from multiple substrates following the original procedure, but to obtain uniformly racemic products, presents a quandary. The possibility that important details are missing for preparing the catalysts or executing the reactions cannot be excluded. Certainly many possibilities exist for generating Br2 under the reaction conditions, and of course, CuBr2 itself is also capable of effecting the dibromination of alkenes at room temperature.
temperature. However, in our opinion, the more likely explanation for the disparity is the authors’ use of chiral shift reagent NMR analysis to determine the enantiomeric composition of the dibromide products. Unfortunately, the spectral data are not provided. Our own attempt to observe signal separation in a racemic sample of 1-(2,3-dibromo-propoxy)-4-methoxybenzene 5a using Eu(hfc)₃ was inconclusive. After portionwise addition of 4 equiv of the chiral shift reagent, some degree of signal separation was observed, showing roughly equal quantities of each enantiomer. However, the level of signal broadening precluded any quantitative determination of enantiomeric ratios.

In conclusion, four dibromination and four chlorohydroxylation reactions of aliphatic ethers catalyzed by chiral mono- or dinuclear palladium(II) complexes reported by Henry and co-workers were repeated. Although the reaction yields were reproduced, the dibromide and chlorohydrin products were generated in racemic form.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b02650.

Full experimental procedures, analyses, characterization data, and NMR data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: sdenmark@illinois.edu.

Notes

The authors declare no competing financial interest.

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