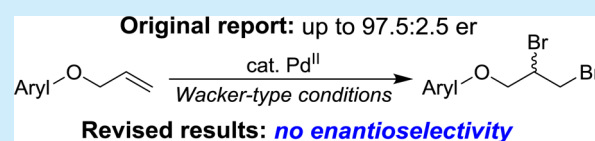# Reinvestigation of a Catalytic, Enantioselective Alkene Dibromination and Chlorohydroxylation

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S *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.

Original report: up to 97.5:2.5 er

Aryl^O$\diagdown$$\diagup$ $\xrightarrow[\textit{Wacker-type conditions}]{\text{cat. Pd}^{\text{II}}}$ Aryl^O$\diagdown$$\diagup$Br$_2$

Revised results: *no enantioselectivity*

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.[1] However, catalytic dihalogenation methods, in which the absolute configuration of the products is controlled from an achiral starting material, have proved elusive until recently.[2] 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.[3]

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 Br$_2$, vicinal dibromides are formed via bromide ion attack on either an alkene−Br$_2$ π-complex or a bromiranium ion, resulting in *anti*-stereospecific addition of Br$_2$ across the double bond.[4] However, strategies for enantioselectivity may be thwarted in a number of ways: (1) A 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−Br$_2$ 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;[5] and (4) the regioselectivity of bromide addition must also be controlled, since attack on either carbon atom of a non-C$_2$-symmetric bromiranium ion intermediate yields enantiomeric products.

In 2011, Nicolaou et al. reported a dichlorination reaction of allylic alcohols using (DHQ)$_2$PHAL as the catalyst and 4-Ph(C$_6$H$_4$)ICl$_2$ as the chlorinating agent.[6] 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(O*i*-Pr)$_3$ as a nucleophilic bromine source, with a TADDOL-derived catalyst.[7] 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.[8]

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.[9] An enantioselective variant of this reaction was subsequently reported by Henry and co-workers, using chiral, nonracemic palladium(II) bisphosphine catalysts **3a** to achieve the enantioselective generation of chlorohydrins **2** from terminal alkenes **1**.[10] 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 O$_2$ uptake.

Enantioselectivity was improved in later work by Henry and co-workers, by the use of dinuclear palladium(II) complexes **4** with bridging triketone ligands, although no direct comparisons to the mononuclear catalysts were made.[11] Terminal olefins **1** were oxidized to chlorohydrins **2** with constitutional site selectivities of 2.3:1−>95:1 and enantioselectivities of 57.5:42.5−97:3 er (Scheme 1b).
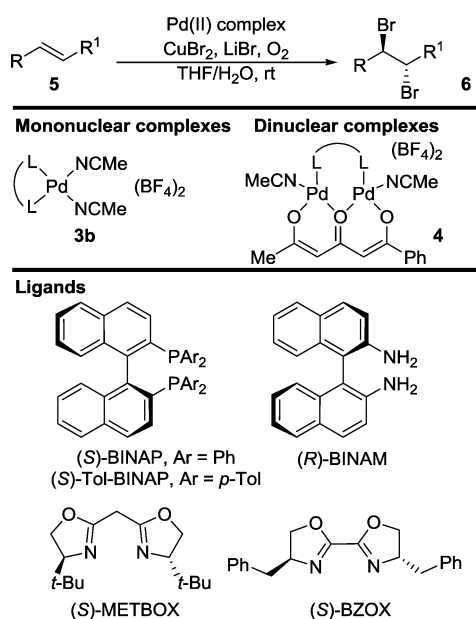
Henry and co-workers later reported an extension of this work to the enantioselective dibromination of olefins, using similar Wacker-type conditions with 2.5−17.7 mol % (per Pd atom) palladium(II) catalyst **3b** or **4** (Scheme 2).[12] The

Scheme 1. Henry's Wacker-Type Chlorohydrin Synthesis
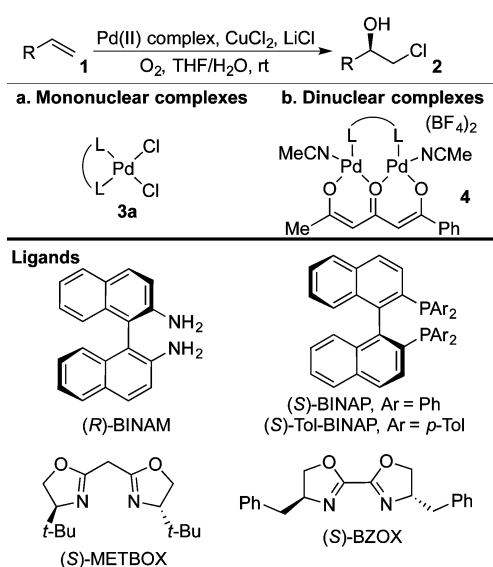
Scheme 2. Henry's Enantioselective Dibromination of Alkenes

reactions were performed in aqueous THF solutions of varying composition, containing copper(II) bromide (~2 M) and lithium bromide (0.13–0.29 M). The concentration of alkene substrate **5** varied between 0.06 and 0.47 M. Since these reaction conditions (i.e., concentrations of LiBr, CuBr$_2$, catalyst, and alkene, and solvent THF/H$_2$O ratio) varied so considerably among substrates, direct comparisons are of limited value. The higher intrinsic nucleophilicity of bromide ion compared to H$_2$O, coupled with the high bromide ion concentrations employed led to the formation of vicinal dibromides **6** rather than bromohydrins as the major products. Although the yields of dibromides reported were highly variable (31–95%),[13] good to excellent enantioselectivities were claimed (90:10–98.5:1.5 er), with the exception of methyl (*E*)-cinnamate (57:43 er). Enantiomeric ratios were determined by ^{1}H NMR spectroscopic analysis using Eu(hfc)$_3$ (europium tris[3-(heptafluoropropyl-hydroxymethylene)-*d*-
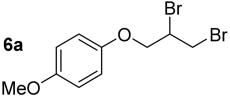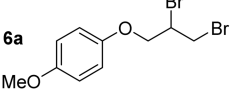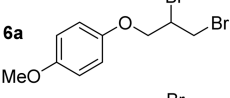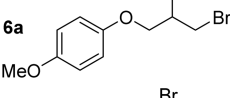
camphorate), although neither spectra nor details of concentrations were given. Optical rotation data were provided for only two of the nine dibromide products.
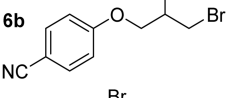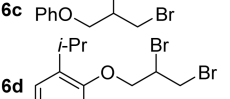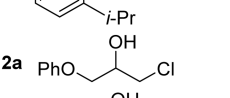
We have attempted to replicate four reactions in the original report from Henry and co-workers (Table 1, entries 1–7). The allylic ether dibromination procedures were repeated as rigorously as the described procedures allow, albeit on a smaller scale (0.25 mmol versus 2.8–3.7 mmol allylic ether in the original work). To confirm that scale was not a critical factor, one tria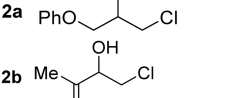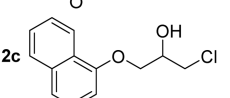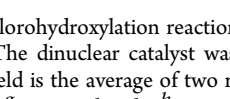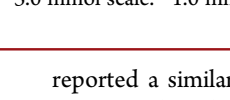l, Table 1, entry 3, was performed on the original 3.0 mmol scale and was allowed to run for the original reaction time of 6 days. Although dibromides **6** revert back to the corresponding allylic ethers **5a–d** over several weeks in light, running reactions and isolating products in the dark affected 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 ^{31}P 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 Et$_3$N was used as a Brønsted base.[11b] This procedure afforded compounds that appeared to be pure by ^{31}P 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 ^{31}P 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)$_4$(BF$_4$)$_2$ and the requisite chiral bisphosphine.[14] The mononuclear catalyst used in Table 1, entry 7 was prepared under Ar and found to be stable in the absence of air and moisture.[15] The reactions were run under positive pressure from an O$_2$ manifold.

Moderate to high yields of dibrominated products **6** were obtained, with small amounts of side products observable in the ^{1}H 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). It is notable that, in our hands, the complete conversion of starting material was achieved in significantly shorter times than those quoted in the original work: 24 or 28 h versus 4–7 days. It is possible that the original reactions were monitored by O$_2$ uptake whereas our experiments were monitored by TLC. A repeat of the dibromination of **5a** was arbitrarily stopped after 6 h (Table 1, entry 4) to determine whether an initial enantioselective process may occur, only to be compromised by epimerization under the reaction conditions. In this case as well the product was racemic.

Table 1. Comparison of Results for the Dibromination and Chlorohydroxylation of Several Substrates (NR = not reported)[a]

Run	Ligand	Complex Type	Complex Nuclearity	Time, d	Product	Yield, %	er	Lit. yield, %	Lit. er
1	(R)-BINAP[b,c]	4	2[d]	1.17	6a	86[e]	50:50	95	98:2
2	(R)-BINAP[b,f]	4	2[d]	1.17	6a	86[e]	50:50	95	98:2
3	(R)-BINAP[b]	3	1[d]	6	6a	78[g]	50:50	95	98:2
4	(R)-BINAP[b]	3	1[d]	0.25	6a	65[e]	50:50	-	-
5	(R)-Tol-BINAP[b]	4	2	1	6b	85[e]	50:50	95	98.5:1.5
6	(R)-BINAP[b,f]	4	2	1	6c	69[e]	50:50	95	97.5:2.5
7	(R)-BINAP[b]	3	1	1	6d	90[e]	50:50	95	97:3
8	(R)-Tol-BINAP	3	1	14	2a	14	50:50	NR	90:10
9	(R)-BINAP[b,c]	4	2	5	2a	40	50:50	92	96.5:3.5
10	(R)-Tol-BINAP	3	1	10	2b	33[h]	50:50	NR	91:9
11	(R)-BINAP[b,c]	4	2	10	2c	29	50:50	95[i]	90:10

[a]Dibromination reactions were performed on a 0.25 mmol scale and chlorohydroxylation reactions on a 0.50 mmol scale unless otherwise specified. [b]The (S)-enantiomer of the ligands was used in the original work. [c]The dinuclear catalyst was prepared according to Henry's procedure. [d]The nuclearity of the catalyst used is ambiguous in the original text. [e]The yield is the average of two runs, each within 2% of the average. [f]The dinuclear catalyst was prepared according to a modification of Henry's procedure. [g]3.0 mmol scale. [h]1.0 mmol scale. [i]The product was mischaracterized in the original work.

In light of these results, four chlorohydroxylation reactions from Henry and co-workers' earlier reports were also investigated (Table 1, entries 8−11).[10] 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 **5**. 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.[16] 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.[12] 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 O_2 uptake.[17] However, measurement of O_2 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 O_2 uptake. However, the amount of recovered starting material is 30% by mass.[12] This inconsistency exemplifies that O_2 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 Br_2 under the reaction conditions, and of course, $CuBr_2$ itself is also capable of effecting the dibromination of alkenes at room

Scheme 3. Catalytic Cycle for Dibromide Formation
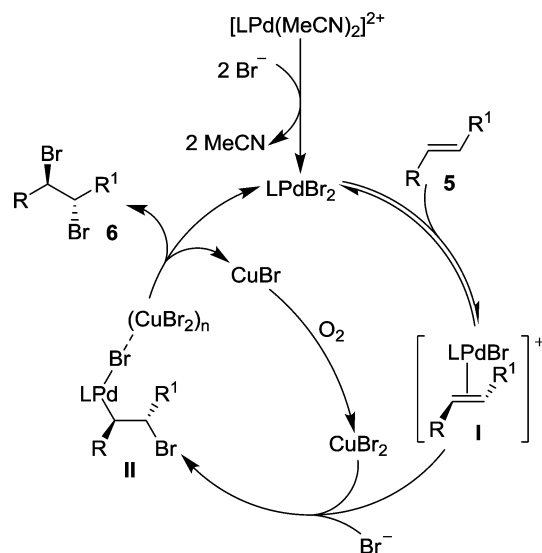
temperature.[18] However, in our opinion, the more likely explanation for the disparity is the authors' use of chiral shift reagent NMR analysis to determine the enantiomeric composition of the dibromide products. Unfortunately, the spectral data are not provided. Our own attempt to observe signal separation in a racemic sample of 1-(2,3-dibromopropoxy)-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 allylic 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.orglett.5b02650.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(13) The true yield of methyl crotonate dibromination is indecipherable. Henry et al. report a yield of 80% based on oxygen uptake, yet 30% of starting material was also recovered.

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