

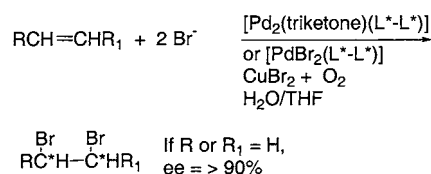
New Palladium(II)-Catalyzed Asymmetric 1,2-Dibromo Synthesis

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ABSTRACT



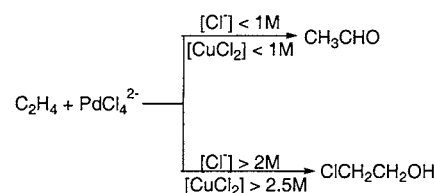
The oxidation of olefins by chiral monometallic and bimetallic Pd(II)–Cu(II) catalysts in bromide-containing aqueous–THF reaction mixtures produced chiral 1,2-dibromides. With α -olefins, the ee's were about 95% while most of the internal alkenes gave somewhat lower enantioselectivities (~80%).

In some reactions of 1,2-dibromides, elimination of HBr occurs with or without substitution,¹ there are many reactions where substitution takes place without elimination.² With chiral 1,2-dibromides, these latter systems could be the basis of new asymmetric syntheses. Yet the use of chiral 1,2-dibromides in asymmetric synthesis is very limited because there are no simple means of preparing these starting materials. Thus, the development of a convenient one-step synthesis of chiral 1,2-dibromides would provide a valuable new tool for asymmetric synthesis.

Previous papers from these laboratories described a palladium(II)-catalyzed asymmetric chlorohydrin synthesis.³ Although Pd(II) salts in aqueous solution oxidize ethene to acetaldehyde under the usual Wacker conditions ($[\text{Cl}^-] \sim 1 \text{ M}$; $[\text{CuCl}_2] \sim 1 \text{ M}$), at higher $[\text{Cl}^-]$ ($> 2 \text{ M}$) and $[\text{CuCl}_2]$ ($> 2.5 \text{ M}$), chlorohydrins become the main product (Scheme 1).

If monometallic or bimetallic catalytic species containing chiral chelating diphosphine or diamine ligands are employed

Scheme 1. Reaction of Ethene under Two Sets of $[\text{Cl}^-]$ and $[\text{CuCl}_2]$ Conditions



(Figure 1), asymmetric induction occurs to give chiral chlorohydrins (Scheme 2). In general, the bimetallic catalysts **B** provided the highest enantioselectivities. In some cases, the ee's were $> 90\%$. The 1/2 ratios ranged from 2.5 to 12

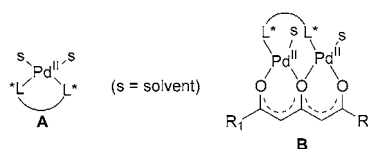


Figure 1. Structures of monometallic and bimetallic catalysts.

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(1) (a) Kashima, C.; Tajima, T.; Omote, Y., *J. Heterocycl. Chem.* **1984**, *21*, 171. (b) Hagiwara, H.; Abe, F.; Uda, H. *J. Chem. Soc., Perkin Trans. I* **1993**, 2651. (c) Fevig, J. M.; Marquis, R. W.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085.

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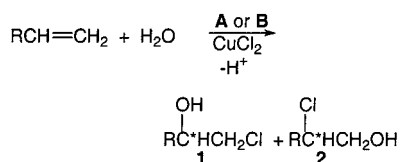
Table 1. Results for the Oxidation of Several Substrates^a

entry	L*–L* ^b	catalyst	[LiBr] (M)	substrate	% yield of 3	% ee of 3	catalyst turnovers
1	(S)-BINAP	B	0.25	<i>p</i> -CH ₃ O-phenyl allyl ether	95	96	85
2	(S)-Tol-BINAP	B	0.13	<i>p</i> -CN-phenyl allyl ether	95	97	88
3	(S)-BINAP	B	0.20	phenyl allyl ether	95	95	148
4	(S)-BINAP	A	0.20	(2,6-diisopropyl)phenyl allyl ether	95	94	80
5	(S)-METBOX	B	0.20	methyl acrylate	84	94	25
6	(S)-BZOX	A	0.30	methyl crotonate	80	84 ^c	13
7	(S)-METBOX	B	0.30	methyl crotonate	80	82 ^c	30
8	(<i>R</i>)-BINDA	B	0.20	cinnamyl alcohol	77	80 ^c	21
9	(<i>R</i>)-BINDA	B	0.0	cinnamyl alcohol	75	34 ^c	20
10	(<i>R</i>)-BINDA	B	0.20	methyl <i>trans</i> -cinnamate	84	14 ^c	10

^a All runs contain 0.05–0.12 mmol of chiral catalyst in 20–30 mL of solvent and 2.0–2.5 M in CuBr₂. Temperature = 25 °C. The solvent was a H₂O/THF mixture containing 54–93% THF by volume. ^b (S)-BINAP = (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, (S)-Tol-BINAP = (S)-(-)-2,2'-bis(ditolylphosphino)-1,1'-binaphthyl, (S)-METBOX = 2,2'-methylenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], (S)-BZOX = 2,2'-methylenebis[(4*S*)-4-benzyl-2-oxazoline], (*R*)-BINDA = (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine. ^c These dibromides have the (*RS*,*SR*) configuration.

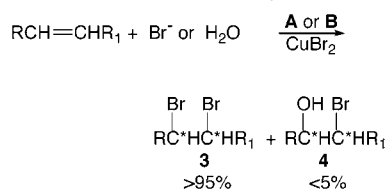
for simple α -olefins but were >90 for allyl ethers. Aldehydes and ketones constituted 5–20% of the total product.

Scheme 2. CuCl₂-Promoted Chlorohydrin Synthesis



This paper reports the results obtained for the reaction in bromide-containing media. Surprising, the oxidation of olefins did not produce the expected bromohydrin. Instead, the predominate products were the 1,2-dibromides (Scheme 3). Furthermore, for α -olefins, the dibromides were obtained

Scheme 3 Dibromo Synthesis



in high enantioselectivity (ee ~95%). Both monometallic, **A**, and bimetallic, **B**, catalysts were effective. Table 1 lists the results for several olefins.

As with the chlorohydrin synthesis, the reaction is a net air oxidation since the CuBr formed in the dibromo reaction is oxidized back to CuBr₂ by oxygen. Catalyst turnovers in

Table 1 ranged from 10 to 150, but the rate did not decrease during the course of the reaction. This raises the possibility that catalyst turnovers could be further increased, though we have yet to demonstrate this experimentally.

The first three runs with para-substituted phenyl allyl ethers test the electronic effects on the oxidation. Since the results for all three runs were very similar, electronic effects have little impact on enantioselectivity in this series of substrates. This result is consistent with other palladium(II) catalytic chemistry.⁴ Entry 4 suggests that steric hindrance is not an important factor.

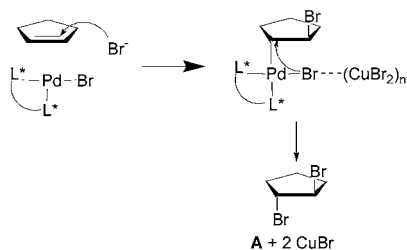
The enantioselectivities for the internal olefins were somewhat poorer than those found for the α -olefins. This could not be due to the variation in chiral ligand. Entries 5 and 6 have the same ligand, but the % ee decreased from 94 for oxidation of methyl acrylate to 82 for the oxidation of methyl crotonate. In addition, the rates, catalyst turnovers, and yields were poorer for the runs with internal alkenes. Entries 8 and 9 demonstrate the important of bromide ion concentration. When no extra bromide is added, the ee drops from 34% from 80%. The low enantioselectivity observed with methyl *trans*-cinnamate is surprising, but similar results were observed for several other runs using this substrate.

These results can be compared with those for the chlorohydrin reaction where internal olefins were completely unreactive. In addition, with α -olefins, a certain minimal concentration of [Cl⁻] had to be present to achieve the maximum enantioselectivities. The dibromo product, **3**, from methyl crotonate, cinnamyl alcohol, and methyl *trans*-cinnamate has the (*RS*,*SR*) configuration. This result is consistent with *trans* addition to the double bond. To establish the stereochemistry of the reaction further a sample of cyclopentene was reacted under the conditions used in Table 1. The main product was the expected 1,2-dibromocyclopentane in 85% yield. The dibromocyclopentane had the *trans* configuration. As shown in Scheme 4, using catalyst **A** for simplicity, the stereochemistry is consistent with anti attack

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Scheme 4. Reaction Pathway for the Oxidation of Cyclopentene



of bromide followed by decomposition involving attack of bromide from the coordination sphere of the Pd(II). It is also possible that the bromide comes from the Cu(II) coordinated to the Pd(II). A similar scheme was postulated for the chlorohydrin product in the chlorine-containing system.^{3b}

The fact that the bromide system produces dibromides rather than bromohydrins almost exclusively can be attributed to the strength of bromide as a nucleophile. The bromide must be a much better nucleophile than chloride or water in palladium(II) catalytic chemistry since, for the examples in Table 1, the concentration of water is at least 200 times the concentration of bromide.

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Supporting Information Available: Procedures and spectra data for chiral syntheses. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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