Coupling Reactions

Catalytic Reductive Coupling of Epoxides and Aldehydes: Epoxide-Ring Opening Precedes Carbonyl Reduction**

*Carmela Molinaro and Timothy F. Jamison**

Transition-metal-catalyzed reductive coupling reactions have attracted considerable interest for several decades since the development of reductive polymerization of carbon monoxide by Fischer and Tropsch.[1] Hydroformylation[2] and the Nozaki–Hiyama–Kishi reaction[3] are other important examples, and in the past decade dozens of nickel- and rhodium-catalyzed reductive coupling reactions have also been described.[4] Represented among these transformations are diverse coupling partners, catalysts, and mechanisms, yet what they have in common is the formation of a carbon–carbon bond. In contrast, with the exception of reductive etherification of carbonyl groups and acetals,[5] catalytic reductive C–O bond formation has remained largely unexplored,[6,7] despite the recent emergence of transition-metal-catalyzed carbon–oxygen bond-forming methods[8] and the importance of oligosaccharides, ribonucleic acids, epoxy resins, natural products, and pharmaceuticals. We now report the first example of such a transformation that employs epoxides (Table 1). Several lines of evidence suggest, perhaps counterintuitively, that carbonyl reduction occurs after epoxide-ring opening.

Recently we reported that a species derived from $[Ni(cod)_2]$ and Bu_3P catalyzes the inter- and intramolecular reductive coupling of alkynes and terminal epoxides to give homoallylic alcohols.[4a,9] To account for several observations, we proposed that epoxide-ring opening occurred prior to carbon–carbon bond formation, possibly by way of a metallaoxetane.[9a,10–11] We reasoned that this species would likely have very different reactivity patterns to those of the epoxide itself, and accordingly we have begun to investigate catalytic reductive coupling reactions of epoxides with other functional groups, including aldehydes.

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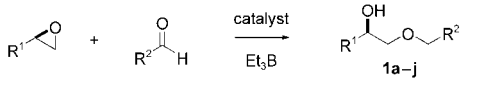
We initially examined a number of nickel(II) and nickel(0) complexes and found that, at room temperature and without added solvent, both $[Ni(cod)_2]/PBu_3$ and $[NiCl_2(PBu_3)_2]$ catalyzed a reductive ring-opening reaction between 1,2-epoxybutane and benzaldehyde in the presence of Et_3B, giving the 1-benzyl ether of 1,2-butanediol with high selectivity (Table 1, entries 1–2). Superior results (Table 1, entries 3–11) were obtained with $[(Ph_3P)_3RhCl]$ (also without added solvent), representing the first use of Et_3B as reductant in a reaction promoted by the Wilkinson catalyst. Sterically

Table 1: Transition-metal-catalyzed reductive coupling of epoxides and aldehydes.[a]



Entry	R^1	R^2	Catalyst	Product	Yield [%]
1	Et	Ph	$[Ni(cod)_2]$, Bu_3P	**1a**	64
2	Et	Ph	$[(Bu_3P)_2NiCl_2]$	**1a**	62
3	Et	Ph	$[(Ph_3P)_3RhCl]$	**1a**	90
4	Ph	Ph	$[(Ph_3P)_3RhCl]$	**1b**	74
5	*i*Pr	Ph	$[(Ph_3P)_3RhCl]$	**1c**	26
6	*t*Bu	Ph	$[(Ph_3P)_3RhCl]$	**1d**	12
7	*i*Pr	Ph	$[(Ph_3P)_3RhCl]$, Et_3N	**1c**	96
8	*t*Bu	Ph	$[(Ph_3P)_3RhCl]$, Et_3N	**1d**	90
9	Et	2-naphthyl	$[(Ph_3P)_3RhCl]$, Et_3N	**1e**	70
10	*n*-hexyl	*p*-anisyl	$[(Ph_3P)_3RhCl]$, Et_3N	**1f**	67
11	*n*-hexyl	2-furyl	$[(Ph_3P)_3RhCl]$, Et_3N	**1g**	57
12	*n*-hexyl	*i*Pr	$[(Ph_3P)_3RhCl]$, Et_3N	**1h**	15

[a] Standard procedure: To the catalyst specified and, where indicated, Et_3N (20 mol%) at room temperature were added the epoxide, aldehyde, Et_3B (200 mol%, dropwise). The mixture was stirred for 16 h and purified by silica-gel chromatography. See Supporting Information for details. cod = cycloocta-1,5-diene.

encumbered epoxides such as *tert*-butyloxirane and isopropyloxirane underwent near-quantitative reductive coupling when a substoichiometric amount of Et_3N was included (Table 1, entries 5–8). Other aromatic and heteroaromatic aldehydes were also effective (Table 1, entries 9–11). The reaction between isobutyraldehyde and 1,2-epoxyoctane proceeded in 15% yield (Table 1, entry 12).[12] Several ketones (benzophenone, acetophenone, cyclohexanone, and 2-octanone) underwent catalytic reductive coupling in 10–25% yield. Despite the large variation in steric and electronic properties of the epoxides in the above examples, the regioselectivity of the ring-opening reaction was universally >95:5, a significant observation as aryl and alkyl oxiranes often undergo ring opening with the opposite sense of regioselectivity.[13–14]

Three examples are worthy of further comment. The one-step Rh-catalyzed reductive coupling shown in Equation (1) demonstrates the tolerance of acid-labile functional groups that would be problematic in a more traditional two-step approach, for example, reduction with $NaBH_4$ and acid-promoted epoxide opening. Complementarity to Jacobsen's methods of enantioselective epoxide opening by oxygen-centered nucleophiles[15] is demonstrated in Equation (2)

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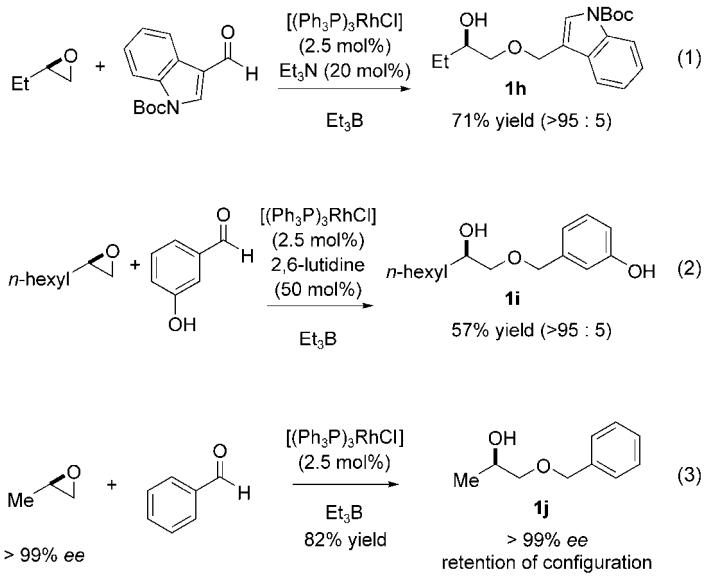
(Boc = *tert*-butoxycarbonyl). Phenolic hydroxy groups are typically more reactive than aliphatic hydroxy groups in [(salen)Co]-catalyzed ring openings,[15e–f] yet in the Rh/Et_3B system the former are unreactive which allows the aldehyde to function as a masked hydroxymethyl group. Finally, as shown in Equation (3), the stereochemical integrity of the epoxide is preserved in these transformations.

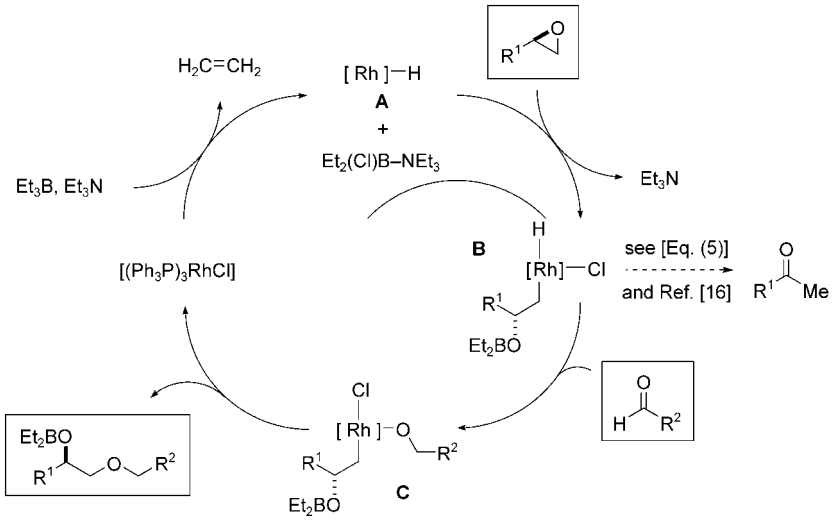


It might be expected that reduction of the aldehyde would initiate these reactions, giving a nucleophilic metal alkoxide that would then open the epoxide. However, we have found no evidence whatsoever to support this mechanistic framework. Reduction of the aldehyde does not occur in the absence of epoxide, even with 50 mol% catalyst [Eq. (4)], and isomerization of the epoxide to a methyl ketone[16] occurs in the absence of aldehyde [Eq. (5)]. It is unlikely that this process is a Lewis acid promoted 1,2-H shift as a terminal epoxide would generally rearrange to an aldehyde.[13b,17]

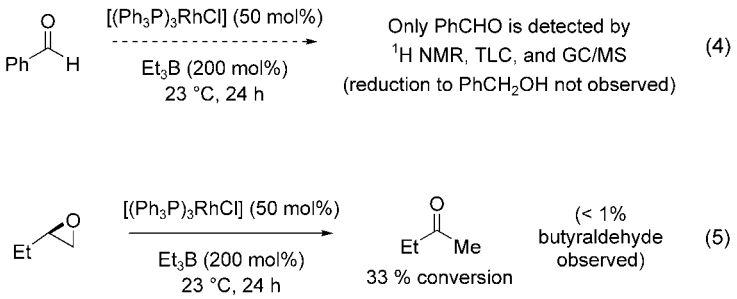
The reactivity of epoxides toward Rh complexes[16,18] [Eq. (5)] and the fact that the aldehyde is not reduced in the absence of epoxide [Eq. (4)] can both be explained by a catalytic cycle in which reduction of the carbonyl follows epoxide opening (Scheme 1).[19] A combination of [$(Ph_3P)_3RhCl$], Et_3B, and Et_3N affords ethylene, $Et_2(Cl)B$-NEt_3 and species **A**, which opens the epoxide,[16] possibly assisted by Et_2BCl, leading to **B** and the regeneration of Et_3N. In other words, Et_3N may serve to temper the Lewis acidity of Et_2BCl.[20] Coordination of the aldehyde to **B**[21] and formal reduction of the carbonyl could occur at this stage to provide **C**, and C–O bond formation through reductive elimination of the product as a borinate ester would complete the catalytic cycle. A similar mechanism involving nickel (Table 1, entries 1–2) can also be envisioned.[9a,10]

Several other experiments and observations also support this proposal. Ethylene is present in the atmosphere above the reaction mixture (^{1}H NMR spectroscopic analysis of head gas samples). In support of **B** (or a related species), ^{11}B NMR spectra of a mixture of all reaction components except for the aldehyde show the appearance of a new signal at $\delta = 53$ ppm (see Supporting Information), representative of Et_2B-OR.[22]

One could also imagine a mechanism in which a Rh species undergoes addition to the aldehyde,[23] the resulting alkoxide opens the epoxide, and then the Rh–C bond is reduced thereafter. To account for the results in Equation (4), therefore, the carbonyl addition would have to be reversible, and the results of Equation (5) and several ^{11}B NMR spectroscopy experiments (see above) would necessarily have to originate from a process not directly involved in the catalytic cycle. Nevertheless, as in the mechanism shown in Scheme 1, epoxide-ring opening still precedes carbonyl reduction in this alternate framework.



Scheme 1. Proposed mechanism for the catalytic reductive coupling of epoxides and aldehydes.



In summary, only off-the-shelf reagents and catalysts are required to effect both a reduction and a carbon–oxygen bond formation in the reductive coupling of two of the most readily available functional groups to provide differentially modified, synthetically useful 1,2-diols in a single catalytic operation. The regioselectivity of this process is very high; none of the

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minor regioisomer can be detected by ^{1}H NMR spectroscopic analysis of the unpurified product mixtures. This method circumvents one of the key problems of catalytic C–O bond formation, β-elimination of a carbinol hydrogen atom to give an aldehyde (or ketone) and an M–H species that is often catalytically inactive.[8d] Moreover, as all evidence suggests that epoxide-ring opening occurs prior to reduction of the aldehyde, other functional groups might also undergo reductive coupling with epoxides by way of proposed intermediate **B**. Thus, these first examples of metal-catalyzed reductive C–O bond formation of epoxides not only are of inherent utility, but also provide a starting point for the development of other useful catalytic reductive C–X coupling methods.

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