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Anionic Zirconaoxiranes as Nucleophilic Aldehyde Equivalents. Application to Intermolecular Pinacol Cross Coupling

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Summary: Selective intermolecular pinacol cross coupling is achieved by reaction of anionic zirconaoxiranes with aromatic aldehydes and ketones, thereby providing an efficient route to unsymmetrical vicinal diols.

The intermolecular reductive coupling of aldehydes or ketones (pinacol coupling) is an attractive method for carbon–carbon bond formation if symmetrical vicinal diols are desired.[1] However, if unsymmetrical diols are required, known methods to accomplish the cross coupling suffer from production of approximately statistical mixtures of products[2] unless one carbonyl component is electronically activated[3] or is a specially functionalized "chelation-accelerated" aldehyde.[4] Other routes to unsymmetrical vicinal diols (e.g., epoxide ring openings,[5] olefin osmylations,[6] and α-hydroxy carbonyl reductions[7]) require the presence of the central carbon–carbon bond in the starting materials.

A potentially general and selective approach to intermolecular pinacol cross coupling is a stepwise one in which one aldehyde is first incorporated into a reactive organometallic complex and then exposed to the second carbonyl component. This forms the basis for the Yb-mediated selective cross coupling of diaryl ketones with aliphatic ketones.[3a,b] However, the intermediate Yb complexes are only formed with diaryl ketones. Other ketones and aldehydes are unreactive.

We have recently obtained general and efficient access to thermally stable anionic zirconocene(η^2-aldehyde) complexes through a route involving transmetalation of zirconocene (α-stannylalkoxide) complexes with methyllithium at low temperature[8] (Figure 1). The structural features of these electron-rich η^2-aldehyde complexes[8] show that the zirconaoxirane resonance structure is an appropriate description thereby indicating that a large amount of electron density resides on the aldehyde fragment. This has led us to explore the applications of these complexes as nucleophilic aldehyde equivalents.

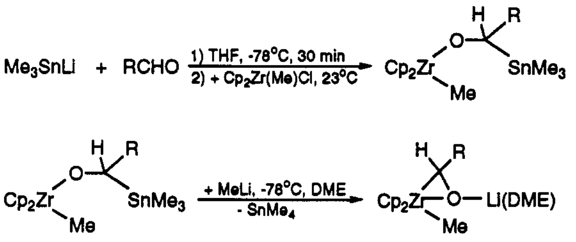
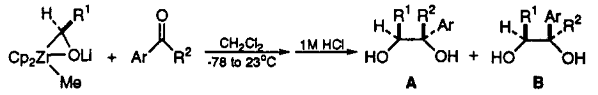


Figure 1.

Table I



R^1	Ar	R^2	A:B	yield[a] (%)
p-tolyl	*p*-tolyl	H	19:1[b]	78
p-tolyl	phenyl	H	19:1[b]	75
p-tolyl	phenyl	phenyl		81
p-tolyl	phenyl	methyl	7:1	77
phenyl	phenyl	methyl	7:1[c]	76
phenyl	phenyl	H	19:1[b]	79
iso-butyl	*p*-tolyl	H	9:1[b]	63
iso-butyl	phenyl	phenyl		67
ethyl	*p*-tolyl	H	3:2[b]	57
ethyl	phenyl	phenyl		61

[a] Combined yield of A + B after isolation by chromatography (silica, ethyl acetate/hexane). [b] Determined by ^{1}H NMR (250 MHz) of the crude reaction mixture after hydrolysis. The ArC*H*(OH) resonance in the threo isomers is consistently upfield of that in the erythro isomers.[16] [c] Erythro compound assigned by comparison of the ^{13}C NMR spectrum to that previously reported.[17]

We now report that anionic zirconaoxiranes are effective nucleophiles toward aromatic aldehydes and ketones. Thus, reaction with 1 equiv of an aromatic aldehyde or ketone proceeds readily in cold dichloromethane solution producing vicinal diols in good yield after acidic hydrolysis (Table I). In reactions where the free and the bound carbonyls are different, only the unsymmetrical diols are observed. Diastereoselectivity is found to favor the threo isomers in all cases and increases as the steric demands

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(8) Askham, F. R.; Carroll, K. M.; Alexander, S. J.; Rheingold, A. L.; Haggerty, B. S. *Organometallics*, in press. Note: Substitution of Bu$_3$SnLi and BuLi for Me$_3$SnLi and MeLi in this synthesis is possible. However, it is critical to completely remove the last traces of SnBu$_4$ since this catalytically decomposes the anionic zirconaoxiranes over 24 h even when isolated as solid materials. Use of Me$_3$SnLi and MeLi avoids this problem since SnMe$_4$ is volatile and is removed completely upon solvent evaporation.

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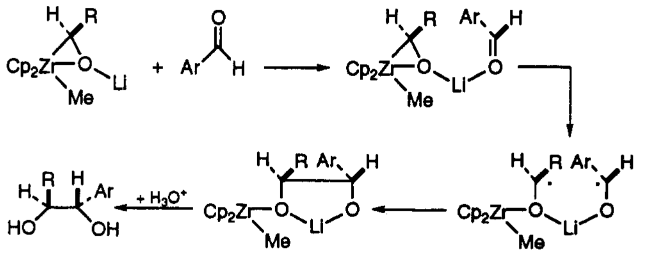

Figure 2.

of the R group increase. This contrasts with the low selectivities found in homocouplings induced by simple reducing agents. For example, reaction of the anionic benzaldehyde complex with free benzaldehyde leads to a 19:1 mixture of *dl*/meso hydrobenzoin after hydrolysis as compared with *dl*/meso diastereoselectivities of 56:44, 13:10, and 1:1 using SmI_2,[1d] $TiCl_3$,[1f] or Zn,[1a] respectively, to reductively couple benzaldehyde. McGarvey has reported reactions of α-lithioethers (generated by transmetalation of α-stannyl ethers) with benzaldehyde which produce monoprotected vicinal diols.[9] Selectivitiy in this system also favors formation of the threo isomer and correlates with the steric bulk of substituents although selectivities are modest (typically 2:1).

In contrast to the successful use of aromatic aldehydes and ketones as the electrophilic partner in our reactions, aliphatic aldehydes or ketones (e.g., isovaleraldehyde or 3-pentanone) fail as substrates. This was surprising since aliphatic aldehydes and ketones are generally more reactive toward alkyllithiums and Grignard reagents than their aromatic analogs.[10] Such a dramatic dependence on the presence of an aromatic functionality could arise if the mechanism requires a reduction of the electrophile to a ketyl radical anion in the rate-determining step. In aprotic solvents, aromatic aldehydes and ketones generally have reduction potentials in the range −1.8 to −2.0 V (vs SCE)[11a] while aliphatic examples are in the range −2.2 to −2.8 V (vs SCE).[11b] In fact, reactions of Grignard reagents with benzophenones have been shown by others to involve a single electron transfer (SET) process while with aliphatic ketones a polar mechanism dominates.[12]

A mechanism for our reaction which incorporates an SET process and also rationalizes the trends we observe in threo selectivities is shown in Figure 2. Note that direct interaction of the electrophile with the zirconium atom is not possible due to coordinative saturation. Several lines of evidence (e.g., the X-ray structure of the isovaleraldehyde complex[8] and the fact that lithium cannot be exchanged for noncoordinating cations such as Bu_4N^+) indicate that lithium forms a tight ion pair with the anionic zirconaoxirane by coordination to oxygen. Complexation of the free carbonyl to the lithium cation in the first step of the mechanism is analogous to the initial coordination of carbonyls to lithium in their reactions with alkyllithiums.[13] In our case, the necessity of electrophile precoordination to lithium is supported by the fact that these reactions fail in tetrahydrofuran (a coordinating solvent) but proceed readily in dichloromethane (a noncoordinating solvent). Coordination to the lithium cation would be expected to lower the reduction potential of the carbonyl compound,[14] thereby facilitating the subsequent SET step. This interaction would also maintain the two C–O bonds approximately parallel as the two carbons approach each other. Minimization of steric interactions in such an intermediate would then lead to the threo product which is always observed as the major isomer. Homocoupling products of the free carbonyl component are not observed in these reactions indicating that C–C bond formation is rapid relative to escape of the ketyl radical anions. This is not surprising since anion radicals are known to form tight ion pairs with alkali metal cations[15] and the two ketyls are formed in close proximity while being bridged by a lithium cation. Significantly, trimetallic reducing agents derived from reduction of titanocene dichloride with zinc or Grignard reagents have been reported to couple benzaldehyde with *dl*/meso selectivities of up to 80:1 through intermediates possessing two bound ketyl radicals.[16]

In summary, anionic zirconaoxiranes have been shown to be effective reagents for selective intermolecular pinacol cross coupling reactions. Presently, the major limitation in this method is the lack of reactivity toward aliphatic aldehydes and ketones. We are currently working to overcome this limitation by increasing the electron density on the anionic zirconaoxiranes by manipulation of the ancillary ligand set.

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Supplementary Material Available: Experimental procedures for the reactions of anionic zirconaoxiranes with aromatic aldehydes and ketones including ^1H and ^{13}C NMR data of the diol products (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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