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Diastereoselective electrophilic substitution of γ-oxy-substituted benzyllithiums[†]

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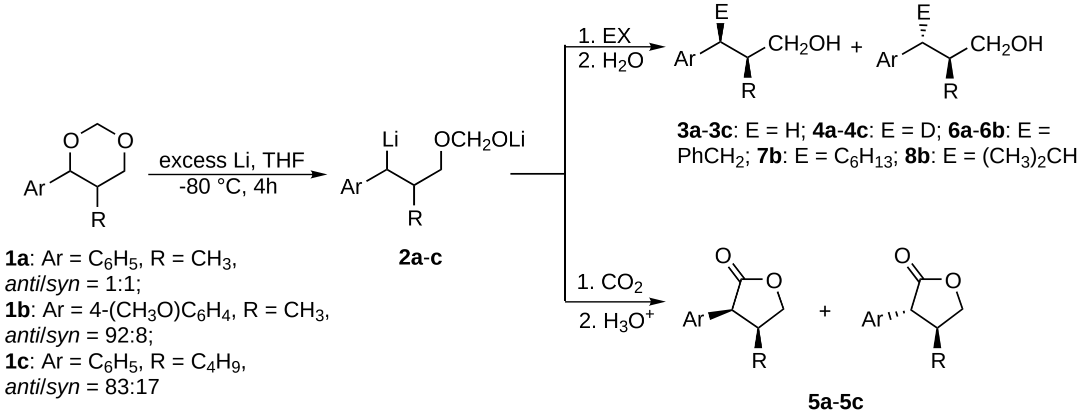
Abstract—Reductive lithiation of diastereoisomeric mixtures of 4-aryl-5-methyl-1,3-dioxanes occurs with epimerization at the benzylic centre. Reaction of intermediate organometals with alkyl halides or CO_2 afforded 2-methyl-3-substituted-3-phenylpropan-1-ols, or the corresponding lactones, with satisfactory yields and satisfactory to high diastereoselectivities. Observed diastereoselectivities strongly depend on the substitution pattern of starting materials. © 2002 Elsevier Science Ltd. All rights reserved.

The configurational stability of chiral α-substituted arylmethyl organometallics and their ability to react with electrophiles in a stereodefined manner is a topic of current interest in organic chemistry.[1–4] Investigations on the carbolithiation of cinnamyl alcohol showed that the alkoxy substitutent is able to coordinate the organometallic centre and to fix its configuration, thus allowing, after thermodynamic equilibration of epimeric intermediates, diastereoselective reaction with electrophiles.[5,6] The reaction was extended to several derivatives of cinnamyl alcohol, showing a strong influence of the coordinative group on the stereochemical result of the electrophilic substitution reaction.[7,8] As a limitation, carbometalation cannot be applied to the synthesis of 3-substituted-2-methyl-3-phenylpropan-1-ols: indeed, no successful addition of CH_3Li to cinnamyl alcohol was reported.[6,9]

We recently reported that reductive lithiation of 4-phenyl-1,3-dioxanes, followed by reaction with electrophiles, affords 3-substituted-3-phenylpropan-1-ols. According to this procedure, a benzylic organometallic reagent is generated together with a potentially coordinative lithiumoxymethyl group.[10] We have now further extended this procedure to the reductive lithiation of diastereoisomeric mixtures of 5-alkyl-4-aryl-1,3-dioxanes **1a**–**c**, and report here interesting observations concerning the dramatic effect of the substitution pat-



Scheme 1. Reductive lithiation and electrophilic substitution of dioxanes **1a**–**c**.

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[†] Dedicated to Professor Giovanni Melloni on the occasion of his 64th birthday.

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tern on the diastereoselective reaction of these intramolecularly coordinated organolithiums with carbon electrophiles (Scheme 1).

According to known procedures,[11,12] dioxanes **1** were obtained by acid catalysed Prins condensation of suitable styrenes with formaldehyde as mixture of diastereoisomers: **1a**, *anti*/*syn* = 1:1; **1b**, *anti*/*syn* = 92:8; **1c**, *anti*/*syn* = 83:17, as determined by ^{1}H NMR spectroscopy.[13,14]

Reductive metalations of dioxanes **1** were conducted under Ar with Li powder (10 equiv.) in the presence of a catalytic amount of naphthalene (10 mol%) in THF at −80°C for 4 h (Scheme 1, Table 1).

Reductive cleavage of 4-phenyl-5-methyl-1,3-dioxane, **1a**, quantitatively afforded alcohol **3a** (Table 1, entry 1). Formation of dilithium intermediate(s) **2a** was evidenced by quenching the reaction mixture with D_2O: under these conditions, alcohol **4a** was obtained as a 51:49 mixture of diastereoisomers (Table 1, entry 2). Quenching the reduction mixture with CO_2 led, after acidic workup, to lactone **5a** as a 86:14 mixture of diastereoisomers, in 64% yield (Table 1, entry 3). According to ^{1}H NMR literature data, we assigned the *anti* configuration to the prevailing diastereoisomer.[15] Furthermore, reaction of intermediate(s) **2a** with $PhCH_2Cl$ afforded alcohol **6a** as a 91:9 mixture of diastereoisomers, in 54% yield (Table 1, entry 4).

Reductive lithiation of 4-*p*-methoxyphenyl-5-methyl-1,3-dioxane, **1b**, followed by aqueous workup, afforded alcohol **3b** (Table 1, entry 5); furthermore, D_2O quenching showed intermediate quantitative formation of dilithium derivative(s) **2b**, leading to alcohol **4b** in a 53:47 diastereoisomeric ratio (Table 1, entry 6). Quenching the reduction mixture with CO_2 afforded, after acidic workup, lactone **5b** as a 82:18 mixture of diastereoisomers, in 50% yield (Table 1, entry 7). The diastereoisomeric ratio of recovered lactone changed from 82:18 to 11:89 under equilibrating conditions (*t*-BuOK/*t*-BuOH in THF); accordingly, we assigned *syn* configuration to the major diastereoisomer of lactone **5b**.[5] Reductive lithiation of dioxane **1b** followed by reaction with $PhCH_2Cl$, $C_6H_{13}Br$ and $(CH_3)_2CHBr$ afforded alcohols **6b**, **7b** and **8b**, respectively, in satisfactory yields and good to satisfactory diastereoselectivities (Table 1, entries 8–10).

Finally, we investigated the reductive lithiation of 4-phenyl-5-butyl-1,3-dioxane, **1c**. Reduction followed by aqueous workup led to quantitative formation of alcohol **3c** (Table 1, entry 11) via intermediate formation of dilithium derivative(s) **2c** (Table 1, entry 12). Reductive lithiation followed by reaction with CO_2 afforded, after acidic workup, lactone **5c** in 69% yield and moderate diastereoselectivity (Table 1, entry 13). The diastereoisomeric ratio of recovered lactone significantly changed (from 76:24 to 6:94) after equilibration with *t*-BuOK/*t*-BuOH in THF, thus showing the *syn* stereochemistry of the major stereoisomer of lactone **5c**.[5]

To rationalize our results, we assume that reductive lithiation of dioxanes **1** occurs with epimerization at the benzylic carbon, thus leading to diastereoisomeric, rapidly interconverting, organolithium intermediates, **2**,[2–4] whose configuration at the benzylic centre is fixed by coordination with the lithiumoxymethyl group (Scheme 2). Epimerization is evidenced by deuteration experiments and is in agreement with the reaction mechanism commonly accepted for the reductive cleavage of benzylic carbon–oxygen bonds, which occurs via intermediate formation of configurationally labile benzylic radicals.[4,16] We therefore assume that deuteration of organolithiums **2** requires an activation energy lower than (or comparable to) the activation energy of their epimerization. At variance with the thermodynamically controlled mechanism suggested for the carbometalation of cinnamyl alcohol,[5,6] we assume that one of the intramolecularly coordinated organolithiums reacts

Table 1. Reductive lithiation and reaction with electrophiles of dioxanes **1**[a]

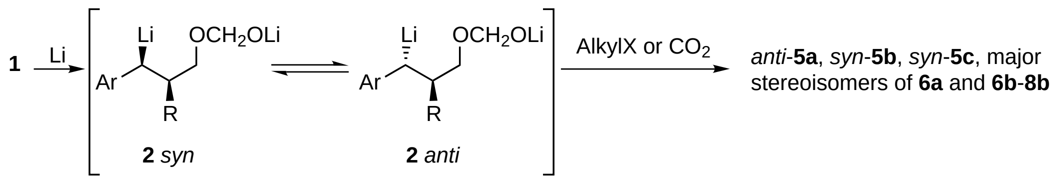
Entry	Compd	EX	Product, E =	Yield (%)[b]	Diastereoisomeric ratio[c]
1	**1a**	H_2O	**3a**, H	>95[c]	–
2	**1a**	D_2O	**4a**, D	>95[c]	51:49
3	**1a**	CO_2	**5a**, COO[d]	64	86:14
4	**1a**	$PhCH_2Cl$	**6a**, $PhCH_2$	54	91:9
5	**1b**	H_2O	**3b**, H	>95[c]	–
6	**1b**	D_2O	**4b**, D	>95[c]	53:47
7	**1b**	CO_2	**5b**, COO[d]	50	82:18
8	**1b**	$PhCH_2Cl$	**6b**, $PhCH_2$	58	93:7
9	**1b**	$C_6H_{13}Br$	**7b**, C_6H_{13}	68	92:8
10	**1b**	$(CH_3)_2CHBr$	**8b**, $(CH_3)_2CH$	70	85:15
11	**1c**	H_2O	**3c**, H	>95[c]	–
12	**1c**	D_2O	**4c**, D	>95[c]	60:40
13	**1c**	CO_2	**5c**, COO[d]	69	76:24

[a] All reactions run at −80°C for 4 h; after this time, the electrophile was added and the mixture stirred for 15 min before aqueous workup. For a general procedure, see Ref. 10.

[b] Isolated yield, unless otherwise indicated.

[c] As determined by ^{1}H NMR and/or GC–MS.

[d] Lactonization occurred during acidic workup.



Scheme 2. Epimerization and kinetic resolution of intermediates **2**.

preferentially and stereoselectively with carbon electrophiles, either under retention or inversion of configuration,[2,3,7,8] i.e. that reaction of our intermediates with carbon electrophiles requires an activation energy higher than the energy of epimerization.

A final remark concerns the relative stereochemistry of the major stereoisomers of recovered lactones (*anti* **5a**; *syn* **5b**; *syn* **5c**; Table 1, entries 3, 7 and 13, respectively), as this evidences a strong influence of the substitution pattern on the kinetic resolution of organolithiums **2**. Indeed, a comparison between intermediates **2a** ($Ar=C_6H_5$; $R=CH_3$) and **2b** ($Ar=4\text{-}(CH_3O)C_6H_4$; $R=CH_3$) shows that the presence of a *para*-methoxy substituent on the aromatic ring led to an inversion of the stereochemical outcome of the carboxylation reaction. From this point of view, it is worth noting that such a substituent on the aromatic ring is known to bias the relative stability of benzylithium derivatives;[17,18] accordingly, it could affect either the relative reactivity of intermediates **2** and/or the relative stereochemistry of the electrophilic substitution (inversion versus retention).

Furthermore, a comparison between intermediates **2a** ($Ar=C_6H_5$; $R=CH_3$) and **2c** ($Ar=C_6H_5$; $R=C_4H_9$) shows that steric bulk at the homobenzylic position influences, besides stereoselectivity, the relative stereochemistry of the major stereoisomer recovered upon carboxylation, a finding not observed in the related carbometalation procedure.[19]

In conclusion, our results show that reductive metalation of 4-aryl-5-methyl-1,3-dioxanes is a suitable procedure for the synthesis of 2-methyl-3-substituted-3-phenylpropan-1-ols with satisfactory to good diastereoselectivities, thus circumventing a drawback of the carbometalation of cinnamyl derivatives.[20]

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19. Carbolithiations of cinnamyl methyl ether with different alkyllithiums, followed by reaction with the same electrophile, result in the formation of major stereoisomers with the same relative stereochemistry; see Ref. 7. For related examples involving carbolithiation of a cinnamyl acetal, see Ref. 6.
20. All new compounds gave analytical and spectral (^1H and ^{13}C NMR, IR, MS) data in agreement with the assigned structures.