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Functionalisation of Chromane by Deprotonative Metallation

Cléo Bastien,^[a] William Erb,^[a] Yury S. Halauko,^{*,[b]} Vadim E. Matulis,^[b] Thierry Roisnel,^[a] Yann Sarazin,^[a] and Florence Mongin^{*,[a]}

Despite the biological interest in chromane derivatives, few studies dedicated to the functionalisation of this heterocycle have been reported. Herein, our objective is to demonstrate the potential of alkali metal bases for the introduction of substituents at its positions 4 and 8, and to explain the observed reactivity based on quantum chemical calculations. Guided by these theoretical results, preliminary optimisation was carried out on 2,3-dihydrobenzofuran before applying the optimal

conditions to chromane. Deprotolithiation at C8 was thus achieved using *n*-butyllithium in hexane at room temperature, while functionalisation at C4 was promoted by a 1:1 mixture of lithium 2,2,6,6-tetramethylpiperide and potassium *tert*-butoxide in tetrahydrofuran at -50°C . Various electrophiles were used to intercept the lithiated intermediates, providing a convenient access to substituted chromane derivatives.

Introduction

Chromane is a heterocycle widely distributed in nature, with vitamin E, renowned for its antioxidant properties, probably being its most notorious derivative^[1] (Figure 1). However, this scaffold can also be found in other important compounds such as flavanols, known to promote memory and vascular health,^[2] and flavanones which display a wide range of biological properties (antimicrobial, antifungal, antihypertensive, antioxidant, anti-inflammatory, cardioprotective, neuroprotective, antidiabetic, antitumor).^[3]

While various synthetic approaches have been designed to access substituted chromanes from well-chosen benzene derivatives,^[4] the functionalisation of bare chromane remains much less explored. The approaches reported are based on SEAr reactions (e.g. acylation, bromination and nitration),^[5] specific photoredox or electrochemical transformations at chromane 6-position^[6] and specific metal-catalysed benzylic reactions (e.g. oxidation,^[7] coupling with alcohols,^[8] carboxylation,^[9] alkenylation,^[10] acylation^[11] and amination^[12]). In recent decades, deprotometallation has been widely used to functionalise aromatic compounds, including heterocycles.^[13] It

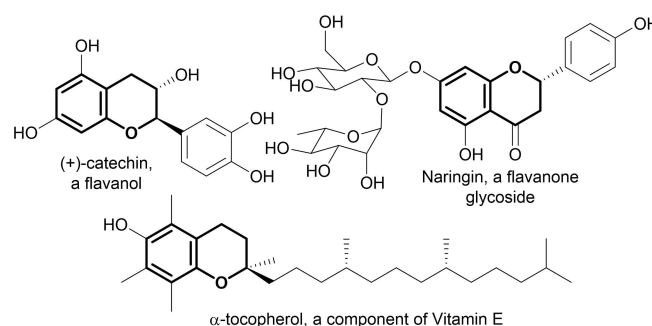


Figure 1. Structures of a few bioactive chromane-based compounds.

is therefore surprising that chromane has rarely been involved in these approaches.

Indeed, the oxygen atom in chromane can coordinate Lewis acidic metals in basic reagents such as alkyllithiums, promoting deprotometallation at a neighbouring site. However, this property was only used once, to reach the corresponding 8-carboxylic acid.^[14] In addition to the aryl hydrogens, chromane also contains a benzyl site that can undergo deprotometallation (Figure 2, left). Controlling the selectivity of benzyl functionalisation compared with aryl functionalisation could require fine-tuning of the reaction conditions (choice of base, solvent, cosolvent/ligand and temperature). It was only very recently that Gutierrez, Thomas and co-workers successfully explored

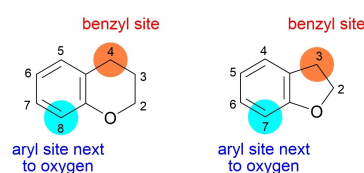


Figure 2. Similarities between chromane (left) and 2,3-dihydrobenzofuran (right).

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such an approach using *tert*-butyllithium under conditions favouring separated ion pairs.^[15]

We describe herein our own efforts on the functionalisation of chromane using alkali metal bases. A preliminary reactivity study was first performed on a cheaper related analogue, 2,3-dihydrobenzofuran (Figure 2, right). Building on this preliminary study, we tackled the selective functionalisation of chromane towards 4- or 8-substituted derivatives and further rationalised the observed reactivity using quantum chemical calculations.

Preliminary Considerations, Atomic Charges and pK_a Values of 2,3-Dihydrobenzofuran (1) and Chromane (2)

In this study, our aim was not only to identify suitable conditions for the functionalisation of chromane using alkali metal bases as key step, but also to provide a better understanding of the deprotonation of this heterocycle. The reactions planned here to functionalise chromane include a key deprotonation step mediated by alkali metal bases.^[13] When the reactions are carried out under kinetic control (typically, using alkylolithiums), the observed regioselectivity generally not only depends on the capacity of the substrate to coordinate the metal of the base, at the stage of a premetallation complex (complex-induced proximity effect)^[16] or/and on the rate-limiting transition state (kinetically enhanced metallation),^[17] but also on hydrogen charges (overriding base mechanism).^[18]

We therefore calculated the atomic charges for the different hydrogens of 2,3-dihydrobenzofuran (1) and chromane (2) by natural population analysis (NPA; Figure 3). Although close values were obtained, they tend to suggest that the hydrogens located at the benzyl site and at the aryl site next to the oxygen would be the most acidic.

It makes little doubt that these calculated hydrogen charges are far from sufficient to rationalise on their own the regioselectivity of reactions under kinetic control. Indeed, coordination of the oxygen atom of these heterocycles to lithium can also decrease the activation energy of deprotonation at neighbouring positions. While such coordination is most likely to occur in nonpolar solvents such as hexane, it was interesting to investigate the ability of these substrates to

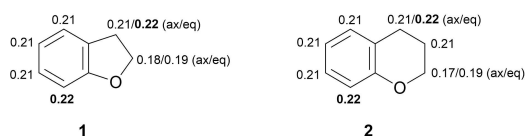


Figure 3. NPA charges on hydrogen atoms in isolated molecules of 2,3-dihydrobenzofuran (1) and chromane (2).

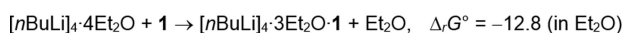


Figure 4. Calculated Gibbs free energy values ($\Delta_r G^\circ$, $\text{kJ}\cdot\text{mol}^{-1}$) for the substitution of the most weakly bonded molecule of THF or Et_2O with the molecule of **1** in tetrasolvated $[\text{BuLi}]_4$ tetramers.

compete with diethyl ether (Et_2O) or tetrahydrofuran (THF) for the coordination onto the metal of the base. We therefore calculated the Gibbs free energy of the reactions involving **1** (Figure 4). To this end, since $n\text{BuLi}$ exists as $[\text{BuLi}]_4 \cdot nS$ tetrameric units in Et_2O and THF,^[19] we only considered substitution of the most weakly bonded solvent molecule (Et_2O or THF) into tetrasolvated $[\text{BuLi}]_4$ tetramers with **1** (see Supporting information for more details). While the Gibbs free energy calculated for the substitution of a THF molecule by **1** is slightly positive (Figure 4, top), the substitution of an Et_2O molecule is accompanied by a decrease in the Gibbs free energy (bottom). This indicates that THF more strongly coordinates the metal of the base than **1** while the latter can successfully compete with Et_2O to coordinate lithium. Thus, from the coordination point of view, we can assume a lower activation energy in Et_2O , and *a fortiori* in hexane, for the abstraction of a hydrogen in the aromatic ring close to the oxygen.

Furthermore, as shown in Figure 5, coordination of the oxygen of the heterocycles **1** and **2** to lithium leads to a significant increase in the calculated charge on the hydrogen atom at the aryl position close to the oxygen, while the calculated charge of the benzyl hydrogens is not altered. Thus, under *kinetic control*, coordination to lithium can decrease the activation energy of deprotonation at the aryl position close to the oxygen.

In contrast, under *thermodynamic control* (e.g. using lithium diethylamide),^[20] reactions should take place at the site with the lowest pK_a value. We therefore calculated these values for 2,3-dihydrobenzofuran (**1**) and chromane (**2**) in THF and hexane within the DFT framework^[21] (Figure 6; see Supporting information for details). It should be noted that the calculated pK_a values in THF are in agreement with the scarce experimental data on related systems such as benzofuran (33.2),^[22] alkoxyphenols (>40)^[23] and xanthene (31.4),^[24] while Bordwell estimated the pK_a of toluene in DMSO to be 42.^[25] Our calculations clearly show that, for 2,3-dihydrobenzofuran (**1**) just like chromane (**2**), deprotonation at the benzyl position is thermodynamically favoured in both THF and hexane.

The coordination of oxygen to lithium is also likely to impact the stability of the derivatives formed by deprotonation. In order to mimic such an interaction, we considered complexes of **1** and **2** with $\text{LiNMe}_2 \cdot 2\text{THF}$ in THF, or with

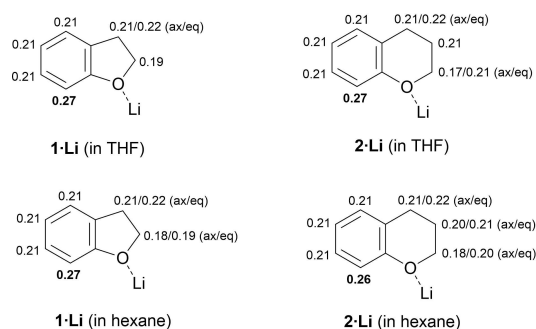


Figure 5. NPA charges on hydrogen atoms in complexes of 2,3-dihydrobenzofuran (**1**) and chromane (**2**) with either $\text{LiNMe}_2 \cdot 2\text{THF}$ (top) or $\text{MeLi} \cdot \text{TMEDA}$ (bottom).

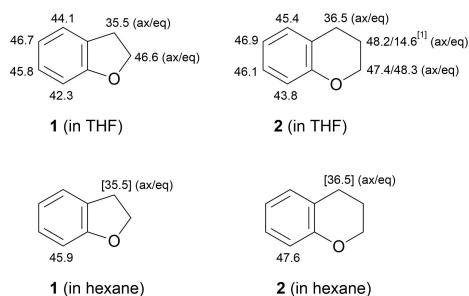


Figure 6. pK_a values calculated for 2,3-dihydrobenzofuran (1) and chromane (2) in THF (top) and hexane (bottom). As references with known pK_a values in hexane were not available, we arbitrarily set the ones for the benzyl position (in square brackets) at C3 (compound 1) and C4 (2) as those calculated in THF. [1] Ring opening expected.

MeLi-TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) in hexane (Figure 7). While the pK_a values calculated for the aryl position next to the oxygen and the benzyl site were found to be closer to each other under these conditions, the lowest pK_a value still remains by far at the benzyl position.

An additional issue able to modify the reaction outcome lies in the stability of the benzylmetal species formed by deprotonation of 1. Indeed, ring opening can lead to a more stable phenolate (Figure 8, top). Although the deprotonation of the β position of chromane (2) should not be favoured according to our calculations, we also evaluated its ring opening for comparison purpose with 1. Similarly, 3-chromanylmetal can also evolve into a much more stable phenolate (Figure 8, bottom). This was confirmed by calculating the ring opening reactions in THF for the naked anions of 2,3-

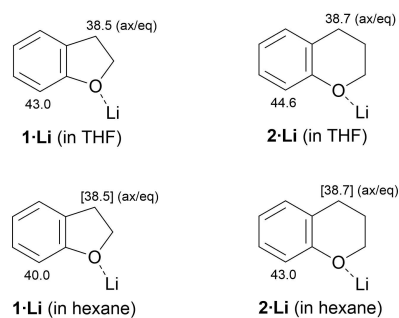


Figure 7. pK_a values calculated for the complexes of 2,3-dihydrobenzofuran (1) or chromane (2) with either $\text{LiNMe}_2 \cdot 2\text{THF}$ in THF (top) or MeLi-TMEDA in hexane (bottom). As references with known pK_a values in hexane were not available, we arbitrarily set the ones for the benzyl position (in square brackets) at C3 (compound 1) and C4 (2) as those calculated in THF.

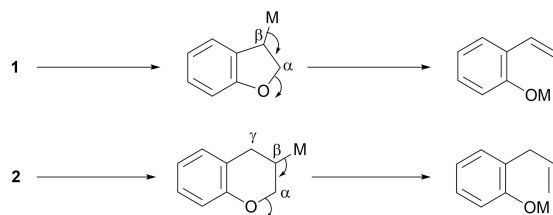


Figure 8. Possible side-processes. M = alkali metal.

dihydrobenzofuran (1) and chromane (2), leading to $\Delta_r G^\circ$ values of -152.7 and -193.3 kJ mol^{-1} for 1 and 2, respectively. The calculations carried out for the corresponding lithium salts led to similar results, the open forms (phenolates) being as expected significantly more stable than the associated cyclic forms (ring opening $\Delta_r G^\circ$ of -171.5 kJ mol^{-1} for 1 and -195.4 kJ mol^{-1} for 2).

In summary, these data tend to show that it should be possible to selectively functionalise either the benzyl site, or the aryl position close to the oxygen, of chromane depending on the reaction conditions. The former will be privileged by deprotonation under thermodynamic control while the latter will occur under kinetic control (possibly favoured by the coordination of the metal of the base by the heteroatom). We therefore next explored this scenario from a synthetic point of view. Although our calculations revealed the instability of the benzylmetal formed from 1, we also included this substrate in our study for comparison purpose.

Functionalisation of 2,3-dihydrobenzofuran

Although direct calcium and rare earth metal-catalysed C-alkylation at the 7-position of 2,3-dihydrobenzofuran (1) has been recently reported,^[26] other C-functionalisations such as palladium-catalysed cyanation^[27] and alkenylation^[28] have led to mixtures of 7- and 5-regioisomers. Deprotolithiation followed by electrophilic trapping therefore remains the most appropriate way to introduce substituents at the 7-position of 2,3-dihydrobenzofuran (1). This is typically achieved regioselectively using TMEDA-activated *n*BuLi in hexane^[29] or cyclohexane^[30] at room temperature (rt), as demonstrated, for example, by subsequent carboxylation. The same chelate was also used in Et_2O at -10°C , to provide the expected ketone after interception with 2-cyanopyridine.^[31] Finally, it is possible to avoid the use of TMEDA, notably by employing Et_2O at rt, as reported during the synthesis of various phosphines^[32] (Figure 9, left).

In these experiments, TMEDA or Et_2O increases the reactivity of the alkyllithium by breaking the aggregates,^[33] and 1 can then compete with TMEDA, or Et_2O , to coordinate the metal of the base as shown in Figure 4 (bottom). Thanks to the proximity effect and the acidification of the neighbouring hydrogen, deprotolithiation can then happen at C7. The reaction being under kinetic (non-reversible) control, electrophilic trapping of this lithiated intermediate finally delivers the 7-functionalised derivative.

We were interested to find out whether 7-lithio-2,3-dihydrobenzofuran could also be prepared in THF, a solvent often used in deprotonation reactions. For this purpose, a

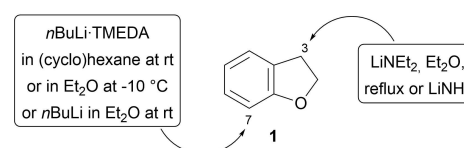


Figure 9. Bases already employed to functionalise 2,3-dihydrobenzofuran (1).

solution of **1** in this solvent was subjected to the action of different lithium bases, before interception with iodomethane (Table 1). When alkyllithiums (*n*BuLi, *s*BuLi or *t*BuLi; 1.2 equiv) were tested at 0 °C for 1 h, moderate to good conversions were noticed. However, two products were obtained, the expected 7-methylated derivative **3a** but also 2-vinylphenol (**4**), with respective ratios of ~3:2 (*n*BuLi), ~7:3 (*s*BuLi) and ~1:1 (*t*BuLi) (entries 1–3). It can be noted that the **3a**:**4** ratios observed here are variable, which argues against thermodynamic control. As shown in Figure 4 (top), coordination of lithium by the oxygen of **1** is less likely in THF than in Et₂O,^[34] explaining why the deprotonation of the benzyl site (followed as expected by ring opening), is here observed. However, interaction between the lithium of the base and the oxygen atom of the substrate cannot be completely ruled out as the resulting acidification of H7 also led to the formation of **3** under these conditions.

The formation of lithium 2-vinylphenolate has already been observed in experiments under thermodynamic control, whether in the presence of lithium diethylamide (LiNEt₂) in Et₂O at reflux,^[35] or with LiNH₂^[36] (Figure 9, right). In these cases, the deprotonation of **1** not only becomes reversible, but the equilibrium could be further driven from the 3-lithiated species to the more stable lithium phenolate. The formation of a 7-substituted derivative after subsequent trapping is thus disfavoured, especially in THF where **1** can hardly compete to

coordinate lithium^[34] (Figure 4; top). Indeed, when similar reactions were carried out using LiNEt₂ (1.2 or 2.2 equiv) in THF at –15 °C for 1 h, followed by quenching with MeI, good conversions and selectivity in favour of **4** were recorded (entries 4 and 5). In order to stabilise the benzylmetal by *in situ* transmetalation of the lithiated intermediate into a more stable zinc species,^[37] and thus avoid ring opening, we also attempted the reaction by adding LiNEt₂ (3 equiv) to a solution of **1** and ZnCl₂·TMEDA (1 equiv), but without success (entry 6).

Compared to diethylamine (p*K*_a value of 31.7 in THF),^[38] 2,2,6,6-tetramethylpiperidine has a higher p*K*_a value (37.3),^[24] but still lower than those calculated for **1**. Hence, it was surprising, only considering the p*K*_a values, that the reaction using lithium 2,2,6,6-tetramethylpiperidide (LiTMP; 1.2 equiv) led to 69% conversion. The 69:31 ratio in favour of **3a** further tends to indicate a reduced degree of thermodynamic control (entry 7), suggesting that the oxygen of **1** is able to coordinate the metal of LiTMP, ultimately leading to an increased acidity of H7.

In order to improve the selectivity in favour of the benzyl site, we chose to combine LiTMP with potassium *tert*-butoxide, expected to generate KTMP *in situ*.^[39] Indeed, it has been reported that these lithium-potassium “superbases” are not significantly influenced by coordinating atoms and instead attack the most acidic positions.^[40] As expected, after 1 h of contact between the “KTMP” thus generated (2.5 equiv) and **1** at –50 °C, a complete conversion to **4** was noticed (entry 8). As diisopropylamine (p*K*_a value of 35.7 in THF)^[24] is less expensive than 2,2,6,6-tetramethylpiperidine, we also tried to use the combination of lithium diisopropylamide (LiDA) and potassium *tert*-butoxide, and similarly observed complete conversion to derivative **4** (entry 9).

Calcium being more oxophilic than lithium, we finally tested calcium bis(hexamethyldisilazide)^[41] in THF at –20 °C for 1 h. However, no conversion was observed under these conditions, likely due to the lower p*K*_a value of bis(trimethylsilyl)amine (25.8 in THF,^[24] entry 10).

To selectively prepare compound **3a**, we finally carried out a few reactions in hexane using TMEDA-activated *n*BuLi.^[29] When the chelate (1.2 equiv) was used at 0 °C for 1 h, moderate conversion was observed and a ~9:1 ratio in favour of **3a** (entry 11). However, by increasing the amount of base to 2.2 equivalents and carrying out the reaction at rt, the formation of **3a** was favoured and the compound could be isolated in 65% yield (entries 12 and 13).

Functionalisation of Chromane

With these results in mind, we then turned our attention to chromane (**2**), a compound accessible by reduction of commercially available 4-chromanone. To synthesise **2**, we first evaluated a protocol using zinc in acetic acid at 100 °C^[42] which, in our hands, only delivered the desired heterocycle in 29% yield. We then performed the reduction using catalytic palladium on charcoal, in the presence of chlorobenzene and polymethylhydrosiloxane (PMHS), in methanol at rt.^[43] This time,

Table 1. Deprotometallation of 2,3-dihydrobenzofuran (**1**) using different bases followed by interception with iodomethane.

| Entry | Base | x | Solvent, conditions | 1 : 3a : 4 ratio ^[a] |
|------------------|--|-----|---------------------|--|
| 1 | <i>n</i> BuLi | 1.2 | THF, 0 °C, 1 h | 24:44:32 |
| 2 | <i>s</i> BuLi | 1.2 | THF, 0 °C, 1 h | 55:33:12 |
| 3 | <i>t</i> BuLi | 1.2 | THF, 0 °C, 1 h | 40:30:30 |
| 4 | LiNEt ₂ | 1.2 | THF, –15 °C, 1 h | 24:4:72 |
| 5 | LiNEt ₂ | 2.2 | THF, –15 °C, 1 h | 6:10:84 |
| 6 ^[b] | LiNEt ₂ | 3 | THF, –15 °C, 1 h | 54:0:46 ^[c] |
| 7 | LiTMP | 1.2 | THF, –15 °C, 1 h | 31:48:21 |
| 8 | LiTMP- <i>t</i> BuOK | 2.5 | THF, –50 °C, 1 h | 0:0:100 |
| 9 | LiDA- <i>t</i> BuOK | 2.5 | THF, –50 °C, 1 h | 0:0:100 |
| 10 | Ca[N(SiMe ₃) ₂] ^[d] | 1 | THF, –20 °C, 1 h | 100:0:0 |
| 11 | <i>n</i> BuLi-TMEDA | 1.2 | hexane, 0 °C, 1 h | 53:41:6 ^[e] |
| 12 | <i>n</i> BuLi-TMEDA | 2.2 | hexane, rt, 1 h | 14:86:0 (65%) ^[f] |
| 13 | <i>n</i> BuLi-TMEDA | 2.2 | hexane, rt, 2 h | 0:100:0 |

[a] Ratio determined by ¹H NMR. Note that 2-vinylanisole was not formed under the conditions used [b] Reaction carried out in the presence of ZnCl₂·TMEDA as an *in-situ* trap [c] The formation of 7-metallated derivative is probably underestimated as arylzinc species react poorly with MeI [d] Isolated Ca[N(SiMe₃)₂]₂(THF)₂^[41] was employed [e] In the absence of TMEDA, no reaction took place (**1** completely recovered); when TMEDA was replaced by *t*BuOK, a complex mixture was formed [f] Yield for **3a**.

and even employing 60% of the recommended amount of PMHS, **2** was isolated in 95% yield as reported.

Very few deprotometallation reactions have been reported to functionalise the position 8 of chromane (**2**). Indeed, before the present study, only the synthesis of 8-chromanecarboxylic acid had been described, by deprotolithiation using *n*BuLi in Et₂O at rt, followed by trapping with carbon dioxide^[14] (Figure 10, left). Under these conditions, similar to those used to functionalise 2,3-dihydrobenzofuran (**1**) at C7, the reaction is irreversible and likely results from the coordination of the chromane oxygen to the metal of the base. Therefore, to improve our understanding of the deprotometallation of **2**, we were eager to apply the reaction conditions used to functionalise **1** (Table 2).

To this end, **2** was first treated with the *n*BuLi-TMEDA chelate (2.2 equiv) in hexane at rt for 2 h, before addition of Mel, leading to the isolation of the 8-methylated product **5a** in 75% yield. As expected, reaction at C4 was not observed under these conditions (entry 1).

With **1**, the use of LiNEt₂ (2.2 equiv) in THF at –15 °C for 1 h mainly led to the formation of the phenol **4**, resulting from a deprotometallation at C3 followed by a ring opening. However, applying these conditions to **2** only provided **5a** with <10% conversion while no reaction was observed in the presence of ZnCl₂-TMEDA (1 equiv) as an *in-situ* trapping reagent (entries 2

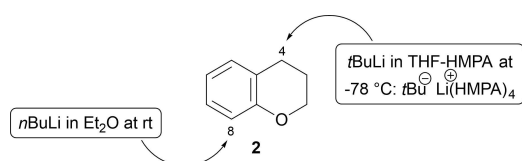


Figure 10. Bases already employed to functionalise chromane (**2**).

Table 2. Deprotometallation of chromane (**2**) using different bases followed by interception with iodomethane.

| Entry | Base | x | Solvent, conditions | 2:5a:6a ratio ^[a] |
|------------------|-----------------------------|------------|--------------------------------------|------------------------------|
| 1 | <i>n</i> BuLi-TMEDA | 2.2 | hexane, rt, 2 h | 0:100:0 (75%) ^[b] |
| 2 | LiNEt ₂ | 2.2 | THF, –15 °C, 1 h | 92:8:0 |
| 3 ^[c] | LiNEt ₂ | 3 | THF, –15 °C, 1 h | 100:0:0 ^[d] |
| 4 | LiTMP | 2 | THF, –15 °C, 1 h | 51:49:0 |
| 5 | LiTMP- <i>t</i> BuOK | 2.5 | THF, –50 °C, 1 h | 17:0:83 (71%) ^[e] |
| 6 | LiDA- <i>t</i> BuOK | 2.5 | THF, –50 °C, 1 h | 57:0:43 ^[f] |
| 7 | LiTMP- <i>t</i> BuOK | 2.5 | THF, –90 °C, 10 min | 52:0:48 |
| 8 | LiTMP then <i>t</i> BuOK | 2.5 2.5 | THF, –15 °C, 1 h then –50 °C, 1 h | 14:0:86 |

[a] The ratio was determined by ¹H NMR [b] Yield for **5a** [c] Reaction carried out in the presence of ZnCl₂-TMEDA as an *in-situ* trap [d] The formation of 8-metallated derivative is probably underestimated as arylzinc species react poorly with Mel [e] Yield for **6a** [f] The degradation of ~10% of **2** was also observed under these conditions.

and 3). This probably results from the use of a base not strong enough to deprotonate the position 8 in an efficient way. Furthermore, as the benzyl position of **2** is γ of the oxygen and not β as in **1**, its deprotonation cannot trigger a ring opening able to shift the deprotolithiation equilibrium. Deprotonation of the position β to oxygen of **2**, which would also lead to a ring opening (see Figure 8), was not observed as not favoured by a coordinating directing group or a sufficiently acidic hydrogen to initiate the reaction.

The use of LiTMP also did not allow the deprotometallation of **2** at C4, a different result from the one noticed from **1**, probably due to the same reasons as those mentioned above (entry 4). However, as observed from **1**, successive treatment of **2** with LiTMP-*t*BuOK in THF at –50 °C for 1 h and Mel led to the expected 4-methylated derivative **6a**, isolated in 71% yield (entry 5). This time, replacing the LiTMP in the combination with LiDA led to a reduced conversion (entry 6).

In an attempt to identify a transient 8-chromanylithium, we tested a short contact time of 10 min at –90 °C between **2** and LiTMP-*t*BuOK before the addition of iodomethane. Under these conditions, **6a** remained the only regioisomer formed (entry 7). We also treated 8-lithiochromane (prepared as in entry 4, using LiTMP in THF at –15 °C for 1 h) with *t*BuOK (2.5 equiv) at –50 °C for 1 h, and similarly observed the exclusive formation of a 4-metallated species (entry 8). These results show that *t*BuOK is capable of promoting anion transfer, as has already been proposed in other contexts.^[44]

Interestingly, Gutierrez, Thomas and co-workers recently reported an alternative way to introduce alkyl substituents at the 4-position of chromane using *t*BuLi in THF at low temperatures. Indeed, they reasoned that the addition of strong Lewis bases such as hexamethylphosphoramide (HMPA) or trispyrrolidinediphosphoramide (TPPA) to the solvent would promote the formation of separated ion pairs, and thus disfavour the interaction between chromane oxygen and metal of the base^[15] (Figure 10, right).

With these conditions in hand, we next evaluated the trapping of the benzylmetal derivative of chromane by different electrophiles. Upon use of 4-anisaldehyde followed by hydrolysis, a yield of 72% was recorded for the alcohol **6b**, isolated as expected as a mixture of stereoisomers.

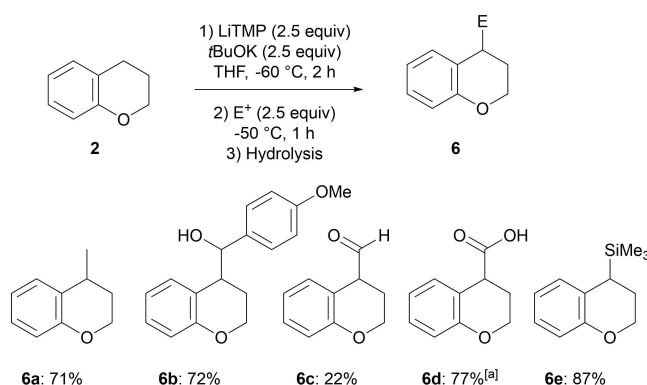
N,N-dimethylformamide (DMF) is commonly used to access aldehydes; however, when we used it to intercept the benzylmetal species obtained as previously, the expected aldehyde **6c** was only isolated in a moderate yield of 22%. Indeed, unexpected products (e.g. chromanone, isolated in 19% yield) were formed under these conditions, a result which could be due to the low stability of **6c**, as already mentioned.^[45]

Conversion to 4-chromanecarboxylic acid (**6d**) was carried out using excess CO₂ gas as an electrophile before acidification. Surprisingly, the tautomeric form **6d'** of the expected product was first isolated (see Supporting information) which, within a few days at rt, afforded the desired carboxylic acid **6d** in 77% yield.

While attempts to use I₂ provided only complex mixtures including 4,4-bichromane, even using reverse addition to the electrophile in order to reduce subsequent nucleophilic

substitution,^[20] we successfully prepared the 4-chromanylsilane **6e** in good yield (Scheme 1).

Access to 4-(2-pyridyl)chromane was explored by Negishi coupling^[47] after transmetalation of 4-chromanylpotassium to the corresponding benzylzinc species using ZnCl₂·TMEDA. To this end, 2-chloropyridine, catalytic PdCl₂ and 1,1'-bis(diphenylphosphino)ferrocene (dppf) were added to the reaction mixture, which was heated to 80 °C.^[48] However, these conditions failed to deliver the target, and instead led to a complex mixture from which *racemic* (Figure 11) and *meso* 4,4'-bichromanes were isolated in yields of 18% and 9%, respectively.



Scheme 1. Functionalisation of chromane (**2**) at C4 by deprotonation-trapping using different electrophiles. [a] Isolated as a tautomeric form.

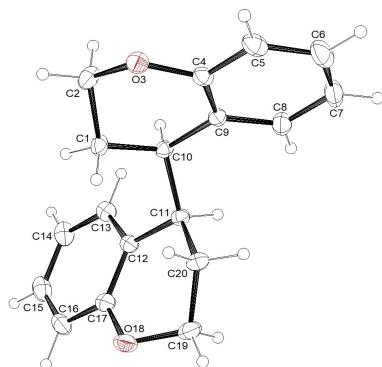
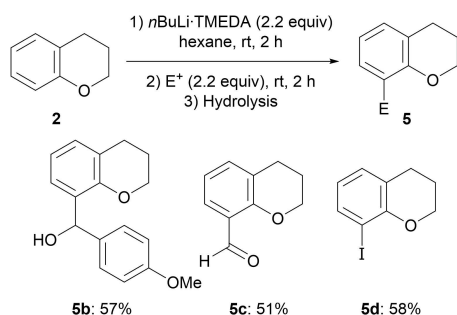


Figure 11. ORTEP diagram (30% probability) of racemic 4,4'-bichromane.^[46]



Scheme 2. Functionalisation of chromane (**2**) at C8 by deprotonation-trapping using different electrophiles.

We next turned our attention to the interception of the 8-deprotonated chromane by different electrophiles (Scheme 2). Thus, after reacting **2** with *n*BuLi·TMEDA (2.2 equiv) in hexane at rt for 2 h, 4-anisaldehyde, DMF and I₂ were added to the reaction mixture. After hydrolysis, the alcohol **5b**, aldehyde **5c** and iodide **5d** (Figure 12, left) were thus obtained in satisfactory yields.

The lithiated derivative of **2** was also transmetalated to the corresponding arylzinc chloride, and the latter involved as above in a Negishi coupling^[47] with 2-chloropyridine in the presence of PdCl₂, dppf and THF (8 h at 80 °C).^[48] Under these conditions, the expected product **5e** was obtained in 36% yield (Scheme 3; Figure 12, right).

Direct introduction of dialkylamino groups onto aromatic heterocycles can be achieved by reaction of the corresponding heteroarylzinc compounds, prepared in THF, with *O*-benzoyl hydroxylamines in the presence of catalytic copper(II) acetate.^[49] Piperidine being present in many biologically active products,^[50] we opted for the synthesis of 8-(*N*-piperidino)chromane. As we had prepared 8-chromanylzinc chloride to access **5e**, we attempted its trapping using *N*-(benzoyloxy)piperidine in the presence of catalytic copper(II) acetate.^[49] However, after 18 h at rt, we only isolated 8-benzoylchromane (**5f**) in a moderate 45% yield, and α -*n*-butyl- α -phenyl-8-chromanemethanol (**5f'**) resulting from addition of an *n*-butylmetal species to this ketone in 31% yield (Scheme 4, top).

To reach the desired 8-(*N*-piperidino)chromane (**7**), we next evaluated the cross-coupling of 8-iodochromane (**5d**) with piperidine. While an attempt using piperidine (2 equiv) in the presence of tripotassium phosphate (2 equiv) and copper(I)

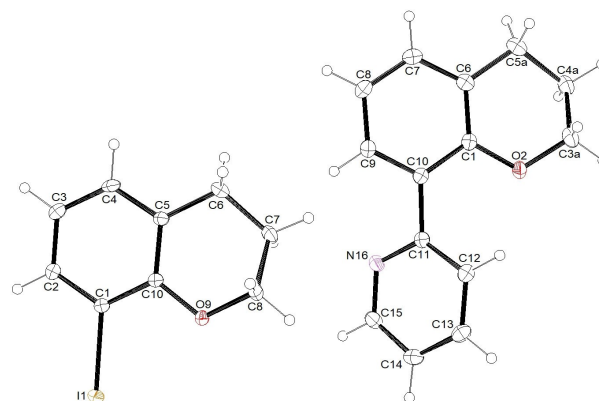
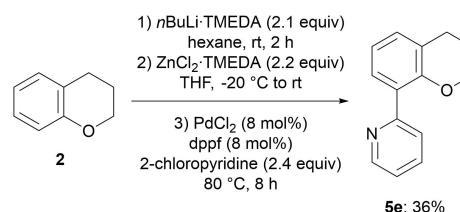
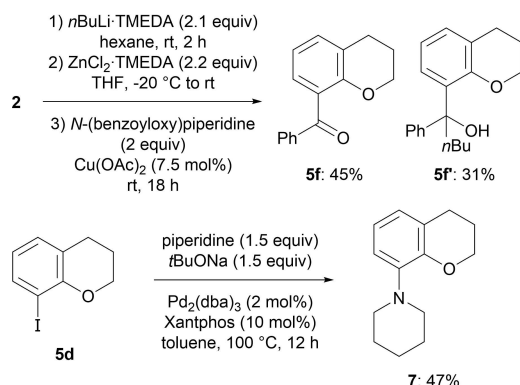


Figure 12. ORTEP diagrams (30% probability) of the chromane derivatives **5d** and **5e**.^[46]



Scheme 3. Functionalisation of chromane (**2**) at C8 by deprotonation-trapping, transmetalation to zinc and Negishi coupling.



Scheme 4. Post-functionalisation towards a piperidine-containing chromane.

iodide (0.2 equiv) in DMSO at 80 °C for 24 h failed (no observed conversion), we finally succeeded in obtaining the desired product **7** by palladium-catalysed amination.^[51] Thus, the reaction of **5d** with piperidine in the presence of sodium *tert*-butoxide, catalytic tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), in toluene at 100 °C,^[52] finally afforded the desired product **7** in 47% yield (Scheme 4, bottom).

Conclusions

We have optimised herein the functionalisation of chromane at its positions 4 and 8 by deprotonation followed by electrophilic trapping. In a non- or weakly polar solvent, coordination of the substrate to lithiated bases is favoured, increasing the acidity of H8, and thus directing the reaction at this position. Provided that the base is strong enough to ensure an unbalanced deprotonation (i.e. kinetic control), the 8-arylmethyl can be accumulated and then converted into 8-substituted derivatives. On the other hand, under conditions allowing equilibrium, or by using a base having a metal more electropositive than lithium (such as potassium), formation of a benzylmetal species drives the reaction, leading to 4-substituted derivatives after following electrophilic trapping. A good agreement between these experimental results and quantum chemical calculations (NPA charges of the lithium-coordinated substrates and pK_a of the molecules) was observed. Therefore, not only this study provides a better understanding of chromane deprotonation, but it also validates the use of calculations to predict the reactivity of substrates for which similar optional site selectivity remains undescribed yet.

Supporting Information Summary

General information, preparation and analyses of the compounds; NMR spectra of the compounds **5a**, **5b**, **5e**, **5f**, **5f'**, **6b**, **6d**, **6d'**, *racemic*-4,4'-bichromane, *meso*-4,4'-bichromane and **7**; Computational details; Cartesian coordinates of DFT optimised

structures. The authors have cited additional references within the Supporting Information.^[53]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Chromane · 2,3-dihydrobenzofuran · Alkali metal base · Acidity · Optional site selectivity

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