Lithiation Chemistry

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Exploiting the Lithiation-Directing Ability of Oxetane for the Regioselective Preparation of Functionalized 2-Aryloxetane Scaffolds under Mild Conditions**

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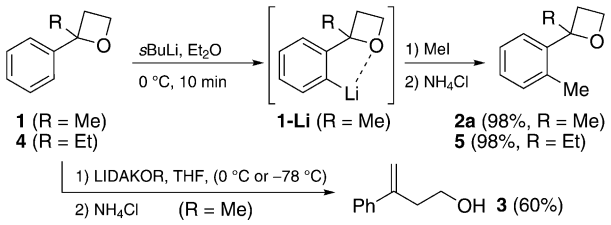
Dedicated to Professor Saverio Florio on the occasion of his retirement

More than seventy years ago, Gilman[1] and Wittig[2] independently observed that the lithiation of an aromatic ring could be achieved *ortho* to a substituent, and hence opened up new horizons for obtaining differently functionalized organolithium derivatives through what is today known as the directed *ortho* metalation (DoM) reaction. Since then, and particularly thanks to seminal contributions from the groups of Hauser, Meyers, Gschwend, Beak, Snieckus, and others,[3] D*o*M methodology, which strikingly complements traditional electrophilic aromatic substitution, has received an extraordinary level of attention in the field of organometallic chemistry.[4] The reaction is proposed to proceed by the involvement of a direct metalation group (DMG) whose ability to effect the *ortho* metalation process has generally been interpreted in terms of an interplay of inductive and complexation effects. The mechanistic rationalization for the DoM reaction, however, still remains elusive and controversial.[5]

Despite the broad range of hetero- and carbon-linked substituents available to synthetic chemists for performing hydrogen/metal permutation processes, saturated ring heterocycles have surprisingly received much less attention as potential DMGs.[6] The oxetane ring motif is an important structural component of several naturally occurring compounds, and oxetane derivatives have received increasing exposure over the years as attractive and versatile modules for both drug discovery and organic synthesis.[7] Herein, we report the first successful use of oxetane as an effective DMG in the regioselective preparation of functionalized 2-aryloxetane scaffolds and explore the scope of such a methodology. On the basis of intra- and intermolecular competition experiments and kinetic evidence, we rank the lithiation-promoting power of oxetane as being equal to that of an aminomethyl group, and support a complex-induced proximity effect (CIPE) as the main mechanism responsible for modulating the *ortho* C–H acidity.

Recently, the search for a new way to access 2-substituted-2-phenyloxetanes has led to the discovery that *s*BuLi in THF at −78 °C is the base of choice to perform a clean α-lithiation/functionalization of 2-phenyloxetane.[8] As for saturated cyclic ethers, it is also known that the electron-donor ability of the oxygen atom is dependent upon the size of the ring, the basicity being in the order four- > five- > six- > three-membered ring.[9] Thus, the intrinsic basicity of an oxetane ring is not only higher than that of an epoxide, but also higher compared with that of tetrahydrofuran. Inspired by this observation, we became intrigued by the possibility that an oxetane ring, in view of its remarkable basicity, could behave as an *ortho*-directing group in the absence of a benzylic proton. Thus, 2-Methyl-2-phenyloxetane **1** was chosen as a model substrate. It was straightforwardly prepared in 90% yield by the reaction of acetophenone with dimethylsulfoxonium methylide (50 °C, 3 days) through a double methylene transfer reaction.[10]

We were pleased to find that treatment of an Et_2O solution (0.2 M) of **1** (1 equiv) at 0 °C with *s*BuLi (1.4 equiv), followed by quenching of the reaction mixture after 10 min with MeI, led to the *ortho*-methylated product **2a** in 98% yield, probably through the putative *ortho*-lithiated intermediate **1-Li**, which proved to be chemically stable for up to 30 min at 0 °C and for up to 10 min even at room temperature (Scheme 1).



Scheme 1. Synthesis of *ortho*-methylated 2-phenyloxetanes **2a** and **5**, and of homoallylic alcohol **3**. LIDAKOR = $iPr_2NLi/tBuOK$.

As for the bases, we also ascertained that *n*BuLi, lithium diisopropylamide (LDA), and lithium 2,2,6,6-tetramethylpiperidide (LTMP) were ineffective (0 °C, Et_2O, 10 min), whereas employing *s*BuLi in THF at 0 °C, followed by quenching with MeI, afforded only an 80% yield of **2a** after

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10 min. This observation can be attributed to the fact that THF partially replaces the activating substituent (the oxetane ring) in coordinating to lithium, thereby reducing its influence in triggering the *ortho*-lithiation.[11] The role of precoordination in such a reaction also becomes apparent by changing the coordination potential of the base: treatment of **1** with a strong non-coordinating base such as LIDAKOR (*i*Pr_2NLi/*t*BuOK) in THF at 0 °C (or at −78 °C) does not promote the *ortho*-lithiation; instead, it results in the formation of homoallylic alcohol **3** in 60% yield, the remaining 40% being starting material only. This may be the result of a β-elimination reaction involving the methyl group and the oxetane ring oxygen (Scheme 1).[12] In Et_2O, there is no reaction.

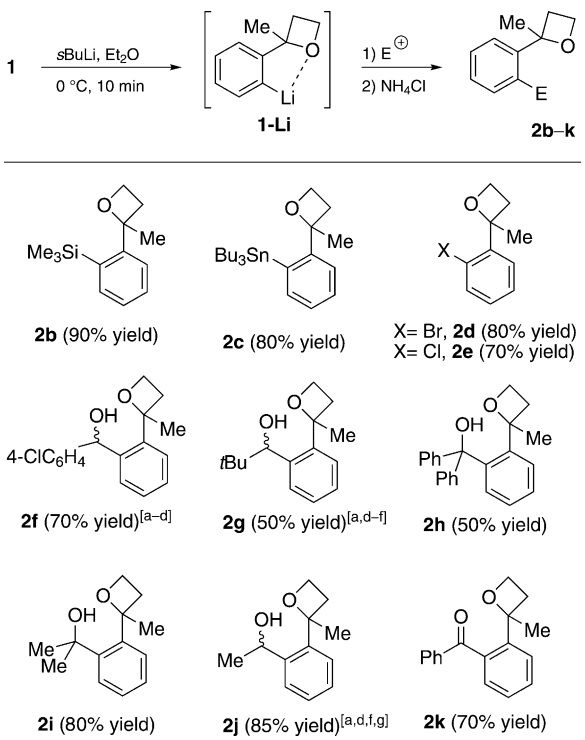
Lithiation proceeds even when the α-position of 2-phenyloxetane is blocked by groups other than methyl: treatment of 2-ethyl-2-phenyloxetane **4** with *s*BuLi in Et_2O at 0 °C, followed by quenching with MeI, gave the *ortho*-methylated compound **5** almost quantitatively (98% yield; Scheme 1).

With the optimal conditions in hand, and in order to test the generality of this new synthetic methodology, the lithiated intermediate **1-Li** was then trapped with a variety of representative electrophiles. Gratifyingly, *ortho* C–H functionalization of **1** was also effective with electrophiles such as Me_3SiCl, Bu_3SnCl, 1,2-dibromoethane, and hexachloroethane, which gave the desired substitution products **2b–e** in high yields (70–90%; Scheme 2). Similarly, the reaction worked well both with aromatic and aliphatic aldehydes and ketones. Enolization, as in the case of acetaldehyde or acetone, did not constitute a problem (Scheme 2); in fact, the expected oxetanyl carbinols **2f–j** all formed in good yields (50–85%; Scheme 2). A functionalized aryl ketone **2k** could also be obtained by this DoM method in 70% yield by reacting **1-Li** with *N*,*N*-dimethylbenzamide (Scheme 2).

Because the quest for biaryl structures is widely pursued today,[13] we next explored the possibility of performing a one-pot DoM-Suzuki–Miyaura cross-coupling reaction combining the oxetane-assisted *ortho* C–H bond activation with a direct Li–B exchange. To the best of our knowledge, the only examples thus far of such one-pot procedures have been reported by Snieckus and co-workers for pyridine derivatives[14] and aryl sulfonamides.[15]

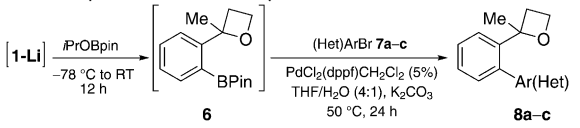
To expand on these precedents, *ortho*-lithiated 2-phenyloxetane **1-Li** was first quenched with the boropinacolate *i*PrOBpin, as an electrophilic boron source, and then reacted with ethyl *p*-bromobenzoate **7a** under the optimized conditions that we had recently determined for the assembly of two aromatic epoxide residues onto a central diborylated phenylene core.[16] To our delight, the putative boronate **6** cleanly underwent cross-coupling, regioselectively giving the desired biaryl **8a** in 50% overall yield (Table 1, entry 1). Under the same conditions, *p*-bromoanisole **7b**, bearing an electron-rich group at the *para* position, also efficiently participated in the coupling process, furnishing the expected oxetanyl-substituted biaryl **8b** in 50% overall yield (Table 1, entry 2). Bromothiazole **7c** could also be successfully partnered to afford the corresponding coupled product **8c** in 45% overall yield (Table 1, entry 3). Interestingly, all of the above cross-couplings took place while leaving the oxetanyl ring intact.

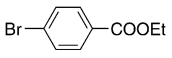
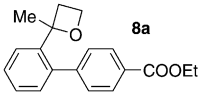
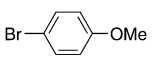
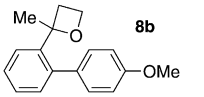
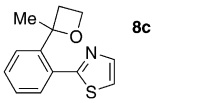
We also wondered whether a ring closure (cyclization) promoted by an oxetanyl carbinol of the type **2f–j** might be conceivable as a means to forge new heterocyclic systems.[17] To this end, *ortho*-hydroxyalkylated phenyl oxetane (±)-**2i**,



Scheme 2. Preparation of *ortho*-substituted 2-methyl-2-phenyloxetanes **2b–k** from 2-methyl-2-phenyloxetane **1**. All yields shown are of products isolated by flash chromatography on silica gel. [a] Overall yield of isolated product for both diastereomers. [b] Diastereomeric ratio = 1.5:1. [c] Separable mixture of diastereomers. [d] Relative configuration has not been assigned. [e] Diastereomeric ratio = 1.2:1. [f] Inseparable mixture of diastereomers. [g] Diastereomeric ratio = 2:1.

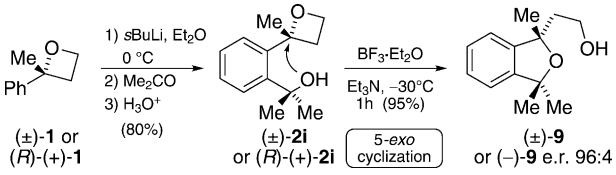
Table 1: One-pot DoM-Suzuki–Miyaura reactions.



Entry	(Het)ArBr **7**	Product **8**	Yield [%][a]
1	 **7a**	 **8a**	50[b]
2	 **7b**	 **8b**	50[b]
3	 **7c**	 **8c**	45[b]

[a] Overall yield of isolated product after flash chromatography on silica gel. [b] Substrate conversions: 66% (**8a**), 55% (**8b**), 50% (**8c**). Dppf = 1,1′-bis(diphenylphosphino)ferrocene, Pin = pinacol.

prepared from (±)-**1**, was selected as a prototypical substrate. Activation of the Lewis basic oxetane oxygen with $BF_3{\cdot}Et_2O$ in Et_2O at −30 °C successfully induced an almost quantitative (95% yield) 5-*exo* cyclization at the phenyl-substituted carbon atom to give 1,3-dihydrobenzo[c]furan (phthalan, (±)-**9**; Scheme 3).[18] In the case of (*R*)-(+)-**2i**, prepared from enantiomerically enriched oxetane (*R*)-(+)-**1** (e.r. 96:4; see



Scheme 3. Synthesis of phthalan **9** by intramolecular cyclization of *ortho*-hydroxyalkylated 2-methyl-2-phenyloxetane **2i**.

the Supporting Information),[19] intramolecular cyclization proceeds with complete preservation of the starting optical purity (e.r. 96:4) at the newly formed quaternary stereogenic center. The high stereochemical fidelity observed in the formation of (−)-**9** is consistent with a stereospecific cyclization (Scheme 3). We assume that an S_N2-type mechanism (inversion of configuration) is followed.[20]

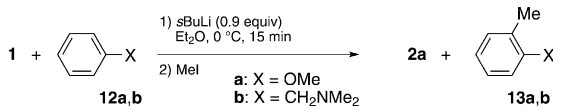
The effect of phenyl ring substitution on the regioselectivity of proton abstraction was also investigated. When *ortho*-chlorophenyloxetane **2e** is treated with *s*BuLi, it smoothly undergoes successive *ortho*-lithiation to give [D_1]-**2e** (98% D) and *ortho*-disubstituted product **10** (98% yield) upon quenching with MeOD and MeI, respectively (Table 2, entries 1 and 2).

meta-Trifluoromethyl-substituted oxetane **2l** could be primarily deprotonated/deuterated at the site *ortho* to the oxetanyl substituent to give [D_1]-**2l** (90% D) instead, despite the cooperative effect of the trifluoromethyl and the oxetanyl groups promoting lithiation between these functional groups (regioselectivity $C_6/C_2 = 9{:}1$; Table 2, entry 3). However, when chlorine is *meta* to the oxetanyl group, as in **2m**, metalation/deuteration exclusively occurred in their mutual *ortho* positions to give [D_1]-**2l** (60% D; regioselectivity $C_6/C_2 = 0{:}10$; Table 2, entry 4).

We then turned our attention to investigating the lithiation of *para*-disubstituted derivatives. Both *p*-(trifluoromethyl) and *p*-(phenylthio)[21] phenyloxetanes **2n**,**p** undergo highly regioselective *ortho*-lithiation at the site nearest the oxetanyl group to give deuterated and methylated derivatives [D_1]-**2n** (70% D) and **11** (90% yield) upon quenching with MeOD and MeI, respectively (Table 2, entries 5 and 6). On the other hand, lithiation of sulfone **2q**[21] with *s*BuLi at 0 °C in THF (this substrate proved to be poorly soluble in Et_2O) occurred only at the *ortho* and *ortho′* positions (C_3 and $C_{2'}$) nearest to the sulfonyl group (see the Supporting Information) to give [D_1]-**2q** (70% D as an equimolar mixture of $C_3/C_{2'}$ regioisomers) upon quenching with MeOD (Table 2, entry 7).

Finally, to assess the relative activation abilities of both aminomethyl groups and alkoxides with respect to the oxetane ring, two intermolecular competition experiments were also performed.[22] Equimolar amounts of 2-methyl-2-phenyloxetane **1** and substituted aromatics such as anisole (**12a**) and *N*,*N*-dimethylbenzylamine (**12b**) were allowed to compete with 0.9 equiv of *s*BuLi in Et_2O. The lithio salts were then trapped by the addition of MeI, and the relative ratios of the corresponding methylated compounds **13a,b** were determined (Table 3). These results suggest that the oxetane ring is more effective at directing *ortho* lithiation than a methoxy substituent (moderate DMG),[3] and almost as strong as the dimethylaminomethyl substituent, which is among one of the most powerful non-acidifying functional groups, with regards to directing ability.[3]

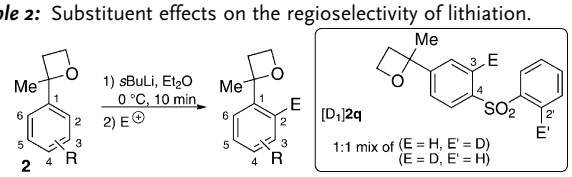
Table 3: Intermolecular competition between **1** and **12a**,**b** for deficient amounts of *s*BuLi.



	Starting Material Yield [%][a]		Methylated Product Yield [%][a]	
X	**1**	**12**	**2a**	**13**
OMe	40	97	60	3
CH_2NMe_2	69	58	31	42

[a] Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

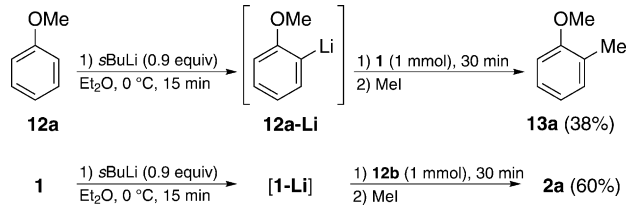
Table 2: Substituent effects on the regioselectivity of lithiation.



Entry	**2**	R	E	Product	Yield [%]	C_6/C_2[a]
1	**2e**	Cl (C_6)	D	[D_1]-**2e**	98[b]	–
2	**2e**	Cl (C_6)	Me	**10**	98[c]	–
3	**2l**	CF_3 (C_3)	D	[D_1]-**2l**	90[b]	9:1
4	**2m**	Cl (C_3)	D	[D_1]-**2m**	60[b,d]	0:10
5	**2n**	CF_3 (C_4)	D	[D_1]-**2n**	70[b,d]	–
6	**2p**	PhS (C_4)	Me	**11**	90[c]	–
7	**2q**	$PhSO_2$ (C_4)	D	[D_1]-**2q**	70[b,e,f]	–

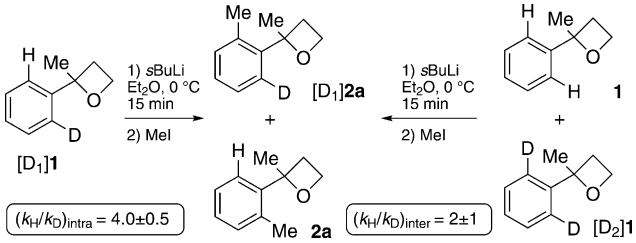
[a] Regioisomeric ratio. [b] Deuteration percentage determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product after flash chromatography on silica gel. [d] Reaction performed at −78 °C. [e] THF solvent. [f] Regioselectivity $C_3/C_{2'} = 1{:}1$ (see box).

To verify that the above methylated products **13a**,**b** result from a direct metalation and not from an anion translocation reaction, two crossover experiments were also performed. Anisole **12a** was *ortho*-lithiated in Et_2O at 0 °C to give **12a-Li**, then treated with oxetane **1**, and finally quenched with MeI; compound **13a** was the only methylated product detected in the crude reaction mixture (38% yield; Scheme 4). In a similar experiment, when *ortho*-lithiated oxetane **1-Li** was reacted with benzylamine **12b** along with a deficiency of *s*BuLi (0.9 equiv), again no translocation occurred and **2a** was the only product formed upon quenching with MeI (60% conversion; Scheme 4).



Scheme 4. Crossover experiments between **12a-Li** and **1-Li** with oxetane **1** and benzylamine **12b**, respectively.

To gain further insight into the number of steps involved, the intra- and intermolecular kinetic isotopic effects (KIEs) were also determined.[5,23] Treatment of [D_1]-**1** (98% D) or an equimolar mixture of **1** and [D_2]-**1** (98% D) with *s*BuLi in Et_2O at 0°C, followed by quenching with MeI, furnished **2a** and [D_1]-**2a** (Scheme 5).



Scheme 5. Determination of inter- and intramolecular KIEs.

An apparent intermolecular KIE of 2 ± 1 was obtained from **1** and [D_2]-**1** at 0°C, whereas the intramolecular KIE calculated from [D_1]-**1** at 0°C was 4.0 ± 0.5 (see the Supporting Information). The fact that two small but measurable values are observed, which are also roughly equal within experimental error, is consistent with a rate-determining proton transfer. Thus, two mechanistic pathways can be suggested: 1) a one-step mechanism via a single transition state arising from simultaneous complexation and proton transfer, or 2) the intervention of a pre-equilibrium complex between the substrate and the organolithium base followed by slow deprotonation (CIPE effect). In light of the effects exerted by solvents (for example, THF) and by noncoordinating bases (for example, LIDAKOR) on the efficacy of deprotonation (see above) and noting that a coordination-driven lithiation pathway has also recently found support in the deprotonation of other small-ring heterocycles, such as epoxides[24] and aziridines,[25] we believe complexation to be the more reasonable pathway.

In conclusion, 2-phenyloxetane is effective in directing both α-lithiation and *ortho*-lithiation, the latter occurring in the absence of benzylic protons.[26] Herein, we have described the first direct *ortho*-lithiation/functionalization of 2-methyl-2-phenyloxetane **1** with a variety of structurally different electrophiles, including aryl and heteroaryl bromides, through a one-pot DoM-Suzuki–Miyaura method. *Ortho*-lithiation proceeds under mild conditions (*s*BuLi in Et_2O at 0°C or room temperature) and without the need for the addition of co-solvents, such as TMEDA.[27] Intra- and intermolecular competition experiments ascertained that an oxetanyl ring is a directing group that is: 1) weaker than those exerting strong acidifying and coordination effects (such as sulfones), 2) stronger than chlorine, trifluoromethyl, phenylthio, and methoxy groups, and 3) as strong as the dimethylaminomethyl group, with respect to directing ability. Comparative KIE studies, together with the screening of bases and solvents, suggest the intervention of a two-step CIPE process rather than a single-step mechanism for the *ortho* C–H lithiation. What adds value to the method described above is the fact that oxetane 1) is a strained small-ring heterocycle transformable to useful targets (such as stereodefined phthlans),[7,17] and 2) does not suffer from attack by the lithiating agent (except in the presence of Lewis acids, the only case in which it becomes vulnerable to nucleophiles).[17] We are confident that in the near future a proper combination of α- and *ortho*-lithiation protocols, together with the control of stereochemistry, will allow for the design of new stereoselective and targeted transformations, which still remain unexplored for aryloxetanes.

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