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Optional *ortho* and lateral lithiations of 4,4-dimethyl-2-(*o*-tolyl)oxazolines

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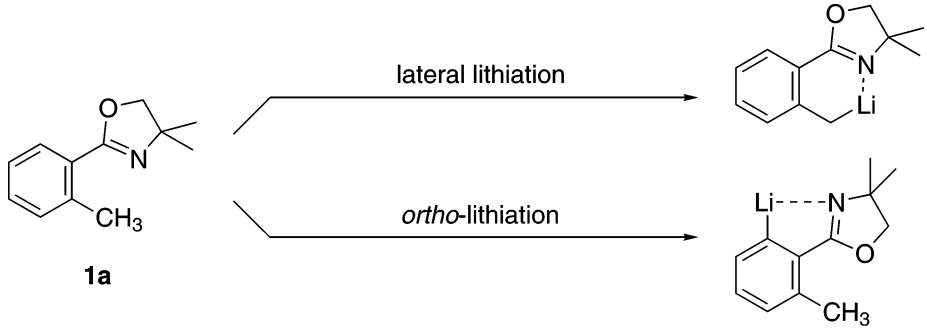
Abstract—4,4-Dimethyl-2-(*o*-tolyl)oxazolines **1** undergo normal lateral lithiation at the benzylic position by treatment with *sec*-BuLi in diethyl ether at −78°C. In contrast, metalation of **1** with *sec*-BuLi/TMEDA in diethyl ether at the same temperature leads to *ortho*-lithiation at the 6′-position. Rationalization for the unusual *ortho*-lithiation of **1** is proposed.

Directed lithiation has been recognized as an excellent method for the synthesis of regiospecifically substituted aromatic compounds.[1] The lithiation of benzene derivatives occurs selectively at the *ortho*-position to a directing group (*ortho*-lithiation). However, if a methyl group exists at the *ortho*-position to the directing group, deprotonation proceeds at the adjacent-benzylic position preferentially due to intrinsic high acidity of the benzylic protons (lateral lithiation).[2] The lateral lithiation is especially facile for *o*-toluic acid and derivatives, such as esters, amides, nitriles, and 2-oxazolines.[2] This may be rationalized by the additional stabilization of the benzylic anion by its extended delocalization to the carbonyl (or its equivalent) moiety. The lateral lithiation of 4,4-dimethyl-2-(*o*-tolyl)oxazoline (**1a**) has been reported by Gschwend and Hamden.[3] We have reinvestigated this reaction and discovered very unusual *ortho*-lithiation of **1a** (Scheme 1).[4] Herein, we report this interesting finding.

The regioselectivity of the lithiation of **1a** was estimated by methylation of the lithio species followed by capillary column GC analysis. Thus, a solution of **1a** (1 mmol) in an appropriate solvent (5 mL) was treated with *sec*-BuLi (1.2 mmol) at −78°C for 1 h and the resulting lithio species were reacted with MeI (3.6 mmol) at −78°C for 3 h. Yields of the recovered **1a**, the lateral methylation product **2**, and the *ortho*-methylation product **3** are shown in Table 1. The lithiation proceeded smoothly in diethyl ether or THF, but it was sluggish in hexane. However, all reactions were highly lateral-selective (entries 1–3). In contrast, when the lithiation was carried out in the presence of TMEDA (1.5 equiv.) in hexane or diethyl ether, the reaction underwent *ortho*-selectively (entries 4 and 5). The remarkable effect of TMEDA was not observed in THF (entry 6). This is apparently due to the strong coordinating ability of THF which overrides the chelating effect of TMEDA.[5] The *ortho*-selectivity was



Scheme 1.

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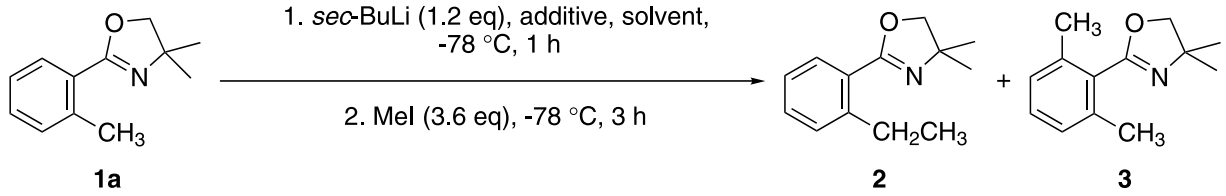
Table 1. Lithiation–methylation of 4,4-dimethyl-2-(*o*-tolyl)oxazoline (**1a**)



Entry	Additive (equiv.)	Solvent	**1a** (%)[a]	**2** (%)[a]	**3** (%)[a]	**2**:**3**
1	None	Hexane	65.4	7.4	0	–
2	None	Et_2O	2.1	81.1	0.7	116:1
3	None	THF	1.9	90.7	4.2	21.6:1
4	TMEDA (1.5)	Hexane	26.9	13.9	50.1	1:3.6
5	TMEDA (1.5)	Et_2O	11.3	14.8	68.3	1:4.6
6	TMEDA (1.5)	THF	0.9	94.6	4.7	20.1:1
7	TMEDA (3.0)	Et_2O	15.0	9.9	67.2	1:6.8
8	TMEDA (5.0)	Et_2O	17.9	8.9	66.4	1:7.5
9	TMEDA (10.0)	Et_2O	23.5	8.1	63.6	1:7.9
10	PMDTA (1.5)	Et_2O	90.0	6.3	1.3	4.8:1
11	Sparteine (1.5)	Et_2O	15.3	82.1	1.1	74.6:1

[a] Yield was determined by capillary column GC analysis using naphthalene as an internal standard.

improved in accord with increasing amount of TMEDA (entries 5, 7–9). A synthetically useful level of selectivity (*ortho* versus lateral = 7.9:1) was achieved by using 10 equiv. of TMEDA (entry 9).[6] The *ortho*-directing effect induced by an external ligand is specific for TMEDA. Other nitrogen ligands, such as *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) and spartein, did not exert the *ortho*-directing effect (entries 10 and 11).

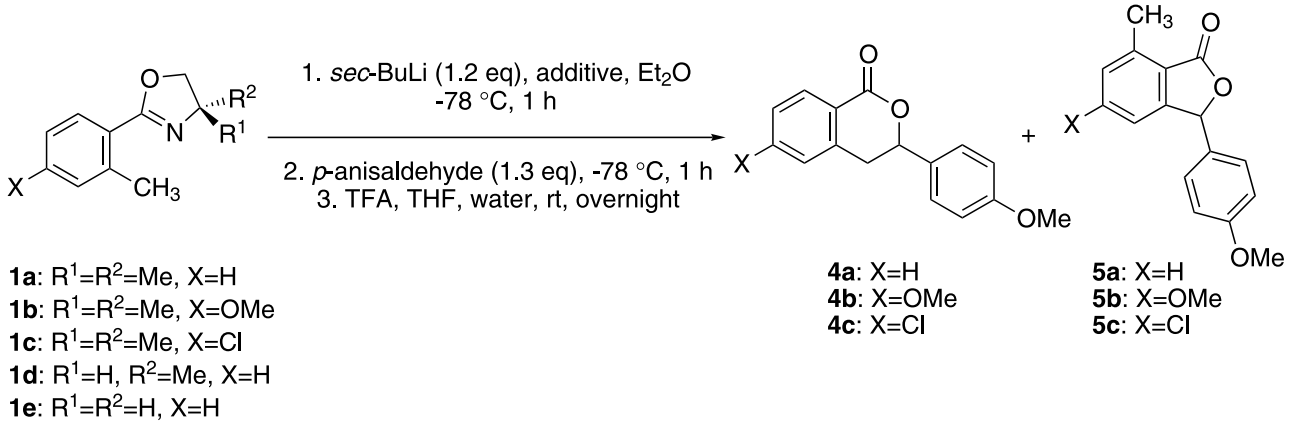
Following these preliminary experiments, we tested the adaptability of these reagent-controlled optional regioselective lithiations[7] to different 2-aryloxazolines **1a**–**e**. Each oxazoline was lithiated with *sec*-BuLi in diethyl ether in the absence or presence of TMEDA. The lithio species was reacted with *p*-anisaldehyde and the crude product was treated with trifluoroacetic acid (TFA) in aqueous THF at room temperature overnight to give a mixture of 3,4-dihydroisocoumarin **4** and 7-methylphthalide **5**.[8] These compounds were readily separated by column chromatography and the isolated yields are shown in Table 2.

First, we checked the effects of the substituent (*p*-OMe or *p*-Cl) on the benzene ring (entries 1–6). In the absence of TMEDA, the oxazolines **1a**,**b** afforded 3,4-dihydroisocoumarins **4a**,**b** almost exclusively to show excellent lateral selectivity in the lithiation step (entries 1 and 2). The selectivity, however, decreased when *p*-chloro derivative **1c** was used (entry 3). This can be accounted for by an inductively electron-withdrawing effect of chlorine,[9] which increases the acidity of the ring protons rather than the lateral protons. In the presence of TMEDA, the lithiation of **1a**–**c** proceeded *ortho*-selectively to give 7-methylphthalides **5a**–**c** as the major products (entries 4–6).[10] Especially in the case of *p*-chloro derivative **1c**, the *ortho*-selectivity was excellent (entry 6).

Next, we examined the effects of the methyl group at the oxazoline 4-position using mono- and non-methylated substrates **1d** and **1e** (entries 7–10). The lateral selectivity of the lithiation of these substrates in the absence of TMEDA was excellent to give 3,4-dihydroisocoumarin **4a** exclusively (entries 7 and 8). On the other hand, the *ortho*-selectivity in the presence of TMEDA decreased considerably (entries 9 and 10). Thus, two methyl groups at the oxazoline 4-position are essential to lead the high *ortho*-selectivity. Based on these critical results, we offer a tentative rationalization for the unusual *ortho*-lithiation of **1** (Fig. 1). Both *ortho* and lateral lithiations may start with initial coordination of the oxazoline nitrogen to the lithium of *sec*-BuLi/TMEDA.[11] A molecular model of the complex of *sec*-BuLi/TMEDA/4,4-dimethyl-2-(*o*-tolyl)oxazoline indicates there is serious steric repulsion between the methyl groups of TMEDA and the methyl groups on the oxazoline ring in a plausible transition state of the lateral lithiation, where the σ orbital of Li–C bond interacts with the σ* orbital of the benzylic C–H bond.[12] Such steric interactions, however, are not remarkable in the transition state of the *ortho*-lithiation. We presume, therefore, the unusual *ortho*-lithiation proceeds much faster than the normal lateral lithiation under these kinetically controlled conditions.

In conclusion, we have discovered unprecedented *ortho*-lithiation of 4,4-dimethyl-2-(*o*-tolyl)oxazolines **1**. Optional *ortho* and lateral lithiations of **1** may open the way to the synthesis of polysubstituted aromatic compounds, which are not readily available by known procedures.

Table 2. Regioselective lithiation of oxazolines **1a–e**



Entry	Substrate	Additive (equiv.)	**4** (%)[a]	**5** (%)[a]
1	**1a**	None	84	2
2	**1b**	None	93	2
3	**1c**	None	64	15
4	**1a**	TMEDA (10)	10	75
5	**1b**	TMEDA (10)	5	75
6	**1c**	TMEDA (10)	1	80
7	**1d**	None	74	0
8	**1e**	None	79	0
9	**1d**	TMEDA (10)	42	34
10	**1e**	TMEDA (10)	26	34

[a] Isolated yield after column chromatography.

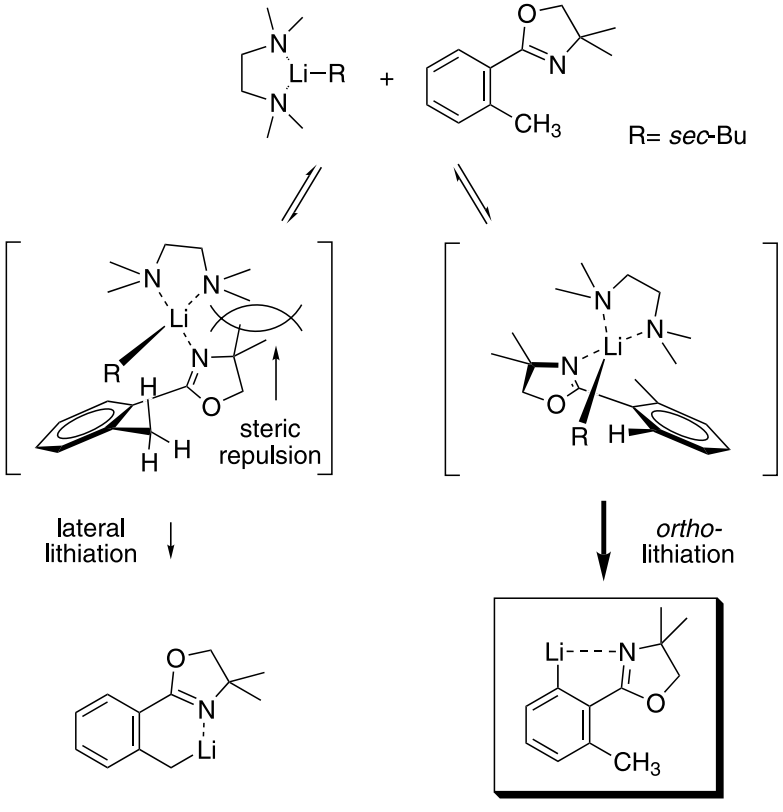


Figure 1.

References

1. For reviews, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1; (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
2. Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.
3. Gschwend, H. W.; Hamden, A. *J. Org. Chem.* **1975**, *40*, 2008.
4. A study on *ortho* versus lateral lithiations of *N*,*N*-diethyl-*o*-alkylbenzamides has been reported, see: Court, J. J.; Hlasta, D. J. *Tetrahedron Lett.* **1996**, *37*, 1335.
5. Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.
6. The dramatic change in regioselectivity by added TMEDA was also confirmed by deuteration experiments. The lithiation of **1a** [*sec*-BuLi (1.2 equiv.), TMEDA (10 equiv.), Et_2O, −78°C, 1 h] followed by MeOD quench afforded 87% recovery of the substrate, in which deuterium content at the *ortho*-position was 81% and that at the lateral position was 12% (^1H NMR analysis). A similar experiment without TMEDA resulted in 102% deuterium incorporation at the lateral position and 5% at the *ortho*-position.
7. For examples of the reagent-controlled optional regioselective lithiations; see: (a) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731; (b) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815; (c) Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430; (d) Schlosser, M.; Maccaroni, P.; Marzi, E. *Tetrahedron* **1998**, *54*, 2763; (e) Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron* **2001**, *57*, 975.
8. (a) Fu, P. P.; Unruh, L. E.; Miller, D. W.; Huang, L. W.; Yang, D. T. C. *J. Org. Chem.* **1985**, *50*, 1259; (b) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991.
9. (a) Schlosser, M.; Marzi, E.; Cottet, F.; Büker, H. H.; Nibberring, N. M. M. *Chem. Eur. J.* **2001**, *7*, 3511; (b) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622.
10. The synthesis of 7-methylphthalides is rather problematic. The best method so far developed employs directed lithiation of tertiary *o*-toluamides, which, however, involves a tedious protection-deprotection sequence, see: Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4386. Compared to this, the method presented herein is straightforward and, therefore, is much more useful for the preparation of this type of phthalides.
11. (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356; (b) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145; (c) Warmus, J. S.; Rodkin, M. A.; Barkley, R.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1993**, 1357; (d) Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628; (e) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092.
12. Schleyer has carried out theoretical studies on the directed lithiations of *ortho*-substituted toluenes and concluded that the preferred site for lithiation is governed by the stabilization of the transition state, rather than by the initial complexation, see: Kremer, T.; Junge, M.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 3345. Ab initio calculations of the transition structures for *ortho* and lateral lithiations of **1** are in progress in our laboratories.