Synthesis of Pyrrolo[1,2-*b*]isoquinolines through Mesityllithium-Mediated Intramolecular Carbolithiation

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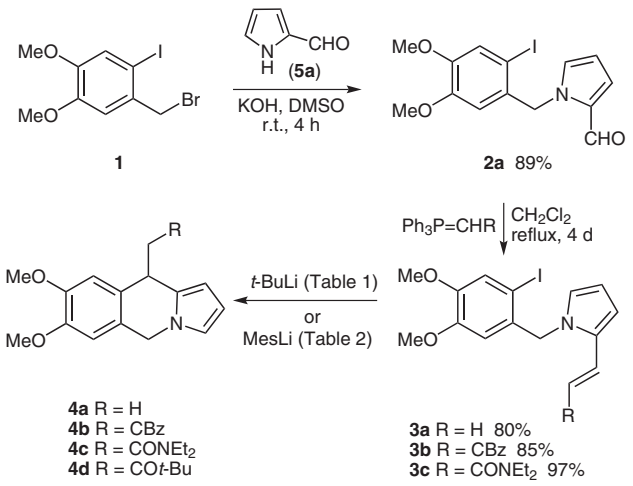
Abstract: Mesityllithium has proven to be an effective iodine–lithium exchange reagent. Thus, carbolithiation reactions on 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrroles have been accomplished avoiding side reactions to afford pyrroloisoquinolines in high yields (80–92%), improving the results obtained with *t*-BuLi. The carbolithiation reaction requires the use of electron-deficient alkenes. Mesityllithium has also been studied as an alternative to *t*-BuLi in Parham cyclization with other internal electrophiles (aldehyde, ketone, ester, amide), proving to be more selective and efficient than *t*-BuLi.

Key words: organolithium, carbanions, carbolithiation, metalation, heterocycles

The synthetic utility of lithium–halogen exchange reaction[1] for the metalation of aromatic substrates, though mechanistically controversial,[2] have been shown in the facile construction of benzo-fused cyclic ring systems via intramolecular reaction of the so-generated aryllithium compounds with internal electrophiles,[3] a metalation–cyclization process known as Parham cyclization.[4,5]

On the other hand, the intramolecular carbolithiation[6] of olefinic organolithiums is rapidly growing in popularity as a preparative method for cyclopentylmethyllithiums and their heterocyclic analogues. The attraction of this methodology lies in the high regio- and stereoselectivity when carbon–carbon bond is formed and in the possibility of trapping the resulting cyclized organolithium with various electrophiles to introduce diverse functionality into the cyclized products. Although many of these carbolithiations involve alkyl- or alkenyllithiums,[7]there are also some examples of cycloisomerization of alkenyl-substituted aryllithiums generated by metal–halogen exchange. Thus, intramolecular carbolithiation reaction of unsaturated aryllithiums is particularly well suited for the construction of five-membered rings through a 5-*exo*-trig cyclization process, as it has been shown in the synthesis of carbocyclic[8] and heterocyclic compounds,[9] even in a diastereoselective[10] or enantioselective fashion.[11,12] However, intramolecular carbolithiation reactions have only been scarcely applied to the synthesis of six-membered rings. To our knowledge, the synthesis of enantiopure 4-substituted tetrahydroisoquinolines achieved by Pedrosa[13] via a diastereoselective carbolithiation of chiral 2-(*o*-bromophenyl)-substituted perhydro-1,3-benzoxazines, derived from (–)-8-aminomenthol is the only example of *6-exo* cyclization process.

Therefore, in connection with our previous studies,[14] we decided to investigate the intramolecular carbolithiation of 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrroles **3**, using alkenes with different substitution patterns as internal electrophiles for the synthesis of pyrrolo[1,2-*b*]isoquinolines **4** (Scheme 1).



Scheme 1 Synthesis and carbolithiation reactions of **3a–c**

The synthetic starting point was the *N*-benzylpyrrole-2-carbaldehyde **2a**, which was prepared by alkylation of commercially available pyrrole-2-carbaldehyde **5a** with the 2-iodo-4,5-dimethoxybenzyl bromide (**1**)[14b] using a standard procedure. The olefination of aldehyde **2a** was achieved via Wittig reaction with the corresponding phosphorus ylides to afford 2-vinyl-substituted *N*-(*o*-iodobenzyl)pyrroles **3a–c** in good overall yields (Scheme 1).

We first studied the carbolithiation reactions of *N*-(*o*-iodobenzyl)pyrroles **3a–c** with *t*-BuLi and TMEDA (Scheme 1, Table 1), starting from previously used conditions.[10a] However, although iodine–lithium exchange occurred efficiently, addition of *t*-BuLi to the unsubstituted alkene in **3a** was competitive with cyclization, isolating **7** and **6** (Table 1, entry 1). The use of equimolecular amounts of *t*-BuLi and TMEDA resulted in a low conver-

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Table 1 Carbolithiation Reactions of **3a–c** with *tert*-Butyllithium

Entry	Substrate	*t*-BuLi (equiv)	TMEDA (equiv)	Temp (°C)	Product	Yield (%)
1	**3a**	2	2	–78 to 0	–[a]	–
2	**3a**	1	1	–78 to 0	–[b]	–
3	**3b**	2	2	–78 to 0	–[c]	–
4	**3b**	2	–	–78	**4b**[d]	39
5	**3b**	1	–	–78	**4b**[d]	38
6	**3b**	2	–	–90	**4b**[d]	42
7	**3c**	2	2	–78	**4c**[e]	27
8	**3c**	1	1	–78	**4c**	39
9	**3c**	1	–	–78	**4c**	41
10	**3c**	1	1	–105	**4c**	31

[a] De-iodinated benzylpyrrole **6** (26%) and addition product **7** (49%) were isolated.
[b] Compound **6** (17%) was isolated.
[c] Addition product **8a** (22%) was isolated.
[d] Addition product **4d** (20–25%) was also isolated.
[e] Addition product **8b** (24%) was also isolated.

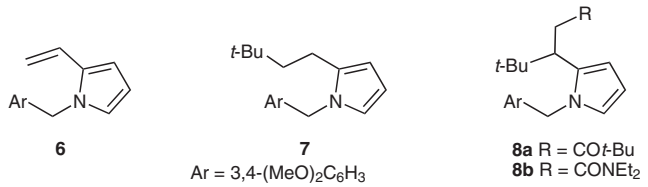


Figure 1 Byproducts from *t*-BuLi-mediated carbolithiation of **3a–c**

sion, and the isolation of de-iodinated **6** (Figure 1), together with unreacted starting material.

Therefore, we studied the carbolithiation reactions on **3b**, where the alkene was substituted with an electron-withdrawing group (CO_2Bn). However, under standard conditions (Table 1, entry 3), the direct addition of *t*-BuLi to both the alkene and the ester moieties was competitive in the presence of TMEDA, yielding a mixture of products where only **8a** was isolated. Although cyclization took place in the absence of TMEDA (entries 4–6), the addition of *t*-BuLi to the ester moiety could not be avoided under various conditions, isolating pyrroloisoquinoline **4d** as a byproduct, together with **4b**, in all cases. Therefore, we tested the possibility of using an amide as electron-withdrawing group (**3c**, R = $CONEt_2$). Thus, when the reaction was carried out in the presence of TMEDA (entry 7), pyrroloisoquinoline **4c** was obtained, although in low yield, due to competitive direct conjugate addition of *t*-BuLi to afford **8b**. The yield of **4c** could be slightly improved in the absence of TMEDA (entry 9) or lowering the temperature or the number of equivalents of organolithium (entries 8 and 10), although variable amounts of **8b** (10–16%) were isolated.

In order to avoid these side reactions in the intramolecular carbolithiation of **3a–c**, we decided to study the possibility of using a more bulky and less nucleophilic reagent for the iodine–lithium exchange reaction. In this context, mesityllithium (MesLi) has been described to be a strongly basic, non-nucleophilic and selective reagent.[15] Mesityllithium has been used in organic synthesis mainly as an LDA equivalent, for deprotonation reactions,[16] and there are only a few examples of its use in aromatic metalation[17] or in halogen–lithium exchange reactions.[18]

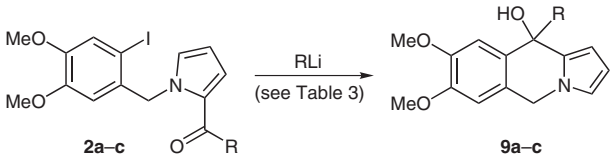
Thus, as shown in Table 2, lithium–iodine exchange was performed efficiently with MesLi, although the unsubstituted alkene **3a** was also unreactive under these conditions (entry 1), isolating the non-iodinated benzylpyrrole **6**, but avoiding the direct addition of the organolithium reagent to the alkene. At higher temperatures (–20 or 0 °C, entries 2 and 3), decomposition of the aryllithium intermediate was observed. On the other hand, we were pleased to find that cyclization of **3b** and **3c** took place smoothly at low temperature and in only 5 minutes to afford pyrroloisoquinolines **4b**,**c** in high yields and avoiding side reactions (entries 4–7).[19]

Table 2 Carbolithiation Reactions of **3a–c** with Mesityllithium

Entry	Substrate	Temp (°C)	Time	Product	Yield (%)
1	**3a**	–78	4 h	**6**	42
2	**3a**	–20	20 h	**6**	16
3	**3a**	0	3 h	–	–
4	**3b**	–78	5 min	**4b**	80
5	**3b**	–105	5 min	**4b**	92
6	**3c**	–78	5 min	**4c**	83
7	**3c**	–105	5 min	**4c**	90

In view of these results, we decided to compare the efficiency of MesLi with *t*-BuLi in this type of reaction using other internal electrophiles. In this context, Kondo had already established the compatibility of MesLi with keto-esters in Parham cyclization.[18] For this purpose, we prepared benzylpyrroles **2b–f** by a standard procedure,[20] which bear different types of carbonyl groups (aldehyde, ketone, ester, and amide) as internal electrophiles.

We first tried the Parham cyclization with **2a**, using an aldehyde as internal electrophile. However, as it could be expected, the aldehyde carbonyl was too reactive under the conditions tested (Scheme 2, Table 3, entries 1–3), and only addition of MesLi to the carbonyl group was observed (compound **10**, Figure 2), besides iodine–lithium exchange. For this reason, the reaction was not tried with *t*-BuLi.



Scheme 2 Parham cyclization of 2-acylpyrroles **2a–c**

Table 3 Parham Cyclization of 2-Acylpyrroles **2a–c**

Entry	Substrate	RLi	Temp (°C)	Time (min)	Product	Yield (%)
1	**2a**	MesLi	–78	60	**10**	9
2	**2a**	MesLi	–78	5	**10**	12
3	**2a**	MesLi	–105	5	**10**	6
4	**2b**	MesLi	–78	5	**11b**	23
5	**2b**	MesLi	–105	5	**11b**	25
6	**2b**	*t*-BuLi	–90	5	**11b**	14
7	**2c**	MesLi	–78	5	**9c**	95
8	**2c**	MesLi	–105	5	**9c**	95
9	**2c**	*t*-BuLi	–105	5	**9c**	95

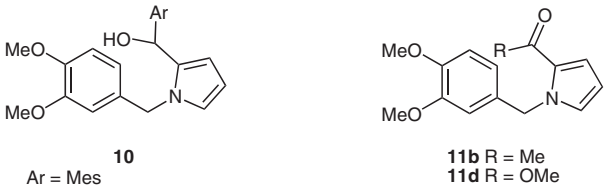
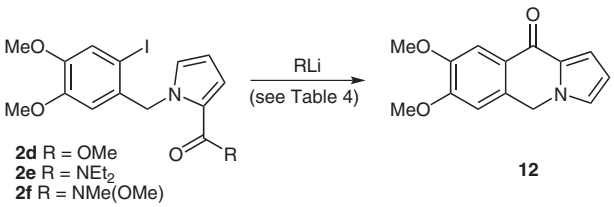


Figure 2 Byproducts from Parham cyclization of **2a–f**

The reaction with an enolizable ketone such as **2b** also failed both with *t*-BuLi and MesLi (Table 3, entries 4–6). In this case, no addition product could be isolated but, although the metalation took place, no cyclization was observed, isolating **11b** in low yields. Probably, competitive α-deprotonation of the ketone precludes cyclization.[21] Thus, cyclization with nonenolizable ketone **2c** took place in high yield in just 5 minutes both with *t*-BuLi and MesLi (Table 3, entries 7–9). On the other hand, MesLi proved to be more selective than *t*-BuLi when an ester (**2d**) was used as electrophile (Scheme 3, Table 4). Thus, when **2d** was treated with *t*-BuLi at –90 °C, no cyclization product was observed, isolating only a moderate yield of noniodinated benzylpyrrole **11d**, together with unreacted **2d** (30%, Table 4, entry 1). A GC-MS analysis of the crude reaction mixture showed also minor amounts of the corresponding *tert*-butyl ketone, result of *t*-BuLi addition to the carbonyl. When the reaction was carried out with MesLi, pyrroloisoquinoline **12** was obtained in moderate yield (54%, entry 2), which was improved working at lower temperature (69%, entry 3). Finally, we had previously shown that amides behave as excellent internal electrophiles in Parham cyclizations with *t*-BuLi.[14] As shown in entries 4–7 (Table 4), MesLi behaves as a more effective metalating agent, improving the yield of **12** and shortening the reaction times.



Scheme 3 Parham cyclization of 2-acylpyrroles **2d–f**

Table 4 Parham Cyclization of 2-Acylpyrroles **2d–f**

Entry	Substrate	RLi	Temp (°C)	Time (min)	Product	Yield (%)
1	**2d**	*t*-BuLi	–90	120	**11d**	37
2	**2d**	MesLi	–78	5	**12**	54
3	**2d**	MesLi	–105	5	**12**	69
4	**2e**	MesLi	–78	5	**12**	79
5	**2e**	*t*-BuLi	–78	180	**12**	79[a]
6	**2f**	MesLi	–78	5	**12**	95
7	**2f**	*t*-BuLi	–78	180	**12**	86[a]

[a] Results previously described in ref. 14b.

In summary, it has been shown that MesLi behaves as an excellent reagent for lithium–iodine exchange reactions, avoiding direct addition to the electrophilic group, and improving the results obtained with *t*-BuLi. Thus, pyrroloisoquinolines **4** have been prepared through MesLi-mediated intramolecular carbolithiation reactions via a 6-*exo* cyclization process, though the alkene is required to be substituted with an electron-withdrawing group. Furthermore, MesLi improves the results obtained with *t*-BuLi in the Parham cyclization with different internal electrophiles allowing the efficient construction of the pyrroloisoquinoline nucleus. While Kondo has reported the application of this type of cyclization to haloaraomatics having alkoxycarbonyl groups using MesLi,[18] only a few successful examples with esters[22] or ketones[23] have been described with the usual organolithiums (*t*-BuLi, *n*-BuLi), due to their high reactivity towards the internal electrophile. As we have shown for the synthesis of pyrroloisoquinolines, the use of MesLi could be an interesting alternative for these metalation reactions.

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(19) **Mesityllithium-Mediated Carbolithiation Reactions of *N*-(*o*-Iodobenzyl)pyrroles 3b,c: Synthesis of Pyrrolo[1,2-*b*]isoquinolines – Typical Procedure for the Synthesis of Benzyl 2-(7,8-Dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetate (4b)**

To a solution of mesityl bromide (0.1 mL, 0.65 mmol) in dry THF (5 mL), *t*-BuLi (1.2 mL of a 1.1 M solution in hexane, 1.3 mmol) was added at –78 °C, and the reaction mixture was stirred at –20 °C for 1 h. *N*-(*o*-Iodobenzyl) pyrroles **3b** (126 mg, 0.32 mmol) in dry THF (5 mL) was added at –105 °C, and the resulting mixture was stirred at this temperature for 5 min. The reaction was quenched by the addition of sat. NH_4Cl (5 mL). Then, Et_2O (10 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, 60% hexane–EtOAc) afforded **4b** as a colorless oil (113 mg, 92%). IR ($CHCl_3$): 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.75 (d, *J* = 7.1 Hz, 2 H), 3.81 (s, 3 H), 3.88 (s, 3 H), 4.61 (t, *J* = 7.1 Hz, 1 H), 4.58 (s, 1 H), 4.61 (s, 1 H), 4.64 (s, 2 H), 6.01 (s, 1 H), 6.18 (t, *J* = 2.8 Hz, 1 H), 6.70 (s, 2 H), 6.82 (s, 1 H), 7.26–

7.35 (m, 5 H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 35.3, 43.6, 47.1, 55.9, 66.2, 103.9, 108.2, 109.0, 110.7, 118.4, 124.1, 128.1, 128.4, 129.9, 135.6, 147.6, 148.1, 171.3. MS (EI): *m/z* (%) = 378(6) [M^+ + 1], 377(21) [M^+], 287(17), 286(83), 242(7), 229(16), 228(100), 212(15), 184(10), 91(16). HRMS: *m/z* calcd for $C_{23}H_{23}NO_4$: 377.1627; found: 377.1638.

(20) *N*-Benzylpyrroles **2b–f** were prepared by alkylation of the corresponding 2-acylpyrrole **5b–f** with bromide **1** under standard conditions (KOH, DMSO) as described in Scheme 1 for **2a**.

(21) In fact, when the reaction described in Table 3, entry 6 (*t*-BuLi, 2 equiv, –90 °C, 5 min) was quenched with MeOD, incorporation of deuterium into the acetyl group could be observed by GC-MS.

(22) For representative examples, see: (a) Paleo, M. R.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1993**, *58*, 2763. (b) Gould, S. J.; Melville, C. R.; Cone, M. C.; Chen, J.; Carney, J. R. *J. Org. Chem.* **1997**, *62*, 320. (c) Moreau, A.; Lorion, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2006**, *71*, 3303.

(23) (a) Aidhen, I. S.; Narasimham, N. S. *Tetrahedron Lett.* **1991**, *32*, 2171. (b) Kihara, M.; Kashimoto, M.; Kobayashi, Y. *Tetrahedron* **1992**, *48*, 67.