Intramolecular Addition of Heteroaryllithium Compounds onto Activated Alkenes: Access to Heterofused Indolizines and Pyrroloazepines

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DOI: **10.1002/ejoc.201700123**

Intramolecular Addition of Heteroaryllithiums onto Activated Alkenes. Access to Heterofused Indolizines and Pyrroloazepines

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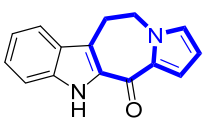
Abstract: Heteroaryllithiums, obtained via MesLi mediated halogen-lithium exchange, undergo intramolecular addition onto acrylamide and acrylate moieties. Both electron rich (thiophenyl) and electron deficient (pyridinyl, quinolinyl) heteroaromatic halides can be used for the formation of six- and seven membered rings, providing an efficient route to fused indolizines and pyrroloazepines in moderate to good yields.

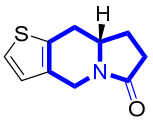
Introduction

Carbolithiation reaction is a powerful method for the synthesis of functionalized molecules, generating new carbon-carbon bonds. Intramolecular carbolithiation, in particular, has become an effective means of preparing carbocycles and heterocycles.[1] Nevertheless, in the specific context of the Parham-type cyclizations,[2] i.e. the intramolecular carbolithiations via aryllithium intermediates generated by halogen-lithium exchange, such cyclization reactions are not without limitations. In most reported cases, these reactions have been applied for the construction of five-membered rings, but there are still few examples of the formation of medium-size rings cycles, and most of them come from our group. The reduced effectiveness of the later processes may have been a consequence of the strain associated with the addition of the aryllithium to the double bond, which would develop in the transition state leading to the cyclic lithiated intermediate.[3] Since the late 2000s, our research group has maintained an interest in intramolecular carbolithiation reactions as a means to generate heterocycles, and we have investigated this transformation in both diastereo- and enantioselective variants.[4] In these studies, the ability of an electron-withdrawing substituent to activate the alkene group as the internal electrophile was identified. These substituents would stabilize the alkyllithium intermediate generated in the addition process, which triggered an 1,4-addition, thus increasing the efficacy of the reaction. Representative of this behavior was the reaction of *N*-alkenyl substituted *o*-iodoanilines, which led to synthesis of 2,4-disubstituted tetrahydroquinolines when an α,β-unsaturated amide moiety served as internal electrophile.[5] The utility of this process was demonstrated in the synthesis of enantiopure tetrahydroquiolines with potential biological activity.[6] Analogous reactions of 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles presented an important question of chemoselectivity, as the conjugate addition reaction of the alkyllithium used for the halogen-lithium exchange on the α,β-unsaturated amide was competitive with the aromatic lithiation reaction.[7] The problem was solved using a bulky non-nucleophilic organolithium as mesityllithium (MesLi) as metalating agent.[8] The methodology showed very broad scope in terms of size of the formed heterocycles, but was limited to cyclization of aryl halides. The procedure could be applied not only for the construction of six-membered rings, pyrrolo[1,2-*b*]isoquinolines, but also seven- and eight-membered rings as pyrrolo-benzazepines and benzazocines.[9] Therefore, we decided to extend this protocol to electron-rich (thiophene) and electron deficient heteroaryl halides (e.g., pyridines and quinolines), which would involve heteroaryllithiums generated by halogen – lithium exchange. Heteroaryllithiums are very versatile intermediates that have been used in different types of organic transformations,[10] as copper-catalyzed α-selective allylic alkylation,[11] palladium catalyzed cross-coupling reactions,[12] conjugate addition,[13] coupling of boronic acids,[14] or Parham-type cycliacylations.[15] These examples illustrate the utility of heteroaryllithiums in heterocycle synthesis, and also demonstrate the possibility of introducing the lithium atom regioselectively at different positions of the ring systems. Nevertheless, their use in carbolithiation reactions is scarce and to our knowledge limited to the intramolecular carbolithiation of alkynes through a 5-exo-*dig* process.[16]

Herein, we report the intramolecular carbolithiation reaction of *N*-(*o*-haloheteroarylalkyl)pyrroles for the synthesis of heterofused indolizidines and pyrroloazepines, important structural motifs that occur in some biological active compounds and have also been found to have potential uses in material science or as building blocks in synthetic chemistry. A notable example is aspastipuline (Figure 1), a natural product recently isolated from *Asparagus stipularis Forssk* roots[17] that shown a moderate antiproliferative activity against the human mammary gland adenocarcinoma cell line MCF-7 (Figure 1). Thieno[3,2-*f*]indolizinone shown in Figure 1 exhibited significant antimutagenic activity,[18] while some pyrrolo[1,2-*g*][1,6]naphthyridine derivatives have been claimed to be calcitonin agonists useful in therapies for osteopenia and osteoporosis.[19] Of particular significance are compounds that bear the pyrido[2,3-*d*]pyrrolo[1,2-*a*]azepine unit, due to their electroluminescent properties.[20]



Aspastipuline



Thieno[3,2-*f*]indolizinone

Figure 1.

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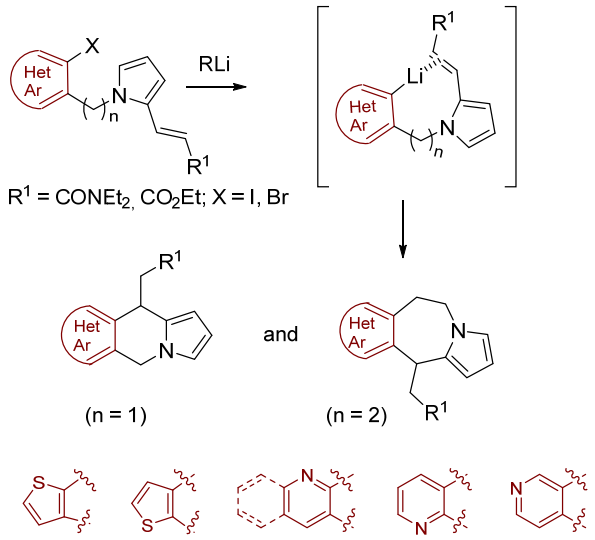
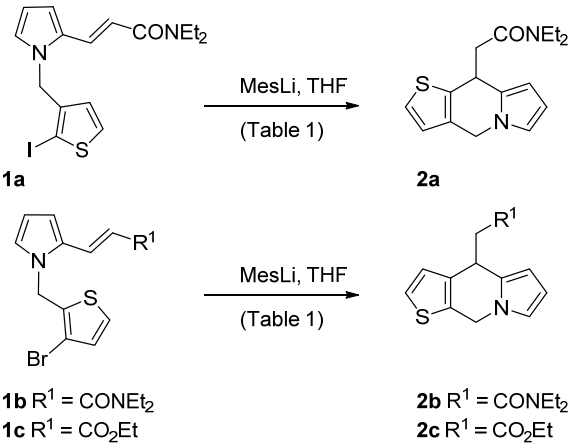
Results and Discussion

For this study of the intramolecular carbolithiation of *N*-(*o*-haloheteroarylalkyl)pyrroles, a series of both electron-rich (thiophene) and electron deficient (pyridines and quinolines) heteroaryl bromides and iodides with different substitution patterns on the heteroaromatic ring were selected. [21] Thus, the behavior of heteroaromatics lithiated at different positions would be evaluated, as well as the nature of the halogen atom (I *vs*. Br) for the exchange reaction (Scheme 1). In all cases, the alkene would be activated with an amide or ester group, to favor the cyclizations through the stabilization of the resulting organolithium. Finally the effect of the ring size ewill also be studied for the formation of six- and seven membered rings.



Scheme 1.

We started studying the cyclization reactions of 2-iodo- and 3-bromothiophenes **1a-c** (Scheme 2, Table 1). First, to establish a comparison with our previous results,[7,9] *t*BuLi was used to effect the iodine-lithium exchange on 2-iodothiophene **1a** at low temperature and in short reaction time (Table 1, entry 1). As could be expected, metalation took place efficiently, but the conjugate addition of *t*BuLi to the acrylamide moiety was competitive with the cyclization, and addition product **3a** (Figure 1) was the major isolated product (64%), together with a minor amount of **3b** (20%).[22] Therefore, the use of a non-nuclephilic metalating agent, such as MesLi, was required to generate the thiophen-3-yl lithium via iodine-lithium exchange. When MesLi was used at -105 °C for 5 min **3b** was obtained (Table 1, entry 2), showing that metalation occurs rapidly but not cyclization. An increase of the temperature to -78 ºC (entry 3) was still not effective, and it was necessary to allow the reaction to reach room temperature to obtain thieno[2,3-*f*]indolizine **2a** (entry 4). Although the conversion was good, **2a** could not be fully characterized due to decomposition under chromatographic conditions, so the yield was estimated by ^{1}H NMR.[23]



Scheme 2. Access to thienoindolizines **2a-c**.

Table 1. Cyclization of thiophenylmethylpyrroles **1a-c**

Entry	Substrate	T (ºC)	t (min)	Product	Yield (%)
1	**1a**	-105[a]	10	**3a**	64[b]
2	**1a**	-105	5	**3b**	91
3	**1a**	-78	15	**3b**	77
4	**1a**	78 to rt	180	**2a**	61[c]
5	**1b**	-78 to rt	180	**-**	[d]
6	**1b**	-78	180	**3c**	41
7	**1b**	-78	360	**2b**	12[e]
8	**1c**	78 to rt	180	**2c**	13
9	**1c**	-78	180	**2c**	61

[a] *t*BuLi/TMEDA was used as metalating agent. [b] 20% of **3b** was also isolated [c] The yield was estimated by ^{1}H NMR. **2a** could not be isolated and characterized.[d] Decomposition. [e] 16% of **3c** was also isolated

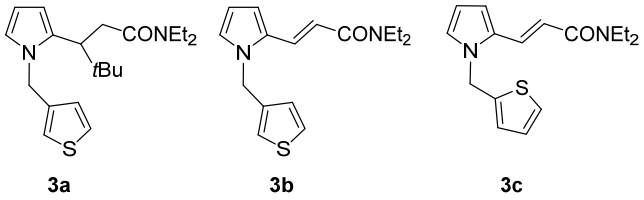
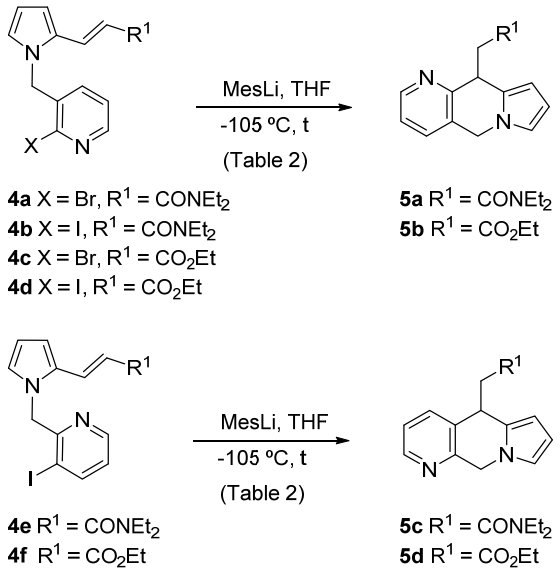


Figure 2. By-products isolated in the cyclizations of **1a,b**.

However, when these reaction conditions were applied to the formation of the thiophen-3-yl lithium derived from the corresponding bromo derivatives **1b** and **1c**, either decomposition products were observed (entry 5) or a low yield of the thieno[3,2-*f*]indolizine **2c** was isolated (entry 8). It is known that 3-lithiothiophenes are unstable as the temperature rises

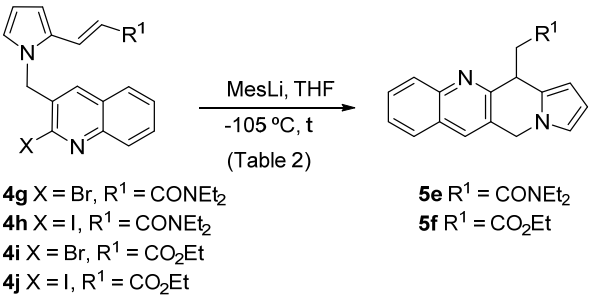
above -78ºC.[10a] So, in these cases, the reactions have to be kept at low temperature (-78 ºC) for 3 h to obtain moderate to good yields of the corresponding thieno[3,2-*f*]indolizines **2b,c** (Table 1, entries 7 and 9). This example illustrates the uytility of the halogen-lithium exchange reaction to introduce the lithium atom at the less acid site of the thiophene, which could not be accomplished by direct deprotonation.

We next studied the cyclizations of the pyridin-2-yllithiums derived from halopyridines **4a-d** (Scheme 3, Table 2). Low temperatures and very short reaction times were required for the formation of this type of heteroaryllithiums. Although *n*BuLi was the most efficient metalating agent for the formation of analogous pyridin-2-yl lithiums in related Parham cyclizations,[15b] in this case gaves 1,4-addition to the acrylamide moiety.[24] Therefore, it was necessary again to use a less nucleophilic metalating agent as MesLi. Thus, treatment of 2-bromopyridine **4a** with MesLi in THF at -105 ºC provided pyrrolonaphthyridine **5a** in just 5 min in low yield (27%), but starting material was recovered (86% conversion) (Table 2, entry 1). Complete conversion and a moderate isolated yield (55%) were accomplished in only 10 min at – 105 ºC (entry 2). A similar yield was obtained if the pyridin-2-yllithium was generated by iodine-lithium exchange from **4b** (entry 3). The reaction was also efficient with the corresponding acrylates **4c,d** to obtain pyrrolonaphthyridine **5b** in moderate yields (entries 4, 5).



Scheme 3. Synthesis of pyrrolonaphthyridines **4a-d**

Next, the formation of the regioisomeric pyrrolonaphthyridines **5c,d** was studied (Scheme 3, Table 2). Although pyridin-3-yl lithiums are reported to be more stable than pyridin-2-yl lithiums,[10e] when acrylamide **4e** and acrylate **4f** were treated under the same reaction conditions, **5c,d** were obtained in low isolated yields (Table 2, entries 6,7). The use of low temperatures and short reaction times was crucial with these pyridinyl lithiums to obtain clean reactions. However, when these conditions were applied to 2-bromoquinoline **4g** (Scheme 4) the conversion was not complete (Table 2, entry 9), and **5e** was isolated in 20% yield. In this case, the extension of the reaction time did not have a significant impact in the yield (entry 10), and a similar result was obtained when the corresponding iodide **4h** was used (entry 11). The cyclization reaction was faster with corresponding acrylates **4i** and **4j**, affording **5f** also in low isolated yield (entries 12 and 13). Therefore, although we have previously shown that the generation and nucleophilic addition of quinoly-2-lithiums to acyl moieties was effective in Parham cycliacylations,[15b] their intramolecular conjugate addition gave poorer results.



Scheme 4. Synthesis of benzopyrrolonaphthyridines **4e-f.**.

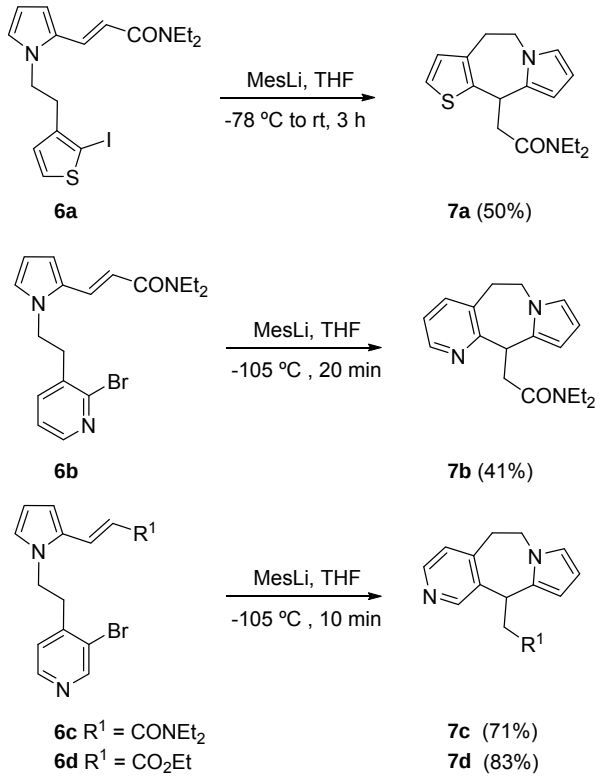
Table 2. Synthesis of pyrrolonaphthyridines **5a-f**

Entry	Substrate	t (min)	Product	Yield (%)[a]
1	**4a**	5	**5a**	27[b]
2	**4a**	10	**5a**	55
3	**4b**	10	**5a**	56
4	**4c**	5	**5b**	47
5	**4d**	5	**5b**	49
6	**4e**	10	**5c**	29
7	**4f**	5	**5d**	26
8	**4f**	10	**5d**	18
9	**4g**	10	**5e**	20[b]
10	**4g**	30	**5e**	25
11	**4h**	30	**5e**	28
12	**4i**	5	**5f**	29
13	**4j**	10	**5f**	30

[a] Yield of pure isolated product. [b] 86% conversion

We then studied the formation of the seven-membered ring to access to heterofused pyrroloazepines. The correspoding thiophen-2-yl lithium was obtained efficiently by treatment of **6a**

with MesLi at – 78 ºC, affording **7a** in 50% isolated yield (Scheme 5),[25] under the same conditions reported for the formation of the six-membered ring (see Table 1, entry 4). Once again, thiophen-2-yl lithium derivative required higher temperature and longer reaction times than the electron deficient pyridinyl lithiums. Thus, pyridin-2-yl lithium obtained from **6b** at -105 ºc was efficiently cyclized to obtain **7b** in only 20 min. Finally, the formation of more stable pyridin-3-yl lithiums derived from **6c** and **6d** resulted in a smooth cylization to afford pyridopyrrolo[1,2-*a*]azepines **7c,d** in high isolated yields.



Scheme 5. Synthesis of heterofused pyrroloazepines **7a-d**.

Conclusions

In conclusion, it has been shown that heteroaryl lithiums obtained via halogen-lithium exchange undergo 6-exo and 7-exo-*dig* cyclizations with alkenes activated with an electron withdrawing group, such as diethyl amide or ethyl ester. As has been described for related systems, the use of mesityl lithium (MesLi) as metalating agent is crucial to avoid the direct 1,4 addition of the metalating agent to the acrylamide or acrylate moieties. Both electron rich (thiophen-2- and 3-yl lithiums) and electron deficient (pyridin-2- and 3-yl lithiums) undergo cyclizations onto the activated alkene, although significant differences on the reactivity have been observed. Thus, electron rich thiophenyllithiums are efficiently generated at low temperature, but both the 6-*exo* and 7-*exo* cyclizations require higher temperature to proceed efficiently. These heteroaryllithium intermediates are thus less reactive than those derived from electron rich methoxylated aromatic rings, which undergo cyclizations at low temperature.[9a] On the other hand, in the case of electron deficient pyridine and quinoline halides, low temperatures and short reaction times are crucial to avoid side reactions. Thus, pyrrolonaphthyridne systems are obtained in modest yields. These results are in contrast with recent calculations for substituted aromatic rings, which point out that an increase of the electron density leads to an increased reactivity.[**¡Error! Marcador no definido.**3c] In the case of heteroaryllithiums studied in this work, electron deficient pyridine-2- and 3-yl, and quinolin-2-yl lithiums, afforded the cyclizations products at lower temperatures and in shorter reaction times. In these cases, the cyclizations can also be efficiently extended to the formation of seven-membered rings. Overall, this anionic cyclyzation allows the synthesis of interesting heterofused indolizidines and pyrroloazepine systems, and could be an alternative to related strategies based on palladium catalyzed reactions, which might present chemoselectivity issues with competitive arylation reactions.[26]

Experimental Section

General experimental methods: Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained in film over NaCl pellets or using an ATR. NMR spectra were recorded at 20-25 ˚C, at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C or at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C in $CDCl_3$ solutions. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Mass spectra were recorded under electron impact (EI) at 70 eV, chemical ionization (CI) at 230 eV, or ESI$^+$ as indicated in each case. Exact mass was obtained using a TOF detector. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was performed on silica gel (230-400 mesh) or on alumina (70-230 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures.[27] *n*- and *t*Butyllithium were titrated with diphenylacetic acid or *N*-benzyl benzamide periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 ˚C) and purged with argon.

MesLi mediated cyclization reactions of acrylates or acrylamides 1a-c, 4a-j and 6a-d General Procedure. To a solution of mesityl bromide (2 mmol) in dry THF (15 mL), *t*BuLi (4 mmol) was added at –78 °C and the reaction mixture was stirred at –20 ºC for 1 h. The reaction mixture was cooled again to –78 °C, and a solution of the acrylate or acrylamide **1a-c, 4a-j** or **6a-d** (1 mmol) in dry THF (15 mL) was added at the temperature indicated. The reaction was quenched at low temperature by the addition of sat. NH_4Cl (10 mL). Et_2O (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*.

2-(4,9-Dihydrothieno[2,3-*f*]indolizin-4-yl)-*N*,*N*-diethylacetamide (2b). (Table 1, entry 7). According to the General Procedure, **1b** (160 mg, 0.44 mmol) was treated with MesLi [0.87 mmol, prepared from mesityl bromide (0.14 mL, 0.87 mmol) and *t*BuLi (1.36 mL of a 1.28 M solution in hexane, 1.74 mmol)] at –78 ºC and the reaction mixture was stirred for 6 h. After work up, flash column chromatography (silica gel, petroleum ether/AcOEt 6/4) afforded **2b** as a yellow oil (15 mg, 12%), and **3c** (20 mg, 16%) (See ESI for characterization data of **3c**). Data for **2b**: IR

(ATR): 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 0.94 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3), 1.16 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3), 2.64 – 2.77 (m, 2H, CH_2CONEt_2), 3.04 – 31.4 (m, 2H, NCH_2CH_3), 3.36 – 3.48 (m, 2H, NCH_2CH_3), 4.83 – 4.88 (m, 1H, H_4), 5.23 (s, 2H, H_9), 6.06– 6.08 (m, 1H, H_5), 6.23 – 6.26 (m, 1H, H_6), 6.66 – 6.71 (m, 1H, H_7), 7.01 (d, *J* = 5.1 Hz, 1H, H_3), 7.20 (d, *J* = 5.1 Hz, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 13.1, 14.2 [$N(CH_2CH_3)_2$], 32.5 (C_4), 40.7 (NCH_2CH_3), 42.1 (NCH_2CH_3 and CH_2CONEt_2)*, 44.6 (C_9), 104.5 (C_5) 109.1 (C_6), 118.2 (C_7), 123.6 (C_2), 127.0 (C_3), 129.2 (C_{9a}), 130.6 (C_{4a}), 136.8 (C_{3a}), 170.2 ($CONEt_2$). * Overlapped signals. MS (ESI^+) *m/z* (rel intensity): 289 (MH^+, 100), 216 (4). HRMS (ESI^+): Calcd. for $C_{16}H_{21}N_2OS$ [MH^+]: 289.1375; found: 289.1370.

Ethyl 2-(4,9-dihydrothieno[2,3-*f*]indolizin-4-yl)acetate (2c). (Table 1, entry 9). According to the General Procedure, **1c** (103 mg, 0.30 mmol) was treated with MesLi [0.60 mmol, prepared from mesityl bromide (0.09 mL, 0.60 mmol) and *t*BuLi (0.93 mL of a 1.30 M solution in hexane, 1.21 mmol)] at –78 ºC and the reaction mixture was stirred for 3 h. After work up, flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **2b** as a pale yellow oil (48 mg, 61%): IR (ATR): 1727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 1.25 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.77 (d, *J* = 6.8 Hz, 2H, CH_2CO_2Et), 4.17 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.61 – 4.69 (m, 1H, H_4), 5.17 – 5.27 (m, 2H, H_9), 6.04 – 6.09 (m, 1H, H_5), 6.23 – 6.28 (m, 1H, H_6), 6.68 – 6.72 (m, 1H, H_7), 6.96 (d, *J* = 5.1 Hz, 1H, H_3), 7.23 (d, *J* = 5.1 Hz, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 14.2 (OCH_2CH_3), 32.1 (C_4), 43.2 (CH_2CO_2Et), 44.6 (C_9), 60.5 (OCH_2CH_3), 104.3 (C_5) 109.0 (C_6), 118.4 (C_7), 123.9 (C_2), 126.1 (C_3), 129.8 (C_{4a}), 129.9 (C_{9a}), 135.8 (C_{3a}), 171.7 (CO_2Et) ppm; MS (ESI^+) *m/z* 262 (MH^+, 100), 174 (4). HRMS (ESI^+): Calcd. for $C_{14}H_{16}NO_2S$ [MH^+]: 262.0902; found: 262.0906.

2-(5,10-Dihydropyrrolo[1,2-*g*][1,6]naphthyridin-10-yl)-*N,N*-diethylacetamide (5a). (Table 2, entry 3). According to the General Procedure, **4b** (100 mg, 0.24 mmol) was treated with MesLi [0.50 mmol, prepared from mesityl bromide (0.08 mL, 0.50 mmol) and *t*BuLi (0.71 mL of a 1.38 M solution in hexane, 0.98 mmol)] at –105 ºC and the reaction mixture was stirred for 10 min. After work up, flash column chromatography (silica gel, hexane/AcOEt 9/1) afforded **5a** as a pale yellow oil (39 mg, 56%): IR (ATR): 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 1.05 – 1.15 (m, 6H, $N(CH_2CH_3)_2$), 2.93 (dd, *J* = 15.1, 6.3 Hz, 1H, $CH_AH_BCONEt_2$), 3.13 – 3.43 (m, 5H, $N(CH_2CH_3)_2$), $CH_AH_BCONEt_2$), 4.79 (t, *J* = 6.3 Hz, 1H, H_{10}), 5.10 (d, *J* = 15.7 Hz, 1H, H_{5A}), 5.20 (d, *J* = 15.7 Hz, 1H, H_{5B}), 6.01 – 6.06 (m, 1H, H_9), 6.17 – 6.22 (m, 1H, H_8), 6.68 – 6.73 (m, 1H, H_7), 7.15 (dd, *J* = 7.7, 4.8 Hz, 1H, H_3), 7.51 (d, *J* = 7.7 Hz, 1H, H_4), 8.45 – 8.52 (m, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 12.9, 14.2 [$N(CH_2CH_3)_2$], 37.7 (CH_2CONEt_2), 37.9 (C_{10}), 40.3, 42.0 [$N(CH_2CH_3)_2$], 47.1 (C_5), 104.2 (C_9) 108.8 (C_8), 118.2 (C_7), 121.2 (C_3), 127.3 (C_{4a}), 130.8 (C_{9a}), 133.6 (C_4), 148.1 (C_2), 156.4 (C_{10a}), 170.2 ($CONEt_2$) ppm; MS (ESI^+) *m/z* (rel intensity): 285 (MH^+ + 1, 16), 284 (MH^+, 100). HRMS (ESI^+): Calcd. for $C_{17}H_{22}N_3O$ [MH^+]: 284.1763; found: 284.1761.

Ethyl 2-(5,10-dihydropyrrolo[1,2-*g*][1,6]naphthyridin-10-yl)acetate (5b). (Table 2, entry 5). According to the General Procedure, **4d** (100 mg, 0.26 mmol) was treated with MesLi [0.50 mmol, prepared from mesityl bromide (0.08 mL, 0.50 mmol) and *t*BuLi (0.68 mL of a 1.53 M solution in hexane, 1.04 mmol)] at –105 ºC and the reaction mixture was stirred for 5 min. After work up, flash column chromatography (silica gel, hexane/AcOEt 8/2) afforded **5b** as a yellow oil (33 mg, 49%): IR (ATR): 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.98 (dd, *J* = 15.8, 6.3 Hz, 1H, $CH_AH_BCO_2Et$), 3.15 (dd, *J* = 15.8, 6.3 Hz, 1H, $CH_AH_BCO_2Et$), 4.13 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.67 (t, *J* = 6.3 Hz, 1H, H_{10}), 5.12 (d, *J* = 15.8 Hz, 1H, H_{5A}), 5.20 (d, *J* = 15.8 Hz, 1H, H_{5B}), 6.03 – 6.11 (m, 1H, H_9), 6.20 – 6.25 (m, 1H, H_8), 6.70-6.75 (m, 1H, H_7), 7.18 (dd, *J* = 7.7, 4.6 Hz, 1H, H_3), 7.53 (d, *J* = 7.7 Hz, 1H, H_4), 8.52 (d, *J* = 4.6 Hz, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 14.1 (OCH_2CH_3), 37.6 (C_{10}), 39.6 ($CH_AH_BCO_2Et$), 47.0 (C_5), 60.4 (OCH_2CH_3), 104.3 (C_9) 109.0 (C_8), 118.5 (C_7), 121.5 (C_3), 127.1 (C_{4a}), 130.0 (C_{9a}), 133.8 (C_4), 148.3 (C_2), 155.4 (C_{10a}), 171.9 (CO_2Et) ppm; MS (ESI^+) *m/z* (rel intensity): 258 (MH^+ + 1, 15), 257 (MH^+, 100). HRMS (ESI^+): Calcd. for $C_{15}H_{17}N_2O_2$ [MH^+]: 257.1290; found: 257.1296.

2-(5,10-Dihydropyrrolo[2,1-*g*][1,7]naphthyridin-5-yl)-*N,N*-diethylacetamide (5c). (Table 2, entry 6). According to the General Procedure, **4e** (101 mg, 0.25 mmol) was treated with MesLi [0.50 mmol, prepared from mesityl bromide (0.08 mL, 0.50 mmol) and *t*BuLi (1.25 mL of a 0.80 M solution in hexane, 1 mmol)] at –105 ºC and the reaction mixture was stirred for 10 min. After work up, flash column chromatography (silica gel, hexane/AcOEt 9/1) afforded **5c** as a pale yellow oil (20 mg, 29%): IR (ATR): 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 0.89 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 1.10 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 2.62 (dd, *J* = 14.7, 7.8 Hz, 1H, $CH_AH_BCO_2Et$), 2.72 (dd, *J* = 14.7, 7.8 Hz, 1H, $CH_AH_BCO_2Et$), 2.98 (q, *J* = 7.1 Hz, 2H, NCH_2CH_3), 3.35 (q, *J* = 7.1 Hz, 2H, NCH_2CH_3), 4.87 (t, *J* = 7.8 Hz, 1H, H_5), 5.22 (s, 2H, H_{10}), 6.05 – 6.09 (m, 1H, H_6), 6.21 (t, *J* = 3.1 Hz, 1H, H_7), 6.72 – 6.78 (m, 1H, H_8), 7.19 (dd, *J* = 7.8, 4.8 Hz, 1H, H_3), 7.79 (dd, *J* = 7.8, 1.6 Hz, 1H, H_4), 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 13.1, 14.2 [$N(CH_2CH_3)_2$], 35.2 (C_5), 40.6 (NCH_2CH_3), 41.9 (CH_2CONEt_2), 42.1 (NCH_2CH_3), 49.9 (C_{10}), 104.4 (C_6) 109.0 (C_7), 118.7 (C_8), 122.5 (C_3), 129.6 (C_{5a}), 132.6 (C_{4a}), 136.6 (C_4), 147.5 (C_2), 152.1 (C_{10a}), 169.5 ($CONEt_2$) ppm; MS (ESI^+) *m/z* (rel intensity): 285 (MH^++1, 22), 284 (MH^+, 100), 169 (1). HRMS (ESI^+): Calcd. for $C_{17}H_{22}N_3O$ [MH^+]: 284.1763; found: 284.1769.

Ethyl 2-(5,10-dihydropyrrolo[2,1-*g*][1,7]naphthyridin-5-yl)acetate (5d). (Table 2, entry 7). According to the General Procedure, **4f** (101 mg, 0.27 mmol) was treated with MesLi [0.50 mmol, prepared from mesityl bromide (0.08 mL, 0.50 mmol) and *t*BuLi (1.25 mL of a 0.80 M solution in hexane, 1 mmol)] at –105 ºC and the reaction mixture was stirred for 10 min. After work up, flash column chromatography (silica gel, hexane/AcOEt 8/2) afforded **5d** as a yellow oil (18 mg, 26%): IR (ATR): 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 1.13 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.63 (dd, *J* = 15.5, 7.1 Hz, 1H, $CH_AH_BCO_2Et$), 2.69 (dd, *J* = 15.5, 7.1 Hz, 1H, $CH_AH_BCO_2Et$), 4.04 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.60 (t, *J* = 7.1 Hz, 1H, H_5), 5.13 (d, *J* = 6.6 Hz, 1H, H_{10A}), 5.17 (d, *J* = 6.6 Hz, 1H, H_{10B}), 5.93 – 6.03 (m, 1H, H_6), 6.14 (t, *J* = 3.2 Hz, 1H, H_7), 6.62 - 6.70 (m, 1H, H_8), 7.15 (dd, *J* = 7.8, 4.8 Hz, 1H, H_3), 7.61 (dd, *J* = 7.8, 1.5 Hz, 1H, H_4), 8.41 (dd, *J* = 4.8, 1.5 Hz, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 14.2 (OCH_2CH_3), 34.8 (C_5), 43.2 (CH_2CO_2Et), 49.9 (C_{10}), 60.7 (OCH_2CH_3), 104.3 (C_6) 108.9 (C_7), 119.0 (C_8), 122.5 (C_3), 128.7 (C_{5a}), 131.7 (C_{4a}), 135.8 (C_4), 147.7 (C_2), 152.5 (C_{10a}), 171.0 (CO_2Et) ppm; MS (ESI^+) *m/z* (rel intensity): 258 (MH^++1, 21), 257 (MH^+, 100), 169 (1). HRMS (ESI^+): Calcd. for $C_{15}H_{17}N_2O_2$ [MH^+]: 257.1290; found: 257.1303.

2-(5,12-Dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridin-12-yl)-*N,N*-diethylacetamide (5e). (Table 2, entry 11). According to the General Procedure, **4h** (100 mg, 0.22 mmol) was treated with MesLi [0.45 mmol, prepared from mesityl bromide (0.07 mL, 0.45 mmol) and *t*BuLi (0.83 mL of a 1.08 M solution in hexane, 0.90 mmol)] at –105 ºC and the reaction mixture was stirred for 30 min. After work up, flash column chromatography (silica gel, hexane/AcOEt 6/4) afforded **5e** as a pale yellow oil (20 mg, 28%): IR (ATR): 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ= 1.16 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 1.25 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 3.03 (dd, *J* = 15.1, 6.1 Hz, 1H, $CH_AH_BCONEt_2$), 3.34 – 3.46 (m, 5H, $CH_AH_BCONEt_2$, $N(CH_2CH_3)_2$), 4.98 (t, *J* = 6.1 Hz, 1H, H_{12}), 5.27 (d, *J* = 15.3 Hz, 1H, H_{5A}), 5.32 (d, *J* = 15.3 Hz, 1H, H_{5B}), 6.04 – 6.09 (m, 1H, H_1), 6.19 (dd, *J* = 3.4, 2.8 Hz, 1H, H_2), 6.76 – 6.78 (m, 1H, H_3), 7.47 – 7.52 (m,

1H, H_8), 7.60-7.68 (m, 1H, H_9), 7.77 (d, J = 8.1 Hz, 1H, H_7), 7.94 – 8.00 (m, 2H, H_6, H_{10}) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 13.1, 14.4 [N(CH_2CH_3)$_2$], 35.8 (CH_2CONEt_2), 39.1 (C_{12}), 40.6, 42.3 [N(CH_2CH_3)$_2$],, 47.8 (C_5), 103.7 (C_1) 108.4 (C_2), 118.5 (C_3), 126.2 (C_{5a}), 126.3 (C_8), 126.6 (C_{6a}), 127.2 (C_7), 129.0 (C_{10}), 129.2 (C_9), 131.3 (C_{12a}), 132.3 (C_6), 147.1 (C_{10a}), 157.9 (C_{11a}), 170.7 ($CONEt_2$) ppm; MS (ESI$^+$) *m/z* (rel intensity): 335 (MH$^+$ + 1, 22), 334 (MH$^+$, 100). HRMS (ESI$^+$): Calcd. for $C_{21}H_{24}N_3O$ [MH$^+$]: 334.1919; found: 334.1926.

Ethyl 2-(5,12-dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridin-12-yl)acetate (5f). (Table 2, entry 13). According to the General Procedure, **4j** (100 mg, 0.23 mmol) was treated with MesLi [0.45 mmol, prepared from mesityl bromide (0.07 mL, 0.45 mmol) and *t*BuLi (0.86 mL of a 1.08 M solution in hexane, 0.93 mmol)] at –105 ºC and the reaction mixture was stirred for 10 min. After work up, flash column chromatography (silica gel, hexane/AcOEt 8/2) afforded **5e** as a pale yellow oil (21 mg, 30%): IR (ATR): 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.08 (dd, J = 15.8, 6.7 Hz, 1H, $CH_AH_BCO_2Et$), 3.33 (dd, J = 15.8, 6.7 Hz, 1H, $CH_AH_BCO_2Et$), 4.14 – 4.27 (m, 2H, OCH_2CH_3), 4.82 (t, J = 6.7 Hz, 1H, H_{12}), 5.27 (d, J = 15.4 Hz, 1H, H_{5A}), 5.33 (d, J = 15.4 Hz, 1H, H_{5B}), 6.07 – 6.12 (m, 1H, H_1), 6.20 – 6.24 (m, 1H, H_2), 6.74 – 6.81 (m, 1H, H_3), 7.50 – 7.54 (m, 1H, H_8), 7.69 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H, H_9), 7.78 (dd, J = 7.7, 1.4 Hz, 1H, H_7), 7.99 (s, 1H, H_6), 8.02 (dd, J = 8.5, 1.4 Hz, 1H, H_{10}) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 14.3 (OCH_2CH_3), 38.2 (CH_2CO_2Et), 38.7 (C_{12}), 47.6 (C_5), 60.5 (OCH_2CH_3), 104.2 (C_1) 108.6 (C_2), 118.8 (C_3), 125.7 (C_{5a}), 126.5 (C_8), 126.6 (C_{6a}), 127.2 (C_7), 129.1 (C_{10}), 129.4 (C_9), 130.3 (C_{12a}), 132.6 (C_6), 147.1 (C_{10a}), 156.8 (C_{11a}), 172.3 (CO_2Et) ppm; MS (ESI$^+$) *m/z* (rel intensity): 308 (MH$^+$ + 1, 18), 307 (MH$^+$, 100). HRMS (ESI$^+$): Calcd. for $C_{19}H_{19}N_2O_2$ [MH$^+$]: 307.1447; found: 307.1453.

2-(4,10-Dihydro-5*H*-pyrrolo[1,2-*a*]thieno[2,3-*d*]azepin-10-yl)-*N*,*N*-diethylacetamide (7a). According to the General Procedure, **6a** (96 mg, 0.22 mmol) was treated with MesLi [0.45 mmol, prepared from mesityl bromide (0.07 mL, 0.45 mmol) and *t*BuLi (1.0 mL of a 0.9 M solution in hexane, 0.9 mmol)] at –78 ºC and the reaction mixture was stirred for 3 h, and then it was allowed to wamp up to rt over 3 h. After work up, flash column chromatography (silica gel, hexane/AcOEt 1/1) afforded **7a** as a solid (34 mg, 50%): mp (hexane/AcOEt): 113-114 ºC; IR (ATR): 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.08-1.12 [m, 6H, N(CH_2CH_3)$_2$], 2.95-3.06 (m, 4H, H_4, $CHCH_2$), 3.17-3.27 (m, 2H, NCH_2CH_3), 3.34-3.41 (m, 2H, NCH_2CH_3), 4.33-4.37 (m, 2H, H_5), 5.09 (t, J = 7.0 Hz, 1H, H_{10}), 5.93-5.95 (m, 1H, H_9), 5.97-5.99 (m, 1H, H_8), 6.56-6.59 (m, 1H, H_7), 6.67 (d, J = 5.1 Hz, 1H, H_3), 7.00 (d, J = 5.1 Hz, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 12.9, 14.2 [N(CH_2CH_3)$_2$], 31.3 (C_4), 34.7 (C_{10}), 40.5 (NCH_2CH_3), 40.7 (CH_2CONEt_2), 41.9 (NCH_2CH_3), 46.4 (C_5), 106.3, 106.4 (C_8, C_9), 121.4 (C_7), 121.8 (C_2), 129.8 (C_3), 134.3 (C_{9a}), 134.6 (C_{3a}), 138.2 (C_{10a}), 169.4 (CO) ppm; MS (CI$^+$) *m/z* (rel intensity): 303 (MH$^+$, 17) 302 (15), 206 (9), 189 (12), 188 (100), 116 (9). HRMS (ESI$^+$): Calcd. for $C_{17}H_{23}N_2OS$ [MH$^+$]: 303.1531; found: 303.1535.

2-(5,11-Dihydro-6*H*-pyrido[2,3-*d*]pyrrolo[1,2-*a*]azepin-11-yl)-*N*,*N*-diethylacetamide (7b). According to the General Procedure, **6b** (93 mg, 0.25 mmol) was treated with MesLi [0.50 mmol, prepared from mesityl bromide (0.08 mL, 0.50 mmol) and *t*BuLi (0.79 mL of a 1.28 M solution in hexane, 1 mmol)] at –105 ºC and the reaction mixture was stirred for 20 min. After work up, flash column chromatography (silica gel, CH_2Cl_2/AcOEt 8/2) afforded **7b** as a yellow oil (30 mg, 41%): (ATR): 1629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.08 (t, J = 7.1 Hz, 3H, NCH_2CH_3), 1.36 (t, J = 7.1 Hz, 3H, NCH_2CH_3), 2.92 (dd, J = 15.1, 4.8 Hz, 1H, $CH_AH_BCONEt_2$), 3.01 (dt, J = 15.5, 5.0 Hz, 1H, H_{5A}), 3.28 - 3.34 (m, 1H, $NCHHCH_3$), 3.40 - 3.42 (m, 1H, $NCHHCH_3$), 3.50 – 3.58 (m, 1H, $NCHHCH_3$), 3.62 – 3.75 (m, 3H, $NCHHCH_3$, H_{5B}, $CH_AH_BCONEt_2$), 4.00 – 4.07 (m, 1H, H_{6A}), 4.52 (dt, J = 13.0, 5.0 Hz, 1H, H_{6B}), 5.23 (dd, J = 9.3, 4.8 Hz, 1H, H_{11}), 5.87 – 5.92 (m, 1H, H_{10}), 6.05 (t, J = 3.2 Hz, 1H, H_9), 6.55 (s, 1H, H_8), 7.02 (dd, J = 7.5, 4.8 Hz, 1H, H_3), 7.41 (dd, J = 7.5, 1.7 Hz, 1H, H_4), 8.26 (dd, J = 4.8, 1.7 Hz, 1H, H_2) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 12.9, 14.3 [N(CH_2CH_3)$_2$], 31.4 (C_5), 32.9 (CH_2CONEt_2), 39.0 (C_{11}), 40.4, 42.2 [N(CH_2CH_3)$_2$], 47.2 (C_6), 104.1 (C_{10}), 107.0 (C_9), 121.6 (C_3), 121.7 (C_8), 132.5, 132.6 (C_{4a}, C_{10a}), 136.4 (C_4), 146.5 (C_2), 159.4 (C_{11a}), 171.1 ($CONEt_2$) ppm; MS (ESI$^+$) *m/z* (rel intensity): 298 (MH$^+$, 100), 225 (54). HRMS (ESI$^+$): Calcd. for $C_{18}H_{24}N_3O$ [MH$^+$]: 298.1919; found: 298.1920.

2-(5,11-Dihydro-6*H*-pyrido[3,4-*d*]pyrrolo[1,2-*a*]azepin-11-yl)-*N*,*N*-diethylacetamide (7c). According to the General Procedure, **6c** (80 mg, 0.21 mmol) was treated with MesLi [0.43 mmol, prepared from mesityl bromide (0.07 mL, 0.43 mmol) and *t*BuLi (0.67 mL of a 1.28 M solution in hexane, 0.85 mmol)] at –105 ºC and the reaction mixture was stirred for 10 min. After work up, flash column chromatography (silica gel, hexane/AcOEt 8/2) afforded **7c** as a yellow oil (45 mg, 71%): (ATR): 1629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.00 – 1.14 (m, 6H, [NCH_2CH_3)$_2$], 2.90 – 3.08 (m, 2H, CH_2CONEt_2), 3.13 – 3.41 [m, 6H, 2 x H_5, N(CH_2CH_3)$_2$], 4.17 – 4.27 (m, 1H, H_{6A}), 4.28 – 4.40 (m, 1H, H_{6B}), 5.01 (t, J = 7.3 Hz, 1H, H_{11}), 5.95 – 6.05 (m, 2H, H_9, H_{10}), 6.51 - 6.57 (m, 1H, H_8), 7.00 – 7.12 (m, 1H, H_4), 8.29 – 8.58 (m, 2H, H_1, H_3) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 12.9, 14.3 [N(CH_2CH_3)$_2$], 33.4 (C_5), 37.6 (C_{11}), 39.2 (CH_2CONEt_2), 40.5, 41.9 [N(CH_2CH_3)$_2$], 46.9 (C_6), 107.2, 107.4 (C_9, C_{10}) 121.9 (C_8), 124.7 (C_4), 132.2 (C_{10a}), 135.5 (C_{11a}), 146.2 (C_{4a}), 147.8 (C_3), 149.3 (C_1), 169.2 ($CONEt_2$) ppm; MS (ESI$^+$) *m/z* (rel intensity): 298 (MH$^+$, 100), 225 (1). HRMS (ESI$^+$): Calcd. for $C_{18}H_{24}N_3O$ [MH$^+$]: 298.1919; found: 298.1925.

Ethyl 2-(5,11-dihydro-6*H*-pyrido[3,4-*d*]pyrrolo[1,2-*a*]azepin-11-yl)acetate (7d). According to the General Procedure, **6d** (104 mg, 0.30 mmol) was treated with MesLi [0.60 mmol, prepared from mesityl bromide (0.09 mL, 0.60 mmol) and *t*BuLi (0.93 mL of a 1.28 M solution in hexane, 1.2 mmol)] at –105 ºC and the reaction mixture was stirred for 10 min. After work up, flash column chromatography (silica gel, CH_2Cl_2/AcOEt 8/2) afforded **7b** as a yellow oil (66 mg, 83%): (ATR): 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.19 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.97 – 3.09 (m, 2H, CH_2CO_2Et), 3.19 – 3.35 (m, 2H, H_5), 4.08 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.17 – 4.27 (m, 1H, H_{6A}), 4.28 – 4.37 (m, 1H, H_{6B}), 4.83 (t, J = 7.9 Hz, 1H, H_{11}), 5.97 – 6.00 (m, 1H, H_{10}), 6.01 – 6.04 (m, 1H, H_9), 6.53 – 6.56 (m, 1H, H_8), 7.05 (d, J = 4.8 Hz, 1H, H_4), 8.37 (d, J = 4.8 Hz, 1H, H_3), 8.44 (s, 1H, H_1) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 14.1 (OCH_2CH_3), 33.1 (C_5), 37.4 (C_{11}), 41.0 (CH_2CO_2Et), 46.8 (C_6), 60.7 (OCH_2CH_3), 107.2, 107.3 (C_9, C_{10}) 122.2 (C_8), 124.6 (C_4), 131.3 (C_{10a}), 135.5 (C_{11a}), 146.4 (C_{4a}), 148.2 (C_3), 148.8 (C_1), 171.0 (CO_2Et) ppm; MS (ESI$^+$) *m/z* (rel intensity): 271 (MH$^+$, 100), 184 (1). HRMS (ESI$^+$): Calcd. for $C_{16}H_{19}N_2O_2$ [MH+]: 271.1447; found: 271.1458.

Supporting Information (see footnote on the first page of this article): Synthesis and characterization of substrates **1a-c**, **4a-j** and **6a-d**, and products **3a-c**. Additional essays with **4a** and **6a**. Copies of ^{1}H and ^{13}C NMR spectra of all compounds described.

Acknowledgements

Ministerio de Economía y Competitividad (CTQ2013-41229-P, CTQ2016-74881-P), Gobierno Vasco (IT1045-16) and Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU are gratefully acknowledged for their financial support. ARA and EC wish to thank Gobierno Vasco for a grant. Technical and human support provided by Servicios Generales

de Investigación SGIker (UPV/EHU, MINECO, GV/EJ, ERDF and ESF) is also acknowledged.

Keywords: Heteroaryllithium • carbolithiation • cyclization • nitrogen heterocycles • carbanion

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[21] See ESI for the synthesis of substrates

[22] See ESI for the characterization of by-products **3a-c.**

[23] The yield was estimated by integration of the corresponding ^{1}H NMR signals with respect to the signals of **3b**, which was obtained as a by-product (39%)

[24] See ESI for details on the reaction of **4a** with *n*BuLi

[25] When the reaction was quenched at low temperature (-105 or -78 ºC), the corresponding deiodinated acrylamide was obtained as the major compound (58-60%), together with **7a** in low yields (7-9%). See ESI for details.

[26] When **1a-b** were treated under Mizoroki-Heck reaction conditions, the corresponding thienoindolizine was isolated in very low yields (0-15%), see: E. Coya, N. Sotomayor, E. Lete, *Adv. Synth. Catal.* **2014**, *356*, 1853–1865.

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