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# C-H Activation / metalation approaches for the synthesis of indolizine derivatives

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**Abstract:** The C-H borylation of indolizines has not previously been reported and in this communication, we describe our preliminary efforts to apply this chemistry to this scaffold and contrast this approach to directed metalation. Through these methodologies were possible obtain a library of substituted indolizines functionalized in both pyridinic and pyrrole ring.

#### Introduction

Indolizines represent a privileged class of heterocycles that have received considerable attention recently due to their significant and broad range of activities (Figure 1). This include roles in many biological active compounds such as anti-inflammatory,<sup>1</sup> anticancer,<sup>2</sup> antimicrobial,<sup>3</sup> and antitubercular agents, among others.<sup>4–12</sup> In addition, owing to the luminescent properties of this ring system, indolizine derivatives have found applications as bioprobes in pH and turn-on/off fluorescent sensors,<sup>13–15</sup> in the detection of volatile organic compounds,<sup>16</sup> lipid droplet accumulation,<sup>17</sup> and in cell labeling.<sup>18</sup> Moreover, substituted indolizines have found roles in organic sensitizer components for photoresponsive materials<sup>19</sup> and dye-sensitized solar cells.<sup>20</sup>

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Figure 1. Some indolizines that present biological activity.

This diversity of function has encouraged the search for new and efficient methods to generate novel analogues. Aromatic indolizines are commonly prepared from pyridines and pyrroles several synthetic strategies including the classic bv Tschitschibabin reaction, cycloaddition reactions, intramolecular cyclizations, and cycloisomerisations.<sup>21-24</sup> However, late stage modification of a preformed indolizine ring can be desirable and several strategies have been described. Given the electron rich nature of the heterocyclic ring electrophilic substitution is relatively facile leading to preferential substitution at C-1 and C-3.25 Selective C-3 substitution can be achieved through palladium catalyzed C-H activation, although this probably also proceeds via a SEAr mechanism. Direct lithiation of the ring is also possible. First reported by Renald and Gubin using 2-phenylindolizine as substrate,<sup>26</sup> this approach can be used to access a range of C-5 functionalized derivatives.<sup>27</sup> One limitation of this approach is functional group tolerance to the bases employed. In this regard we have been exploring the direct metalation of indolizines as well as other N-heterocycles<sup>28</sup> using lithium and the mixed lithiummagnesium bases TMPMgCI·LiCl and TMP2Mg·2LiCl (TMP= 2,2,6,6-tetramethylpiperidinyl).<sup>29</sup> Using indolizine-1-carboxylates as a model substrates the selective synthesis of a variety of C-2 and C-5 difunctionalized indolizines could be achieved.28e An alternative functional group tolerant approach to C-H activation that is gaining significant popularity is C-H borylation mediated by Iridium tris-boryl complexes.<sup>30</sup> The C-H borylation of indolizines has not previously been reported and in this communication, we describe our preliminary efforts to apply this chemistry to this scaffold and contrast this approach to directed metalation.

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#### **Results and Discussion**

With the aim of comparing the two C-H activation procedures we selected a small focused set of indolizines containing functional groups that have previously been shown to enable directed metalation chemistry. The nitriles (5, 6) and diester 9 could easily be prepared through cycloaddition of pyridine derived ylid and the acrylonitrile and dimethyl fumarate respectively.<sup>31</sup>

With substrates in hand we then considered their borylation using as a standard reagent, the catalyst derived from [Ir(OMe)cod]<sub>2</sub>/ dtbpy (4,4'-di-t-butylbipyridine) and B<sub>2</sub>Pin<sub>2</sub> as the source of boron.<sup>32,33</sup> As the Ir catalyzed borylation of the parent indolizine has not been previously reported we initially explored this substrate to ascertain if there was any intrinisic selectivity within this heterocyclic scaffold. Surpringly, given the latent azole within the indolizine structure this proved to be a rather reluctant substrate requiring elevated temperatures (80°C) to observe any significant reactivity. Moreover, in line with many unsubstitued polycyclic arenes, at this temperature, the unhindered nature of the substrate led to a complex mixture of both mono- and bisborylated products. Introduction of an additional heteratom into the five membered ring (compounds 1 and 3) enhanced the reactivity with borylation occurring remote from the azinyl nitrogen as would be expected.<sup>34</sup> In both cases the initially formed boronate ester proved difficult to purify and confirmation of regiochemistry was obtained by in situ Suzuki-Miyaura cross coupling reactions that afforded products 2 and 4 in 31 and 41% yields, respectively (Scheme 1).



Scheme 1. C-H borylations of 1 and 3 followed by Suzuki-Miyaura cross coupling reactions.

The addition of an electron withdrawing substituent is also well known to be strongly activating towards borylation. In particular, benzonitriles are viable substrates in which the substituent has only a limited steric influence. In line with this precedent, 2-cyanoindolizine **5** reacted to afford a complex mixture of monoborylated and di-borylated products (Scheme 2, equation a). Within this, substitution at C-1 and C-3 in the five membered ring was favored consistent both with the known propensity for a nitrile to activate *ortho* C-H bonds to borylation and the high reactivity of azole rings. Whilst at higher temperatures and longer reactions time 1-cyanoindolizine **6** gave a similar output, lowering both the reaction temperature and time led to the formation of only two regioisomers at C-3 (compound **7a**) or C-6 (compound **8a**), albeit with only low conversion (45% by GC/MS).

As isolation of the boronate esters was challenging it proved more practical to undertake a one pot conversion to the corresponding biaryls (7a, 7b, 8a and 8b) which could be achieved in moderate overall yields (Scheme 2, equations b and c). Subsequently, we then turned to explore the diester 9. Pleasingly, this combination of greater steric influence coupled with a strong electron withdrawing effect proved to be successful. After some experimentation, the best combination of selectivity and conversion (87% by GC/MS) was achieved using MTBE as solvent with 5 mol% of [Ir(OMe)cod]<sub>2</sub>, 10 mol% dtbpy and 1.0 equivalent of B<sub>2</sub>Pin<sub>2</sub> at 80°C for 4h. This led to a mixture of borylated products that proved difficult to resolve so a one pot tandem C-H borylation Suzuki-Miyaura cross coupling process was established. In this, following completion of the borylation step, the reaction mixture was concentrated in vacuo and Pd(dppf)Cl<sub>2</sub>, K<sub>3</sub>PO<sub>2</sub> and dimethylacetamide (DMAc)/H<sub>2</sub>O (2:1) added.<sup>35</sup> As shown in equation d (Scheme 2), this led to the formation of two arylated indolizine regioisomers (compounds 10 and 11) and a di-arylated product 12 with the major product being the C-5 arylated product 10 (48% isolated yield). The formation of the C-5,6 diarylated derivative 12 was particularly intriguing as the possibility of formation of an intermediate with ortho Bpin groups is normally sterically inhibited.



Scheme 2. C-H borylation of 5, 6 and 9 followed by Suzuki-Miyaura cross coupling reactions.

Having demonstrated that the borylation of indolizines was possible we then turned to examine the substituted indolizines (5, 6 and 9) in the direct metalation process. In all cases we used the trapping reaction with iodine as a standard marker of selectivity. We had previously employed the directed regioselective metalation of 1-ester-substituted indolizines using LDA and TMPMgCI-LiCI under mild conditions. Application of this strategy allowed the synthesis of a variety of C-2 and C-5 difunctionalized indolizines after reaction of the corresponding organometallic

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intermediates with different electrophiles.<sup>28e</sup> In a similar fashion, we evaluated the reactivity of diester 9 using lithium and magnesium amides. Interesting, albeit no reaction was observed using LDA or TMPLi, the metalation occurred smoothly at room temperature within 5h using 2 equivalents of TMPMgCI·LiCI, as verified by CG-MS analysis of the crude reaction mixtures quenched with iodine. On a preparative scale, solvent extraction and purification with flash chromatography allowed iodide 13a to be isolated in 87% yield (Table 1, entry 1). Moreover, quenching intermediate with dimethylformamide gave the trisubstituted indolizine bearing an aldehyde group at C-5 position 13b with 60% yield (Table 1, entry 2). Remarkably, as already observed in other indolizine substrates,<sup>29</sup> a regioselectivity dependent upon the electrophile was observed when the reaction was quenched with diphenyldisulfide to give 14a (Table 1, entry 3). The same regioselectivity was observed in palladium-catalyzed coupling reactions, important tools to functionalize aromatics and heterocyclic substrates.<sup>36</sup> After, transmetalation of the organomagnesium intermediate with ZnCl<sub>2</sub>, Negishi crossreactions with iodobenzene or 1-bromo-4coupling (trifluoromethyl)benzene in the presence of [Pd(PPh<sub>3</sub>)<sub>4</sub>] (10mol%) produced the C-3 arylated derivatives 14b or 14c in 64 and 76% yields, respectively (Table 1, entries 4 and 5).



Table 1. Selective metalation of 5 followed by reaction with electrophiles.





This divergence in selectivity potentially arises through a dynamic equilibrium between the anionic species since pKa calculations (computed at B3LYP/6-31+G(d,p) level in Gaussian 03 software)37 indicate similar acidity of the hydrogens at C-3 and C-5 positions (Scheme 3). We speculate that the generation of the C-3 anion is favored by chelation of the magnesium counter-ion by the proximal ester. Consistent with this hypothesis, in situ trapping<sup>38</sup> experiments with chlorotrimethylsilane afforded the corresponding 3-silylated derivative as the major product (see SI). Disruption of the chelate by a coordinating electrophile (iodide) allows anion equilibration and leads to formation of the sterically less hindered anion and formation of the 5-substituted product. In contrast reaction with non-coordinating reagents (ZnCl<sub>2</sub>) traps the coordinated anion faster than exchange can occur. Whilst a base mediated halogen dance<sup>39</sup> provides an alternative mechanism that leads to the formation of iodide 13a, that cannot be excluded, the order of events with addition of the electrophile (I2) only occurring after complete metalation leads us to favor the former scenario.



Scheme 3. Dynamic equilibrium of anionic species derived from the reaction of 9 with TMPMgCI-LiCI

With 1-cyanoindolizine 6, complete metalation was achieved within 30 min using 1.4 equivalents of LDA at 0°C leading, on reaction with iodine, and isobutyraldehyde to the C-5 indolizine derivatives 15a-b, respectively (Scheme 4, equations a and b). This result is consistent with simple pKa calculations (See SI) which reveal that the C-5 hydrogen is the more acidic (pKa 26.0). On switching to the magnesium bases, an ortho metalation effect enabled by the cyano group was expected leading to the formation of the C-2 substituted products. However, a dependence on the electrophile was again observed with the isobutyraldehyde reacting at C-2 to give 16a (Scheme 4, equation c) possibly via a chelate mechanism, whilst the iodide, as previously noted, disrupted the weak chelation to the nitrile group leading to rapid anion isomerization and formation of the C-5 product 15a (Scheme 4, equation d). The metalation of 2-cyanoindolizine 5 was best achieved using the mixed lithium magnesium bases TMPMgCI LiCI and TMP<sub>2</sub>Mg·2LiCl. As before, the ultimate product isolated depended on the nature of the electrophile. Thus, reaction of 5 with 3 equivalents of TMPMgCI LiCl for 1 hour followed by addition of trimethylsilyl chloride gave the C-3 silylated derivative 17b in 67% yield (Scheme 4, equation e). Functionalization at C-3 position was also observed when the same reaction was quenched with hexachloroethane, allowing the isolation of chloride 17b in 62% yield (Scheme 4, equation f). A very similar result was obtained when the diamide TMP<sub>2</sub>Mg·2LiCl was used as a base (2 equiv),

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leading to the same product **17b** in 63% yield (Scheme 4, equation g). In contrast, quenching the reaction with iodine afforded the C-5 substituted product **18a** in 47% yield (Scheme 4, equation h).



Scheme 4. Selective metalation of cyanoindolizines 5 and 6

### Conclusions

In this report, we have described for the first time the C-H borylation of indolizines, which allowed the synthesis of arylated derivatives after *in situ* Suzuki-Miyaura cross coupling reactions. Directed metalation of the same substrates followed by reaction with electrophiles afforded the functionalized derivatives in reasonable to good yields, with the

regioselectivity of the reactions being dependent upon the base and electrophile used. DFT calculations illustrated how the substituents affect the acidity of the aromatic hydrogens. In summary, these two strategies enable the selective access to a set of substituted indolizines functionalized in either pyridinic or pyrrole ring. The scope of these methodologies and their applicability towards the synthesis of biologically active molecules are currently being investigated in our laboratories.

### Experimental Section

The solvents were purified according to standard procedures. The starting materials were purchased from Sigma-Aldrich Corp. All airsensitive and/or water-sensitive reactions were carried out with dry solvents under anhydrous conditions and under nitrogen atmosphere. Standard syringe techniques were applied for the transfer of dry solvents and air-sensitive reagents. The reactions were monitored by TLC on Merck silica gel (60 F 254) by using UV light as a visualizing agent and 5% vanillin in 10% H<sub>2</sub>SO<sub>4</sub> with heating as a developing agent. Sigma- Aldrich silica gel (particle size 0.040-0.063 nm), pre-packed silica Redisep® Rf cartridges and pre-packed C18 silica Redisep® Rf cartridges (Teledyne Isco CombiFlash Rf machine) were used for flash chromatography. NMR spectra were recorded with a Bruker DPX 300, 400, 500 and 600 (at 300, 400, 500 and 600 MHz for <sup>1</sup>H and 75, 100, 125 and 151 MHz for <sup>13</sup>C, respectively.) instrument while using CDCl<sub>3</sub> or DMSO-d<sub>6</sub> as solvent. The chemical shifts are reported as  $\delta$  units in parts per million (ppm) relative to the solvent residual peak as the internal reference. Infrared (IR) spectra of all synthesized compounds were recorded on Perkin-Elmer- mod.1420 in KBr pellets or in a Diamond ATR (attenuated total reflection) accessory (Golden Gate). Assigned peaks are reported in wavenumbers (cm<sup>-1</sup>). Mass spectra (MS) were measured with Shimadzu GCMS-QP2010 mass spectrometer. HRMS spectra were measured with a Bruker Daltonics micrOTOF QII/ESI-TOF, LTQFT mass spectrometer or QToF mass spectrometer. Dimethyl indolizine-1,2-dicarboxylate, indolizine-1carbonitrile, indolizine-2-carbonitrile and [Ir(OMe)cod]<sub>2</sub> were prepared as previously reported.30

**General Procedure 1A:** In a glovebox, a premixed solution of  $[Ir(COD)OMe]_2$  (1.5 mol%), dtbpy (3 mol%) and  $B_2pin_2$  (0.5 equiv) (or HBpin (1.0 equiv) where stated) in MTBE (2.5 mL) was added to a thick-walled microwave synthesis vial containing the stated heterocycle (1.0 equiv). The mixture was shaken vigorously to ensure complete mixing, and then the mixture was stirred at room temperature or heated at 80 °C for the stated time. In-situ NMR reaction monitoring was carried out. The reaction was stirred for 16h at room temperature before being concentrated in vacuo. A tandem Suzuki-Miyaura cross-coupling reaction was then carried out. To the crude borylation mixture under N<sub>2</sub>, was added Pd(Amphos)Cl<sub>2</sub> (40 mg, 0.056 mmol), Na<sub>2</sub>CO<sub>3</sub>(aq) (2M, 197 mg, 1.86 mmol), 3-iodo-fluorobenzene (248 mg, 1.12 mmol) in DME (3 mL) at 80°C for 3h. The reaction mixture was diluted with water and extracted into EtOAc. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to give the crude product.

3-(3-fluorophenyl)pyrazolo[1,5-a]pyridine 3-(3-2: From fluorophenyl)pyrazolo[1,5-a]pyridine (110 mg, 0,93 mmol) and 3iodofluorobenzene (248 mg, 1.12 mmol). Purification by reverse phase chromatography using pre-packed C18 silica Redisep® Rf cartridges and a 0-100% MeOH in H<sub>2</sub>O (containing 0.1% HCOOH) gradient elution, constant of flow 35 mL/min. Yield: 61 mg, (31%), pale yellow oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25°C) δ 8.38 (d, J = 7.7, 1H), 8.03 (s, 1H), 7.69 (d, J = 7.7, 1H), 7.35 (m, 2H), 7.24 (m, 1H), 7.16 (t, J = 7.7, 1H), 6.95 (m, 1 H), 6.77 (t, J = 7.7, 1H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 163.4 (d, J<sub>F,C</sub> = 246.0 Hz), 140.6, 137.1, 135.5, 130.6, 129.3, 124.5, 122.7, 117.4, 113.7 (d, J = 22.0), 113.0 (d, J<sub>F,C</sub> = 21.1 Hz), 112.3, 111.9 (d, J<sub>F,C</sub> = 2.3 Hz). IR vmax (ATR) 1634, 1613, 1584, 1546, 1531, 1453, 1366, 1260, 1217, 1178,

1017, 904 cm  $^{-1}$  . HRMS (ESI) m/z ([M+H]^+ calcd for  $C_{13}H_{10}N_2F$  213.0828, found 213.0814.

**General Procedure 1B :** In a glovebox, a premixed solution of  $[Ir(COD)OMe]_2$  (1.5 mol%), dtbpy (3 mol%) and  $B_2pin_2$  (1.0 equiv) (or HBpin (1.0 equiv) where stated) in MTBE (2.5 mL) was added to a thick-walled microwave synthesis vial containing pyrazolo[1,2-a]pyridine **3** (118 mg, 1 mmol). The mixture was shaken vigorously to ensure complete mixing, and then the mixture was stirred at 80 °C for 24h. Insitu NMR reaction monitoring was carried out. The 3-(Bpin) desire product was obtained in 85% conversion (<sup>1</sup>H NMR). The Suzuki-Miyaura step was carried out for 2h with Pd(Amphos)Cl<sub>2</sub> (39 mg, 0.05 mmol), K<sub>3</sub>PO<sub>4</sub> (425 mg, 2 mmol), 3-iodoanisole (257 mg, 1.1 mmol) in DMAc:H<sub>2</sub>O (10:1) (2.5 mL) at 50°C. The reaction mixture was diluted with water and extracted into EtOAc. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to give the crude product.

**3-(3-methoxyphenyl)imidazo[1,2-a]pyridine 4:** From pyrazolo[1,2-a]pyridine **3** (118 mg, 1 mmol) and 3-iodoanisole (257 mg, 1.1 mmol). Purification was achieved using automated Teledyne Isco CombiFlash Rf machine with a pre-packed silica Redisep® Rf cartridges (ethyl acetate/hexane 0-50%) at a constant flow rate of 35 mL/min. Yield: 92 mg (41%), grey amorphous solid. <sup>1</sup>H NMR (700 MHz, CDCI<sub>3</sub>, 25 °C)  $\delta$  8.37 (d, *J* = 7.6, 1H), 7.70 (s, 1H), 7.67 (d, *J* = 7.6, 1H), 7.43 (t, *J* = 7.9, 1H), 7.20 (m, 1H), 7.15 (d, *J* = 7.9, 1H), 7.09 (m, 1H), 6.96 (dd, *J* = 7.9, 1.9, 41H), 6.81 (t, *J* = 7.6, 1H), 3.87 (s, 3H); <sup>13</sup>C NMR (176 MHz, CDCI<sub>3</sub>)  $\delta$  160.2, 146.2, 132.6, 130.6, 130.2, 125.6, 124.2, 123.5, 120.2, 118.3, 113.7, 113.5, 112.5, 55.4. IR vmax (ATR) 1602, 1580, 1501, 1299, 1283, 1237, 1165, 1047 cm<sup>-1</sup>; HRMS (ESI) m/z ([M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O 225.1030, found 225.1019.

#### General Procedure 1C: One-pot C-H borylation/Suzuki-Miyaura Crosscoupling of substituted indolizines

A thick-walled microwave synthesis vial was charged with the corresponding indolizine (0.5 mmol, 1.0 equiv) and degassed MTBE (1mL) (vial A). A separate vial was charged with [Ir(COD)OMe]2 (5 mol%), dtbpy (10 mol%), B2pin2 (1.0 equiv) and it was evacuated and placed under N2 with three evacuation/refill cycles, before degassed MTBE was added. The vial was sealed with a crimp top septum cap and shaken to develop a deep red colour. Once it was homogeneous, the solution of vial A was added to vial B. The vial was heated (vide Scheme 2) for 1h or 4h. Upon completion (determinated by GC-MS) the volatiles were removed in vacuo to afford the crude boronate product. Pd(dppf)Cl<sub>2</sub> (10 mol%), K<sub>2</sub>PO<sub>3</sub> (1 equiv.) and aryl halide (Scheme 2; 1.3 equiv) were added, and the vial was sealed and purged with three evacuation/refill (Ar) cycles. DMAc/H<sub>2</sub>O (2mL/1 mL) was added, and the mixture was heated to 80°C for 12h in an oil bath. The reaction mixture was diluted with water (10 mL) and extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous MgSO<sub>4</sub>, filtered through Celite, and concentrated in vacuo to afford the crude product. The residue was purified by pre-packed silica Redisep® Rf cartridges with the stated solvent gradient and at a constant flow rate of 35 mL/min using an automated Teledyne Isco CombiFlash Rf machine.

**3-phenylindolizine-1-carbonitrile 7a:** From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and iodobenzene (0.07 mL, 0.65 mmol), pre-packed silica Redisep® Rf cartridges (ethyl acetate/hexane 2/8), yield: 33 mg (30%), brown oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$  8.28 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.55 – 7.50 (m, 4H), 7.46 – 7.42 (m, 1H), 7.09 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.05 (s, 1H), 6.74 (td, *J* = 6.8, 1.3 Hz, 1H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  138.6, 130.4, 129.4, 128.9, 128.8, 127.1, 126.7, 123.9, 122.5, 118.4, 117.1, 116.4, 113.2, 82.4. Accurate mass (EI): calcd for C1<sub>5</sub>H<sub>10</sub>N<sub>2</sub> 218.0844, found 218.0927.

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**6-phenylindolizine-1-carbonitrile 8a:** From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and iodobenzene (0.07 mL, 0.65 mmol), pre-packed silica Redisep® Rf cartridges (ethyl acetate/hexane 1/9), yield: 11 mg (10%), brown oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25°C) δ 8.20 (t, *J* = 1.3 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.48 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.44 – 7.39 (m, 1H), 7.34 (dd, *J* = 9.3, 1.6 Hz, 1H), 7.31 (d, *J* = 3.0 Hz, 1H), 7.06 (d, *J* = 2.9 Hz, 1H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 129.3, 128.3, 127.6, 127.0, 123.4, 120.4, 118.0, 117.6, 117.0, 114,5. Accurate mass (EI): calcd for C<sub>18</sub>H<sub>10</sub>N<sub>2</sub> 218.0844, found 218.0952.

**3-(4-(trifluoromethyl)phenyl)indolizine-1-carbonitrile 7b**: From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and 1-bromo-4-(trifluoromethyl)benzene (0.09 mL, 0.65 mmol), pre-packed silica Redisep® Rf cartridges (ethyl acetate/hexane 2/8), yield: 42 mg (33%), pale yellow solid, mp: 157-158°C. <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>, 25°C) δ 8.29 (dt, *J* = 7.1, 1.1 Hz, 1H, H-5), 7.80 – 7.76 (m, 2H), 7.72 (dt, *J* = 9.0, 1.2 Hz, 1H, H-2'), 7.68 – 7.64 (m, 2H), 7.14 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H, H-7), 7.12 (s, 1H, H-3), 6.81 (td, *J* = 6.9, 1.3 Hz, 1H, H-6). <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>) δ 139.0, 133.9, 130.5 (q, *J<sub>F,C</sub>* = 32,7 Hz, C-4') 128.80, 126.4 (q, *J<sub>F,C</sub>* = 3.7 Hz, 2C, C-3', C-5'), 125.5, 124.8 (q, *J<sub>F,C</sub>* = 72 Hz, CF<sub>3</sub>), 123.6, 123.2, 123.1, 118.6, 117.3, 116.5, 113.8, 83.1. Accurate mass (EI): calcd for C<sub>16</sub>H<sub>3</sub>F<sub>3</sub>N<sub>2</sub> 286.0718, found 286.0820.

**6-(4-(trifluoromethyl)phenyl)indolizine-1-carbonitrile 8b**: From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and 1-bromo-4-(trifluoromethyl)benzene (0.09 mL, 0.65 mmol), pre-packed silica Redisep® Rf cartridges (ethyl acetate/hexane 2/8), yield: 17 mg (12%), brown oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25°C) δ 8.11 (dd, *J* = 7.1, 0.9 Hz, 1H, H-5), 7.87 (dd, *J* = 1.8, 0.9 Hz, 1H. H-8), 7.77 – 7.72 (m, 4H), 7.30 (d, *J* = 3.1 Hz, 1H, H-3), 7.08 (d, *J* = 2.9 Hz, 1H, H-2), 7.04 (dd, *J* = 7.2, 1.9 Hz, 1H, H-7). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 141.7, 137.9, 133.8, 130.5 (q, *J*<sub>F,C</sub> = 32.6 Hz, C-4'), 127.08, 126.86, 126.1 (q, *J*<sub>F,C</sub> = 3.7 Hz, C-3', C-5'), 124.17 (q, *J*<sub>F,C</sub> = 272 Hz, CF<sub>3</sub>), 117.98, 116.81, 115.56, 114.19, 112.58, 83.31. Accurate mass (EI): calcd for C<sub>16</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub> 286.0718, found 286.0805.

**Dimethyl-5-(4-(trifluoromethyl)phenyl)indolizine-1,2-dicarboxylate 10:** From dimethyl indolizine-1,2-dicarboxylate (116.5 mg, 0.5 mmol) and 1-bromo-4-(trifluoromethyl)benzene (0.09 mL, 0.65 mmol), prepacked silica Redisep® Rf cartridges (ethyl acetate/hexane 1/9), yield: 90 mg (48%), pale yellow solid, mp: 147°C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25°C) δ 8.21 (ddd, J = 9.2, 1.2, 0.6 Hz, 1H, H-8), 7.83 (dt, J = 8.1, 0.8 Hz, 2H, H-3', H-5'), 7.73 – 7.70 (m, 2H,H-2', H-6'), 7.57 (d, J = 0.7 Hz, 1H, H-3), 7.17 (dd, J = 9.3, 6.8 Hz, 1H, H-7), 6.72 (dd, J = 6.8, 1.2 Hz, 1H, H-6), 3.93 (s, 3H), 3.87 (s, 3H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  165.2, 164.4, 137.3, 137.1, 136.6, 132.5, 132.3, 132.0 (q,  $J_{F,C} = 32.8$  Hz, C-4') 130.4, 129.4, 126.4 (q,  $J_{F,C} = 3.7$  Hz, C-3', C-5'),126.6 (q,  $J_{F,C} = 272$  Hz, CF<sub>3</sub>), 123.33, 122.91, 121.90, 120.32, 115.17, 114.86, 114.12, 103.75, 52.34, 51.57. Accurate mass (EI): calcd for C<sub>19</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>4</sub> 377.0875, found 377.0965.

#### Dimethyl-6-(4-(trifluoromethyl)phenyl)indolizine-1,2-

**dicarboxylate 11:** From dimethyl indolizine-1,2-dicarboxylate (116.5 mg, 0.5 mmol) and 1-bromo-4-(trifluoromethyl)benzene (0.09 mL, 0.65 mmol), pre-packed silica Redisep® Rf cartridges (ethyl acetate/hexane 1/9), yield: 33 mg (12%), pale yellow solid, mp: 172-173°C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$  8.23 (dt, *J* = 9.5, 0.8 Hz, 1H, H-8), 8.16 (dd, *J* = 1.6, 1.0 Hz, 1H, H-5), 7.77 – 7.72 (m, 2H, H-3', H-5'), 7.72 (s, 1H, H-3), 7.67 (dt, *J* = 8.0, 0.8 Hz, 2H, H-2', H-6'), 7.33 (dd, *J* = 9.5, 1.6 Hz, 1H, H-7), 3.93 (d, *J* = 1.0 Hz, 6H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  164.8, 164.1, 140.4, 135.2, 130.3 (q, *J*<sub>F,C</sub> = 32.6 Hz, C-4'), 127.1, 126.6, 126.1 (q, *J*<sub>F,C</sub> = 3.9 Hz, C-3', C-5'), 126.11, 126.1, 124.0 (q, *J*<sub>F,C</sub> = 272 Hz, CF<sub>3</sub>), 123.5, 123.3, 123.1, 122.3, 121.0, 117.5, 103.3, 52.2, 51.4. Accurate mass (EI): calcd for C<sub>19</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>4</sub> 377.0875, found 377.0965.

Dimethyl-5,6-bis(4-(trifluoromethyl)phenyl)indolizine-1,2dicarboxylate 12: From dimethyl indolizine-1,2-dicarboxylate (116.5

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mg, 0.5 mmol) and 1-bromo-4-(trifluoromethyl)benzene (0.09 mL, 0.65 mmol), pre-packed silica Redisep® Rf cartridges (ethyl acetate/hexane 1/9), yield: 31 mg (12%), yellow solid, mp: 203-204°C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$  8.50 (d, *J* = 1.6 Hz, 1H, H-8), 7.90 – 7.85 (m, 2H), 7.83 – 7.77 (m, 4H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 0.6 Hz, 1H, H-3), 7.02 (d, *J* = 1.9 Hz, 1H, H-7), 3.95 (s, 3H), 3.89 (s, 3H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) 165.4, 164.8, 142.2, 137.5, 137.4, 135.2, 132.4, 132.2, 130.5, 130.3, 130.2, 129.3, 127.6, 127.0, 126.5 (q, *J<sub>F,C</sub>* = 3.6 Hz, 2C), 126.0 (q, *J<sub>F,C</sub>* = 3.7 Hz, 2C), 125.4, 124.0 (q, *J<sub>F,C</sub>* = 272 Hz, CF<sub>3</sub>), 123.5 (q, *J<sub>F,C</sub>* = 298 Hz, CF<sub>3</sub>), 118.1, 115.7, 114.7, 105.2, 52.8, 52.1. Accurate mass (EI): calcd for C<sub>26</sub>H<sub>17</sub>F<sub>6</sub>NO<sub>4</sub> 521.1062, found 521.1141.

**General Procedure 2 - Preparation of TMPMgCI-LiCI in THF:** In a dry and nitrogen-flushed Schlenk flask equipped with a magnetic stirring bar and was charged with *i*-PrMgCI-LiCI (1.0 M in THF, 20 mL, 20 mmol). Then, 2,2,6,6-tetramethylpiperidine (3.52 mL, 21 mmol) was added dropwise through a syringe within 3 min. The mixture was stirred until the gas evolution ceased (24–48h). Titration against benzoic acid in THF (0°C) in the presence of 4- (phenylazo)diphenylamine as the indicator showed the base concentration ranged from 0.90 to 0.98 M.

General Procedure 3: Selective Magnesiation of indolizines: In a dry round-bottom flask sob N<sub>2</sub> under magnetic stirring containing 2 mL of THF and start material (0.50 mmol), amounts of TMPMgCi-LiCl (vide **Table 1** and **Scheme 3**) was added dropwise to the reaction mixture. After stirring for 1h to 5h (see **Table 1** and **Scheme 3**) a solution of an appropriate electrophile (1.8 equiv) in THF (1.0 mL) was added, and the reaction mixture was kept under stirring for 6h (for iodine) to 12h (other electrophiles). The reaction was quenched with saturated aqueous NH<sub>4</sub>CI, the products were extracted with ethyl acetate (3 × 15 mL), and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduction pressure. The residue was purified by flash column chromatography (silica gel, ethyl acetate/hexanes).

**Dimethyl-5-iodoindolizine-1,2-dicarboxylate 13a:** From dimethyl indolizine-1,2-dicarboxylate (116.5 mg, 0.5 mmol) and  $I_2$  (342.6.4 mg, 0.9 mmol), silica gel (ethyl acetate/hexane: 2/8), yield: 156 mg (87%), brown solid, mp: 91-93°C. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ , 25°C)  $\delta$  8.04 (d, J = 9.1 Hz, 1H, H-8), 7.97 (s, 1H, H-3), 7.53 (dd, J = 7.1, 1.1 Hz, 1H, H-6), 6.98 (dd, J = 9.1, 7.0 Hz, 1H, H-7), 3.83 (s, 3H), 3.80 (s, 3H).<sup>13</sup>C NMR (101 MHz, DMSO - $d_6$ )  $\delta$  164.3, 163.4, 135.6, 125.9, 124.4, 121.0, 120.7, 118.8, 103.6, 91.5, 52.1, 51.3. HRMS (ESI) *m*/z ([M+H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>INO<sub>4</sub> 359.9655, found 359.9729.

**Dimethyl-5-formylindolizine-1,2-dicarboxylate 13b:** From dimethyl indolizine-1,2-dicarboxylate (116.5 mg, 0.5 mmol) and DMF (0.12 mL, 1.5 mmol), silica gel (ethyl acetate/hexane: 3/7), yield: 78 mg (60%), brown oil. <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ , 25°C)  $\delta$  9.95 (d, *J* = 10.5 Hz, 1H), 8.99 (s, 1H, H-3), 8.31 (d, *J* = 9.0 Hz, 1H, H-8), 7.95 – 7.85 (m, 1H, H-6), 7.43 (dd, *J* = 9.0, 7.0 Hz, 1H, H-7), 3.84 (d, *J* = 4.2 Hz, 6H). <sup>13</sup>C NMR (126 MHz, DMSO- $d_6$ )  $\delta$  187.0, 163.9, 163.1, 135.0, 131.0, 128.6, 125.7, 122.4, 122.1, 117.8, 104.5, 52.0, 51.5. HRMS (ESI) *m/z* ([M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>11</sub>NO<sub>5</sub> 262.0637, found 262.0713.

**Dimethyl-3-(phenylthio)indolizine-1,2-dicarboxylate** 14a: From dimethyl indolizine-1,2-dicarboxylate (116.5 mg, 0.5 mmol) and diphenylsulfane (131.0 mg, 0.6 mmol), silica gel (ethyl acetate/hexane: 3/7), yield: 128 mg (75%), orange oil. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ , 25°C)  $\delta$  8.44 (dd, J = 7.0, 1.2 Hz, 1H, H-8), 8.16 (dt, J = 9.0, 1.3 Hz, 1H, H-5), 7.43 (ddd, J = 9.1, 6.9, 1.1 Hz, 1H, H-6), 7.31 – 7.24 (m, 2H), 7.24 – 7.17 (m, 1H, H-7), 7.14 – 7.06 (m, 3H), 3.86 (s, 3H), 3.82 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO- $d_6$ )  $\delta$  165.6, 163.0, 136.8, 133.7, 131.6, 129.9, 127.3, 127.3, 126.7, 125.1, 119.6, 115.4, 110.1, 101.6, 53.0,

51.7. HRMS (ESI) m/z ([M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>15</sub>NO<sub>4</sub>S 342.0722, found 342.0796.

**5-iodoindolizine-1-carbonitrile and 2-iodoindolizine-1-carbonitrile 15a and regioisomer**: From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and I<sub>2</sub> (228.4 mg, 0,9 mmol), silica gel (ethyl acetate/hexane: 8/2.).<sup>1</sup>H NMR (400 MHz, CDCI<sub>3</sub>, 25°C)  $\delta$  8.10 (dd, *J* = 7.0 Hz, 1Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1.07 H), 7.62 (dd, *J* = 9.0 Hz, 1.0 Hz, 0.92 H), 7.55 (d, *J* = 3.0 Hz, 0.92 H), 7.29 (d, *J* = 7.0 Hz, 1.20 H), 7.21 (s, 0.93 H), 7.10-7.14 (m, 1.96 H), 6.91 (t, *J* = 6.8 Hz, 1.17 H), 6.80 (dd, *J* = 9.0 Hz, 7.0 Hz, 1.02 H). <sup>13</sup>C NMR (100 MHz, CDCI<sub>3</sub>)  $\delta$  140.4, 138.3, 127.2, 125.3, 125.2, 122.7, 122.4, 119.1, 117.7, 117.6, 116.5, 115.7, 113.8, 88.1, 84.7. Note: proportional integration of H. 96:4 (product 15a).

**5-iodoindolizine-1-carbonitrile 15a**: From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and l<sub>2</sub> (228.4 mg, 0.9 mmol), silica gel (ethyl acetate/hexane: 8/2.), yield: 104 mg (78%), green solid, mp: 131°C, IR (KBr): 2976, 2917, 2211, 1490, 1293, 1179, 765, 725, 684. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C ) δ 7.66 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 3.0 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.80 (dd, *J* = 8.8 Hz, 7.0 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 138.3, 125.3, 122.4, 119.1, 117.6, 116.5, 113.8, 88.1, 84.6. HRMS (ESI) *m/z* 268.9570 ([M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>5</sub>IN<sub>2</sub>: 268.9573.

**2-(1-hydroxy-2-methylpropyl)indolizine-1-carbonitrile 16a:** From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and isobutyraldehyde (0.09 mL, 0.9 mmol), silica gel (ethyl acetate/hexane: 3/7), yield: 88 mg (82%), brown oil. IR (KBr): 3429, 2962, 2873, 2211, 1513, 1461, 1368, 1311, 1162, 1011, 829, 745. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 25°C)  $\delta$  8.34 (d, *J* = 7.0 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.05 (ddd, *J* = 9.0 Hz, 7.0 Hz, 0.8 Hz, 1H), 6.87 (s, 1H), 6.76 (td, *J* = 7.0 Hz, 1.1 Hz, 1H), 4.59 (d, *J* = 8.0 Hz, 1H), 2.29 (sext, *J* = 6.7 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 6.86 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  138.6, 126.8, 125.4, 122.2, 117.6, 117.1, 115.0, 112.5, 80.1, 72.5, 31.9, 19.7, 18.6. HRMS (ESI) *m/z* ([M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O + Na<sup>+</sup> 237.0998, found 237.100.

**3-(trimethylsilyl)indolizine-2-carbonitrile 17a:** From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and TMSCI (0.12 mL, 0.9 mmol), silica gel (ethyl acetate/hexane: 8/2.), yield: 72 mg (67%), grey oil. IR (KBr): 3128, 3055, 2960, 2226, 1519, 1422, 1349, 1310, 1249, 1120, 772, 627. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$  8.03 (dd, J = 7.1 Hz, 1.0 Hz, 1H), 7.41 (dt, J = 9.0 Hz, 1.1 Hz, 1H), 6.83 (ddd, J = 9.0 Hz, 6.5 Hz, 1.0 Hz, 1H), 6.77 (s, 1H), 6.63 (m, 1H), 0.52 (s, 9H), <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  136.1, 128.9, 126.2, 120.0, 119.6, 118.0, 112.8, 105.8, 105.4, -0.77 (3C). HRMS (ESI) m/z ([M+H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>Si 215.0999, found 215.1005.

**3-chloroindolizine-2-carbonitrile 17b:** From indolizine-1-carbonitrile (71 mg, 0.5 mmol) and hexachloroethane (214 mg, 0.9 mmol), silica gel (ethyl acetate/hexane: 8/2.), yield: 45 mg (51%), grey oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C) δ 7.91 (d, *J* = 7.0 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 6.77-6.86 (m, 2H), 6.73 (s, 1H), <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 131.7, 121.6, 119.8, 119.3, 114.4, 113.7, 112.5, 102.0, 96.6. HRMS (ESI) m/z ([M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>5</sub>CIN<sub>2</sub> 177.0141, found 177.0160.

General Procedure 4: Selective magnesiation of indolizines followed by Negishi Cross Coupling Reaction: After magnesiation step (according to GP3), the temperature was warmed at 0°C, and ZnCl<sub>2</sub> (1.0 M in THF, 2.0 equiv) was added dropwise to the reaction mixture. The temperature was kept for 30 min. Then, a THF solution of [Pd(PPh<sub>3</sub>)<sub>4</sub>] (10 mol%) and 1 mL of a THF solution of appropriate electrophile (1.8 equiv) were added, and the reaction mixture was kept under stirring for 12h at 60°C. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl; the products were extracted with ethyl acetate (3 × 15 mL), and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduction pressure. The residue was

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purified by flash column chromatography (silica gel, ethyl acetate/hexanes). Results are presented in Table 1.

**Dimethyl 3-phenylindolizine-1,2-dicarboxylate 14b:** From dimethyl indolizine-1,2-dicarboxylate (116.5 mg, 0.5 mmol) and iodobenzene (0.10 mL, 0.9 mmol) silica gel (ethyl acetate/hexane 2/8), yield 99 mg (64%), green oil.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$  8.23 (dt, *J* = 9.1, 1.3 Hz, 1H), 8.05 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.51 (dd, *J* = 4.2, 0.8 Hz, 4H), 7.49 – 7.45 (m, 1H), 7.13 (ddd, *J* = 9.2, 6.6, 1.1 Hz, 1H), 6.72 (td, *J* = 6.9, 1.4 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.0, 164.4, 135.4, 130.1, 129.2, 129.0, 125.2, 123.7, 122.2, 120.5, 113.6, 102.1, 52.6, 51.4. HRMS (ESI) m/z ([M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>15</sub>NO4 310.1001, found 310. 1069.

**Dimethyl 3-(4-(trifluoromethyl)phenyl)indolizine-1,2-dicarboxylate 14c**: From dimethyl indolizine-1,2-dicarboxylate (116.5 mg, 0.5 mmol) and 1-bromo-4-(trifluoromethyl)benzene (0.12 mL, 0.9 mmol), silica gel (ethyl acetate/hexane 2/8), yields 143 mg (76%).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C) δ 8.26 (dt, J = 9.1, 1.2 Hz, 1H, H-8), 8.03 (dt, J = 7.2, 1.1 Hz, 1H, H-5), 7.81 – 7.74 (m, 2H), 7.70 – 7.63 (m, 2H), 7.21 – 7.13 (m, 1H, H-7), 6.78 (td, J = 6.9, 1.3 Hz, 1H, H-6), 3.91 (s, 3H), 3.82 (s, 3H).<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 166.64, 164.19, 135.72, 130.42, 126.3 (q,  $J_{F,C}$ = 3.1, 2.7 Hz, 2C, C-3', C5'), 124.1 (q,  $J_{F,C} = 272$  Hz, CF<sub>3</sub>), 120.8, 114.1, 102.7, 52.8, 51.6. HRMS (ESI) m/z ([M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>4</sub> 378.0875, found 378.0941.

General Procedure 5: Selective Lithiation of indolizines using LDA: In a dry round-bottom flask under magnetic stirring, LDA was prepared by addition of n-butyllithium (2.35 M in hexanes, 0.70 mmol, 0.30 mL, 1.4 equiv) to a solution of diisopropylamine (0.77 mmol, 0.10mL, 1.54 equiv) in THF (1 mL) at -70°C. After 15 min, the reaction mixture was warmed to 0°C and stirred for 20 min at the same temperature. After, indolizine-carbonitrile (71 mg, 0.5 mmol) in THF (2 mL) was added dropwise to the reaction mixture. After stirring for 30 min at 0°C, a solution of an appropriate electrophile (1.8 equiv) in THF (1.0 mL) was added, and the reaction mixture was kept under stirring for 2h (for iodine) and 12h (other electrophiles). The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl, the products were extracted with ethyl acetate (3 × 15mL), and the organic layers were dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate). Results are presented in Scheme 3.

**5-(1-hydroxy-2-methylpropyl)indolizine-1-carbonitrile 15b**: From indolizine-1-carbonitrile (71 mg, 0,5 mmol) and isobutyraldehyde (0.09 mL, 0.9 mmol), silica gel (ethyl acetate/hexane: 3/7), yield: 79 mg (74%), brown oil. IR (KBr): 3426, 3104, 2962, 2928, 2867, 2203, 1520, 1464, 1389, 1259, 1159, 1010, 787, 695.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C) δ 7.44-7.46 (m, 2H), 7.05 (dd, J = 8.9 Hz, J = 6.8 Hz, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.81 (d, J = 6.7 Hz, 1H), 4.70 (d, J = 6.4 Hz, 1H), 2.29 (sext, J = 6.6 Hz, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 139.5, 138.9, 122.1, 117.2, 116.4, 116.3, 112.4, 111.1, 81.1, 77.3, 77.0, 76.6, 75.9, 30.1, 19.7, 17.3. HRMS (ESI) *m/z* ([M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O + Na<sup>+</sup> 237.0998 found 237.1003.

General Procedure 6: Selective Magnesiation of indolizines using TMP<sub>2</sub>MgCl·2LiCl: In a dry round-bottom flask under magnetic stirring, TMP<sub>2</sub>MgCl·2LiCl was prepared by addition of *n*-butyllithium (2.48 M in hexanes, 1.0 mmol, 0.40 mL) to a solution of TMPMgCl·LiCl ( 1.05 mmol, 0.18 mL) in THF (2 mL) at -70 °C. After 5 min, the reaction mixture was warmed to 0°C and stirred for 30 min at the same temperature. A solution of TMPMgCl·LiCl (1.0 M in THF, 1.0 mmol, 1mL) was added dropwise to the reaction mixture. The temperature was held at 0°C for 15 min and warmed up to room temperature. After 30 min, a solution of indolizine-2-carbonitrile (71 mg, 0.5 mmol in THF (2 mL) was added. After stirring for 1h at room temperature, a solution of an appropriate electrophile (1.8 equiv) in THF (1.0 mL) was added, and the reaction mixture was kept under stirring for 2h (for iodine) and 12h (other electrophiles). The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl, the products were extracted with ethyl acetate (3 × 15mL), and the organic layers were dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, ethyl acetate/hexanes). Results are presented in Scheme 3.

**5-iodoindolizine-2-carbonitrile 18a:** From dimethyl indolizine-2-carbonitrile (71 mg, 0,5 mmol) and I<sub>2</sub> (228.4 mg, 0,9 mmol), silica gel (ethyl acetate/hexane: 8/2.), yield: 104 mg (78%), pale yellow solid, mp: 140-142°C. IR (KBr): 3133, 3119, 2962, 2229, 1493, 1288, 1207, 1125, 788, 721. <sup>1</sup>H NMR (400 MHz, CDCI3, 25°C)  $\delta$  7.95 (m, 1H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.19 (dd, *J* = 6.9 Hz, 1.0 Hz, 1H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.56 (dd, *J* = 9.0 Hz, 6.9 Hz, 1H). <sup>13</sup>C NMR (400 MHz, CDCI<sub>3</sub>)  $\delta$  133.2, 125.5, 122.9, 119.9, 119.6, 115.9, 105.0, 97.2, 85.8. HRMS (ESI) m/z ([M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>5</sub>IN<sub>2</sub> 268.9570, found 268.9574.

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**Keywords:** C-H borylation • C-H metalation • Indolizines • Suzuki-Miyaura cross coupling • Negishi cross coupling

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Indolizines represent a privileged class of heterocycles with several applications in Organic Synthesis and Medicinal Chemistry. In this work, the C-H borylation of aryl indolizines is described for the first time and contrasted to directed metalation. These complementary approaches allowed us to obtain a variety of substituted indolizines functionalized in both pyridinic and pyrrole ring.

#### Functionalized indolizines

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C-H Activation / metalation approaches for the synthesis of indolizine derivatives