Synthesis of α - and β -Carbolines by a Metalation/Negishi Cross-Coupling/ S_NAr Reaction Sequence

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Carbolines are considered to be privileged scaffolds in medicinal chemistry. An efficient method for the synthesis of α - and β -carbolines from fluoropyridines and 2-haloanilines is reported. This streamlined procedure consists of a four-step directed ortho-lithiation, zincation, Negishi cross-coupling, and intramolecular nucleophilic aromatic substitution, providing access to a diverse set of functionalized carbolines. While the procedure is applicable to batch conditions, the generation of arylzinc intermediates in continuous flow has been demonstrated.

While β -carbolines (pyrido[3,4-*b*]indoles) are found in numerous natural products, which are widely distributed among plants, marine organisms, insects, mammals, and human tissues,¹ α -carbolines (pyrido[2,3-*b*]indoles) are considerably less well investigated.² However, the significance of both classes of molecules is exemplified by their bioactivity in various disease-related pathways, thus meriting them as anticancer, neuropharmacological, anti-inflammatory, antibacterial and antiviral agents. Specific examples include the neuro-protective alkaloid mescengricin,³ the cytotoxic marine natural products grossularine-1 and -2,⁴ and the naturally occurring anticancer agent harmine (Figure 1).⁵ In addition to their diverse biological activity,

carbolines have found interesting applications in material science.⁶ Thus, the efficient preparation of this class of alkaloids from readily available starting materials is of considerable interest.

Figure 1. Examples of naturally occurring bioactive α - and β -carbolines.

Among common synthetic approaches towards the preparation of carbolines,⁷ several cross-coupling procedures have been developed, including methods that utilise sequential palladium-catalysed aryl amination followed by intramolecular arylation.⁸ Alternative procedures have been reported that generate first the C–C bond followed by Buchwald-Hartwig amination,⁹ condensation,¹⁰ thermal¹¹ or metal-catalysed¹² nitrene insertion, or nucleophilic aromatic substitution.¹³ Typically, these reactions employ harsh reaction conditions and high catalyst loadings (3–10 mol%) while often relying on elaborated, not readily available reagents.

In light of these challenges, a complementary approach towards the synthesis of α - and β -carbolines was envisaged. We have previously demonstrated a valuable methodology for the synthesis of 2-fluorobiaryls under continuous flow conditions.¹⁴ Building up on this experience and inspired by Queguiner's and Achab's approaches towards the synthesis of carbolines (Scheme 1a),¹³ a reaction sequence comprising four synthetic operations was envisioned (Scheme 1b): 1) Directed *ortho*-lithiation of fluoropyridine **1**; 2) zincation of the organolithium species; 3) Negishi cross-coupling of arylzinc **2** with 2-haloanilines to generate 2-aminobiaryl **3**; 4) intramolecular nucleophilic aromatic substitution (S_NAr) of **3** to provide carboline **4**. We anticipated that XPhos-based palladium precatalyst **6**, which has previously been shown to facilitate efficient C(sp²)–C(sp²) Negishi cross-coupling reactions, would allow for rapid activation and high reactivity even at low catalyst loading.¹⁵ Furthermore, we were confident that the first two steps for the generation of arylzinc intermediate **2** would be suitable to be

conducted under continuous flow conditions, enabling rapid generation and safe handling of thermally unstable organolithium intermediates.¹⁶ A comparable procedure for the formation of (hetero)aryl zincates in flow followed by Negishi cross-coupling under batch conditions has been reported by Knochel and co-workers.¹⁷ The synthesis of *ortho-ortho* substituted biaryl compounds **3** is interesting in its own right, as it has been reported that these structurally diverse species are currently underrepresented in medicinal chemistry.¹⁸ Finally, the intramolecular S_NAr would provide access to different classes of carbolines. Herein, we describe the protection group-free preparation of α - and β -carbolines via a telescoped metalation/cross-coupling/S_NAr reaction sequence.

a) *Previous work:*

b) *This work:*

Scheme 1. a) Previously reported S_NAr conditions for the synthesis of carbolines. b) Synthesis of carbolines by a lithiation/zincation/Negishi cross-coupling/S_NAr reaction sequence; XPhos (**5**) and third generation palladium precatalyst (**6**).

We initiated our studies by generating a diverse set of 2-aminobiaryls **3** as precursors for **4**. The directed lithiation of various fluoropyridines (**1**) with lithium diisopropylamide (LDA) has previously been reported to occur with high regioselectivity in *ortho*-position to the fluorine directing group at the most acidic proton.¹⁹ For the directed lithiation of **1** under batch conditions with LDA, we found that 5 min at –25 °C was an excellent compromise between reaction time and temperature. Increasing the lithiation temperature above –25 °C led to a dark

Table 1. Scope of 2-aminobiaryls **3**.^a

^a1.0 mmol scale; reaction conditions: 1) fluoropyridine (1.1–1.2 equiv), LDA (1.3 equiv), THF (0.5 M), –25 °C, 5 min; 2) ZnCl₂ (1.3 equiv), then –25 °C → rt; 3) 2-bromoaniline (1.0 equiv) and precatalyst **6** (1.0 mol%) in THF (1.0 M), 60 °C, 20 min. ^b2.0 mol% of precatalyst **6**. ^c2-Chloroaniline applied as coupling partner. ^d2-Iodoaniline applied as coupling partner. ^eLithiation at –78 °C for 30 min.

brown discoloration of the reaction mixture, which indicated the decomposition of the aryllithium species. Instead of commercially available LDA solution, the amide base could also be generated *in situ* by addition of *n*-butyllithium to a mixture of **1** and diisopropylamine in THF to provide comparable results.²⁰

Transmetalation of the organolithium intermediates with ZnCl₂ generated arylzinc species **2**, which were cross-coupled with a variety of 2-haloanilines. Biaryl **3a** was obtained from 2-bromo- or 2-iodoaniline in excellent yield after 20 min at 60 °C applying only 1.0 mol% of precatalyst **6** (Table 1). Though, using 2-chloroaniline as coupling partner necessitated a higher catalyst loading of **6** (2.0 mol%) to give **3a** in 77% yield. Protection of the free aniline was not required since no competing dimerisation of 2-haloanilines could be detected. As a range of functionalized 2-bromoanilines is commercially available, these substrates were our preferred coupling partners for the following studies.

The substrate scope for a variety of fluoropyridine and 2-bromoaniline combinations was explored applying the optimised reaction conditions (Table 1). 2-Fluoropyridine could efficiently be coupled with a diverse set of substituted 2-bromoanilines carrying either electron withdrawing or donating substituents (**3b-f**). Substitution in all positions of the coupling partner was tolerated. 2-Chloro-6-fluoropyridine was selectively metalated in the 5-position *ortho* to the fluorine substituent to afford **3g** in 57% yield after cross-coupling. Applying the reaction conditions to 2,6-difluoropyridine with differentially substituted 2-bromoanilines provided **3h-l** in 70-86% yield. 2,4-Difluoropyridine and 2-fluoro-5-methylpyridine were selectively functionalized in 3-position to give **3m** and **3n**, respectively. 3-Fluoropyridine, 3-fluoro-2-methylpyridine, and 3,5-difluoropyridine required a higher catalyst loading of **6** (2.0 mol%) to give 2-aminobiaryls **3o-r**. Here, lower yields were attributed to thermal decomposition of the corresponding arylzinc species **2** during the cross-coupling step at elevated temperatures. Furthermore, for 3-fluoro-2-methylpyridine the lithiation procedure had to be adapted (30 min at -78 °C) as under standard conditions metalation predominately occurred in the benzylic position. Finally, metalation of 2,3- and 2,5-difluoropyridine occurred selectively in the 4-position providing regioisomerically pure 2-aminobiaryls **3s-w** after cross-coupling in 67-90% yield.

Next, we focused our efforts on the intramolecular S_NAr of **3a**. While Queguiner and co-workers reported acidic conditions using refluxing anhydrous pyridinium hydrochloride (bp 222–224 °C) to access all classes of carbolines,^{13a} Achab and co-workers applied a variety of bases (NaH, K₂CO₃ or KH, catalytic 18-crown-6) at 100 °C in DMF to synthesise α -carbolines

from 2-aminobiaryl substrates (Scheme 1a).^{13b} Building upon these unlike procedures, we were curious if the intramolecular S_NAr could also be conducted under neutral conditions. For biaryl **3a**, we found that simple heating to 200 °C in a solution of 1,2-dichlorobenzene in a sealed tube was sufficient to facilitate the ring-closure. α -Carboline **4a** was afforded in 84% yield without the need for acidic or basic additives (Scheme 2).

Scheme 2. Two-step process for the synthesis of α -carboline **4a** via metalation/Negishi cross-coupling followed by intramolecular S_NAr .

With these optimised reaction conditions for the S_NAr step, we were interested in streamlining the two-step process to access carbolines directly from commercially available fluoropyridines and 2-haloanilines without purification of 2-aminobiaryls **3**. We found that all four synthetic operations could be conducted as a one-pot procedure, changing the reaction solvent from THF to 1,2-dichlorobenzene after the Negishi cross-coupling to give α -carboline **4a** in 60% yield. However, higher yields were obtained by applying an aqueous work-up after biaryl formation, followed by intramolecular S_NAr . Under these conditions, **4a** was obtained in 85% isolated yield from readily available reagents requiring just a single purification step (Table 2). Next, the telescoped procedure was applied to a range of 2-fluoropyridines **1** in combination with a variety of 2-bromoanilines or 2-iodoaniline to provide α -carbolines **4b-m**. Most of these substrates were obtained in similar yields compared to their 2-aminobiaryl precursors **3** (*cf.* Table 1), indicating that the intramolecular S_NAr occurred in nearly quantitative yields. However, the formation of undesired side products led to reduced yields for carbolines **4i**, **4j** and **4l**. When we applied the reaction sequence to 2,4-difluoropyridine, an inseparable 5:1 mixture α -carboline **4m** along its regioisomeric γ -carboline was obtained.²⁰ Carrying an electron donating methyl group at the pyridine ring, thermal S_NAr under neutral conditions for the generation of **4n** was unsuccessful. In this case, base-mediated activation (NaHMDS) was employed to afford **4n** in 77% yield.

Table 2. Scope of α -carbolines via telescoped metalation/cross-coupling/ S_NAr reaction sequence.^a

^a1.0 mmol scale; reaction conditions: 1) fluoropyridine (1.2 equiv), LDA (1.3 equiv), THF (0.5 M), –25 °C, 5 min; 2) $ZnCl_2$ (1.3 equiv), then –25 °C → rt; 3) 2-bromoaniline (1.0 equiv) and precatalyst **6** (1.0 mol%) in THF (1.0 M), 60 °C, 20 min, followed by aqueous work-up; 4) 1,2-dichlorobenzene (0.3 M), 200 °C, 18 h, sealed tube. ^b2.0 mol% of precatalyst **6**. ^c2-Iodoaniline applied as coupling partner. ^dObtained as inseparable 5:1 mixture of α - and γ -carboline determined by ^{19}F NMR. ^eObtained after treatment with NaHMDS (3.0 equiv) in THF at rt for 18 h.

Next, the synthesis of β -carbolines was examined. Applying neutral reaction conditions to 2-aminobiaryls **3o-w** (1,2-dichlorobenzene, 200 °C, 18 h), no conversion to the corresponding β -carbolines was observed. To promote the intramolecular nucleophilic aromatic substitution, we applied basic conditions as previously shown for α -carboline **4n**. Best results were obtained from purified 2-aminobiaryls in the presence of an excess of NaHMDS to provide β -carbolines **4o-w** in 18-66% yield (Table 3). This two-step reaction sequence starting from commercially available 3-fluoropyridines and 2-haloanilines represents to the best of our knowledge the shortest synthesis of the naturally occurring β -carbolines norharmane (**4o**) and harmine (**4p**).

Table 3. β -Carbolines synthesised via base-mediated S_NAr .^a

^aReaction conditions: 1) 2-aminobiaryl **3** (1.0 equiv), NaHMDS (1.9–3.0 equiv), THF (0.1 M), 70 °C, 15 min – 18 h, sealed tube. ^bReaction conducted at rt.

Finally, we envisioned to apply continuous flow conditions for the generation of arylzinc intermediates **2**. Based on our previous experience, high dilution and rapid flow rates were essential to avoid fouling and clogging of the reactor during the generation of these organometallic species.¹⁴ The optimised flow process for the generation of **2** is depicted in Scheme 3.²⁰ Precise temperature and time control, enabled by continuous flow technology, allowed us to conduct the *ortho*-lithiation of 2-fluoropyridine and 2,5-difluoropyridine with LDA at 0 °C in just 20 s. This is significantly faster than our optimised batch procedure (–25 °C, 5 min) and in strong contrast to previous conditions reported in the literature (–78 °C for several hours).¹⁹ After transmetalation of the organolithium intermediate with ZnCl₂, arylzinc species **2** was collected in a flask under an inert atmosphere and subjected in batch to Negishi cross-coupling and intramolecular S_NAr as previously described (see Table 2 and 3).

Scheme 3. Experimental setup for the synthesis of arylzinc species **2** by directed *ortho*-lithiation and zincation.

Neither fouling nor clogging of the flow reactor was observed under the optimised conditions. Thus, a representative set of carbolines (α -carbolines **4a**, **4c**, and **4e** and β -carboline **4v**) was prepared in similar yields compared to the ones obtained under batch conditions (Table 4). Here, the clear advantage of the continuous flow procedure is the potential to be reproducibly scaled up.²¹

Table 4. Scope of carbolines prepared in a semi-batch process.^a

^aReactions conducted on 1.0 mmol scale; see the Supporting Information for details.

In summary, we have developed a highly efficient route towards the synthesis of α - and β -carbolines. Fluoropyridines were subjected to a directed *ortho*-lithiation followed by zincation and Negishi cross-coupling with 2-haloanilines to afford 2-aminobiaryls. α -Carbolines were obtained after intramolecular S_NAr under neutral condition, while the formation of β -carbolines required base. This reaction sequence was extended to a semi-batch process, employing continuous flow technology for the preparation of arylzinc intermediates. Our methodology

takes advantage of readily available starting materials, mild reaction conditions, very low catalyst loading and excellent atom economy to provide a diverse range of carbolines. Currently, the expansion of this methodology to γ - and δ -carbolines is under investigation.

Conflicts of interest

The authors declare no competing financial interest.

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References

- (1) (a) Cao, R.; Peng, W.; Wang, Z.; Xu, A. β -Carboline Alkaloids: Biochemical and Pharmacological Functions. *Curr. Med. Chem.* **2007**, *14*, 479–500. (b) Peduto, A.; More, V.; de Caprariis, P.; Festa, M.; Capasso, A.; Piacente, S.; De Martino, L.; De Feo, V.; Filosa, R. Synthesis and Cytotoxic Activity of New β -Carboline Derivatives. *Mini-Rev. Med. Chem.* **2011**, *11*, 486–491.
- (2) Wadsworth, A. D.; Naysmith, B. J.; Brimble, M. A. A Review of the Synthesis of α -Carbolines. *Eur. J. Med. Chem.* **2015**, *97*, 816–829.
- (3) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. Structure of Mescengricin, a Novel Neuronal Cell Protecting Substance Produced by *Streptomyces griseoflavus*. *Tetrahedron Lett.* **1997**, *38*, 3431–3434.

- (4) Moquin-Patthey, C.; Guyot, M. Grossularine-1 and Grossularine-2, Cytotoxic α -Carbolines from the Tunicate: *Dendrodoa grossularia*. *Tetrahedron* **1989**, *45*, 3445–3450.
- (5) Patel, K.; Gadewar, M.; Tripathi, R.; Prasad, S.; Patel, D. K. A Review on Medicinal Importance, Pharmacological Activity and Bioanalytical Aspects of beta-Carboline Alkaloid “Harmine”. *Asian Pac. J. Trop. Biomed.* **2012**, *2*, 660–664.
- (6) (a) Lee, C. W.; Lee, J. Y. Above 30% External Quantum Efficiency in Blue Phosphorescent Organic Light-Emitting Diodes Using Pyrido[2,3-*b*]indole Derivatives as Host Materials. *Adv. Mater.* **2013**, *25*, 5450–5454. (b) Son, Y. H.; Kim, Y. J.; Park, M. J.; Oh, H.-Y.; Park, J. S.; Yang, J. H.; Suh, M. C.; Kwon, J. H. Small Single-Triplet Energy Gap Bipolar Host Materials for Phosphorescent Blue and White Organic Light Emitting Diodes. *J. Mater. Chem. C* **2013**, *1*, 5008–5014.
- (7) Zhang, H., Zhang, R.-H.; Wang, L.-X.; Li, Y.-J.; Liao, S.-G.; Zhou, M. Synthesis Strategies for α -, β -, γ - and δ -Carbolines. *Asian J. Org. Chem.* **2021**, *10*, 429–452.
- (8) (a) Iwaki, T.; Yasuhara, A.; Sakamoto, T. Novel Synthetic Strategy of Carbolines via Palladium-Catalyzed Amination and Arylation Reaction. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1505–1510. (b) Hostyn, S.; Van Baelen, G.; Lemièrre, G. L. F.; Maes, B. U. W. Synthesis of α -Carbolines Starting from 2,3-Dichloropyridines and Substituted Anilines. *Adv. Synth. Catal.* **2008**, *350*, 2653–2660. (c) Laha, J. K.; Petrou, P.; Cuny, G. D. One-Pot Synthesis of α -Carbolines via Sequential Palladium-Catalyzed Aryl Amination and Intramolecular Arylation. *J. Org. Chem.* **2009**, *74*, 3152–3155. (d) Namjoshi, O. A.; Gryboski, A.; Fonseca, G. O.; Van Linn, M. L.; Wang, Z.; Deschamps, J. R.; Cook, J. M. Development of a Two-Step Route to 3-PBC and β CCt, Two Agents Active Against Alcohol Self-Administration in Rodent and Primate Models. *J. Org. Chem.* **2011**, *76*, 4721–4727. (e) Dhara, S.; Singha, R.; Ahmed, A.; Mandal, H.; Ghosh, M.; Nuree, Y.; Ray, J. K. Synthesis of α , β and γ -Carbolines via Pd-Mediated C_{sp}²-H/N-H Activation. *RSC Adv.* **2014**, *4*, 45163–45167. (f) Mineno, M.; Sera, M.; Ueda, T.; Mizufune, H.; Zanka, A.; O'Bryan, C.; Brown, J.; Scorch, N. Integrated Cross-Coupling Strategy for an α -Carboline-Based Aurora B Kinase Inhibitor. *J. Org. Chem.* **2015**, *80*, 1564–1568.
- (9) (a) Hung, T. Q.; Hieu, D. T.; Van Tinh, D.; Do, H. N.; Nguyen Tien, T. A.; Van Do, D.; Son, L. T.; Tran, N. H.; Van Tuyen, N.; Tan, V. M.; Ehlers, P.; Dang, T. T.; Langer, P. Efficient Access to β - and γ -Carbolines from a Common Starting Material by Sequential

- Site-Selective Pd-Catalyzed C–C, C–N Coupling Reactions. *Tetrahedron* **2019**, *75*, 130569. (b) Hung, T. Q.; Dang, T. T.; Janke, J.; Villinger, A.; Langer, P. Efficient Synthesis of α - and δ -Carbolines by Sequential Pd-Catalyzed Site-Selective C–C and Twofold C–N Coupling Reactions. *Org. Biomol. Chem.* **2015**, *13*, 1375–1386.
- (10) Yan, Q.; Gin, E.; Banwell, M. G.; Willis, A. C.; Carr, P. D. A Unified Approach to the Isomeric α -, β -, γ -, and δ -Carbolines via their 6,7,8,9-Tetrahydro Counterparts. *J. Org. Chem.* **2017**, *82*, 4328–4335.
- (11) (a) Das, S. K.; Roy, S.; Khatua, H.; Chattopadhyay, B. Ir-Catalyzed Intramolecular Transannulation/C(sp²)–H Amination of 1,2,3,4-Tetrazoles by Electrocyclization. *J. Am. Chem. Soc.* **2018**, *140*, 8429–8433. (b) Pumphrey, A. L.; Dong, H.; Driver, T. G. Rh^{II}₂-Catalyzed Synthesis of α -, β -, or δ -Carbolines from Aryl Azides. *Angew. Chem. Int. Ed.* **2012**, *51*, 5920–5923.
- (12) (a) Smith, P. A. S.; Boyer, J. H. The Synthesis of Heterocyclic Compounds from Aryl Azides. II. Carbolines and Thienindole. *J. Am. Chem. Soc.* **1951**, *73*, 2626–2629. (b) Pudlo, M.; Csányi, D.; Moreau, F.; Hajós, G.; Riedl, Z.; Sapi, J. First Suzuki–Miyaura Type Cross-Coupling of *Ortho*-Azidobromobenzene with Arylboronic Acids and its Application to the Synthesis of Fused Aromatic Indole-Heterocycles. *Tetrahedron* **2007**, *63*, 10320–10329.
- (13) (a) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. Connection Between Metalation and Cross-Coupling Strategies. A New Convergent Route to Azacarbazoles. *Tetrahedron* **1993**, *49*, 49–64. (b) Achab, S.; Guyot, M.; Potier, P. A Short Entry into the Pyrido[2,3-*b*]indole Ring System. Synthesis of the Tetracyclic Segment of the Marine Antitumor Agents: Grossularines-1 and -2. *Tetrahedron Lett.* **1993**, *34*, 2127–2130.
- (14) Roesner, S.; Buchwald, S. L. Continuous-Flow Synthesis of Biaryls by Negishi Cross-Coupling of Fluoro- and Trifluoromethyl-Substituted (Hetero)arenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 10463–10467.
- (15) (a) Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. Mild and General Conditions for Negishi Cross-Coupling Enabled by the Use of Palladacycle Precatalysts. *Angew. Chem. Int. Ed.* **2013**, *52*, 615–619. (b) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. Synthesis of Solid 2-Pyridylzinc Reagents and Their Application in Negishi Reactions. *Org. Lett.* **2013**, *15*, 5754–5757.

- (16) (a) Colella, M.; Nagaki, A.; Luisi, R. Flow Technology for the Genesis and Use of (Highly) Reactive Organometallic Reagents. *Chem. Eur. J.* **2020**, *26*, 19–32. (b) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.
- (17) (a) Becker, M. R.; Knochel, P. Practical Continuous-Flow Trapping Metalations of Functionalized Arenes and Heteroarenes Using TMPLi in the Presence of Mg, Zn, Cu, or La Halides. *Angew. Chem. Int. Ed.* **2015**, *54*, 12501–12505. (b) Becker, M. R.; Ganiek, M. A.; Knochel, P. Practical and Economic Lithiations of Functionalized Arenes and Heteroarenes Using Cy₂NLi in the Presence of Mg, Zn or La Halides in a Continuous Flow. *Chem. Sci.* **2015**, *6*, 6649–6653. (c) Becker, M. R.; Knochel, P. High-Temperature Continuous-Flow Zincations of Functionalized Arenes and Heteroarenes Using (Cy₂N)₂Zn·2LiCl. *Org. Lett.* **2016**, *18*, 1462–1465.
- (18) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443–4458.
- (19) (a) Gupta, L.; Hoepker, A. C.; Ma, Y.; Viciu, M. S.; Faggin, M. F.; Collum, D. B. Lithium Diisopropylamide-Mediated Ortholithiation of 2-Fluoropyridines: Rates, Mechanisms, and the Role of Autocatalysis. *J. Org. Chem.* **2013**, *78*, 4214–4230. (b) Bobbio, C.; Schlosser, M. Selective Functionalization of 2-Fluoropyridine, 2,3-Difluoropyridine, and 2,5-Difluoropyridine at Each Vacant Position. *J. Org. Chem.* **2005**, *70*, 3039–3045. (c) Schlosser, M.; Rausis, T. The Structural Proliferation of 2,6-Difluoropyridine through Organometallic Intermediates. *Eur. J. Org. Chem.* **2004**, 1018–1024. (d) Gribble, G. W.; Saulnier, M. G. Regioselective *Ortho* Lithiation of Halopyridines. *Tetrahedron Lett.* **1980**, *21*, 4137–4140.
- (20) See the Supporting Information for a detailed description.
- (21) Menges-Flanagan, G.; Deitmann, E.; Gössl, L.; Hofmann, C.; Löb, P. Scalable Continuous Synthesis of Organozinc Reagents and Their Immediate Subsequent Coupling Reactions. *Org. Process Res. Dev.* **2021**, *25*, 427–433.