

Cite this: *Chem. Sci.*, 2021, 12, 6143

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 1st March 2021
Accepted 24th March 2021

DOI: 10.1039/d1sc01208h

rsc.li/chemical-science

Regioselective difunctionalization of pyridines via 3,4-pyridynes[†]

Benjamin Heinz,^{‡a} Dimitrije Djukanovic,^{‡a} Paolo Filipponi,^b Benjamin Martin,^b Konstantin Karaghiosoff^a and Paul Knochel^{†a}

A new regioselective 3,4-difunctionalization of 3-chloropyridines via 3,4-pyridyne intermediates is reported. Regioselective lithiation of 3-chloro-2-ethoxypyridine and a related 2-thio-derivative followed by treatment with aryl- and alkylmagnesium halides as well as magnesium thiolates at $-78\text{ }^{\circ}\text{C}$ produced 3,4-pyridynes during heating to $75\text{ }^{\circ}\text{C}$. Regioselective addition of the Grignard moiety in position 4 followed by an electrophilic quench in position 3 led to various 2,3,4-trisubstituted pyridines. This method was adapted into a continuous flow set-up. As an application, we have prepared a key intermediate for (\pm)-paroxetine.

Introduction

Pyridines are important heterocycles present in numerous biologically relevant molecules.¹ As a consequence, many synthetic methods have been developed for the functionalization of such N-heterocycles.² Especially, the regioselective metalation of pyridines has been broadly used.³ Also, highly unsaturated intermediates such as pyridynes (analogs of arynes^{4,5}) offer a unique possibility of adjacent regioselective double functionalization.⁶

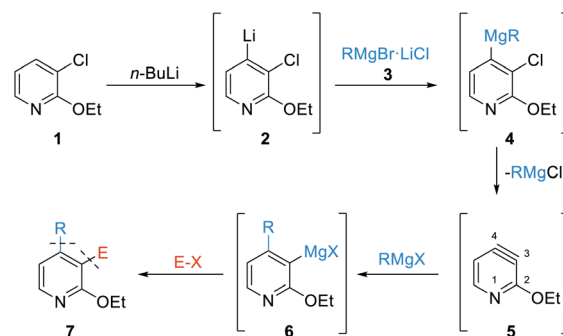
However, pyridyne chemistry is relatively unexplored. The generation of pyridynes often requires elaborated precursors and their further reactions with nucleophiles were of limited scope and complicated by a lack of regioselectivity.⁷ Garg showed, that the introduction of a substituent in position 2 significantly improved the regioselectivity of the nucleophilic addition using the aryne distortion model.⁸ However, the starting material preparation was lengthy and the reactivity of such 3,4-pyridynes was limited to cycloadditions and aminations.⁸ To overcome some of the previously described drawbacks, we have chosen, according to Hegarty,⁹ to use readily prepared 3-chloro-2-ethoxypyridine (**1**) as a precursor of 3,4-pyridyne, achieving an effective synthesis of highly decorated pyridines.

Thus, the regioselective lithiation of the pyridine **1** with *n*-BuLi will afford the 4-lithiated pyridine **2**.¹⁰ Transmetalation with an

organomagnesium halide $\text{RMgBr}\cdot\text{LiCl}$ of type **3** will produce mixed diorganomagnesiums of type **4**. At elevated temperatures, an elimination should proceed leading to the 3,4-pyridyne **5**. After the regioselective addition of RMgX ($\text{RMgBr}\cdot\text{LiCl}$ or RMgCl), affording magnesiated pyridines of type **6**, quenching with various electrophiles (E-X) should produce the desired polyfunctional pyridines of type **7** (Scheme 1).

Results and discussion

Herein, we report the successful outcome of this synthetic approach. In preliminary experiments, we have treated **1** with *n*-BuLi in THF at $-78\text{ }^{\circ}\text{C}$ and found that a fully regioselective lithiation towards **2** was achieved within 2 h. Addition of 4-anisylmagnesium bromide ($\text{AnMgBr}\cdot\text{LiCl}$, **3a**) at $-78\text{ }^{\circ}\text{C}$, which was prepared by the reaction of 4-anisyl bromide with magnesium turnings in the presence of LiCl ,¹¹ led tentatively to the mixed diorganomagnesium reagent **4**. The optimum for the



Scheme 1 General reaction sequence towards difunctionalized pyridines of type **7** starting from 3-chloro-2-ethoxypyridine (**1**) via the 3,4-pyridyne intermediate **5**.

^aLudwig-Maximilians-Universität München, Department Chemie, Butenandtstraße 5-13, 81377 Munich, Germany. E-mail: paul.knochel@cup.uni-muenchen.de

^bNovartis Pharma AG, Chemical Development, Fabrikstraße, 4002 Basel, Switzerland. E-mail: benjamin.martin@novartis.com

[†] Electronic supplementary information (ESI) available. CCDC 2057612, 2057613 and 2057614. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc01208h

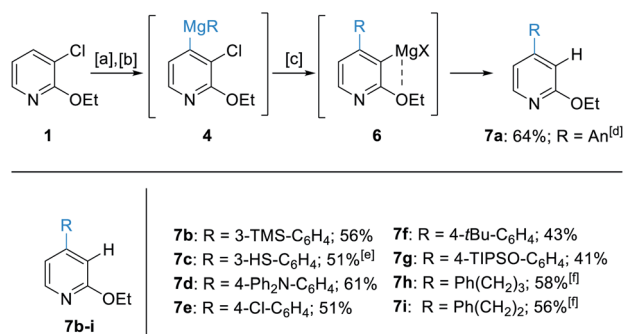
[‡] These authors contributed equally to this work.



elimination of **4** providing the corresponding pyridyne occurred at 75 °C in a sealed tube with 1 h reaction time.¹² Also, the use of 2 equivalents of 4-anisylmagnesium bromide (An-MgBr) was required to achieve a high yield.¹³ The regioselectivity of the organomagnesium addition to the pyridyne intermediate was explained by a coordinating effect of the ethoxy group at position C2. Therefore, the stabilized 3-magnesiated species **6** gave regioselectively the pure 4-arylated pyridine **7a** (64% yield) after quenching the reaction mixture with sat. aq. NH₄Cl. This procedure was quite general and a range of arylmagnesium bromides added regioselectively at position 4. After aqueous workup, the 4-arylated pyridines **7b–g** were obtained in 41–61% yield.¹⁴ Additionally, the use of alkylmagnesium halides (5.0 equiv.) provided the desired pyridines **7h–i**, bearing an alkyl substituent at position 4, in 56–58% yield (Scheme 2). The missing material was a result of the instability of the pyridine intermediate which may oligomerize or polymerize.¹⁵

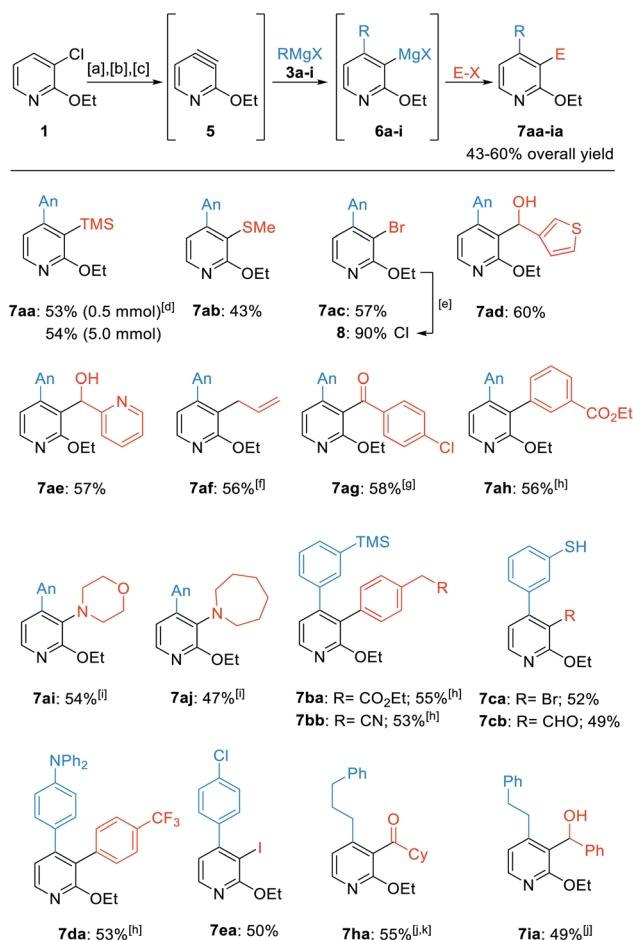
With these optimized conditions, we have trapped the newly generated pyridylmagnesium halides of type **6** with various electrophiles leading to 3,4-difunctionalized pyridines of type **7** (Scheme 3).

As previously described, we treated **1** with *n*-BuLi followed by addition of AnMgBr (**3a**, An = 4-MeO-C₆H₄). Heating to 75 °C in a sealed tube for 1 h led to the pyridyne formation. Regioselective addition of **3a** afforded the 3-pyridylmagnesium species **6a**. Addition of TMSCl (2.5 equiv., 25 °C, 12 h) gave the 3,4-difunctionalized pyridine **7aa** in an overall yield of 53% (0.5 mmol scale, Scheme 3). A scale-up to 5 mmol provided a similar yield (54%). Thiolation with *S*-methyl methanesulfonylthioate and bromination with (CCl₂Br)₂ led to the thioether **7ab** in 43% yield and the 3-halogenated pyridine **7ac** in 57% yield. A further derivatization of the previously prepared trisubstituted pyridines (**7ac**) was made. This pyridine was treated with POCl₃ and DMF leading to the trisubstituted 2-chloropyridine **8** in 90% yield.¹⁶ Quenching the pyridylmagnesium bromide **6a** with both, electron-rich and electron-poor heterocyclic aldehydes afforded the benzylic alcohols **7ad** and **7ae** in 57–60% yield. Copper(i)-catalyzed



[a] *n*-BuLi (1.1 equiv), 2 h, -78 °C. [b] RMgBr·LiCl (2.0 equiv), 0.5 h, -78 °C. [c] 75 °C (sealed tube), 1 h, quench with aq. sat. NH₄Cl. [d] An = 4-MeO-C₆H₄. [e] 3-MeS-C₆H₄MgBr·LiCl (2.0 equiv) [f] AlkylMgBr·LiCl (5.0 equiv)

Scheme 2 Regioselective lithiation of 3-chloro-2-ethoxypyridine (**1**) and subsequent transmetalation to diorganomagnesium reagents of type **4** leading to 4-arylated pyridines of type **7** via the 3,4-pyridyne **5**.



[a] *n*-BuLi (1.1 equiv), -78 °C, 2 h. [b] RMgBr·LiCl (2.0 equiv), -78 °C, 30 min. [c] 75 °C (sealed tube), 1 h. [d] The regioselectivity was determined by crystal structure analyses, see Supporting Information [e] POCl₃ (3.0 equiv), DMF, 0 °C, 1 h, then 100 °C (sealed tube), 4 h. [f] CuCN·2LiCl (10 mol%), 0 °C, 10 min, then allyl bromide (2.5 equiv), 25 °C, 12 h [g] CuCN·2LiCl (2.0 equiv), 0 °C, 10 min, then acyl chloride (2.5 equiv), 25 °C, 12 h. [h] ZnCl₂ (2.0 equiv), 0 °C, 10 min, then a mixture of aryl halide (2.5 equiv), Pd(OAc)₂ (5 mol%) and SPhos (10 mol%), 25 °C, 12 h. [i] ZnCl₂ (1.0 equiv), 0 °C, 10 min, then *N*-hydroxylamino benzoates (2.0 equiv) and Cu(OTf)₂ (10 mol%), 0 °C to 25 °C, 12 h. [j] AlkylMgBr·LiCl (5.0 equiv). [k] CuCN·2LiCl (5.0 equiv), 0 °C, 10 min, then acyl chloride (5.5 equiv), 25 °C, 12 h.

Scheme 3 Regioselective difunctionalization of 3-chloro-2-ethoxypyridine (**1**) towards the pyridines **7aa–7ia** via the 3,4-pyridyne **5**.

allylation gave the pyridine **7af** in 56% yield. Additionally, copper(i)-mediated acylation with 4-chlorobenzoyl chloride led to the biaryl ketone **7ag** in 58% yield. Negishi cross-coupling¹⁷ of the magnesium species **6a**, after transmetalation with ZnCl₂, with ethyl 3-bromobenzoate in the presence of 5 mol% Pd(OAc)₂ and 10 mol% SPhos¹⁸ led to the 3,4-bis-arylated pyridine **7ah** in 56% yield. A Cu-catalyzed electrophilic amination with *N*-hydroxylamino benzoates afforded the 3-aminated pyridines **7ai** and **7aj** in 47–54% yield.¹⁹

Next, cross-coupling reactions of 4-(3-(trimethylsilyl)phenyl)-3-pyridylmagnesium bromide (**6b**) led to the highly functionalized pyridines **7ba** and **7bb** in 53–55% isolated yield. Using the 3-pyridylmagnesium compound **6c** gave the thiols **7ca** and **7cb** in 49–52% yield by quenching with either (CCl₂Br)₂ or DMF.¹⁴ A cross-coupling of **6d** with 4-iodobenzotrifluoride gave



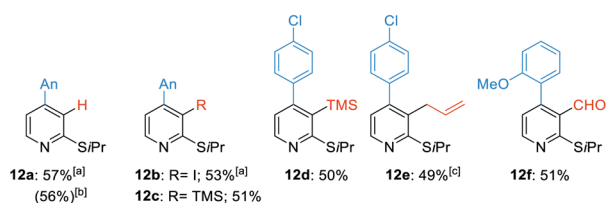
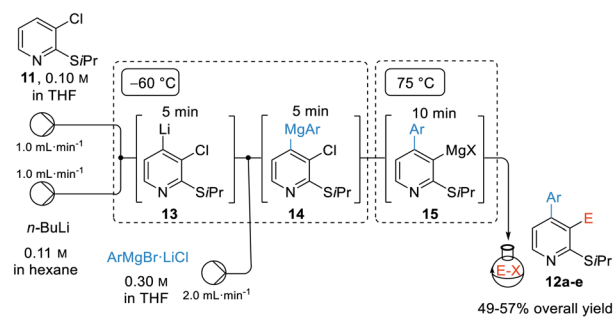
the expected trisubstituted pyridine **7da** in 53% yield. Iodolysis of 3-magnesiated pyridine **6e** gave the iodinated pyridine **7ea** in 50% yield.

Finally, the 4-alkylated pyridylmagnesium species **6h** and **6i** were further functionalized either by acylation affording the ketone **7ha** in 55% yield or quench with benzaldehyde leading to the alcohol **7ia** in 49% overall yield.

In order to extend the scope of these difunctionalizations, we investigated the use of magnesium thiolates. These nucleophiles proved to be excellent reaction partners and the treatment of the lithiated pyridine **2** with $\text{RSMgX} \cdot \text{LiCl}^{20}$ gave regioselectively, after heating to 75 °C for 1 h in a sealed tube, 4-thiolated pyridines such as **10a–b** in 69–72% yield (Scheme 4). Further quenching of the intermediate **9a** with various electrophiles such as TMSCl , DMF, benzaldehyde and benzophenone gave the 2,3,4-trifunctionalized pyridines **10aa–ad** in 50–71% yield. Additionally, the treatment of **9a** with ethyl 2-formylbenzoate produced the phthalide **10ae** in 71% yield. Further, a palladium-catalyzed cross-coupling on the sterically demanding substrate **9b** gave, after 3,4-pyridyne formation, the pyridine **10ba** in 67% isolated yield.

The performance of multi-step organometallic reactions in a continuous flow set-up using microreactors often proved to be advantageous, allowing a much better reaction control than in batch with milder and more selective reactions conditions.²¹ Thus, we examined the arylation of 2-isopropylthio-3-chloropyridine (**11**) and subsequent trapping with electrophiles.²² In a calibration experiment in batch, we treated **11** with *n*-BuLi (−60 °C, 10 min) followed by the addition of AnMgBr (**3a**, 6.0 equiv., −60 °C, 0.5 h, then 75 °C, 1 h) leading to the desired 2,4-disubstituted pyridine **12a** in 56% yield.

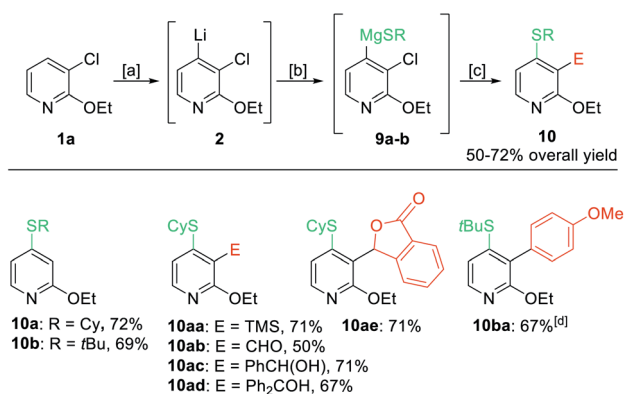
We transposed this reaction sequence into a continuous flow set-up as shown in Scheme 5. Mixing *n*-BuLi with the starting material **11** afforded the lithiated species **13** after 5 min residence time at −60 °C. Adding various arylmagnesium bromides of type **3** via a third pump gave the transient magnesium species



[a] The regioselectivity was determined by crystal structure analyses, see SI. [b] yield in batch. [c] $\text{CuCN} \cdot 2\text{LiCl}$ (10 mol%), 0 °C, 10 min, then allyl bromide (2.5 equiv), 25 °C, 12 h.

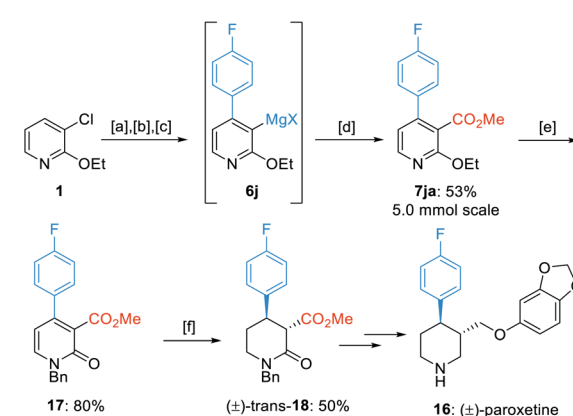
Scheme 5 Continuous flow set-up for the difunctionalization of 3-chloro-2-(isopropylthio)pyridine **11** via pyridyne formation and subsequent quenching of the generated 3-pyridylmagnesium reagent **15** with various electrophiles.

of type **14** which were heated to 75 °C for 10 min. This very reproducible procedure provided the stable 3-pyridylmagnesium species **15** which was directly pumped into a round bottom flask containing various electrophiles. Quenching with sat. aq. NH_4Cl gave the pyridine **12a** in 57% isolated yield. Alternatively, iodination (with I_2), silylation (with TMSCl), allylation (with allyl bromide) and formylation (with DMF) gave the expected 2,3,4-trisubstituted pyridines **12b–f** in 49–53% overall yield. For this multi-step procedure, the flow set-up proved to be advantageous for its high reproducibility, good temperature control and its potential for easy scale up for eventual industrial applications.



[a] *n*-BuLi (1.1 equiv), 2 h, −78 °C. [b] $\text{RSMgCl} \cdot \text{LiCl}$ (2.0 equiv), 0.5 h, −78 °C. [c] 75 °C (sealed tube), 1 h, quench with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ or E-X . [d] ZnCl_2 (2.0 equiv), 0 °C, 0.5 h, then $\text{Pd}(\text{OAc})_2$ (10 mol%), SPhos (20 mol%) and 4-iodoanisole (2.5 equiv), 0 °C to 25 °C, 12 h.

Scheme 4 Selective lithiation of 3-chloro-2-ethoxy pyridine (**1**) and subsequent transmetalation towards the diorganomagnesium reagents of type **9** leading to 4-thiolated pyridines of type **10**.



[a] *n*-BuLi (1.1 equiv), −78 °C, 2 h. [b] $4\text{-F-C}_6\text{H}_4\text{MgBr} \cdot \text{LiCl}$ (3.0 equiv), −78 °C, 30 min. [c] 75 °C (sealed tube), 1 h. [d] methyl cyanoformate (5.0 equiv), 0 °C to 25 °C, 12 h. [e] BnBr (neat), microwave irradiation, 120 °C, 30 h, [f] 5% Pd/C (100 mol%), 1 atm H_2 , MeOH , 25 °C, 18 h.

Scheme 6 Route towards the key intermediate **18** of the synthesis of (±)-paroxetine (**16**).



Next, we applied this method for the preparation of a key intermediate of the synthesis of (\pm)-paroxetine (**16**).²³ Thus, starting from 3-chloro-2-ethoxypyridine (**1**), we have prepared the trisubstituted pyridine (**7ja**) on a 5 mmol scale with 53% overall yield. Treatment of **7ja** with neat benzyl bromide at 120 °C for 30 h afforded the *N*-benzylated pyridone **17** in 80% yield.²⁴ Then, a selective hydrogenation of the pyridone **17** using H₂ gas and Pd/C gave the desired *trans*-substituted piperidone **18** in 50% yield (Scheme 6).²⁵

Conclusions

In conclusion, we have developed a new regioselective 3,4-difunctionalization of 3-chloropyridines *via* 2-alkoxy or 2-alkylthiol 3,4-pyridyne intermediates using as nucleophiles aryl- and alkylmagnesium halides as well as magnesium alkylthiolates. The resulting 3-pyridylmagnesium species were quenched with various electrophiles, producing polyfunctional 2,3,4-substituted pyridines.

In addition, this methodology was converted into a convenient continuous flow set-up. As an application, we have prepared a key intermediate for the synthesis of the antidepressant (\pm)-paroxetine **16**.

Author contributions

B. H. and D. D. performed the experiments and analysed the data. P. F. and B. M. discussed the results. K. K. measured and analyzed the crystal structures. P. K. conceived the project and wrote the paper. B. H., D. D., P. F. and B. M. contributed to the editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

B. Heinz thanks the Novartis Pharma AG for the fellowship. We thank Albermarle (Hoechst, Germany) and BASF for the generous gift of chemicals and Vapourtec for technical support. Helpful discussions with Dr B. Schenkel, Dr F. Mandrelli and Dr S. Mostarda (Novartis Pharma) are gratefully acknowledged.

Notes and references

- (a) V. Bisai and R. Sarpong, *Org. Lett.*, 2010, **12**, 2551–2553; (b) D. F. Fischer and R. Sarpong, *J. Am. Chem. Soc.*, 2010, **132**, 5926–5927; (c) J. N. Newton, D. F. Fischer and R. Sarpong, *Angew. Chem., Int. Ed.*, 2013, **52**, 1726–1730; (d) G. Rouquet, D. C. Blakemore and S. V. Ley, *Chem. Commun.*, 2014, **50**, 8908–8911; (e) G. Rouquet, D. E. Moore, M. Spain, D. M. Allwood, C. Battilocchio, D. C. Blakemore, P. V. Fish, S. Jenkinson, A. S. Jessiman, S. V. Ley, G. McMurray and R. A. Storer, *ACS Med. Chem. Lett.*, 2015, **6**, 329–333; (f) L.-G. Xie, S. Shaaban, X. Chen

and N. Maulide, *Angew. Chem., Int. Ed.*, 2016, **128**, 13056–13059.

- (a) L. C. Campeau, S. Rousseaux and K. Fagnou, *J. Am. Chem. Soc.*, 2005, **127**, 18020–18021; (b) J. Yin, B. Xiang, M. A. Huffman, C. E. Raab and I. W. Davies, *J. Org. Chem.*, 2007, **72**, 4554–4557; (c) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 5451–5455; (d) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642–2713; (e) J. L. Jeffrey and R. Sarpong, *Org. Lett.*, 2012, **14**, 5400–5403; (f) Q. Chen, X. Mollat du Jourdin and P. Knochel, *J. Am. Chem. Soc.*, 2013, **135**, 4958–4961; (g) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald and P. Knochel, *Org. Lett.*, 2013, **15**, 5754–5757; (h) A. K. Steib, S. Fernandez, O. M. Kuzmina, M. Corpet, C. Gosmini and P. Knochel, *Synlett*, 2015, **26**, 1049–1054.
- (a) D. L. Comins and M. O. Killpack, *J. Org. Chem.*, 1990, **55**, 69–73; (b) P. Gros, Y. Fort, G. Queguiner and P. Caubère, *Tetrahedron Lett.*, 1995, **36**, 4791–4794; (c) S. Choppin, P. Gros and Y. Fort, *Eur. J. Org. Chem.*, 2001, **2001**, 603–606; (d) M. Balkenhohl, C. François, D. S. Roman, P. Quinio and P. Knochel, *Org. Lett.*, 2017, **19**, 536–539; (e) M. Balkenhohl and P. Knochel, *SynOpen*, 2018, **2**, 78–95; (f) M. Balkenhohl, B. Heinz, T. Abegg and P. Knochel, *Org. Lett.*, 2018, **20**, 8057–8060; (g) A. B. Bellan and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 1838–1941.
- For aryne chemistry starting with direct lithiation, see: (a) K. H. Reuter and W. J. Scott, *J. Org. Chem.*, 1993, **58**, 4722–4726; (b) P. Stanetty and B. Krumpak, *J. Org. Chem.*, 1996, **61**, 5130–5133; (c) J. Pawlas and M. Begtrup, *Org. Lett.*, 2002, **4**, 2689–2690; (d) E. P. Jones, P. Jones, A. J. P. White and A. G. M. Barrett, *Beilstein J. Org. Chem.*, 2011, **7**, 1570–1576; (e) E. P. Jones, P. Jones and A. G. M. Barrett, *Org. Lett.*, 2011, **13**, 1012–1015; (f) T. Truong and O. Daugulis, *J. Am. Chem. Soc.*, 2011, **133**, 4243–4245; (g) T. Truong and O. Daugulis, *Org. Lett.*, 2011, **13**, 4172–4175; (h) T. Truong and O. Daugulis, *Org. Lett.*, 2012, **14**, 5964–5967; (i) T. Hamura, Y. Chuda, Y. Nakatsuji and K. Suzuki, *Angew. Chem., Int. Ed.*, 2012, **51**, 3368–3372.
- For other methods to generate arynes, see: (a) E. R. Biehl, S. M. Smith and P. C. Reeves, *J. Org. Chem.*, 1971, **36**, 1841–1842; (b) H. Y. Xin and E. R. Biehl, *J. Org. Chem.*, 1983, **48**, 4397–4399; (c) H. Hart, K. Harada and C.-J. F. Du, *J. Org. Chem.*, 1985, **50**, 3104–3110; (d) K. Harada, H. Hart and C.-J. F. Du, *J. Org. Chem.*, 1985, **50**, 5524–5528; (e) T. Ghosh and H. Hart, *J. Org. Chem.*, 1988, **53**, 3555–3558; (f) F. Leroux and M. Schlosser, *Angew. Chem., Int. Ed.*, 2002, **41**, 4272–4274; (g) I. Sapountzis, W. Lin, M. Fischer and P. Knochel, *Angew. Chem., Int. Ed.*, 2004, **43**, 4364–4366; (h) W. Lin, I. Sapountzis and P. Knochel, *Angew. Chem., Int. Ed.*, 2005, **44**, 4258–4261; (i) C.-G. Dong and Q.-S. Hu, *Org. Lett.*, 2006, **8**, 5057–5060; (j) A. T. Biju and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 9761–9764; (k) S. Bronner, J. L. Mackey, K. N. Houk and N. K. Garg, *J. Am. Chem. Soc.*, 2012, **134**, 13966–13969; (l) J.-A. Garcia-Lopez, M. Cetin and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2015, **54**, 2156–2159; (m) S. Niu, J. Hu, K. He, Y. Chen and Q. Xiao, *Org. Lett.*,



- 2019, **21**, 4250–4254; (n) S. Cho and Q. Wang, *Org. Lett.*, 2020, **22**, 1670–1674.
- 6 (a) G. W. Gribble and M. G. Saulnier, *Heterocycles*, 1993, **35**, 151–169; (b) W. Lin, L. Chen and P. Knochel, *Tetrahedron*, 2007, **63**, 2787–2797; (c) A. E. Goetz, S. M. Bronner, J. D. Cisneros, J. M. Melamed, R. S. Paton, K. N. Houk and N. K. Garg, *Angew. Chem., Int. Ed.*, 2012, **51**, 2758–2762; (d) A. E. Goetz and N. K. Garg, *J. Org. Chem.*, 2014, **79**, 846–851; (e) J. M. Medina, M. K. Jackl, R. B. Susick and N. K. Garg, *Tetrahedron*, 2016, **72**, 3629–3634.
- 7 (a) M. Tsukazaki and V. Snieckus, *Heterocycles*, 1992, **33**, 533–536; (b) K. Vinter-Pasquier, B. Jamart-Grégoire and P. Caubère, *Heterocycles*, 1997, **45**, 2113–2119.
- 8 (a) A. E. Goetz and N. K. Garg, *Nat. Chem.*, 2013, **5**, 54–60; (b) J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 15798–15805.
- 9 S. J. Connon and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1245–1249.
- 10 (a) S. Choppin, P. Gros and Y. Fort, *Eur. J. Org. Chem.*, 2001, **2001**, 603–606; (b) J. S. Dhau, A. Singh, Y. Kasetti, S. Bhatia, P. V. Bharatam, P. Brandão, V. Félix and K. N. Singh, *Tetrahedron*, 2013, **69**, 10284–10291.
- 11 F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm and P. Knochel, *Angew. Chem., Int. Ed.*, 2008, **47**, 6802–6806.
- 12 For the optimization of the reaction conditions, see ESI.†
- 13 For the optimization of the stoichiometry of nucleophiles, see ESI.†
- 14 We have observed that by using of 3-methylthiophenylmagnesium bromide the resulting product **6g** bears a free thiol group. We assumed that a magnesiation of the methylthio group takes place during the reaction, resulting into a magnesium carbenoid which decomposed under the reaction conditions (75 °C).
- 15 (a) W. E. Bachmann and H. T. Clarke, *J. Am. Chem. Soc.*, 1927, **49**, 2089–2098; (b) L. S. Chen, G. J. Chen and C. Tamborski, *J. Org. Chem.*, 1980, **193**, 283–292; (c) M. Fossatelli and L. Brandsma, *Synthesis*, 1992, 756.
- 16 (a) T. R. Kasturi, H. R. Y. Jois and L. Mathew, *Synthesis*, 1984, **9**, 743–746; (b) M. Shiao, L. Shyu and K. Tarng, *Synth. Commun.*, 1990, **20**, 2971–2977.
- 17 (a) G. Manolikakes, C. M. Hernandez, M. A. Schade, A. Metzger and P. Knochel, *J. Org. Chem.*, 2008, **73**, 8422–8436; (b) L. Melzig, A. Metzger and P. Knochel, *J. Org. Chem.*, 2010, **75**, 2131–2133.
- 18 (a) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685–4696; (b) R. A. Altmann and S. L. Buchwald, *Nat. Protoc.*, 2007, **2**, 3115–3121.
- 19 (a) A. M. Berman and J. S. Johnson, *J. Am. Chem. Soc.*, 2004, **126**, 5680–5681; (b) A. M. Berman and J. S. Johnson, *J. Org. Chem.*, 2006, **71**, 219–224; (c) Y.-H. Chen, S. Graßl and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 1108–1111.
- 20 B. Heinz, M. Balkenhohl and P. Knochel, *Synthesis*, 2019, **51**, 4452–4462.
- 21 (a) Z. He and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2014, **53**, 3353–3357; (b) A. Nagaki, D. Ichinari and J. Yoshida, *J. Am. Chem. Soc.*, 2014, **136**, 12245–12248; (c) A. Khadra and M. G. Organ, *J. Flow Chem.*, 2016, **6**, 293–296; (d) M. Teci, M. Tilley, M. A. McGuire and M. G. Organ, *Org. Process Res. Dev.*, 2016, **20**, 1967–1973; (e) J. Schwan, M. Kleoff, B. Hartmayer, P. Heretsch and M. Christmann, *Org. Lett.*, 2018, **20**, 7661–7664; (f) Z. Tan, Z. Li, G. Jin and C. Yu, *Org. Process Res. Dev.*, 2019, **23**, 31–37.
- 22 The continuous flow set-up was not applicable for the reaction starting from 3-chloro-2-ethoxy pyridine (**1**) due to longer reaction times and pressure limitations. For a detailed continuous flow/batch comparison, see ESI.†
- 23 (a) C. De Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente and V. Zanirato, *Tetrahedron: Asymmetry*, 2008, **19**, 131–155; (b) S. Ötvös, M. Pericàs and C. O. Kappe, *Chem. Sci.*, 2019, **10**, 11141–11146; (c) S. Jara, S. Sarkar and S. A. Morris, *Tetrahedron*, 2020, **76**, 131215.
- 24 W. R. Bowman and C. F. Bridge, *Synth. Commun.*, 1999, **29**, 4051–4059.
- 25 (a) S. Maris and N. Castagnoli, *J. Org. Chem.*, 1996, **61**(1), 309–313; (b) J. Wysocki, C. Schkepphorst and F. Glorius, *Synlett*, 2015, **26**, 1557–1562; (c) B. Zacharie, S. D. Abbott, C. B. Baigent, C. Doyle and R. S. Yalagala, *Eur. J. Org. Chem.*, 2018, **46**, 6486–6493; (d) Z. Nairoukh, M. Wollenburg, C. Schleppehorst, K. Bergander and F. Glorius, *Nat. Chem.*, 2019, **11**, 264–270.

