



Flow Chemistry Hot Paper

# Preparation of Functionalized Aryl, Heteroaryl, and Benzylic Potassium Organometallics Using Potassium Diisopropylamide in Continuous Flow

Johannes H. Harenberg<sup>+</sup>, Niels Weidmann<sup>+</sup>, and Paul Knochel<sup>\*</sup>

In memory of Rolf Huisgen

**Abstract:** We report the preparation of lithium-salt-free KDA (potassium diisopropylamide; 0.6 M in hexane) complexed with TMEDA (*N,N,N',N'*-tetramethylethylenediamine) and its use for the flow-metalation of (hetero)arenes between  $-78^{\circ}\text{C}$  and  $25^{\circ}\text{C}$  with reaction times between 0.2 s and 24 s and a combined flow rate of  $10\text{ mL min}^{-1}$  using a commercial flow setup. The resulting potassium organometallics react instantaneously with various electrophiles, such as ketones, aldehydes, alkyl and allylic halides, disulfides, Weinreb amides, and  $\text{Me}_3\text{SiCl}$ , affording functionalized (hetero)arenes in high yields. This flow procedure is successfully extended to the lateral metalation of methyl-substituted arenes and heteroaromatics, resulting in the formation of various benzylic potassium organometallics. A metalation scale-up was possible without further optimization.

Of all the alkali metals, lithium has by far received the most attention in organic synthesis.<sup>[1]</sup> However, the use of sodium and potassium organometallic intermediates has been explored since more than a century<sup>[2]</sup> and presents several specific advantages such as enhanced reactivity, low prices, and moderate toxicity of these alkali organometallics as well as opportunities for new metalation selectivities.<sup>[3]</sup> Recently, we have reported that the use of continuous flow techniques<sup>[4]</sup> considerably facilitates the use of sodium bases such as NaDA (sodium diisopropylamide) for the selective sodiation of aromatics and heterocycles.<sup>[5]</sup> Herein, we wish to report a new metalation procedure making it possible to perform arene and heteroarene metalations as well as lateral metalations using potassium diisopropylamide (KDA) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in continuous flow in a hexane/tetrahydrofuran (THF) mixture.

[\*] J. H. Harenberg,<sup>[+]</sup> N. Weidmann,<sup>[+]</sup> Prof. Dr. P. Knochel  
Department Chemie, Ludwig-Maximilians-Universität München  
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)  
E-mail: paul.knochel@cup.uni-muenchen.de

[+] These authors contributed equally.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:  
<https://doi.org/10.1002/anie.202003392>.

© 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial, and no modifications or adaptations are made.

How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 12321–12325

International Edition: [doi.org/10.1002/anie.202003392](https://doi.org/10.1002/anie.202003392)

German Edition: [doi.org/10.1002/ange.202003392](https://doi.org/10.1002/ange.202003392)

Whereas KDA was usually prepared by the Schlosser method by mixing LDA (lithium diisopropylamide) with *t*BuOK,<sup>[6]</sup> we have envisioned preparing this base in the absence of any lithium salts, using a modified procedure described by Collum for the preparation of NaDA.<sup>[7]</sup> Thus, small slices of oil-free solid potassium suspended in hexane were mixed with diisopropylamine. The resulting suspension was cooled to  $0^{\circ}\text{C}$  and isoprene was added dropwise. After 30 min of stirring at  $0^{\circ}\text{C}$ , the suspension was warmed to  $25^{\circ}\text{C}$ , leading after 6 h reaction time to a dark solution (Table 1, entries 1–6). The resulting KDA/TMEDA solution was titrated with a standardized solution of 0.40 M *n*-butanol in hexane. In most cases, an excess of potassium (ca. 3 equiv) was used and the KDA/TMEDA yield was calculated based on diisopropylamine (1.0 equiv). We have varied the equivalents of TMEDA and isoprene (entries 1–4) and found that 1.0 equiv of TMEDA and 0.5 equiv of isoprene resulted in the best yield after 6 h reaction time (entry 4).<sup>[6a]</sup> Stirring for longer times did not improve the yield. Such KDA/TMEDA solutions were stable for at least one week at  $25^{\circ}\text{C}$ . Similar yields were obtained using cyclohexane instead of hexane (entry 5). A quantitative yield was reached by setting potassium as the limiting reagent (1.0 equiv) and adding an excess of diisopropylamine (DIPA, 3.0 equiv), TMEDA (3.0 equiv), and isoprene (1.5 equiv; entry 6). Attempts to extend this preparation to 2,2,6,6-tetramethylpiperidine

**Table 1:** Optimization of the preparation of potassium amide bases using solid potassium, secondary amides, TMEDA and isoprene in hexane.

Entry	$\text{K}_{\text{solid}}$ (excess)	+ $\text{R}_2\text{NH}$ (X equiv)	1) hexane, TMEDA (X equiv) 2) isoprene (X equiv)		$t$ [h]	Molarity (K base)	Yield [%]
			30 min, $0^{\circ}\text{C}$	$0^{\circ}\text{C} - 25^{\circ}\text{C}$ , $t$ [h]			
1		DIPA	2.7	0.5	6	0.33	33
2		DIPA	1.0	1.0	6	0.40	40
3		DIPA	2.7	1.0	6	0.50	50
4		<b>DIPA</b>	<b>1.0</b>	<b>0.5</b>	<b>6</b>	<b>0.56</b>	<b>56</b>
5		DIPA	1.0	0.5	18	0.57 (0.49)	57 (49) <sup>[a]</sup>
6		<b>DIPA</b>	<b>3.0</b>	<b>1.5</b>	<b>18</b>	<b>0.33</b>	<b>99<sup>[b]</sup></b>
7		TMPH	1.0	0.5	6	0.20	20
8		HNCy <sub>2</sub>	1.0	0.5	6	0.28	28

[a] Yield of KDA/TMEDA in cyclohexane. [b] Potassium was used as the limiting reagent, DIPA was used in excess (3.0 equiv).

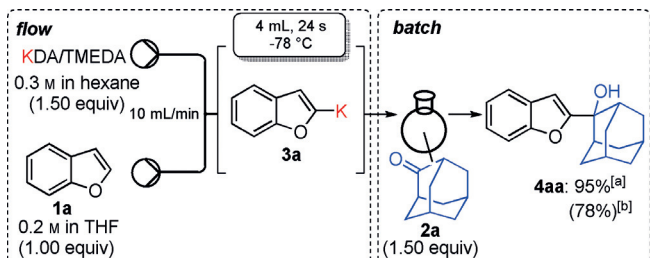
(TMPH) or  $\text{Cy}_2\text{NH}$  led to significantly lower yields (entries 7 and 8). For subsequent experiments performed in continuous flow, we have used the KDA/TMEDA preparation conditions described in entry 4.


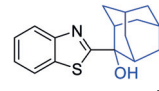
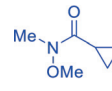
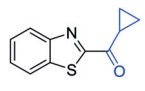

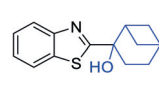
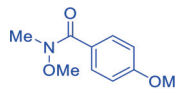
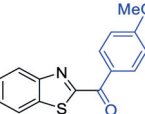
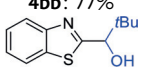
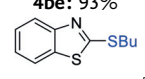
In preliminary experiments, we have optimized the reaction conditions for performing metalations with KDA/TMEDA in hexane and in continuous flow using benzofuran (**1a**) in THF as the substrate and adamantanone (**2a**) as the quenching reagent. We have varied the temperature, the flow rate, and the reactor size (reactor volume) and have found that it was best to perform the metalation at  $-78^\circ\text{C}$  using 1.5 equiv of KDA/TMEDA, a 4 mL tube reactor, and a combined flow rate of  $10\text{ mL min}^{-1}$ , leading to a reaction time of 24 s for the metalation.<sup>[8]</sup> The resulting potassium organometallic **3a** was then quenched with adamantanone (**2a**, 1.5 equiv) at  $-40^\circ\text{C}$  for 10 min, leading after workup to the tertiary alcohol **4aa** in 95% isolated yield (Scheme 1).

These potassium organometallics display a high reactivity and the metalation of benzothiazole under optimum conditions<sup>[9]</sup> (flow rate:  $10\text{ mL min}^{-1}$ ; reaction time: 0.18 s; reactor volume: 0.03 mL; reaction temperature:  $-78^\circ\text{C}$ ) furnished the potassium intermediate **3b**, which was trapped with various electrophiles such as ketones (adamantanone (**2a**) and norcamphor (**2b**)), leading to the tertiary alcohols **4ba** and **4bb** in 74–77% yield (Table 2, entries 1 and 2).

Using Barbier-type conditions,<sup>[10]</sup> that is, metalation of a mixture of **1b** (1.00 equiv) with **2a** (1.50 equiv) with KDA/TMEDA (1.50 equiv) under the same flow conditions, led to the alcohol **4ba** in 74% yield (entry 1). Quenching of **3b** with pivaldehyde (**2c**) afforded the alcohol **5bc** in 75% yield. Weinreb amides were excellent acylation reagents for potas-

**Table 2:** Metalation of benzothiazole (**1b**) using KDA/TMEDA in continuous flow and subsequent batch quenching with various electrophiles of type **2** leading to functionalized benzothiazole derivatives of type **4**.



Entry	Electrophile of type <b>2</b>	Product of type <b>4</b> <sup>[a]</sup>	Entry	Electrophile of type <b>2</b>	Product of type <b>4</b> <sup>[a]</sup>
1			4		
2			5		
3	pivaldehyde ( <b>2c</b> )		6	$\text{Bu}_2\text{S}_2$ ( <b>2f</b> )	

[a] Yield of analytically pure isolated product. [b] Barbier-type reaction using a premixed solution of benzothiazole (1.00 equiv) and electrophile (1.50 equiv), instant quenching with  $\text{NH}_4\text{Cl}$ .

sium organometallics and the trapping of **3b** with **2d** and **2e** gave the corresponding ketones in 91–93% yield (entries 4 and 5). Thiolation of **3b** with  $\text{Bu}_2\text{S}_2$  (**2f**) led to the thioether **4bf** in 92% yield. The corresponding Barbier reaction proceeded in this case with only 47% yield (entry 6).

We have extended the reaction scope to various heterocyclic and aromatic substrates. For example, benzothiophene derivatives **1c** and **1d** were metalated with KDA/TMEDA and quenched with iodine (**2g**) or the aromatic aldehyde **2h** as well as the disulfide **2i**, leading to the expected products (**4cg**, **4dh**, and **4di**) in 63–98% yield (Table 3, entries 1–3). Complete regioselectivity of the metalation of 3-octylthiophene (**1e**) was observed and addition to dicyclopropyl ketone (**2j**) gave the tertiary alcohol **4ej** in 65% yield (entry 4). Similarly, 2-phenylthiophene **1f** was metalated with KDA/TMEDA and trapped with **2a**, affording **4fa** in 80% yield (entry 5). 2-Methoxypyrazine (**1g**) was regioselectively metalated at position 3 with KDA/TMEDA ( $-78^\circ\text{C}$ , 0.18 s using a combined flow rate of  $10\text{ mL min}^{-1}$ ). Addition of ketone **2a** gave the desired alcohol **4ga** in 81% yield (entry 6).

Extension to various aromatic substrates was possible. Electron-poor trifluoromethylbenzene (**1h**) was metalated in *ortho*-position with KDA/TMEDA ( $-78^\circ\text{C}$ , 24 s reaction time,  $10\text{ mL min}^{-1}$  combined flow rate), providing after addition of **2a** the alcohol **4ha** in 42% yield (entry 7). Electron-rich substrates such as 1,3-dimethoxybenzene (**1i**) and 1,2,4-trimethoxybenzene (**1j**) were metalated with KDA/TMEDA and gave after batch quenching with aldehydes **2k**

**Scheme 1.** Metalation of benzofuran (**1a**) with KDA/TMEDA and subsequent trapping with adamantanone (**2a**) in continuous flow. [a] Isolated yield of analytically pure product. [b] Cyclohexane was used as solvent.

**Table 3:** Metalation of (hetero)arenes of type **1** using KDA/TMEDA in continuous flow and subsequent batch quench with various electrophiles of type **2** leading to functionalized (hetero)arenes of type **4**.

Entry	Substrate of type <b>1</b> ; <i>T</i> [°C], <i>t</i> [s], Flow rate [mL min <sup>-1</sup> ]	Electrophile of type <b>2</b> <sup>[a]</sup>	Product of type <b>4</b> <sup>[b]</sup>
1	 <b>1c</b> : -78, 24, 10	 <b>2g</b>	 <b>4cg</b> : 63% <sup>[c]</sup>
2	 <b>1d</b> : -78, 0.18, 10	 <b>2h</b>	 <b>4dh</b> : 98%
3	 <b>1d</b> : -78, 0.18, 10  <b>C<sub>8</sub>H<sub>17</sub></b>	 <b>2i</b>	 <b>4di</b> : 93%
4	 <b>1e</b> : -78, 0.18, 10	 <b>2j</b>	 <b>4ej</b> : 65%
5	 <b>1f</b> : -78, 0.18, 10	 <b>2a</b>	 <b>4fa</b> : 80%
6	 <b>1g</b> : -78, 0.18, 10	 <b>2a</b>	 <b>4ga</b> : 81%
7	 <b>1h</b> : -78, 24, 10	 <b>2a</b>	 <b>4ha</b> : 42%
8	 <b>1i</b> : -78, 24, 10	 <b>2k</b>	 <b>4ik</b> : 82%
9	 <b>1i</b> : -78, 24, 10	 <b>2f</b>	 <b>4if</b> : 73%
10	 <b>1j</b> : -78, 0.18, 10	 <b>2h</b>	 <b>4jh</b> : 71%

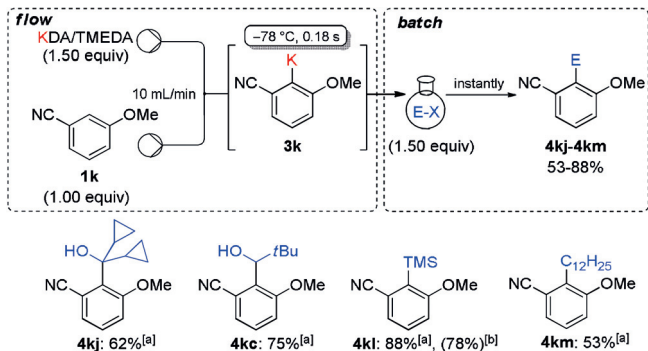
[a] 1.50 equiv of electrophile was used. [b] Yield of analytically pure isolated product. [c] KDA/TMEDA was prepared in cyclohexane.

[d] Barbier-type reaction using a premixed solution of 1,3-dimethoxybenzene (**1i**, 28 mg, 0.20 mmol, 1.00 equiv) and adamantanone (**2a**, 45 mg, 0.30 mmol, 1.50 equiv), instant quenching with NH<sub>4</sub>Cl.

and **2h** and Bu<sub>2</sub>S<sub>2</sub> (**2f**) the corresponding adducts **4ik**, **4if**, and **4jh** in 71–82% yield (entries 8–10).

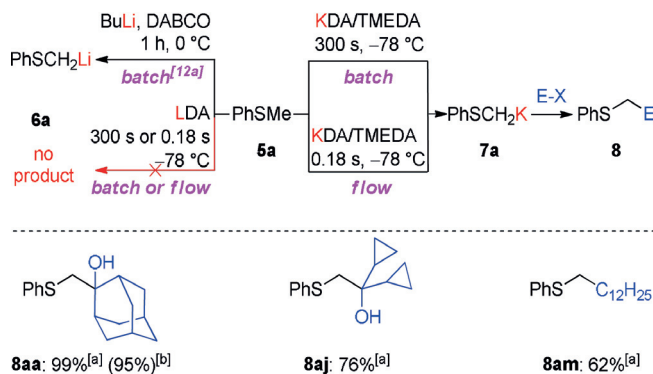
Remarkably, aromatic nitriles were tolerated in such metalations and 3-methoxybenzonitrile (**1k**) was deprotonated at the 2-position by KDA/TMEDA (-78°C, reaction time: 0.18 s). The resulting arylpotassium derivative **3k**

reacted with various electrophiles (ketone **2j**, pivaldehyde (**2c**), and TMS-Cl (**2l**)), leading to the expected products **4kj**, **4kc**, and **4kl** in 62–88% yield. Batch metalation of **1k** with KDA/TMEDA followed by Me<sub>3</sub>SiCl quenching afforded the product **4kl** in 78% yield. A Wurtz-type coupling<sup>[11]</sup> using primary alkyl iodides such as dodecyl iodide (**2m**) led to the alkylated 3-methoxybenzonitrile **4km** in 53% yield. (Scheme 2).



**Scheme 2.** Metalation of 3-methoxybenzonitrile (**1k**) with KDA/TMEDA in continuous flow and subsequent trapping with various electrophiles. [a] Yield of analytically pure isolated product. [b] Yield of analytically pure isolated product obtained under batch conditions.

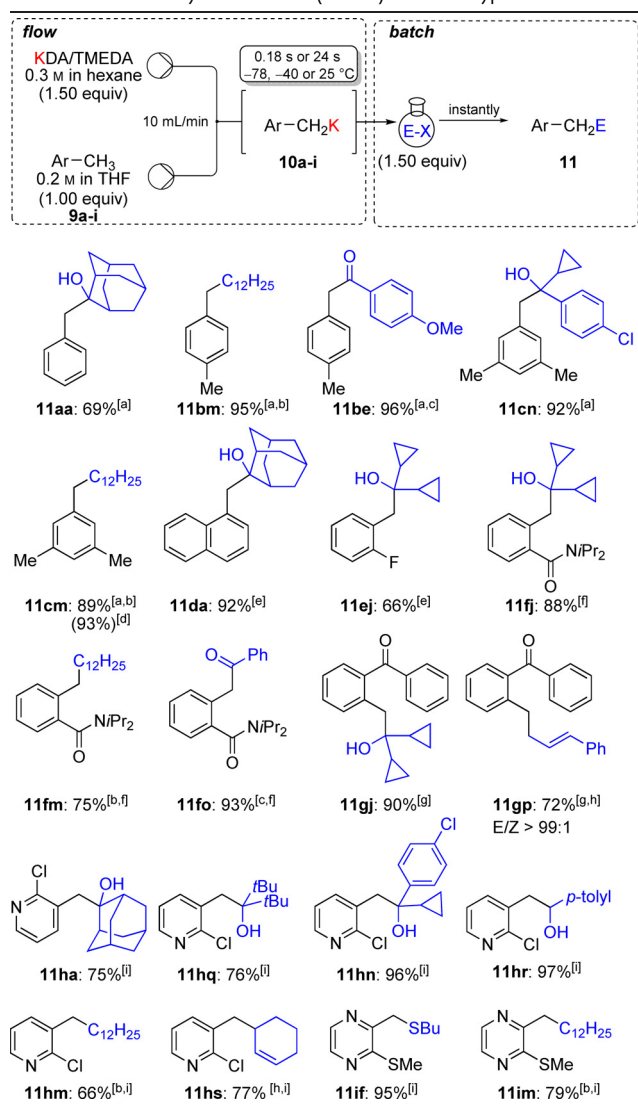
Then, we turned our attention to substrates able to undergo lateral metalation. Thus, thioanisole (**5a**) was previously lithiated with BuLi and DABCO or HMPA leading to PhSCH<sub>2</sub>Li (**6a**).<sup>[12]</sup> However, LDA did not achieve a lithiation, neither under batch nor under flow conditions.<sup>[13]</sup> On the other hand, KDA/TMEDA successfully deprotonated **5a** under batch as well as flow conditions (Scheme 3) affording PhSCH<sub>2</sub>K (**7a**), which was quenched with ketones **2a** and **2j** and alkyl iodide **2m** resulting in the desired products **8aa**, **8aj**, and **8am** in 62–99% yield.



**Scheme 3.** Metalation of thioanisole (**5a**) using various lithium and potassium bases under batch and flow conditions. [a] Yield of analytically pure isolated product obtained in continuous flow. [b] Yield of analytically pure isolated product obtained under batch conditions.

Whereas lateral alkali-metalations of arenes were well described under batch conditions,<sup>[14]</sup> the corresponding reactions in flow are rare.<sup>[15]</sup> The use of KDA/TMEDA was quite advantageous for the metalation of methyl-substituted arenes (Table 4). Preliminary results show that a 0.2M solution of toluene (**9a**) led to unsatisfactory results; however, the

**Table 4:** Lateral metalation of methyl-substituted (hetero)arenes using KDA/TMEDA in continuous flow leading to organopotassium species of type **10**. Subsequent batch trapping with various electrophiles afforded functionalized methyl-substituted (hetero)arenes of type **11**.



Yields of analytically pure isolated products. [a] Substrate (neat), E-X (0.30 mmol, 1.00 equiv), KDA/TMEDA (1.10 equiv), 25 °C, 24 s, 10 mL min<sup>-1</sup>. [b] Wurtz-type coupling with the corresponding iodide. [c] From the corresponding Weinreb amide. [d] Scale-up to 2.0 mmol using the optimized flow conditions. [e] 25 °C, 24 s, 10 mL min<sup>-1</sup>. [f] -40 °C, 24 s, 10 mL min<sup>-1</sup>. [g] 40 °C, 0.18 s, 10 mL min<sup>-1</sup>. [h] 10 mol% CuCN·2LiCl. [i] -78 °C, 0.18, 10 mL min<sup>-1</sup>.

injection of neat toluene (**9a**) considerably improved the flow metalation with KDA/TMEDA. Interestingly, this metalation was performed at 25 °C (in contrast to previously described metalations of arenes and heteroarenes). In this case, the reaction time was increased to 24 s at a flow rate of 10 mL min<sup>-1</sup>. Under these convenient conditions, the subsequent batch-trapping with ketone **2a** gave **11aa** in 69% yield. Similarly, *p*-xylene (**9b**) provided the monopotassium derivative **10b**, which after quenching with dodecyl iodide (**2m**) or Weinreb amide **2e** afforded the products **11bm** and **11be** in 95–96% yield. Mesitylene (**9c**) was metalated neat and after

quenching with ketone **2n** and dodecyl iodide (**2m**) gave the arenes **11cn** and **11cm** in 89–92% yield. In the case of the Wurtz-type coupling with **2m**, the reaction was scaled up tenfold to a 3 mmol scale,<sup>[16]</sup> providing **11cm** in 93% yield. For 1-methylnaphthalene (**9d**), a 0.2 M solution in THF was used and standard KDA/TMEDA metalation led after trapping with ketone **2a** to the corresponding naphthylmethyl alcohol **11da** in 92% yield. Functionalized substrates such as 2-fluorotoluene (**9e**) were metalated at the benzylic position, affording the potassium organometallic **10e**, which after quenching with ketone **2j** led to the tertiary alcohol **11ej** in 66% yield. *N,N*-diisopropyl-2-methylbenzamide (**9f**) led upon reaction with KDA/TMEDA at -40 °C (reaction time: 24 s) solely to the lateral metalated species **10f**, completely avoiding *ortho* metalation.<sup>[1d,17]</sup> Trapping with various electrophiles such as ketone **2j**, alkyl iodide **2m**, and Weinreb amide **2o** gave the expected products **11fj**, **11fm**, and **11fo** in 75–93% yield. Further, ketones were tolerated. For example, lateral metalation of ketone **9g** using KDA/TMEDA proceeded smoothly at -40 °C within 0.18 s using a flow rate of 10 mL min<sup>-1</sup>. Batch trapping with ketone **2j** and cinnamyl bromide (**2p**) in the presence of 10% CuCN·2LiCl resulted in the tertiary alcohol **11gj** and the allylated ketone **11gp** in 72–90% yield. We further extended the substrate scope to methyl-substituted heterocycles such as 2-chloro-3-methylpyridine (**9h**). Metalation of **9h** at the *meta*-methyl substituent using KDA/TMEDA led to the corresponding organopotassium species **10h**, which after batch quenching with various carbonyl electrophiles (**2a**, **2q**, **2n**, and **2r**) gave the corresponding alcohols **11ha**, **11hq**, **11hn**, and **11hr** in 75–97% yield.

Trapping **10h** with alkyl iodide **2m** and cinnamyl bromide **2p** (in the presence of 10% CuCN·2LiCl) led to the corresponding products **11hm** and **11hs** in 66–77% yield. Pyrazine **9i** was metalated in continuous flow with KDA/TMEDA. We have found that after metalation at the methyl substituent, the heterobenzylic potassium organometallic **10i** was obtained. Batch trapping with dibutyl disulfide (**2f**) and dodecyl iodide (**2m**) gave the functionalized pyrazines **11if** and **11im** in 79–95% isolated yield.

In summary, we have reported a preparation of the potassium base KDA/TMEDA in the absence of lithium salts and have demonstrated its utility for the metalation of (hetero)arenes containing sensitive functional groups using a flow setup. The resulting potassium organometallics react upon batch quenching instantly with various electrophiles, affording functionalized (hetero)arenes in high yields. This flow procedure was successfully extended to the lateral metalation of methyl-substituted arenes and heteroarenes, resulting in benzylic potassium organometallics, which were trapped with a range of electrophiles. Scaling up was possible without further optimization. Further investigations of flow metalations using KDA/TMEDA are currently under way in our laboratories.

## Acknowledgements

N.W. thanks the German Academic Scholarship Foundation for a fellowship. We thank the DFG and LMU for financial support. We further thank BASF (Ludwigshafen) and Albe-marle (Frankfurt) for the generous gift of chemicals and Uniqsis for technical support.

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** arenes · flow chemistry · heteroarenes · lateral metalation · potassium

- [1] a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Pergamon, Oxford, **2002**; b) T. Rathman, J. A. Schwindeman, *Org. Process Res. Dev.* **2014**, *18*, 1192; c) G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596; d) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; e) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; *Angew. Chem.* **2004**, *116*, 2256.
- [2] a) D. Seyferth, *Organometallics* **2006**, *25*, 2; b) D. Seyferth, *Organometallics* **2009**, *28*, 2; c) G. B. Buckton, *Proc. R. Soc. London* **1859**, *9*, 685; d) G. B. Buckton, *Liebigs Ann. Chem.* **1859**, *112*, 220; e) W. H. Carothers, D. D. Coffman, *J. Am. Chem. Soc.* **1930**, *52*, 1254; f) J. A. Wanklyn, *Liebigs Ann. Chem.* **1858**, *108*, 67.
- [3] a) Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2019**, *84*, 9051; b) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544; c) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470; *Angew. Chem.* **2013**, *125*, 11682; d) M. Schlosser, *Organometallics in Synthesis*, Wiley, Hoboken, **2013**; e) M. Schlosser, J. Hartmann, M. Stähle, J. Kramer, A. Walde, A. Mordini, *Chimia* **1986**, *40*, 306.
- [4] a) H. Kim, A. Nagaki, J.-i. Yoshida, *Nat. Commun.* **2011**, *2*, 264; b) C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blakemore, S. V. Ley, *Nat. Chem.* **2016**, *8*, 360; c) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463; *Angew. Chem.* **2016**, *128*, 10619; d) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process Res. Dev.* **2016**, *20*, 1967; e) B. Gutmann, C. O. Kappe, *J. Flow Chem.* **2017**, *7*, 65; f) J. Britton, T. F. Jamison, *Nat. Protoc.* **2017**, *12*, 2423; g) G. A. Price, A. R. Bogdan, A. L. Aguirre, T. Iwai, S. W. Djuric, M. G. Organ, *Catal. Sci. Technol.* **2016**, *6*, 4733; For recent reviews about flow chemistry see: h) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796; i) M. Colella, A. Nagaki, R. Luisi, *Chem. Eur. J.* **2020**, *26*, 19.
- [5] a) N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748; *Angew. Chem.* **2018**, *130*, 10908.
- [6] a) The crystal structure of KDA complexed with 1.0 equiv of TMEDA was reported: W. Clegg, S. Kleditzsch, R. E. Mulvey, P. O'Shaughnessy, *J. Organomet. Chem.* **1998**, *558*, 193; b) L. Lochmann, J. Trekoval, *J. Organomet. Chem.* **1979**, *179*, 123; c) L. Lochmann, J. Pospíšil, D. Lim, *Tetrahedron Lett.* **1966**, *7*, 257; d) A. Mordini, D. Peruzzi, F. Russo, M. Valacchi, G. Reginato, A. Brandi, *Tetrahedron* **2005**, *61*, 3349; e) L. Lochmann, M. Janata, *Cent. Eur. J. Chem.* **2014**, *12*, 537; f) for preparation of KTMP using Me<sub>3</sub>SiCH<sub>2</sub>K see: B. Conway, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, J. G. Alvarez, *Angew. Chem. Int. Ed.* **2010**, *49*, 3182; *Angew. Chem.* **2010**, *122*, 3250.
- [7] Y. Ma, R. F. Algera, D. B. Collum, *J. Org. Chem.* **2016**, *81*, 11312.
- [8] Commercially available equipment from Uniqsis was used. For a detailed optimization, see pp. 8–9 in the Supporting Information.
- [9] Optimization studies of the flow conditions were conducted separately for each substrate.
- [10] a) P. Barbier, *Compt. Rend.* **1899**, *128*, 110; b) P. Barbier, *C. R. Acad. Sci. Paris* **1899**, *128*, 110; c) C. Blomberg, F. A. Hartog, *Synthesis* **1977**, 18.
- [11] a) A. Wurtz, *Ann. Chim. Phys.* **1955**, *44*, 275; b) A. Wurtz, *Ann. Chim. Phys.* **1855**, *96*, 364.
- [12] a) E. J. Corey, D. Seebach, *J. Org. Chem.* **1966**, *31*, 4097; b) M. F. Semmelhack, J. W. Herndon, *Organometallics* **1983**, *2*, 363; c) The use of TMEDA and 2.2 equiv of nBuLi leads to dimetalation of thioanisole; S. Cabiddu, C. Floris, S. Melis, *Tetrahedron Lett.* **1986**, *27*, 4625.
- [13] For detailed screening conditions, see pp. 6–7 in the Supporting Information.
- [14] a) P. Fleming, D. F. O'Shea, *J. Am. Chem. Soc.* **2011**, *133*, 1698; b) A. Manvar, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2015**, *80*, 8727; c) F. Gualtieri, A. Mordini, S. Pecchi, S. Scapecchi, *Synlett* **1996**, *5*, 447; d) M. A. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. FAMILONI, V. Snieckus, *Eur. J. Org. Chem.* **2018**, 440; e) J. Fässler, J. A. McCubbin, A. Roglans, T. Kimachi, J. W. Hollett, R. W. Kunz, M. Tinkl, Y. Zhang, R. Wang, M. Campbell, V. Snieckus, *J. Org. Chem.* **2015**, *80*, 3368; f) S. L. MacNeil, O. B. FAMILONI, V. Snieckus, *J. Org. Chem.* **2001**, *66*, 3662; g) D.-D. Zhai, X.-Y. Zhang, Y.-F. Liu, L. Zheng, B.-T. Guan, *Angew. Chem. Int. Ed.* **2018**, *57*, 1650; *Angew. Chem.* **2018**, *130*, 1666.
- [15] a) F. Venturoni, N. Nikzad, S. V. Ley, I. R. Baxendale, *Org. Biomol. Chem.* **2010**, *8*, 1798; b) J. Y. F. Wong, J. M. Tobin, F. Vilela, G. Barker, *Chem. Eur. J.* **2019**, *25*, 12439; c) H.-J. Lee, H. Kim, D.-P. Kim, *Chem. Eur. J.* **2019**, *25*, 11641.
- [16] a) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Chem. Eur. J.* **2016**, *22*, 17407; b) A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni, J. Sedelmeier, *Org. Process Res. Dev.* **2016**, *20*, 1833.
- [17] a) L. Balloch, A. R. Kennedy, R. E. Mulvey, T. Rantanen, S. D. Robertson, V. Snieckus, *Organometallics* **2011**, *30*, 145; b) K. J. Singh, A. C. Hoepker, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 18008.

Manuscript received: March 5, 2020

Version of record online: April 30, 2020