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

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Dedicated to Prof. Dr. Rolf Huisgen for his 100th birthday

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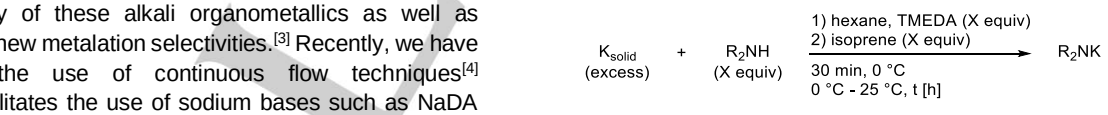
Abstract: *We report the preparation of lithium salt free KDA (potassium diisopropylamide; 0.6 M in hexane) complexed with TMEDA (N,N,N',N'-tetramethylethylenediamine) and its use for the flow-metalation of (hetero)arenes between -78 °C and 25 °C with reaction times between 0.2 s and 24 s and a combined flow rate of 10 mL/min using a commercial flow set-up. The resulting potassium organometallics react instantaneously with various electrophiles, such as ketones, aldehydes, alkyl and allylic halides, disulfides, Weinreb amides and Me_3SiCl, 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.*

From all the alkali metals, lithium has by far received the most applications in organic synthesis.[1] However, the use of sodium and potassium organometallic intermediates has been explored since more than a century[2] 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.[3] Recently, we have reported that the use of continuous flow techniques[4] considerably facilitates the use of sodium bases such as NaDA (sodium diisopropylamide) for the selective sodiation of aromatics and heterocycles.[5] Herein, we wish to report a new metalation procedure allowing both 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.

Whereas KDA was usually prepared by the Schlosser method by mixing LDA (lithium diisopropylamide) with *t*BuOK,[6] we have envisioned to prepare this base in the absence of any lithium salts, using a modified procedure of Collum for the preparation of NaDA.[7] Thus, small slices of oil-free solid potassium suspended in hexane were mixed with diisopropylamine. The resulting suspension was cooled to 0 °C and isoprene was added dropwise. After 30 min of stirring at 0 °C, the suspension was warmed to 25 °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 equivalent of TMEDA and 0.5 equivalent of isoprene resulted in the best yield after 6 h reaction time (entry 4).[6a] Longer stirring did not improve the yield. Such KDA/TMEDA solutions were stable for at least one week at 25 °C. Similar yields were obtained using cyclohexane instead of hexane (entry 5). A quantitative yield was reached by setting potassium as 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 (TMPH) or Cy_2NH led to significantly lower yields (entries 7-8). For subsequent experiments performed in continuous flow, we have used the KDA/TMEDA preparation conditions described in entry 4.

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



Entry	R_2NH 1.0 equiv	TMEDA X equiv	Isoprene X equiv	t [h]	Molarity (K-base)	Yield (%)
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	**DIPA**	**1.0**	**0.5**	**6**	**0.56**	**56**
5	DIPA	1.0	0.5	18	0.57 (0.49)	57 (49)[a]
6	**DIPA**	**3.0**	**1.5**	**18**	**0.33**	**99[b]**
7	TMPH	1.0	0.5	6	0.20	20
8	$HNCy_2$	1.0	0.5	6	0.28	28

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

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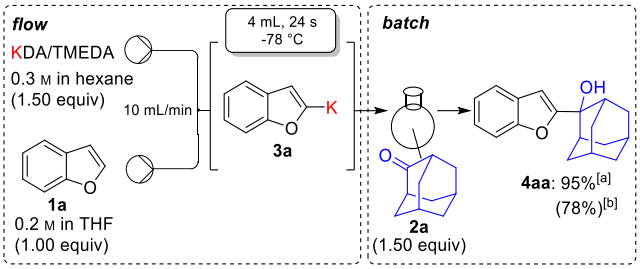
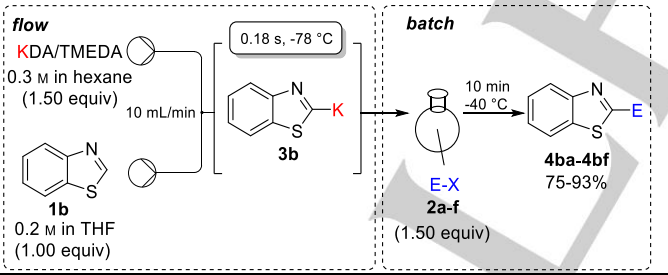
In preliminary experiments, we have optimized the reaction conditions for performing metalations with KDA/TMEDA in hexane and in continuous flow using benzofuran (**1a**) in THF as substrate and adamantanone (**2a**) as quenching reagent. We have varied the temperature, the flow rate and the reactor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



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.

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

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



entry	electrophile of type **2**	product of type **4**[a]	entry	electrophile of type **2**	product of type **4**[a]
1	**2a**	**4ba**: 77%, (74%)[b]	4	**2d**	**4bd**: 91%
2	**2b**	**4bb**: 77%	5	**2e**	**4be**: 93%
3	**2c** (Pivaldehyde)	**4bc**: 75%	6	**2f** (Bu_2S_2)	**4bf**: 92%, (47%)[b]

[a] Yield of analytically pure isolated product. [b] Barbier-type reaction using a pre-mixed solution of benzothiazole (1.00 equiv) and electrophile (1.50 equiv), instant quench with NH_4Cl.

Using Barbier-type conditions,[10] *i.e.* 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 potassium organometallics and the trapping of **3b** with **2d** and **2e** gave the corresponding ketones in 91-93% yield (entries 4-5). Thiolation of **3b** with Bu_2S_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). A 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 °C, 0.18 s using a combined flow rate of 10 mL/min). Addition of ketone **2a** gave the desired alcohol **4ga** in 81% yield (entry 6).

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 **1** T [°C], t [s], flow rate [mL/min]	electrophile of type **2**[a]	product of type **4**[b]
1	**1c:** -78, 24, 10	**2g** (I_2)	**4cg:** 63%[c]
2	**1d:** -78, 0.18, 10	**2h**	**4dh:** 98%
3	**1d:** -78, 0.18, 10	**2i**	**4di:** 93%
4	**1e:** -78, 0.18, 10	**2j**	**4ej:** 65%
5	**1f:** -78, 0.18, 10	**2a**	**4fa:** 80%
6	**1g:** -78, 0.18, 10	**2a**	**4ga:** 81%
7	**1h:** -78, 24, 10	**2a**	**4ha:** 42%
8	**1i:** -78, 24, 10	**2k**	**4ik:** 82%

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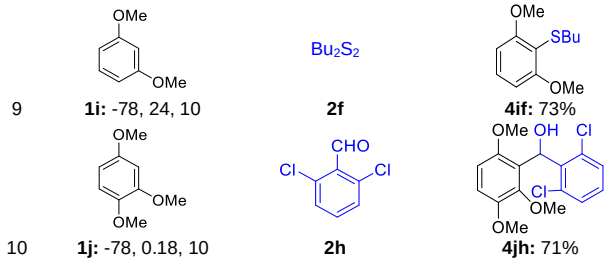
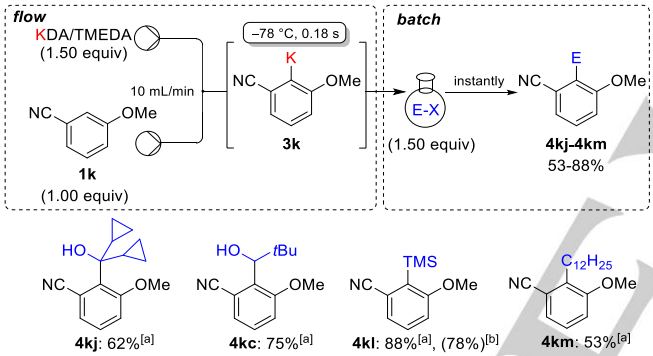


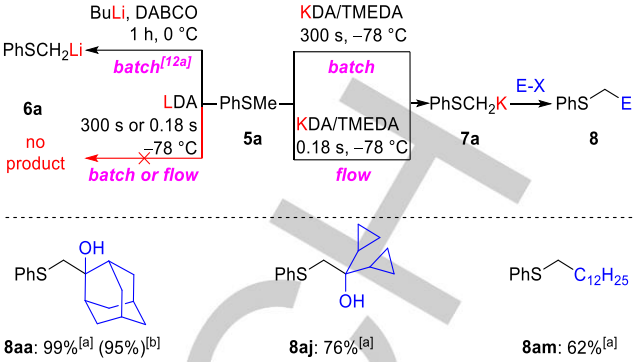
[a] 1.50 equiv of electrophile were used. [b] Yield of analytically pure isolated product. [c] KDA/TMEDA was prepared in cyclohexane. [d] Barbier-type reaction using a pre-mixed solution of 1,3-dimethoxybenzene (**1i**, 28 mg, 0.20 mmol, 1.00 equiv) and adamantanone (**2a**, 45 mg, 0.30 mmol, 1.50 equiv), instant quench with NH_4Cl.

Extension to various aromatic substrates was possible. Electron-poor trifluoromethylbenzene (**1h**) was metalated in *ortho*-position with KDA/TMEDA (-78 °C, 24 s reaction time, 10 mL/min 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** and **2h** and Bu_2S_2 (**2f**) the corresponding adducts **4ik**, **4if** and **4jh** in 71-82% yield (entries 8-10).



Scheme 2. Metalation of 3-methoxy benzonitrile (**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.

Remarkably, aromatic nitriles were tolerated in such metalations and 3-methoxybenzonitrile (**1k**) was deprotonated at position 2 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. Performing the metalation of **1k** with KDA/TMEDA in batch followed by Me_3SiCl quenching afforded the product **4kl** in 78% yield. A Wurtz-type coupling[11] using primary alkyl iodides such as dodecyl iodide (**2m**) led to the alkylated 3-methoxybenzonitrile **4km** in 53% yield. (Scheme 2). Then, we turned our attention to substrates being able to undergo lateral metalation. Thus, thioanisole (**5a**) was previously lithiated with BuLi and DABCO or HMPA leading to $PhSCH_2Li$ (**6a**).[12] However, LDA did not achieve a lithiation neither in batch nor in flow.[13] On the other hand, KDA/TMEDA successfully deprotonated **5a** in batch as well as in flow (Scheme 3) affording $PhSCH_2K$ (**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 in batch,[14] the corresponding reactions in flow were rare.[15] The use of KDA/TMEDA was quite advantageous for the metalation of methyl-substituted arenes (Table 4). Preliminary results show, that a 0.2 M solution of toluene (**9a**) led to unsatisfactory results, however the injection of neat toluene (**9a**) improved considerably 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. Under these convenient conditions, a subsequent batch-trapping with ketone **2a** gave **11aa** in 69% yield. Similarly, *p*-xylene (**9b**) provided the mono-potassium 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 ten-fold scaled up to a 3 mmol scale,[16] 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.[1d, 17] 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. 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-methyl-pyridine (**9h**). Metalation of **9h** at the meta-methyl substituent using KDA/TMEDA led to the corresponding organopotassium species **10h**, which after batch quench with various carbonyl

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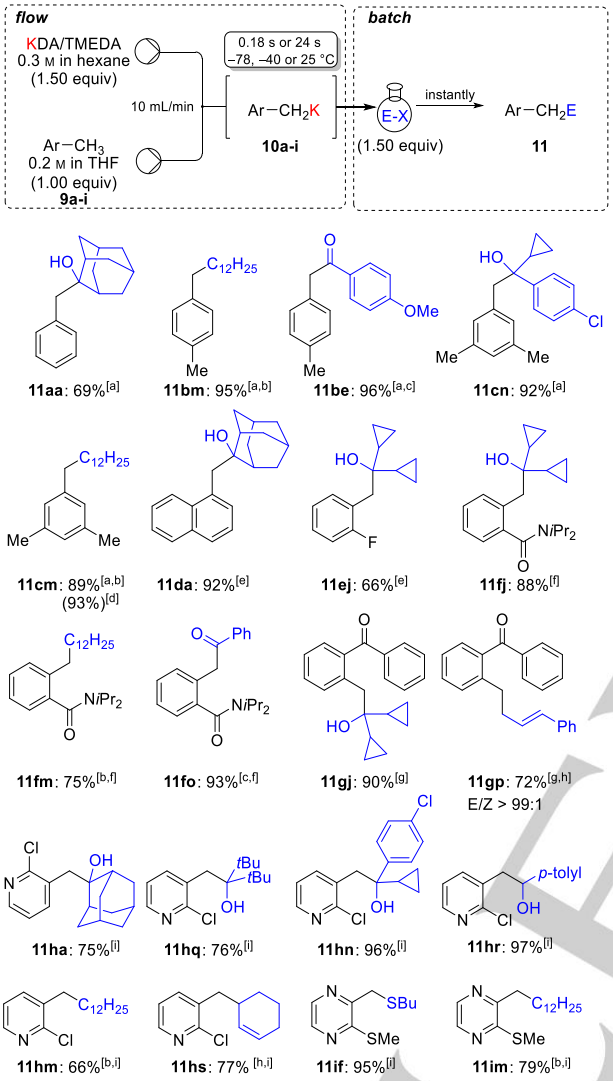
electrophiles (**2a**, **2q**, **2n** and **2r**) gave the corresponding alcohols **11ha**, **11hq**, **11hn** and **11hr** in 75-97% yield.

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. [b] Wurtz-type coupling from 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 [f] -40 °C, 24 s, 10 mL/min. [g] 40 °C, 0.18 s, 10 mL/min. [h] 10 mol% CuCN·2LiCl. [i] -78 °C, 0.18, 10 mL/min.

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 any lithium salts and have demonstrated its utility for the metalation of (hetero)arenes containing sensitive functional groups using a flow set-up. The resulting potassium organometallics react upon batch quench 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 heteroaromatics resulting in benzylic potassium organometallics, which were trapped with a range of electrophiles. A scale-up was possible without further optimization. Further investigations of flow metalations using KDA/TMEDA are currently under way in our laboratories.

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Keywords: flow chemistry • lateral metalation • potassium• arene • heteroarene

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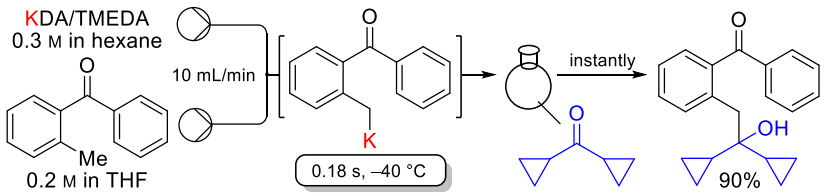

Potassium in Flow: A metalation of functionalized (hetero)arenes with KDA (potassium diisopropylamide)/TMEDA was performed using a commercial continuous flow set-up leading to the corresponding potassium organometallics. Trapping with various electrophiles gave polyfunctionalized (hetero)aromatics in good yields. Further, the flow procedure was extended to the lateral metalation of methyl-substituted (hetero)arenes resulting in benzylic potassium organometallics, which were trapped with various electrophiles.

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