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Ultrafast Halogen Dance Reactions of Bromoarenes Enabled by Catalytic Potassium Hexamethyldisilazide

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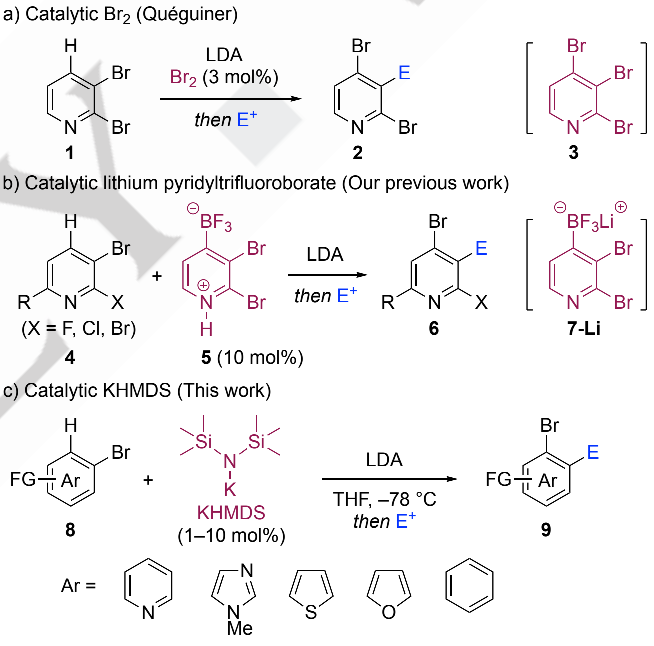
Abstract: Lochmann–Schlosser base, a stoichiometric combination of *n*BuLi and KO*t*Bu, is commonly used as a superbase for deprotonating a wide range of organic compounds. In the present study, we report that catalytic potassium hexamethyldisilazide (KHMDS) exhibits higher catalytic activity than KO*t*Bu for successive bromine–metal exchanges. Accordingly, 1–10 mol% of KHMDS dramatically enhances halogen dance reactions to introduce various electrophiles to bromopyridine, bromoimidazole, bromothiophene, bromofuran, and bromobenzene derivatives with the bromo group translocated from the original position. A dual catalytic cycle is proposed to explain the ultrafast bromine transfer.

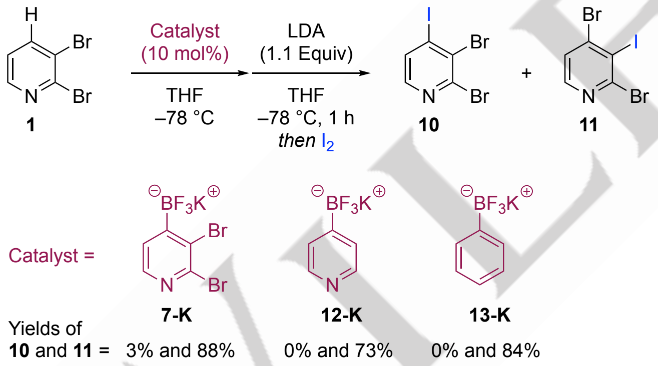
Multiply substituted arenes are an important class of compounds in pharmaceuticals, agrochemicals, natural products, and functional materials.[1] Their physical and biological properties are largely influenced by the positioning of the substituents on the aromatic ring(s).[2] Thus, methods for accessing arenes with diverse substitution patterns – a formidable challenge owing to the inherent regioselectivities of their reactions – are in high demand. Transposition reactions[3] are emerging as an especially powerful tool by which to directly access compounds with multiple substitution patterns. Among such transposition reactions, the halogen dance reaction (or rearrangement),[4] which generally involves bromine transfer, is superior to other transposition reactions owing to the wide range of reliable transformations[5] available for the bromo group. However, although halogen dance reactions of thiophene,[6] pyridine,[7] and ferrocene[8] are well known, there are few examples of their successful application to other arenes.[9] Recently, much of our efforts have been devoted to extending the limited substrate scope and utilizing the hitherto unutilized arylmetal species of the halogen dance reaction of thiophene,[10a,b] azole,[10c] pyrrole,[10d–g] and benzene.[10h,i] Nevertheless, the general conditions remain underdeveloped, even for bromopyridines, which are the most investigated halogen dance reaction substrates. This situation prompted us to explore the identification and/or development of a highly active and durable catalyst for the halogen dance reaction.



Scheme 1. Examples of halogen dance reactions and their catalysts.

Quéguiner and co-workers reported that catalytic bromine accelerates the halogen dance reaction of 2,3-dibromopyridine (**1**) (Scheme 1a).[11a] Treatment of **1** with lithium diisopropylamide (LDA) as a base and 3 mol% bromine followed by electrophilic trapping provided 2,4-dibromopyridines **2**. On the basis of the mechanistic studies on similar halopyridines such as 3-bromo-2-chloropyridine and 3-bromo-2-fluoropyridine,[11b–d] the bromination of the 4-pyridyllithium would provide tribromopyridine **3**, which is considered to be the real catalyst.[4] Recently, we reported that lithium pyridyltrifluoroborate shows high catalytic activity for the halogen dance reaction (Scheme 1b).[12] Treatment of 3-bromopyridines **4** and precatalyst **5** with LDA selectively provided 4-bromopyridines **6**. Density functional theory (DFT) calculations indicated that lithium pyridyltrifluoroborate **7-Li** generated from precatalyst **5** promotes the halogen dance. Accordingly, as a continuation of our work, we thoroughly explored a more active catalyst besides bromopyridines. Among the catalysts screened, an unprecedented combination of LDA and catalytic potassium hexamethyldisilazide (KHMDS) dramatically enhanced the halogen dance reactions of various bromoarenes (Scheme 1c). Specifically, at a KHMDS loading of 1–10 mol%, the bromo group attached to bromoarenes **8** was translocated within 1 min and subsequent electrophilic trapping afforded functionalized bromoarenes **9**. Furthermore, catalytic KHMDS was found to be applicable not only to bromopyridine, but also to bromothiophene, bromoimidazole, bromofuran, and bromobenzene.

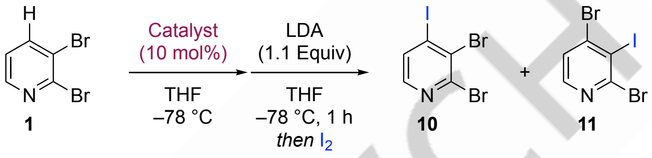
We first explored the catalytic activity of potassium aryltrifluoroborates[13] rather than lithium aryltrifluoroborates (Scheme 2). Treatment of 2,3-dibromopyridine (**1**) and potassium pyridyltrifluoroborate **7-K** with LDA followed by iodine furnished 4-iodopyridine **10** and 3-iodopyridine **11** in 3% and 88% yields, respectively. Potassium pyridyltrifluoroborate **7-K** also proved to be an effective halogen dance catalyst, although its tetrabutylammonium counterpart was less effective.[12] Moreover, the structurally simpler potassium aryltrifluoroborates **12-K** (no bromo substituents) and **13-K** (no bromo substituents nor pyridyl nitrogen) provided 3-iodopyridine **11** in 73% and 84% yields, respectively. These results indicate that the halogen dance reaction with potassium aryltrifluoroborates would proceed via a different pathway from that with lithium aryltrifluoroborate **7-Li**, which acts successively as a brominating and bromine-abstraction catalyst.[12]



Scheme 2. Halogen dance reactions catalyzed with potassium aryltrifluoroborates.

These results encouraged us to expand our exploration of potassium catalysts for the halogen dance reaction (Table 1). As a control experiment, a THF solution of pyridine **1** was treated with LDA at −78 °C for 1 h without a potassium source, and subsequent iodination gave 3-iodopyridine **11** in 8% yield (entry 1). We then tried to accelerate the sluggish halogen dance with a potassium salt. First, potassium *tert*-butoxide (KO*t*Bu), which is a component of the Lochmann–Schlosser base (*n*BuLi/KO*t*Bu),[14] was used to enhance the reactivity of the organolithium intermediate, providing 3-iodopyridine **11** exclusively in 92% yield (entry 2). Alternatively, KOH resulted in a lower yield of **11** (entry 3), and potassium salts such as K_2CO_3, KOAc, KF, and KI were also less effective (entries 4–7). After intensive optimization, KHMDS proved to be a highly active catalyst, affording 3-iodopyridine **11** in 94% yield (entry 8). Strong bases such as KHMDS and KO*t*Bu dramatically enhanced the halogen dance reaction. However, the use of NaHMDS and LiHMDS instead of KHMDS decreased the yield of 3-iodopyridine **11** (entries 9 and 10). These results indicate that potassium ions are essential for high catalytic activity.

Table 1. Screening of halogen dance catalysts[a]

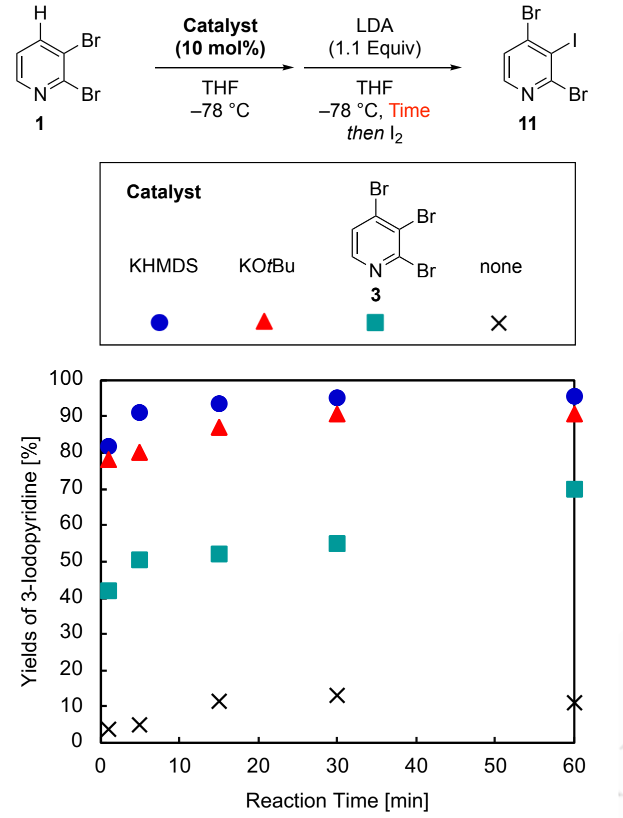


Entry	Catalyst	**10** [%][b]	**11** [%][b]
1	none	77	8
2	KO*t*Bu	–[c]	92
3	KOH	70	12
4	K_2CO_3	74	12
5	KOAc	63	21
6	KF	66	15
7	KI	64	24
8	KHMDS	–[c]	94 (86[d])
9	NaHMDS	8	64
10	LiHMDS	54	15

[a] Reaction conditions: 2,3-dibromopyridine (**1**; 1.0 equiv, 3.0 mmol), catalyst (10 mol%, 0.30 mmol), THF (30 mL), then LDA (1.1 equiv, 3.3 mmol), −78 °C, 1 h, then I_2 (2.0 equiv, 6.0 mmol), −78 °C, 1 h. [b] Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c] Not observed. [d] Isolated yield.

The catalytic activity of KHMDS was compared with that of KO*t*Bu and tribromopyridine **3** by performing a kinetic analysis (Figure 1a). When using 10 mol% of KHMDS, 3-iodopyridine **11** was obtained in 82% yield within 1 min. Applying KO*t*Bu under the same conditions, product **11** was generated in 78% yield. A time-course study revealed that KHMDS shows higher catalytic activity than KO*t*Bu. Conditions with 10 mol% tribromopyridine **3**[11a] and those without a catalyst resulted in decreased yields of 3-iodopyridine **11**. Next, we investigated the effects of catalytic loading (Figure 1b). The plot of 3-iodopyridine **11** yield vs. catalyst loading shows that even 1 mol% KHMDS promotes the halogen dance reaction, providing 3-iodopyridine **11** in 87% yield in 1 h. When KO*t*Bu was used, the yields of the product were lower than those with KHMDS. Moreover, reducing the amount of tribromopyridine **3** (1 mol%) yielded 15% of iodopyridine **11**. Thus, KHMDS shows higher catalytic activity than KO*t*Bu and tribromopyridine **3**.

a) Yields of 3-iodopyridine vs. reaction time



b) Yields of 3-iodopyridine vs. catalyst loading

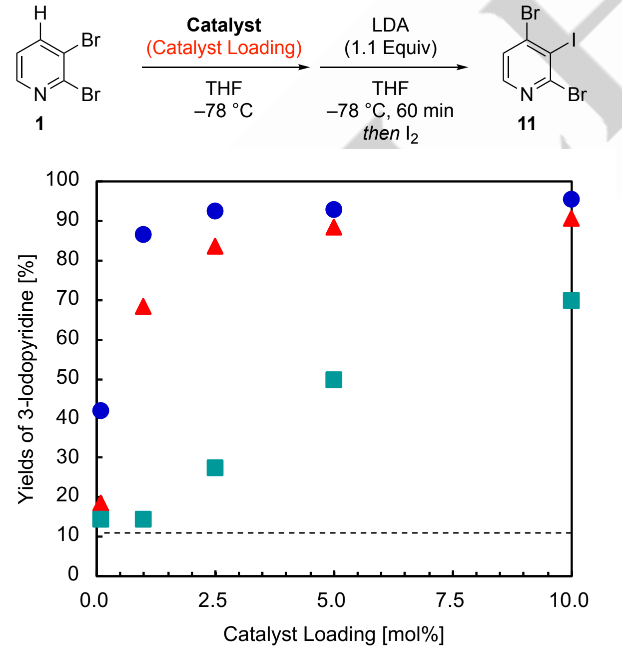
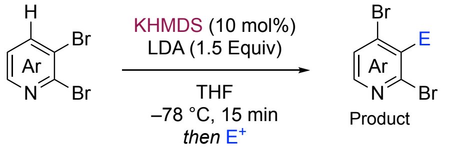
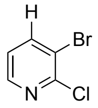
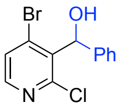
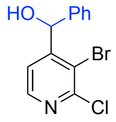
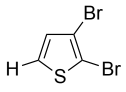
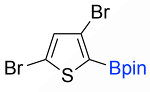
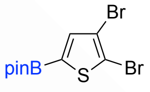
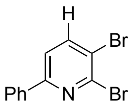
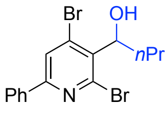
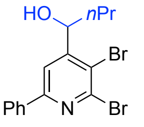
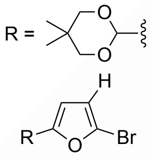
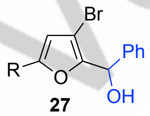
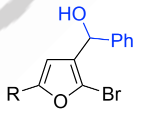
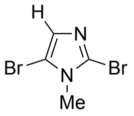
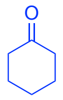
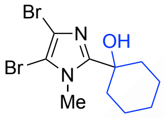
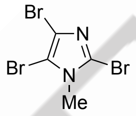
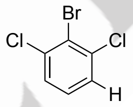
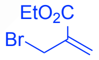
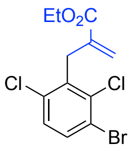
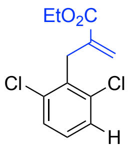


Figure 1. Kinetic analysis of KHMDS-catalyzed halogen dance reactions. [a] Plots of the yields of 3-iodopyridine **11** (average of two runs) vs. reaction time upon treatment of 2,3-dibromopyridine (**1**; 1.0 equiv) and a catalyst (10 mol%) in THF with LDA (1.1 equiv), −78 °C, 1–60 min, then I_2 (2.0 equiv), −78 °C, 1 h. [b] Plots of the yields of 3-iodopyridine **11** (average of two runs) vs. catalyst loading upon treatment of 2,3-dibromopyridine (**1**; 1.0 equiv) and a catalyst (0.1–10 mol%) in THF with LDA (1.1 equiv), −78 °C, 1 h, then I_2 (2.0 equiv), −78 °C, 1 h.

The combination of LDA and catalytic KHMDS was found to be applicable to various bromoarenes (Table 2). A mixture of 3-bromo-2-chloropyridine (**14**) and KHMDS (10 mol%) was treated with LDA (1.5 equiv) at −78 °C for 15 min, then reacted with benzaldehyde (2.0 equiv) for 2 h to give the adduct **15** exclusively in 72% yield. However, when KHMDS was absent from the reaction, the adduct **15** was generated in 16% yield along with undesired isomer **16** in 63% yield. Moreover, a reaction without KHMDS for a prolonged time (5 h) also resulted in the formation of isomer **16** in 67% yield. The results confirm that KHMDS is a superior catalyst for ultrafast bromine transfer. Performing the halogen dance reaction for 6-phenylpyridine **17** with catalytic KHMDS and electrophilic trapping with butanal provided the desired adduct **18** in 66% yield. The reaction without KHMDS provided product **18** and undesired isomer **19** in 49% and 32% yields, respectively. Furthermore, this ultrafast halogen dance was found to be applicable to five-membered bromoheteroarenes. A toluene solution of dibromoimidazole **20** and KHMDS (10 mol%) was treated with LDA, then reacted with cyclohexanone to give imidazolylcyclohexanol **21** in 89% yield. In the absence of KHMDS, although isomeric cyclohexanols were not detected, the reaction intermediate **22**[4,12] was obtained in 60% yield. The optimized conditions were applied to bromothiophene **23**. At a KHMDS loading of 10 mol%, the borylation with pinB(O*i*Pr)[15] afforded the desired pinacol boronate **24** in 86% yield. Similarly, performing the borylation without KHMDS furnished an inseparable mixture of pinacol boronates **24** and **25** in 55% and 43% yields, respectively. Moreover, the halogen dance reaction of bromofuran **26**[16] was found to be feasible using catalytic KHMDS. A combination of 1.5 equiv lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and 19 mol%[17] KHMDS resulted in complete consumption of starting furan **26**, and subsequent reaction with benzaldehyde gave 3-bromofuran **27** exclusively in 38% yield. In the absence of KHMDS, isomer **28** was selectively obtained in 47% yield with the recovery of 25% of substrate **26**. The complete deprotonation with KHMDS indicates that the combination of LiTMP and catalytic KHMDS facilitates not only bromine–metal exchange, but also deprotonation as the Lochmann–Schlosser-type base. Compared with normal Lochmann–Schlosser conditions, i.e., with stoichiometric KO*t*Bu,[16,18] only a catalytic amount of KHMDS was utilized in this ultrafast halogen dance. The optimized conditions were also found to be suitable for bromobenzene. Performing the bromine transfer of bromobenzene **29** for 5 h followed by copper-mediated allylation[19] afforded ethyl (bromophenyl)acrylate **30** in 53% yield. In the absence of KHMDS, an inseparable mixture of ethyl (bromophenyl)acrylate **30** and a substantial amount of debrominated product **31** were obtained. This was most likely due to allylation of the intermediate organolithium species.[4,12] In general, we have found that the combination of LDA and catalytic KHMDS generates a new type of mixed aggregate[20] that very effectively facilitates successive bromine–metal exchanges in halogen dance reactions of various bromoarenes.

Table 2. Range of bromoarenes synthesized by the KHMDS-catalyzed halogen dance reaction.[a]

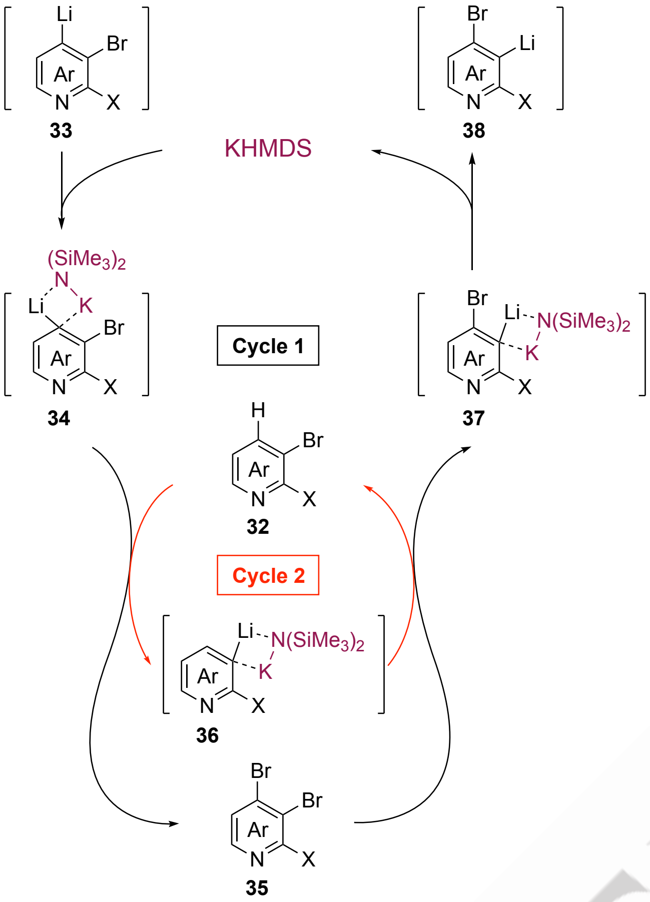


Substrate	E+	Product [%][b]	Byproduct [%][b]	Substrate	E+	Product [%][b]	Byproduct [%][b]
 **14**	PhCHO	 **15**	 **16**	 **23**	pinBO*i*Pr	 **24**	 **25**
With KHMDS		72 (72[c])	3	With KHMDS[h]		86 (57[c])	2
Without KHMDS		16	63	Without KHMDS[h]		55	43
Without KHMDS[d]		16	67				
 **17**	*n*PrCHO	 **18**	 **19**	 **26**	PhCHO	 **27**	 **28**
With KHMDS[e,f]		66 (61[c])	13	With KHMDS[f,i]		38[j] (27[c])	4[j]
Without KHMDS[e,f]		49	32	Without KHMDS[f,i]		–[j,k]	47[j]
 **20**		 **21**	 **22**	 **29**		 **30**	 **31**
With KHMDS[f,g]		89 (80[c])	11	With KHMDS[l]		53 (42[c])	4
Without KHMDS[f,g]		23	60	Without KHMDS[l]		40	29

[a] Reaction conditions: bromoarene (1.0 equiv, 0.30 mmol), KHMDS (10 mol%, 0.03 mmol), THF (3 mL), then LDA (1.5 equiv, 0.45 mmol), −78 °C, 15 min, then electrophile (2.0 equiv, 0.60 mmol), −78 °C, 2 h. [b] Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] Reaction time was 5 h. [e] Reaction time was 1 h. [f] Reaction using 0.15 mmol of bromoarene. [g] Reaction was performed in toluene. [h] Reaction was performed in toluene/THF (60:1). [i] Reaction with KHMDS (19 mol%, 0.03 mmol) and LiTMP (1.5 equiv, 0.23 mmol). [j] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [k] Not observed. [l] Reaction conditions: bromobenzene (**29**; 1.0 equiv, 0.30 mmol), KHMDS (10 mol%, 0.03 mmol), THF (3 mL), then LDA (1.5 equiv, 0.45 mmol), −78 °C, 5 h, then CuCN·2LiCl (1.5 equiv, 0.45 mmol) and ethyl 2-(bromomethyl)acrylate (2.1 equiv, 0.62 mmol), −78 °C to RT, 2 h.

Mechanistically, we propose a dual catalytic cycle[13g,21] involving both KHMDS and bromopyridine **32** for this ultrafast halogen dance on the basis of the literature precedents on mixed aggregates of organolithium and KO*t*Bu[14] (Scheme 3). First, deprotonation of bromopyridine **32** with LDA provides 4-pyridyllithium **33**, which would coordinate KHMDS to give mixed aggregate **34** bearing both lithium and potassium ions. The bromine–metal exchange of the activated organometallic species **34** and bromopyridine **32** provides dibromopyridine **35** and organometallic species **36**, which undergoes subsequent bromine–metal exchange with dibromopyridine **35** to afford the thermodynamically more stable organometallic species **37** with regeneration of bromopyridine **32**. The release of KHMDS from mixed aggregate **37** furnishes organolithium **38** to complete the dual catalytic cycle. According to the results of our previously reported DFT calculations,[12] the first bromine–metal exchange of the mixed aggregate **34** and substrate **32** would be the rate-determining step, and this would be facilitated by the highly reactive mixed aggregate **34**. Thus, we propose that the mixed aggregate formed with catalytic KHMDS further accelerates bromine–metal exchange, while the Lochmann–Schlosser-type base generated from stoichiometric KO*t*Bu is utilized for deprotonation.[14]

In conclusion, an ultrafast halogen dance reaction enabled by catalytic KHMDS has been developed. KHMDS exhibits higher catalytic activity than KO*t*Bu. The developed method is applicable not only to bromopyridines, but also to bromoimidazole, bromothiophene, bromofuran, and bromobenzene derivatives. The combination of LDA and catalytic KHMDS facilitates successive bromine–metal exchanges through a dual-cycle mechanism involving a reactive mixed aggregate. To the best of our knowledge, this is the first report of catalytic KHMDS accelerating bromine–metal exchange besides deprotonation.



Scheme 3. Plausible mechanistic pathway for the ultrafast halogen dance reaction, which proceeds through a dual catalytic cycle.

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Keywords: Dual catalysis • Halogen dance • Potassium hexamethyldisilazide • Rearrangement • Synthetic methods

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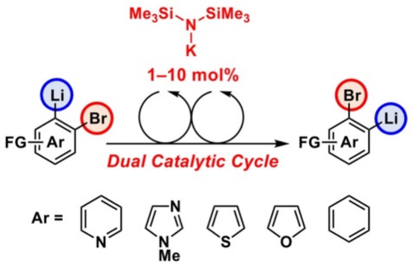
Entry for the Table of Contents



Catalytic KHMDS dramatically enhances halogen-dance-type reactions to provide bromoarenes without aryne formation. KHMDS exhibits higher catalytic activity than KO*t*Bu, which is used stoichiometrically in the Lochmann–Schlosser base. A dual catalytic cycle is proposed, demonstrating the potential of new catalytic reactions based on highly reactive mixed organometallic species.