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(Citation)
ChemCatChem,16(14):e202400408

(Issue Date)
2024-07-22

(Resource Type)
journal article

(Version)
Accepted Manuscript

Catalytic Approaches to the Halogen Dance Reaction for Molecular Editing

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Dedication ((optional))

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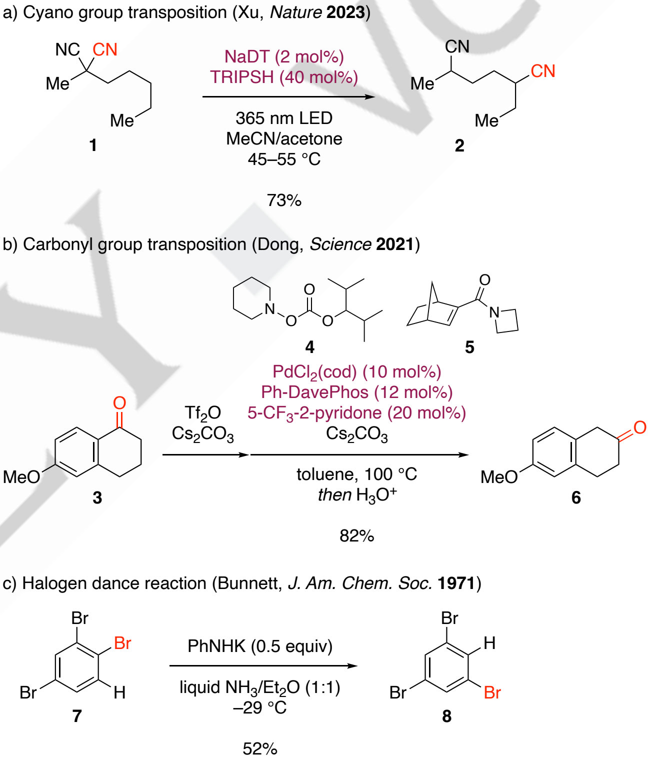
Abstract: Transposition reactions, i.e., switching the position of functional groups, are a powerful tool for molecular editing. The transposition of a halogen atom attached to an aromatic ring, referred to as the halogen dance reaction, has great potential in the fields of pharmaceuticals, agrochemicals, natural products, and functional materials. However, the substrate scope of this reaction is limited owing to the intrinsic difficulty in facilitating multiple catalytic cycles involving several aryllithium species. In this concept paper, recent advances in halogen dance catalysis that have expanded the substrate scope of this reaction are highlighted.

Introduction

Molecular editing[1] is an emerging technology for rapidly increasing molecular complexity and diversity. In addition to the skeletal editing, transposition reactions[2] involving functional group transfer play significant roles in the construction of complex molecules. For instance, Xu and co-workers recently reported the photocatalytic transposition reaction of a cyano group, whereby malononitrile derivative **1** was treated with sodium decatungstate (NaDT) and 2,4,6-triisopropylbenzenethiol (TRIPSH) under 365-nm LED irradiation to provide the transferred product **2** in 73% yield (Scheme 1a).[3] Furthermore, Dong and co-workers developed a palladium-catalyzed carbonyl 1,2-transposition reaction, in which α-tetralone **3** was treated with Tf_2O under basic conditions to form the corresponding enol triflate, which was subjected to reaction with a palladium catalyst, pyridone catalyst, carbonate **4**, and norbornene **5** at 100 °C to furnish β-tetralone **6** in 82% yield after acidic hydrolysis of the corresponding enamine (Scheme 1b).[4] These catalytic transposition reactions demonstrate that the migration of synthetically useful cyano and carbonyl groups can provide direct access to their constitutional isomers. The transposition of a halogen atom attached to an aromatic ring via aryllithium, referred to as the base-catalyzed halogen dance reaction,[5] provides broader scope for further transformations than the transposition of aryl,[2a,b] alkene,[2c,d] and ester[2e] groups. For instance, Bunnett reported the halogen dance reaction of bromobenzene derivatives, in which treatment of 1,2,4-tribromobenzene (**7**) with PhNHK in liquid ammonia/Et_2O provided 1,3,5-tribromobenzene (**8**) in 52% yield (Scheme 1c).[6a]


a) Cyano group transposition (Xu, *Nature* **2023**)

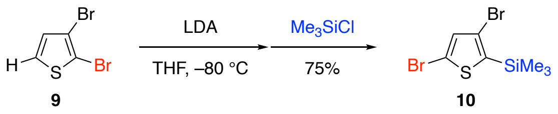
b) Carbonyl group transposition (Dong, *Science* **2021**)

c) Halogen dance reaction (Bunnett, *J. Am. Chem. Soc.* **1971**)

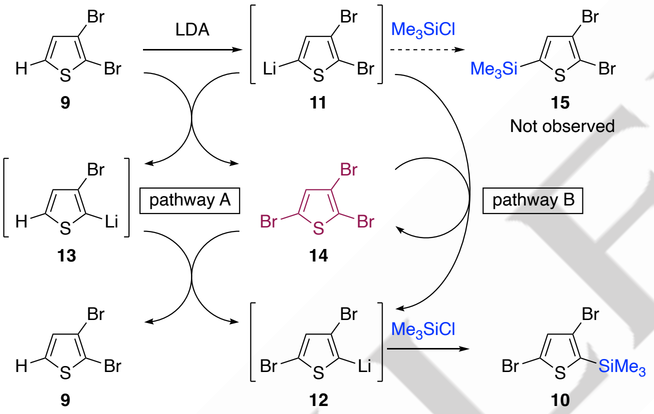
Scheme 1. Transposition reactions of synthetically useful functional groups.

The halogen dance reaction proceeds through a complex catalytic cycle involving several carbanions. Fröhlich revealed that 2,3-dibromothiophene (**9**) undergoes the halogen dance reaction through multiple halogen–metal exchanges (Scheme 2).[7] In their work, a THF solution of 2,3-dibromothiophene (**9**) was treated with LDA at −80 °C followed by silylation with trimethylsilyl chloride to give 3,5-dibromothiophene (**10**) in 75% yield.

A reaction pathway for the isomerization of thienyllithium **11** to **12**, catalyzed by the starting thiophene **9**, was proposed (Scheme 3, pathway A). Deprotonative lithiation of dibromothiophene **9** generates 2,3-dibromothienyllithium **11**, which undergoes bromine–lithium exchange with substrate **9** to furnish 3-bromothienyllithium **13** and tribromothiophene **14** as a key intermediate. This catalytic cycle is completed by subsequent bromine–lithium exchange to provide 3,5-dibromothienyllithium **12** with the regeneration of thiophene **9**. In addition to pathway A, pathway B, catalyzed by the key intermediate **14**, was also proposed (Scheme 3, pathway B).[8] The bromine–lithium exchange of the generated thienyllithium **11** and tribromothiophene **14** provides thienyllithium **12**, regenerating catalyst **14**. During the course of the reaction, the formation of silylated thiophene **15** is suppressed due to the fast halogen dance reaction of thienyllithium **11**. In marked contrast to the photocatalyst[3] (Scheme 1a) and the transition-metal catalyst[4] (Scheme 1b), the starting thiophene **9** and *in situ*-generated tribromothiophene **14**, which is the requisite intermediate for both pathways A and B, act as halogen dance catalysts. Although there has been much discussion[5b,9] around another route involving aryne formation, pathways A and B are becoming increasingly accepted as the most likely mechanism.[5]



Scheme 2. The halogen dance reaction of 2,3-dibromothiophene.



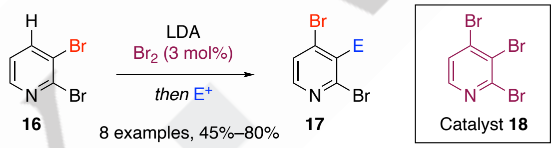
Scheme 3. Reaction pathway for the halogen dance reaction of 2,3-dibromothiophene.

Mechanistically, poorly reactive aryllithium species undergo the bromine–lithium exchange sluggishly, while highly reactive aryllithium species undergo undesired decomposition or aryne formation.[10] Accordingly, the scope of the halogen dance reaction has hitherto been limited, typically to bromothiophenes,[11] halopyridines,[12] iodoferrocenes,[13] and several halobenzenes.[5b,6,9] Since Nord's first report on the halogen dance reaction of thiophene[11a] in 1951, Bunnett, Gronowitz, Quéguiner, Fröhlich, Sammakia, Stanetty, Poisson, Jubault, Legros, Bandar, Mongin, Erb, Halauko, Hurvois, and our group have devoted considerable research effort to improving this narrow substrate scope.[14] Herein, this concept paper summarizes recently developed catalysts that realize novel catalytic cycles for the halogen dance reaction. Furthermore, we present a brief summary of the current challenges facing the application of this reaction.

Brominating Catalysts

Facilitating Halogen Dance Reaction of Bromoarenes

It is of great importance that the catalyst generates a brominated substrate (for instance, tribromothiophene **14** in Scheme 3) to boost halogen–lithium exchange. Pioneering work by Quéguiner has revealed the identity of the bromine catalyst for the halogen dance reaction of dihalopyridine (Scheme 4).[15] In their work, a THF solution of 2,3-dibromopyridine (**16**) was treated with LDA and catalytic bromine (3 mol%) followed by electrophilic trapping to provide 2,4-dibromopyridine derivative **17**. Here, the generated pyridyllithium is brominated to form the real catalyst **18**, which facilitates halogen–lithium exchange.[16] Our group has performed this reaction in the absence of catalytic bromine with subsequent iodination to obtain a small amount (9%) of 2,4-dibromo-3-iodopyridine, as described in Scheme 12. Although this experiment is not directly comparable with Quéguiner's work, our result indicates that bromine exhibits essential catalytic activity for the halogen dance reaction.



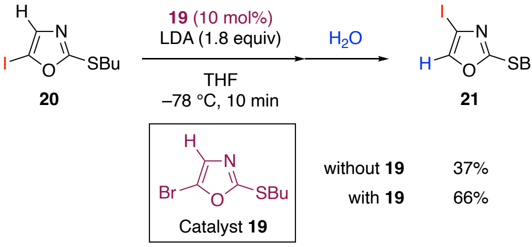
Scheme 4. Bromine catalyst for the halogen dance reaction of 2,3-dibromopyridine.

Kengo Inoue was born in Fukuoka in 1997. He received his Ph.D. in 2024 from Kobe University under the direction of Professors Atsunori Mori and Kentaro Okano. During his M.S. and Ph.D. studies, he has worked on the development of catalysts for the halogen dance reactions. In 2022, he visited Professor Brian Stoltz's group at California Institute of Technology as a visiting graduate student.

Kentaro Okano received his B.S. in 2003 from Kyoto University under the supervision of Professor Tamejiro Hiyama. He then moved to Professor Tohru Fukuyama's group at The University of Tokyo. In 2007, he joined the faculty at Tohoku University in Professor Hidetoshi Tokuyama's group. In 2014, he visited Professor Amir Hoveyda's group at Boston College as a visiting researcher. In 2015, he moved to Kobe University, where he is currently an Associate Professor. His research interests include the development of new synthetic methodologies and natural product synthesis.

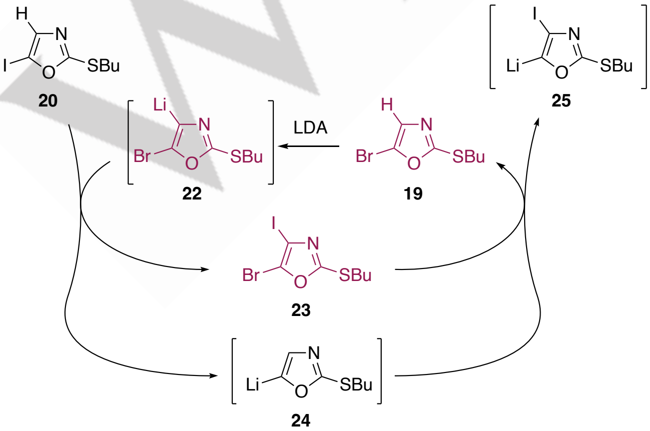
Facilitating Halogen Dance Reaction of Iodoarenes

On the basis of the reaction mechanism, an iodinating catalyst is required for the halogen dance reaction of iodoarenes. Nevertheless, a brominating catalyst with no iodine atom was found to be applicable for this reaction. Specifically, Stambuli and co-workers developed bromooxazole **19** as a catalyst for the halogen dance reaction of iodooxazole (Scheme 5).[17] Treatment of 5-iodooxazole **20** with LDA and quenching with water provided 4-iodooxazole **21** in 37% yield, along with 31% of reduced 2-(butylthio)oxazole. To avoid the undesired reduction of the iodo group, the brominating catalyst **19** was employed, which resulted in the formation of the desired iodooxazole **21** in 66% yield. These results indicate that catalyst **19** facilitates the halogen dance reaction in addition to the background halogen dance reaction.



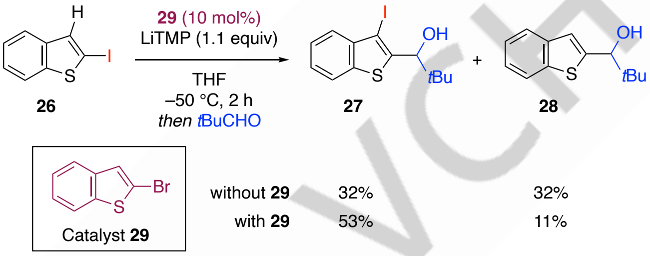
Scheme 5. The halogen dance reaction of iodooxazole catalyzed by bromooxazole.

In their paper, the significant yield improvement was explained in terms of a catalytic cycle involving iodine– and bromine–lithium exchange reactions (Scheme 6). Deprotonation of catalyst **19** with LDA, which proceeds faster than that with **20**, furnishes bromooxazolyllithium **22**. The iodine–lithium exchange of the starting iodooxazole **20**, which is faster than the bromine–lithium exchange of catalyst **19**, generates brominated iodooxazole **23** and oxazolyllithium **24**. Subsequent bromine–lithium exchange affords the thermodynamically more stable iodooxazolyllithium **25** with the regeneration of catalyst **19**. Oxazolyllithium **24**, which would essentially provide the undesired 2-(butylthio)oxazole, is stransformed into iodooxazolyllithium **25**. This reaction pathway was demonstrated by means of a crossover experiment in which the bromine and iodine atoms were scrambled between iodooxazole **20** and catalyst **19**.



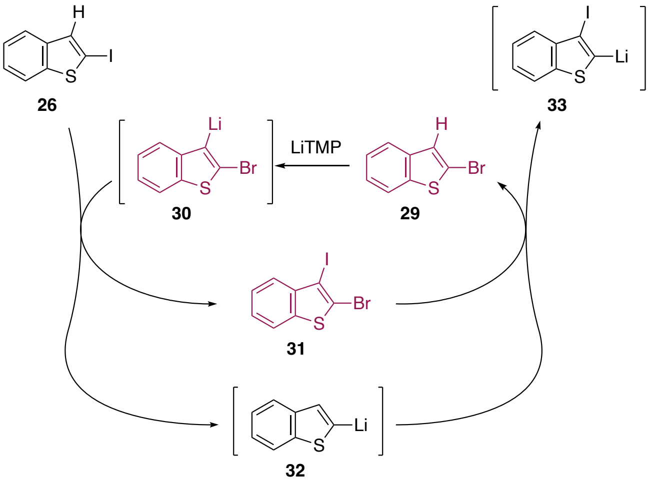
Scheme 6. A catalytic cycle for the halogen dance reaction involving the bromooxazole catalyst.

Mongin and co-workers reported that the bromobenzothiophene catalyst also promoted the halogen dance reaction of iodobenzothiophene (Scheme 7).[18] A THF solution of 2-iodobenzothiophene (**26**) was treated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) followed by reaction with pivalaldehyde to provide a mixture of the desired product **27** and the reduced benzothiophene **28** both in 32% yields. On the basis of Stambuli's approach, 2-bromobenzothiophene catalyst **29** (10 mol%) was employed to suppress the undesired reduction, namely, loss of the iodo group, furnishing the desired product **27** in 53% yield along with 11% of the undesired product **28**.



Scheme 7. The halogen dance reaction of iodobenzothiophene catalyzed by bromobenzothiophene.

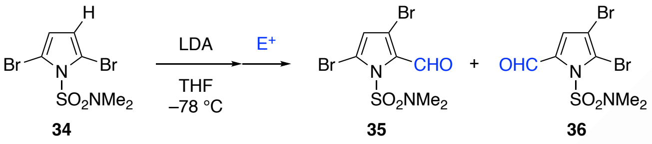
The catalytic cycle was described in their report (Scheme 8). First, bromobenzothiophene catalyst **29** is deprotonated by LiTMP to give bromobenzothienyllithium **30**, which undergoes iodine–lithium exchange with the starting iodobenzothiophene **26** to provide brominated iodobenzothiophene **31** and benzothienyllithium **32**. Subsequent bromine–lithium exchange generates bromobenzothiophene catalyst **29** and iodobenzothienyllithium **33**, followed by reaction with pivalaldehyde to afford the desired product **27**. When using catalyst **29**, a lower amount (11%) of the undesired product **28** was obtained, presumably by facilitating the conversion of benzothienyllithium **32** into iodobenzothienyllithium **33** with the transient brominated catalyst **31** through this catalytic cycle in addition to the background halogen dance reaction.



Scheme 8. A catalytic cycle for the halogen dance reaction involving the bromobenzothiophene catalyst.

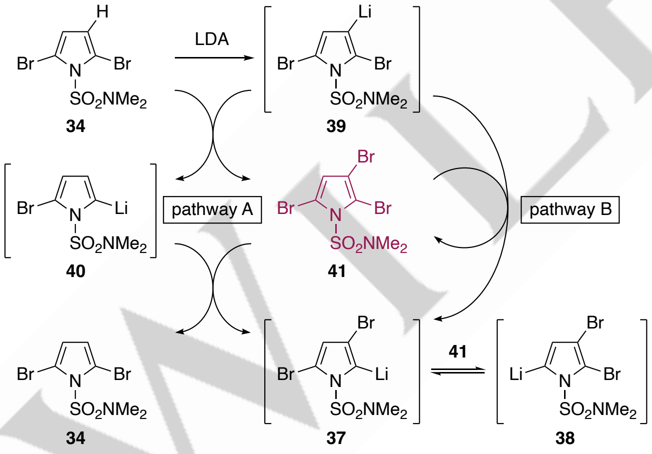
Switching the Regioselectivity of the Halogen Dance Reaction

While the aforementioned brominating catalysts promote the halogen dance reaction, their ability to switch its regioselectivity has also been presented. Our group has reported that the selective halogen dance reaction (1,2- or 1,3-halogen dance reaction) of dibromopyrrole **34** was achieved simply by using the appropriate electrophiles, providing formyl pyrroles **35** and **36** (Scheme 9).[19] Deprotonation of the pyrrole bearing *N*,*N*-dimethylsulfamoyl protecting group **34** with LDA and subsequent formylation with ethyl formate afforded 3,5-dibromopyrrole **35** in 66% yield, during which a small amount (5%) of 2,3-dibromopyrrole **36** was generated. Furthermore, the use of DMF led to formylation at the C5 position to give 2,3-dibromopyrrole **36** exclusively in 49% yield. These results indicate that two dibromopyrrolyllithium species, corresponding to the products **35** and **36**, are selectively trapped by each electrophile. To the best of our knowledge, this was the first report of the regioselective introduction of an electrophile upon halogen dance reaction, although that upon proton transfer has been reported.[12c,20]



	35	36
E$^+$ = HCO$_2$Et	66%	5%
E$^+$ = DMF	–	49%

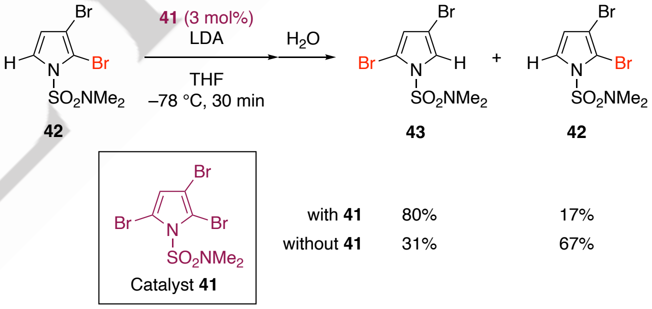
Scheme 9. Selective trapping of pyrrolyllithium species in the halogen dance reaction.



Scheme 10. Reaction pathways A and B for the halogen dance reaction of 2,5-dibromopyrrole.

A rationale for the regioselective formylation was proposed based on reaction pathways A and B involving the equilibrium between pyrrolyllithium species **37** and **38** (Scheme 10). The reaction of 2,5-dibromopyrrole **34** with dibromopyrrolyllithium **39** provides bromopyrrolyllithium **40** and tribromopyrrole **41**, which undergo bromine–lithium exchange to give the starting dibromopyrrole **34** and pyrrolyllithiums **37** or **38**. On the basis of the observed regioselectivity, pyrrolyllithiums **37** and **38** exist in equilibrium through bromine–lithium exchange with tribromopyrrole **41**. When using the more reactive ethyl formate, the equilibrium favoring pyrrolyllithium **37** being transformed into 3,5-dibromopyrrole **35** is established, while the less reactive DMF favors the less congested and thermodynamically unstable pyrrolyllithium **38**, selectively giving the formylated 2,3-dibromopyrrole **36**. A key to this highly regioselective C5 formylation is the rapidly established equilibrium between the two pyrrolyllithium species, which prevents the undesired reaction of the sterically demanding and less reactive pyrrolyllithium **37**. Of the protecting groups screened, the *N*,*N*-dimethylsulfamoyl group proved to be the most effective for accelerating not only bromine–lithium exchanges through pathways A and B, but also the equilibrium between dibromopyrrolyllithium species **37** and **38**.

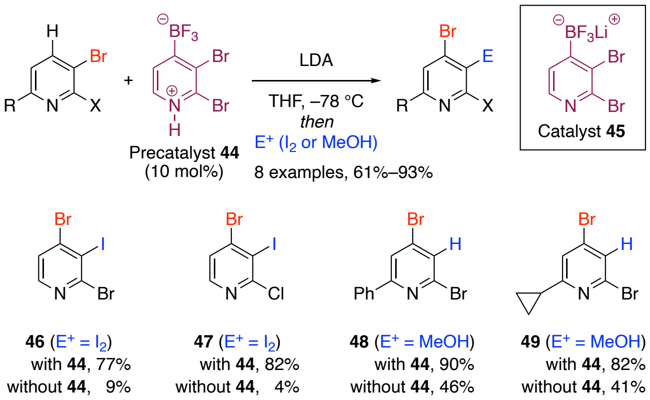
We experimentally confirmed that the equilibrium between pyrrolyllithium species **37** and **38** is facilitated by catalytic tribromopyrrole **41** (Scheme 11). A mixture of 2,3-dibromopyrrole **42** and catalyst **41** (3 mol%) was treated with LDA at −78 °C, followed by proton quenching to give the thermodynamically favored product **43** in 80% yield, with recovery (17%) of 2,3-dibromopyrrole **42**. In the absence of catalyst **41**, the yield of the isomer **43** was 31%, resulting in the recovery (67%) of 2,3-dibromopyrrole **42**. These results indicate that *N*,*N*-dimethylsulfamoyl tribromopyrrole **41** acts as the active catalyst for promoting the isomerization of pyrrolyllithium **38**, which selectively provides thermodynamically favored pyrrolyllithium **37**.



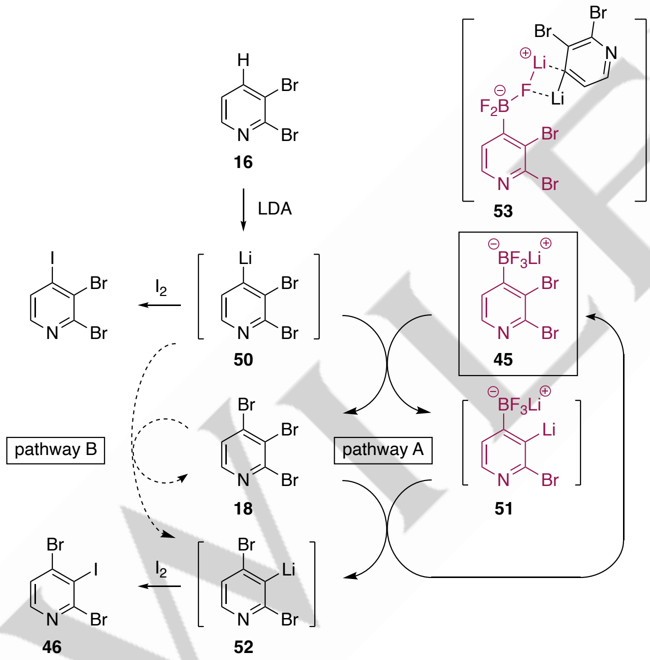
Scheme 11. Equilibrium of the two dibromopyrrolyllithium species catalyzed by the *N*,*N*-dimethylsulfamoyl tribromopyrrole.

Lithium Aryltrifluoroborate Catalyst

Our group has recently reported a new type of halogen dance catalyst.[21] We initially screened Lewis acids for switching the deprotonation site and regioselectivity of the halogen dance reaction.[22] Among the Lewis acids tested, a catalytic amount (10 mol%) of BF_3·OEt_2 unexpectedly, specifically, and dramatically facilitated the reaction, although it did not influence the migratory aptitude of the bromo group. Experimental and theoretical studies revealed that pyridinium trifluoroborate precatalyst **44** provides lithium aryltrifluoroborate **45** by deprotolithiation with LDA, catalyzing the halogen dance reaction of various 2,3-dihalopyridines (Scheme 12). A mixture of 2,3-dibromopyridine and precatalyst **44** (10 mol%) was treated with LDA at −78 °C followed by iodine to give 2,4-dibromo-3-iodopyridine (**46**) in 77% yield. In the absence of precatalyst **44**, the corresponding product **46** was obtained in 9% yield along with 77% of 2,3-dibromo-4-iodopyridine. Reaction of 3-bromo-2-chloropyridine with precatalyst **44** also provided 3-iodopyridine **47** in 82% yield, whereas the reaction without precatalyst **44** afforded 4% of 3-iodopyridine **47**. The optimized reaction conditions were applied to 2,3-dibromo-6-phenylpyridine and 2,3-dibromo-6-cyclopropylpyridine, which furnished products **48** and **49** in 90% and 82% yields, respectively. In the case of the 6-substituted pyridines, reactions without precatalyst **44** resulted in decreased yields of products **48** and **49**. Lithium aryltrifluoroborate **45** was found to be a highly active catalyst for the halogen dance reaction.



Scheme 12. Lithium aryltrifluoroborate catalyst for the halogen dance reaction.

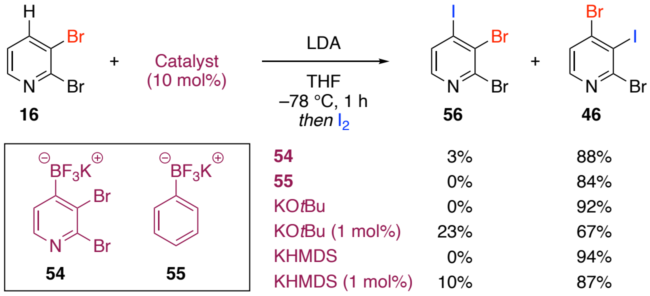


Scheme 13. Plausible reaction pathway for the halogen dance reaction catalyzed by lithium aryltrifluoroborate.

A reaction pathway was proposed involving successive bromine–lithium exchanges (Scheme 13, pathway A). First, deprotonative lithiation of 2,3-dibromopyridine (**16**) generates dibromopyridyllithium **50**, which undergoes bromine–lithium exchange with catalyst **45** to give tribromopyridine **18** and pyridyllithium catalyst **51**. Subsequent bromine–lithium exchange of tribromopyridine **18** and pyridyllithium catalyst **51** then provides the thermodynamically favored dibromopyridyllithium **52** with regeneration of catalyst **45**. Pathway A is completely different from the classical pathway B,[15] where catalytic tribromopyridine **18** facilitates isomerization of dibromopyridyllithium **50** to **52**. Density functional theory calculations revealed that the rate-determining step is the first bromine–lithium exchange of dibromopyridyllithium **50** and catalyst **45**, whose activation energy was calculated to be +23.0 kcal mol^{-1}. The activation energy for the bromine–lithium exchange of dibromopyridyllithium **50** and tribromopyridine **18** was calculated to be +26.7 kcal mol^{-1}. These calculations indicated that catalyst **45** induces the formation of organometallic aggregate **53**, facilitating the rate-determining bromine–lithium exchange through F−Li interactions.[23] The positive effect of the lithium cation was confirmed by a control experiment using the tetrabutylammonium counterpart, which showed much lower catalytic activity than precatalyst **44**. Although aryltrifluoroborate has been widely used as a stoichiometric reagent for cross-coupling reactions,[24] photoredox reactions,[25] and other reactions,[26] we revealed the potential of lithium aryltrifluoroborate as an organocatalyst.

KHMDS Catalyst

We explored potassium aryltrifluoroborates,[24–26] which are more widely available than their lithium counterparts.[27] First, the catalytic activities of potassium aryltrifluoroborates **54** and **55** in the halogen dance reaction of 2,3-dibromopyridine **16** were assessed (Scheme 14). Treatment of pyridine **16** and catalyst **54** with LDA and subsequent iodination provided 4-iodopyridine **56** and 3-iodopyridine **46** in 3% and 88% yields, respectively. Compared with the reaction in the absence of catalyst (Scheme 12), potassium pyridyltrifluoroborate **54** proved to be highly active. Despite bearing no bromine or nitrogen atoms, potassium phenyltrifluoroborate **55** furnished 3-iodopyridine **46** in 84% yield. This result indicates that bromine and nitrogen atoms are not essential for catalytic activity, indicating that potassium aryltrifluoroborates accelerate the halogen dance reaction through a different reaction pathway to pathway A in Scheme 13. Accordingly, we screened potassium salts, among which 10 mol% *tert*-butoxide (KO*t*Bu), a stoichiometric component of Lochmann–Schlosser base,[28] showed high catalytic activity to give 3-iodopyridine **46** exclusively in 92% yield.[29] Nevertheless, 1 mol% KO*t*Bu was less effective. Meanwhile, potassium hexamethyldisilazide (KHMDS) dramatically facilitated the halogen dance reaction to give 3-iodopyridine **46** exclusively in 94% yield. Intriguingly, the reaction with 1 mol% KHMDS was almost completed within 1 h, resulting in the formation of 87% 3-iodopyridine **46**. A time-course study (1 to 60 min) also demonstrated that KHMDS is a more active catalyst than KO*t*Bu.

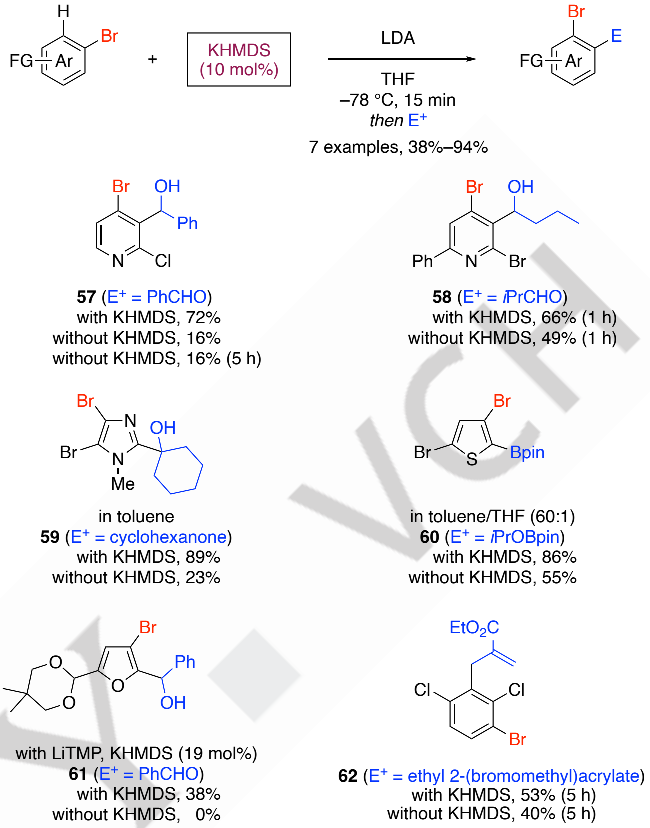


Catalyst	56	46
54	3%	88%
55	0%	84%
KO*t*Bu	0%	92%
KO*t*Bu (1 mol%)	23%	67%
KHMDS	0%	94%
KHMDS (1 mol%)	10%	87%

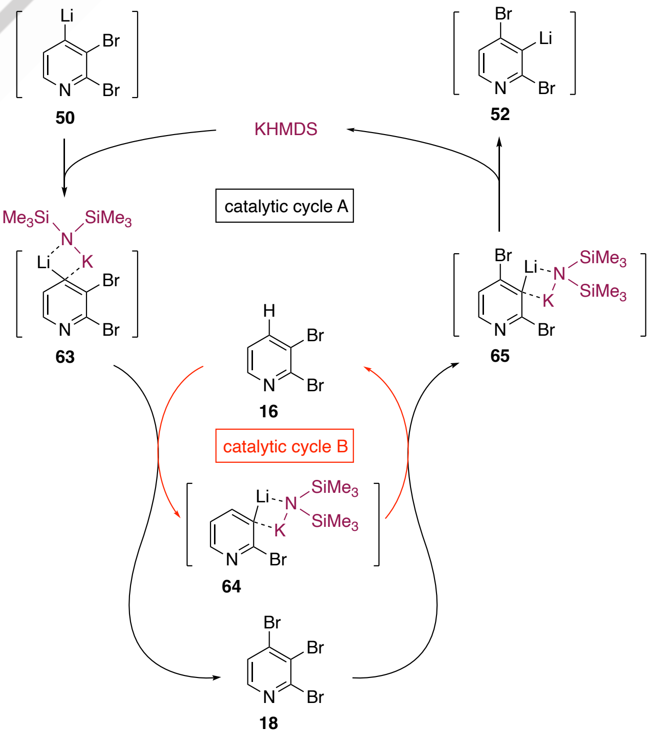
Scheme 14. Potassium catalysts for the halogen dance reaction.

This Lochmann–Schlosser-type base generated from catalytic KHMDS was found to be applicable to the halogen dance reaction of various bromoarenes (Scheme 15). At a 10 mol% loading of KHMDS, a THF solution of 3-bromo-2-chloropyridine was treated with LDA at −78 °C for 15 min then reacted with benzaldehyde to give the desired adduct **57** in 72% yield. In contrast, the reaction without KHMDS provided **57** in 16% yield. Even when the reaction was conducted for 5 h, the yield of product **57** was not improved, indicating that KHMDS is an extremely active catalyst. Performing the halogen dance reaction of 2,3-dibromo-6-phenylpyridine with 10 mol% KHMDS followed by trapping with butanal furnished the desired alcohol **58** in 66% yield. The yield of alcohol **58** was decreased to 49% in the absence of KHMDS. Catalytic KHMDS also facilitated halogen dance reactions of bromoimidazole, bromothiophene, and bromofuran. A toluene solution of 2,5-dibromo-1-methyl-1*H*-imidazole and KHMDS (10 mol%) was reacted under the optimized conditions, followed by reaction with cyclohexanone to obtain the adduct **59** in 89% yield. It is noteworthy that a substantial amount (60%) of 2,4,5-tribromoimidazole, which is considered to be the reaction intermediate,[5,16] was obtained in the absence of KHMDS, along with 23% of product **59**. In the case of 2,3-dibromothiophene, borylation with *i*PrOBpin[30] gave pinacol boronate **60** in 86% yield. For the reaction without KHMDS, a mixture of the product **60** and 2,3-dibromo-5-borylthiophene was obtained in 55% and 43% yields, respectively. The halogen dance of 2-(5-bromofuran-2-yl)-5,5-dimethyl-1,3-dioxane[31] with a combination of LiTMP and KHMDS (19 mol%) was conducted with benzaldehyde to furnish 3-bromofuran **61** in 38% yield, while the isomeric 2-bromofuran was exclusively obtained in 47% in the absence of KHMDS. The optimized conditions were applied to bromobenzene derivative. The KHMDS-catalyzed 1,3-halogen dance reaction of 1-bromo-2,6-dichlorobenzene followed by copper-mediated allylation[32] provided the desired ethyl 2-(3-bromo-2,6-dichlorobenzyl)acrylate (**62**) in 53% yield. The allylation without KHMDS resulted in the formation of product **62** and ethyl 2-(2,6-dichlorobenzyl)acrylate in 40% and 29% yields, respectively. During the process, the reduced benzene was generated by protonation of the corresponding aryllithium intermediate.

A dual catalytic cycle[33] was proposed to rationalize the KHMDS-catalyzed ultrafast halogen dance reaction, using 2,3-dibromopyridine as an example (Scheme 16). The reaction begins with the deprotonative lithiation of the starting 2,3-dibromopyridine (**16**) to generate the corresponding dibromopyridyllithium **50**. On the basis of published literature,[28,34] coordination with KHMDS would form the highly reactive mixed aggregate **63** (catalytic cycle A), which readily undergoes bromine–metal exchange with another molecule of dibromopyridine **16** to give tribromopyridine **18** and the mixed aggregate **64** (catalytic cycle B). Catalytic cycle B is subsequently accomplished by bromine–metal exchange to furnish mixed aggregate **65**, regenerating dibromopyridine **16**. Consequently, catalytic cycle A is completed by the release of KHMDS to afford the thermodynamically more stable pyridyllithium **52**. During the catalytic process, the rate-determining bromine–metal exchange of the starting pyridine **16** would be boosted by the synergic effect[35] of the highly reactive mixed aggregate **63**. Although the Lochmann–Schlosser base, a combination of *n*BuLi and stoichiometric KO*t*Bu, has been commonly used for deprotonation of various organic compounds, the newly developed mixed aggregate formed with catalytic KHMDS dramatically facilitates successive bromine–metal exchanges.



Scheme 15. KHMDS-catalyzed halogen dance reaction of bromoarenes.



Scheme 16. A plausible dual catalytic cycle for the KHMDS-catalyzed halogen dance reaction of 2,3-dibromopyridine.

Summary and Outlook

In conclusion, recently reported halogen dance catalysts and their catalytic cycles have been summarized in this concept paper. Compared with the conventional use of catalytic bromine for the halogen dance reaction, Quéguiner-type brominating catalysts have been employed for the halogen dance reaction of iodoarenes. Moreover, regioselective functionalization has been kinetically and thermodynamically controlled through the fast equilibrium catalyzed by the brominating catalyst. Moreover, our group has reported that lithium aryltrifluoroborate exhibits high catalytic activity. The catalytic cycle proceeds through successive bromine–lithium exchanges boosted by F−Li interactions, offering the novel possibility of organotrifluoroborates as organocatalysts. As a continuation of this work, KHMDS was found to be the most effective halogen dance catalyst. During the course of the reaction, the halogen dance reaction was completed with 1 mol% KHMDS, which is in marked contrast to KO*t*Bu, a stoichiometric component of a Lochmann–Schlosser base. These results indicate that the Lochmann–Schlosser-type mixed aggregate generated with catalytic KHMDS has a synergetic effect, dramatically facilitating successive bromine–metal exchanges with the dual catalytic cycle.

Substantial efforts have been devoted over the past 70 years since the first halogen dance reaction by Nord in 1951; however, its substrate scope is still limited. Thus, further investigation and modification of these catalysts are required to develop more active and robust catalysts that promote multiple halogen–metal exchanges involving the thermodynamically unfavorable step. We believe that this concept will pave the way for the rational design of novel catalysts for the halogen dance reactions of hitherto unamenable substrates.

Acknowledgements

This work was supported by JSPS KAKENHI Grants JP19H02717 in Scientific Research (B) (to K.O.) and JP22J21420 in JSPS Fellows (to K.I.). We thank Dr Jay Freeman at Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Keywords: Borates • Carbanions • Halogen dance reaction • Halogen–metal exchange • Organocatalysis

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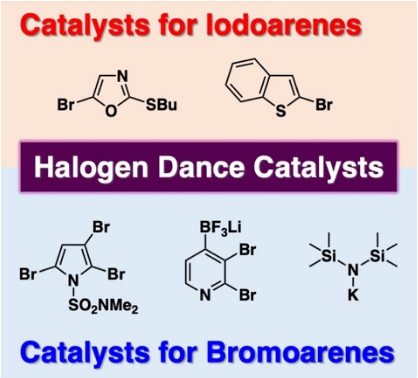

Recent advances in catalysts for a transposition process of bromine or iodine atoms on haloarenes, referred to as the halogen dance reaction, are highlighted. In this concept paper, we shed light on their catalytic cycles involving multiple aryllithium species.

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