金属交換を鍵としたブロモアレーンのハロゲンダンス

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Halogen Dance of Bromoarenes Using In Situ Transmetalation

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目次

略 語 一 覧

Ac	Acetyl
Ar	Aryl
^{n}Bu, Bu	Normal butyl
^{s}Bu	Secondary butyl
^{t}Bu	Tertiary butyl
BuMeEDA	*N*,*N*-Di-*tert*-butyl- *N'*,*N'*-dimethylethylenediamine
Cod	1,5-Cyclooctadiene
COX-2	Cyclooxygenase-2
Cy	Cyclohexyl
dba	Dibenzylideneacetone
dcype	1,2-Bis(dicyclohexylphosphino)ethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DFT	Density functional theory
DMF	*N*,*N*-Dimethylformamide
DMP	1,3-Dimorpholinopropane
DMSO	Dimethyl sulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
E^{+}	Electrophile
EDA	Ethylenediamine
Et	Ethyl
Equiv	Equivalent
FG	Functional group
IC_{50}	50% Inhibitory concentration
KHMDS	Potassium hexamethyldisilazide
Li^{t}BuSA	Lithium *tert*-butyl(*tert*-butyldimethylsilyl)amide
LDA	Lithium diisopropylamide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
*m*CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
pin	Pinacolate
Ph	Phenyl
^{i}Pr	Isopropyl
^{n}Pr	Normal propyl
rt	Room temperature

SEM	2-(Trimethylsilyl)ethoxymethyl
TBS	*Tert*-butyldimethylsilyl
TEEDA	*N*,*N*,*N*′,*N*′-Tetraethylethylenediamine
Temp	Temperature
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMCDA	*N*,*N*,*N*′,*N*′-Tetramethylcyclohexane-1,2-diamine
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidinyl

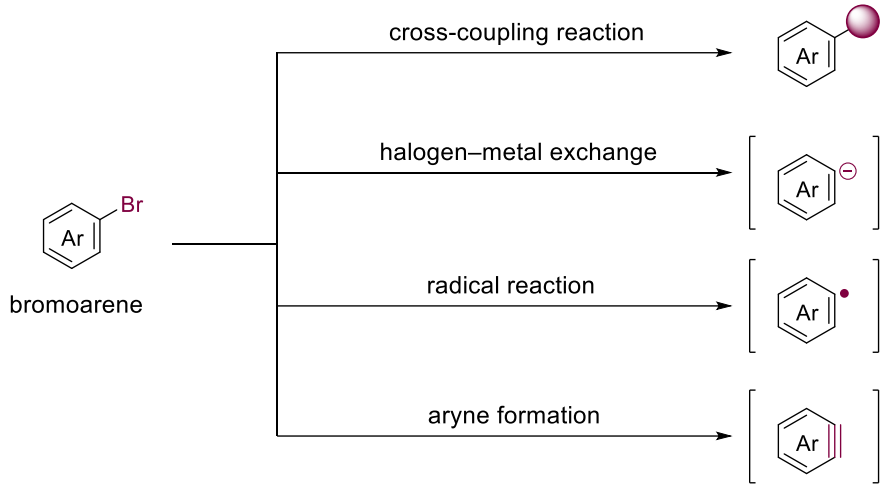
第一章

序論

1-1　ブロモアレーンの合成化学的価値

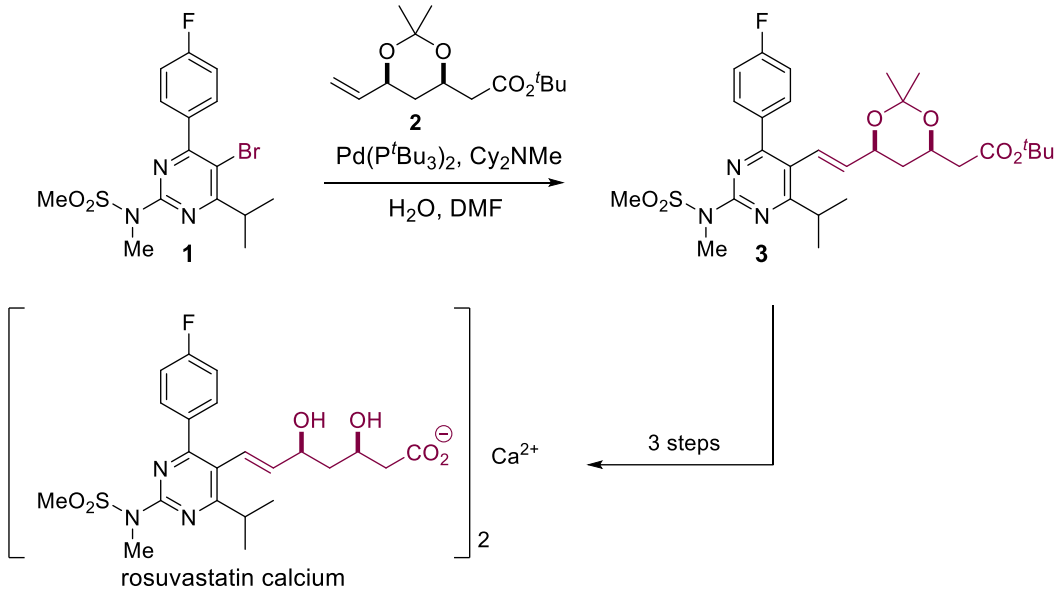
ベンゼンに代表される芳香環に臭素原子が置換した化合物をブロモアレーンという。ブロモアレーンの臭素原子は，クロスカップリング反応[1]によって，幅広い置換基へ変換できるため非常に有用である (Scheme 1–1)。また，ハロゲン–金属交換[2]，ラジカル反応[3]によって，炭素アニオン，炭素ラジカルとしても利用できる。臭素原子は，アライン形成[4]の起点にもなるため，ブロモアレーンは合成化学上きわめて重要な化合物である。

Scheme 1–1. Examples of Chemical Reactions Using Bromoarene

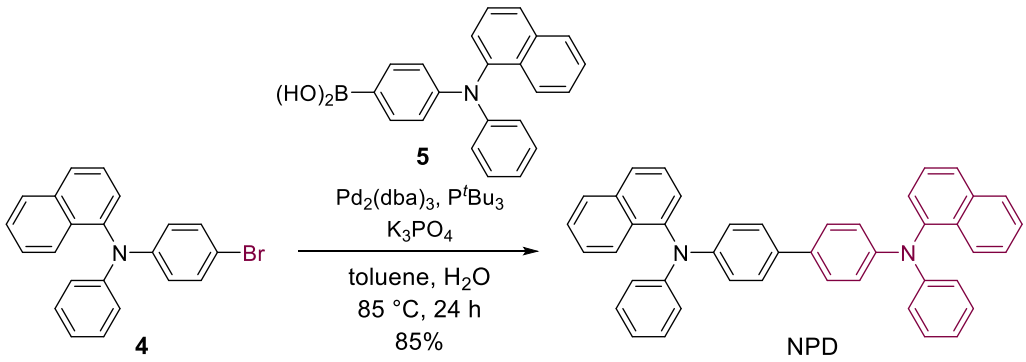


実際に，ブロモアレーンを用いて，様々な医薬品や有機電子材料が合成されている。その例の一つに，AstraZeneca 社が報告したロスバスタチンカルシウムの合成が挙げられる (Scheme 1–2)[5]。ブロモピリミジン **1** を前駆体として，ビニル化合物 **2** との溝呂木–Heck 反応[6]によって，ロスバスタチンカルシウム前駆体 **3** を得ている。前駆体 **3** は三工程を経て，ロスバスタチンカルシウムへと導かれている。また，東ソー有機化学株式会社は，ブロモベンゼンを用いて，低分子半導体の正孔輸送材料として利用される NPD (*N,N'*-ビス(1-ナフチル)-*N,N'*-ジフェニルベンジジン)の合成を達成している (Scheme 1–3)[7]。ブロモベンゼン **4** を出発化合物とし，ボロン酸 **5** とパラジウム触媒を作用させ，85 °C に加熱することで，NPD を収率 85%で得ている。以上のように，ブロモアレーンのブロモ基を化学変換の起点として，複雑な有機化合物が簡便に合成されている。

Scheme 1–2. Synthesis of Rosuvastatin Calcium by Using a Bromopyrimidine



Scheme 1–3. Synthesis of NPD by Using a Bromobenzene



医薬品や有機電子材料として利用される多置換芳香族化合物を合成する際，その生物活性や材料物性は置換基の位置によって大きく変化するため[8]，置換基の位置のみが異なる異性体（構造異性体）の網羅的な合成が重要となる。

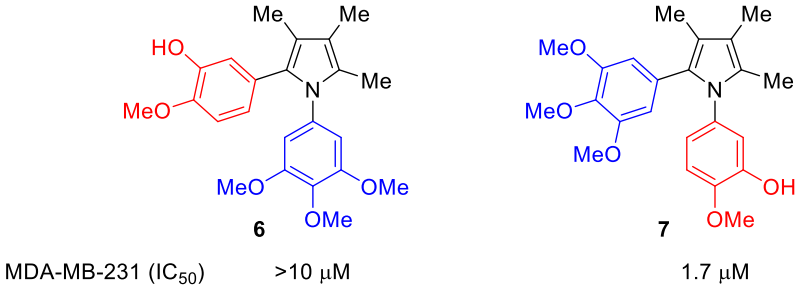


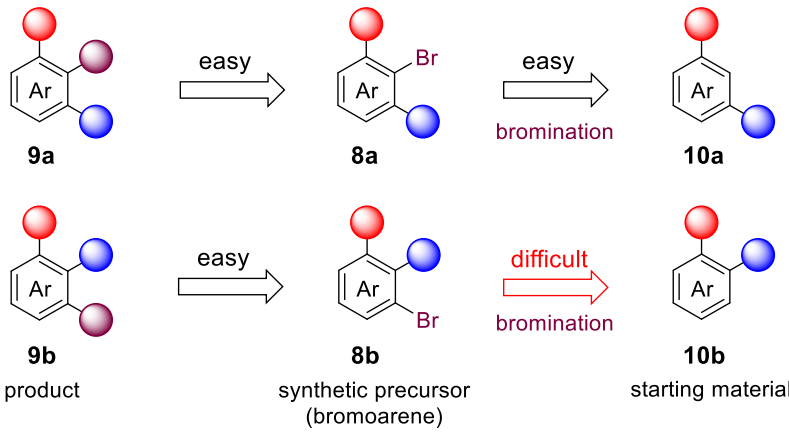
Figure 1–1. Biological activity of pyrrole analogues

Borker らは，二つの芳香環が置換したピロール **6** において，芳香環の位置を入れ替えると，生物活性が向上したことを報告している (Figure 1–1)[9]。ピロール **6** の細胞株 MDA-MB-231 に対する 50%阻害濃度(IC_{50})が 10 μM を超えていた一方で，ピロール **7** の IC_{50} は 1.7 μM と低く，高い生物活性を示している。したがって，置換基の位置が異なった構造異性体の網羅的な合成法の開発は，高い生物活性をもつ医薬品や材料物性に優れた有機電子材料の探索プロセスにおいて非常に重要である。著者は，構造異性体の網羅的合成において，ブロモアレーンが優れた合成前駆体となると考えた。

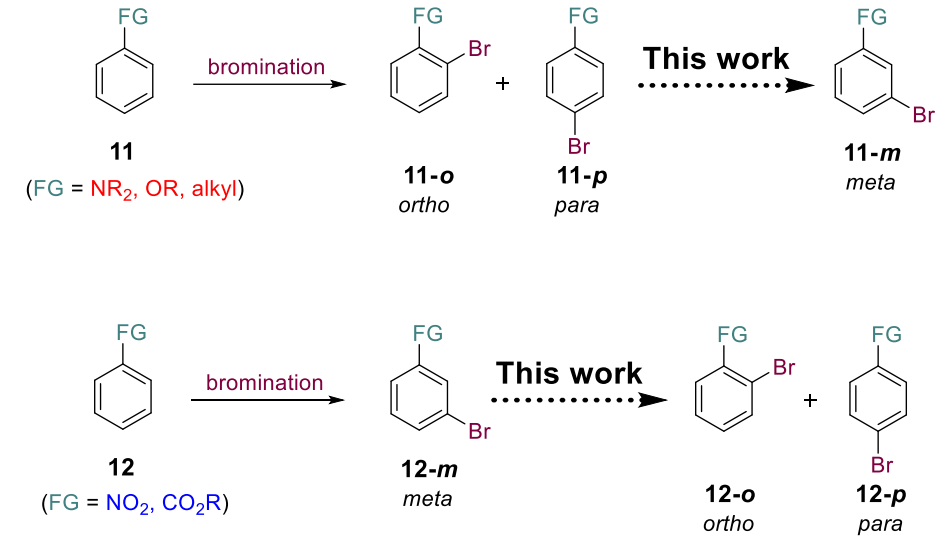
1-2　ブロモアレーン合成における課題

構造異性体を網羅的に合成する際，ブロモアレーンは，優れた合成前駆体となる可能性がある (Scheme 1–4)。すなわち，幅広い置換様式をもつブロモアレーン **8a** や **8b** を合成中間体として供給できれば，後の変換が容易なブロモ基の化学変換[1–4]を用いて，多置換芳香族化合物 **9a** およびその構造異性体 **9b** を簡便かつ網羅的に合成できる。しかし，ブロモアレーンは，ブロモ基の置換位置次第でその合成難易度が大きく異なる。例えば，臭素化によってブロモアレーン **8a** と **8b** を合成する際に，出発化合物 **10a** の臭素化は容易であるが，出発化合物 **10b** の臭素化が難しい場合がある。具体例として，一般的なブロモアレーンの合成法として知られる芳香族化合物の求電子的な臭素化反応では，単純な一置換ベンゼン **11** でさえ，オルト位，パラ位，メタ位に臭素が導入された三種類の構

Scheme 1–4. Bromoarene as a Synthetic Precursor for Multiply Substituted Arenes



Scheme 1–5. Bromination of Mono-Substituted Benzene



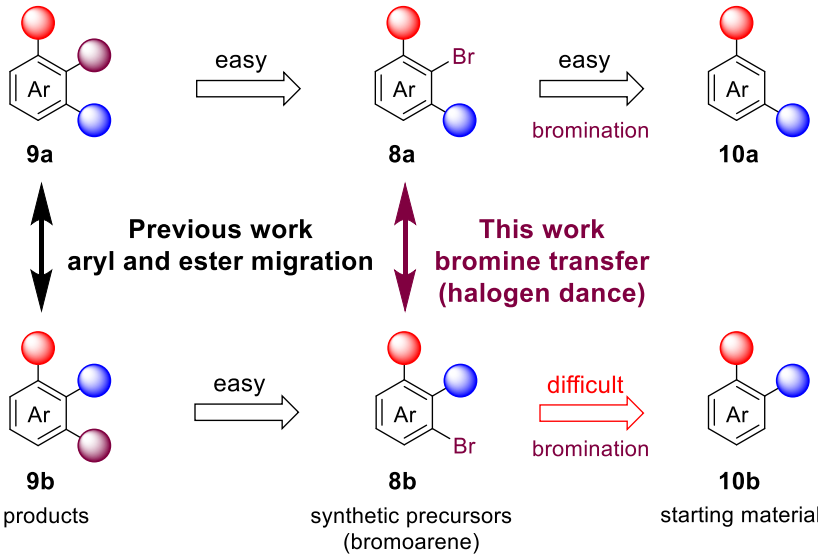
造異性体が考えられる (Scheme 1–5)。臭素化の選択性は，すでに導入されている官能基 FG の種類によって異なり，電子供与性の官能基 (FG = NR_2, OR, alkyl) をもつベンゼン **11** であれば，オルト–パラ選択的に進行し，**11-*o*** や **11-*p*** が得られる。一方で，電子求引性の官能基 (FG = NO_2, CO_2R)をもつベンゼン **12** であれば，メタ選択的に臭素原子が導入され，**12-*m*** を与える。したがって，電子供与性の官能基をもちながら，メタ位に臭素原子をもつブロモアレーン **11-*m*** や，電子求引性の官能基をもちながらオルト位またはパラ位に臭素原子をもつブロモアレーン **12-*o*** や **12-*p*** の合成は難しい。求電子的な臭素化反応ではなく，配向基を用いたオルト位選択的な脱プロトン反応 (DoM: Directed *ortho*-metalation)[10]を経由した臭素化を用いれば，配向基として利用されるエステルやアミドのオルト位を選択的に臭素化できるが，配向基を反応の後から除去することは通常難しい。したがって，構造異性体の関係にあるオルト，メタ，パラ位に臭素原子が導入された三種類のブロモアレーンは，それぞれ多置換芳香族化合物を合成する上で重要なビルディングブロックとなるにもかかわらず，その網羅的な合成法は今まで確立されていなかった。本論文では，構造異性体の関係にあるブロモアレーンを網羅的に供給するために，官能基のなかでも化学変換が容易で有用性が高いブロモ基を，後から移動させる戦略に着目した。すなわち，ブロモアレーン **11-*o*** や **11-*p*** の臭素原子をメタ位に，もしくはブロモアレーン **12-*m*** の臭素

原子をオルトまたはパラ位に移動できれば，通常の臭素化の選択性では実現できない置換様式をもつ **11-*m*** や **12-*o***，**12-*p*** が合成できるようになると考えた。

1-3　ハロゲンダンス

前節では，構造異性体の関係にあるブロモアレーンを供給するために，ブロモ基の移動反応に着目した (Scheme 1–6)。構造異性体の関係にあるブロモアレーン **8a** と **8b** をそれぞれ構造異性体の関係にある出発化合物 **10a** と **10b** から臭素化によって合成するのではなく，ブロモアレーン **8a** を合成した後に臭素原子を移動させ，**8b** へ変換できれば，同一の出発化合物 **10a** を用いて構造異性体 **9a** や **9b** を網羅的に合成できる。臭素原子は様々な置換基へ変換できるため，臭素原子の移動反応は，近年報告されている芳香環[3b,11]やエステル[12]，カルボニル基[13]，その他の官能基[14]の移動反応よりも優れている。したがって，ブロモアレーン **8a** から **8b** へのブロモ基の移動反応を鍵とし，後の化学変換によって様々な置換基をもつ多置換芳香族化合物 **9a** や **9b** の網羅的な合成をめざした。

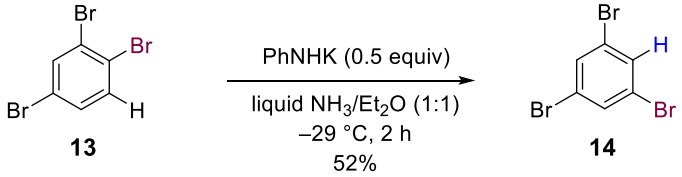
Scheme 1–6. Transposition Reactions for the Synthesis of Multiple Arenes with Diverse Substitution Patterns



臭素原子を移動させる反応として，ハロゲンダンス[15]とよばれる反応が知られている。Bunnett らは，ブロモベンゼンのハロゲンダンスを報告している (Scheme 1–7)[16]。液体アンモニア，ジエチルエーテル溶媒中で，1,2,4-トリブロモベンゼン

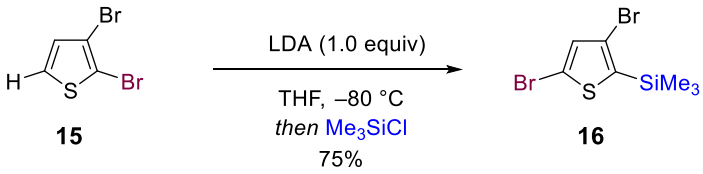
(**13**)に対して，PhNHK を作用させ，1,3,5-トリブロモベンゼン(**14**)を収率 52%で得ている。ハロゲンダンスを利用し，トリブロモベンゼン **13** の置換様式を変換することに成功している。

Scheme 1–7. Halogen Dance of 1,2,4-Tribromobenzene



また，Fröhlich らは，ヘテロ芳香環としてブロモチオフェンのハロゲンダンスを報告している (Scheme 1–8)[17]。THF 溶液中で 2,3-ジブロモチオフェン(**15**)に LDA を−80 °C で作用させ，Me_3SiCl を加えると，3,5-ジブロモチオフェン **16** を収率 75%で得ている。なお，その他のハロゲンダンスの例については，Stanetty[15f]や，Mongin[15g]，著者ら [15h] が総説を執筆している。以上のようにハロゲンダンスは，ブロモアレーンの置換様式を簡便に変換できるためきわめて有用である。しかし，ブロモアレーンの種類によって報告例が限られている点が課題であった。

Scheme 1–8. Halogen Dance of 2,3-Dibromothiophene



ハロゲンダンスの報告数をブロモアレーンごとに分類した (Figure 1–2)[18]。ヘテロ芳香環として，チオフェン[19]，ピリジン[20]のハロゲンダンスは多くの報告例が知られている。また，Mongin や Erb らが，フェロセン[21]のハロゲンダンスについて近年盛んに研究している。一方で，チアゾール[22]やオキサゾール[23]，キノリン[24]などのヘテロ芳香環に加えて，芳香環として最も一般的なベンゼン [16,25]のハロゲンダンスは，限定的な例にとどまっていた（第二章，第三章参照）。以上のように，従来のハロゲンダンスは，ブロモアレーンの置換様式を変換できるため非常に有用ではあるものの，適用可能なブロモアレーンの種類がきわめて限

定的であった。したがって，本研究では，幅広いブロモアレーンに適用可能な一般性の高いハロゲンダンスの開発をめざした。

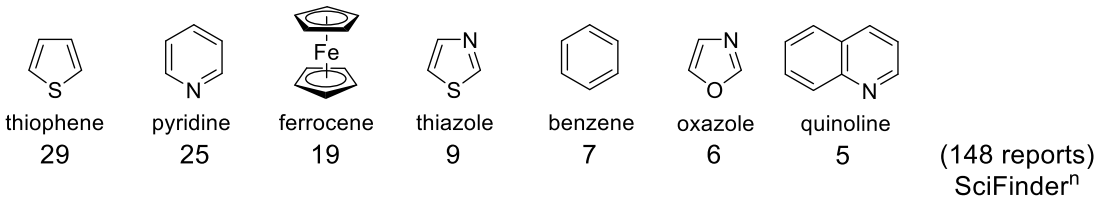


Figure 1–2. Number of reports on halogen dance reactions

研究および文献検索を進める中で，従来ハロゲンダンスが進行しなかったブロモアレーンを三種類に分類できることがわかった (Figure 1–3)。従来報告されていたハロゲンダンスが進行しやすい基質として，チオフェン[19]やフラン[26]，アゾール[22,23,27]，フルオロ基やクロロ基をもつピリジン[20a,b,28]が挙げられる (Figure 1–2)。一方で，反応中間体が不安定で分解反応が競合するブロモアレーンや，ハロゲン原子の移動が遅いブロモアレーンのハロゲンダンスは達成されていなかった。本論文は，上記の未解決課題に取り組み，ハロゲンダンスが進行する基質

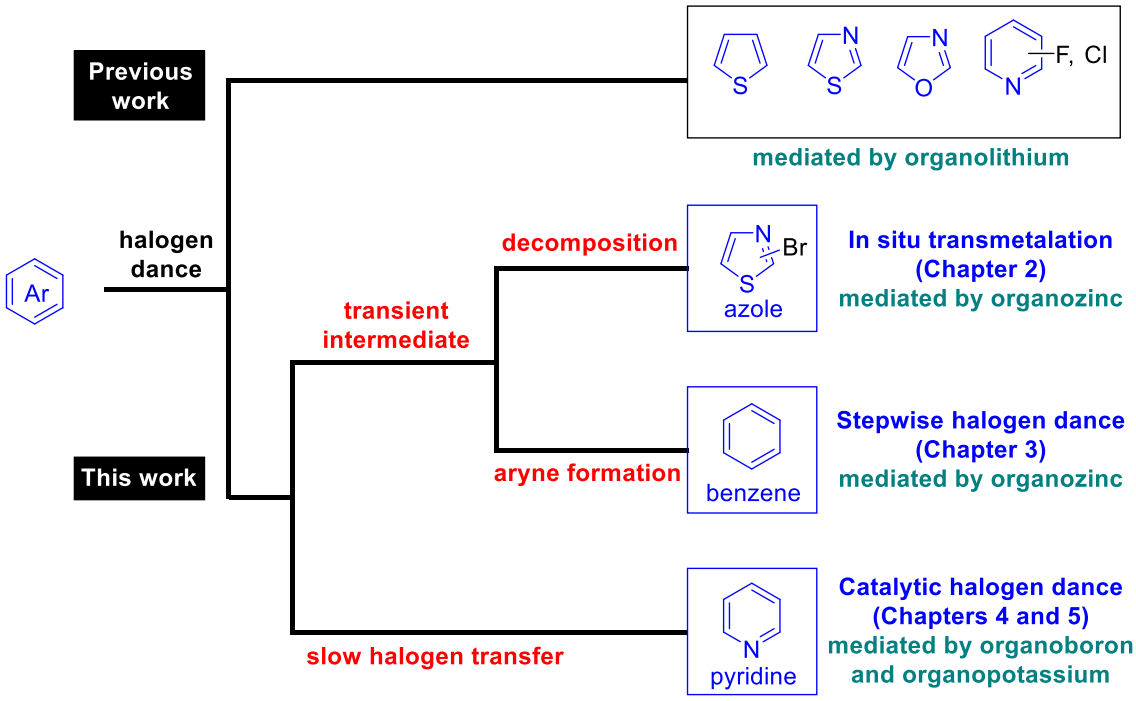


Figure 1–3. This work: halogen dance of various bromoarenes

の一般性を向上させることを目的とした (Figure 1−3)。研究の結果，分解反応が進行するブロモチアゾール（第二章参照），アライン形成が進行するベンゼン（第三章参照），ブロモ基の転位が遅いピリジン（第四章，第五章参照）のハロゲンダンスを達成した。従来のハロゲンダンスは，反応中間体として有機リチウムが一般的であった [15] が，第二章と第三章ではリチウムを亜鉛へ，第四章ではリチウムをホウ素へ，第五章ではリチウムをカリウムへ金属交換し，従来進行しなかったハロゲンダンスを実現した。

1-4　本研究の目的と構成

本研究では，様々な置換様式をもつ多置換芳香族化合物とその構造異性体を対応するブロモアレーンから網羅的に合成するため，従来の反応条件では進行しなかったブロモアレーンのハロゲンダンスを検討し，基質一般性の向上をめざした。従来の反応条件では分解反応が進行するブロモアゾール（第二章），アライン形成が進行するブロモベンゼン（第三章），ブロモ基の転位が遅いブロモピリジンのハロゲンダンス（第四章，第五章）の反応条件をそれぞれ新たに見出し，一般性の高いハロゲンダンスの開発に成功したことを報告する。

第二章：Inoue, K.; Feng, Y.; Mori, A.; Okano, K. “Snapshot” Trapping of Multiple Transient Azolyllithiums in Batch. *Chem. Eur. J.* **2021**, *27*, 10267–10273.

第二章では，医薬品や機能性材料のビルディングブロックとなるブロモアゾールのハロゲンダンスを達成した。チアゾールから脱プロトン的に発生させた有機リチウムは短寿命であり，ハロゲンダンスと競合して分解反応が進行した。そこで，ジアミンを配位させた塩化亜鉛で有機リチウムを選択的に捕捉する in situ トランスメタル化を開発し，今まで不安定で利用されたことのなかったハロゲンダンス前後の有機リチウムを有機亜鉛反応剤に変換することで，それぞれに対応する構造異性体を網羅的に供給した。開発した手法は，チアゾールだけでなく，イミダゾール，オキサゾールにも適用でき，ハロゲンダンスにおけるブロモアゾールの基質一般性を大幅に向上させた。さらに，非ステロイド抗炎症薬として知られるオキサゾールまたはチアゾール誘導体と，それらの構造異性体の短段階合成に成功した。

第三章：Inoue, K.; Mori, A.; Okano, K. Formal Halogen Transfer of Bromoarenes via Stepwise Reactions. *Org. Lett.* **2023**, *25*, 6693–6698.

第三章では，アライン形成が進行するベンゼンのハロゲンダンスを達成した。ベンゼンから脱プロトン的に発生させた有機リチウムは短寿命であり，アラインが形成し，分解反応が進行した。ベンザイン形成を抑制しながらハロゲンダンスを達成するために，二段階の段階的ハロゲンダンスを考案した。第二章で報告した in situ トランスメタル化によって有機リチウムから発生させた有機亜鉛反応剤を臭素化し，その後エチルグリニャール反応剤を用いた選択的マグネシオ化と求電子剤による捕捉によって，二段階の形式的なハロゲンダンスを達成した。段階的ハロゲンダンスは，芳香環として最も一般的なベンゼンだけでなく，ヘテロ芳香環として合成化学上有用なピリジン，キノリン，ピリミジン，チアゾールにも適用でき，今まで報告されたなかで最も一般性の高いハロゲンダンスの反応条件を確立できた。

第四章：Inoue, K.; Hirano, K.; Fujioka, S.; Uchiyama, M.; Mori, A.; Okano, K. Lithium Aryltrifluoroborate as a Catalyst for Halogen Transfer. *ACS Catal.* **2023**, *13*, 3788–3793.

第四章では，ブロモ基の転位が遅いブロモピリジンのハロゲンダンスを触媒的に加速させた。条件検討の結果，三フッ化ホウ素がハロゲンダンスを触媒的に促進することを新たに見出した。実験的，計算的アプローチから，本反応の真の触媒が，有機リチウムと三フッ化ホウ素が反応し発生した，ピリジンの炭素原子に三フッ化ホウ素が導入されたアート型ホウ素錯体（トリフルオロボラート）であることを明らかにした。通常，トリフルオロボラートは化学量論量の反応剤として，クロスカップリング反応や光レドックス反応に利用されるが，今回，ブロモ基の移動反応を触媒的に加速させる有機分子触媒としての新たな可能性を見出した。

第五章：Inoue, K.; Mori, A.; Okano, K. Ultrafast Halogen Dance Reactions Enabled by Catalytic Potassium Hexamethyldisilazide. *ChemRxiv* **2023**, in press, DOI: 10.26434/chemrxiv-2023-n89mz.

第五章では，第四章で報告したトリフルオロボラートに加えて，通常，カリウムアミド塩基として利用される KHMDS が，触媒としてハロゲンダンスを大幅に加速させることを見出した。KHMDS 触媒は非常に高活性で，触媒量を 10 mol%とした場合，反応時間を 1 分にまで短縮でき，従来報告されたいずれの触媒よりも触媒活性が優れているとわかった。KHMDS を触媒とするハロゲンダンスは，ピリジン，イミダゾール，チオフェン，フラン，ベンゼンなどの幅広いブロモアレーンに適用でき，様々な置換様式をもつブロモアレーンの網羅的な供給を可能とした。

第六章では，第二章から第五章の内容を総括し，本研究の応用先について議論する。

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第二章

ハロゲンダンスにおける
短寿命アゾリルリチウムの選択的捕捉

2-1　緒言

医薬品の重要骨格として知られている多置換アゾールの優れた合成前駆体として，ブロモアゾールのハロゲンダンスをめざした。変換が容易なブロモ基を二つもつジブロモチアゾールを基質とし，脱プロトン的に発生させた有機リチウムのハロゲンダンスを検討したが，分解反応が進行した。そこで，有機リチウムの捕捉剤として，塩化亜鉛ジアミンのジアミン配位子を適切に選択すると，ハロゲンダンス前後で発生する複数の有機リチウムを有機亜鉛反応剤として選択的に捕捉でき，ブロモ基の置換様式が異なる複数の構造異性体を合成できた。

2-2　アゾールの脱プロトン的官能基化

2-2-1　アゾールの化学修飾

アゾールは，1 つ以上のピリジン窒素(–N=)に加えて，ヘテロ原子として，硫黄(–S–)，ピロール窒素(–NR–)，酸素(–O–)などを含む 5 員環ヘテロ芳香環である(Figure 2−1)。窒素原子の位置によって 1,3-アゾールと 1,2-アゾールに分類されるが，本研究は，より一般的な 1,3-アゾールを対象とする。多置換アゾールは，ビタミン B1，高血圧治療薬として知られているカンデサルタン，カルシウムイオノフォアとして機能するカルシマイシンとして利用されるため，重要な化合物である (Figure 2−2)。したがって，多置換アゾールの簡便な合成法の開発が求められている。

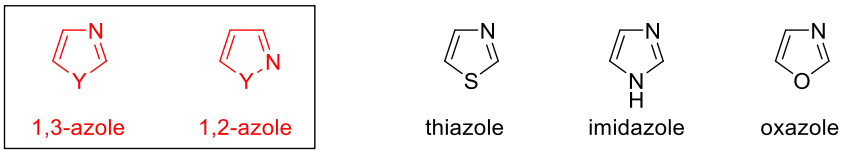


Figure 2–1. Classification of azoles

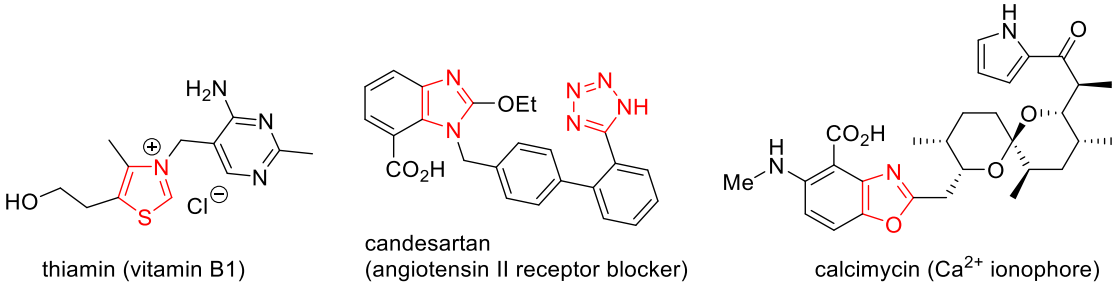


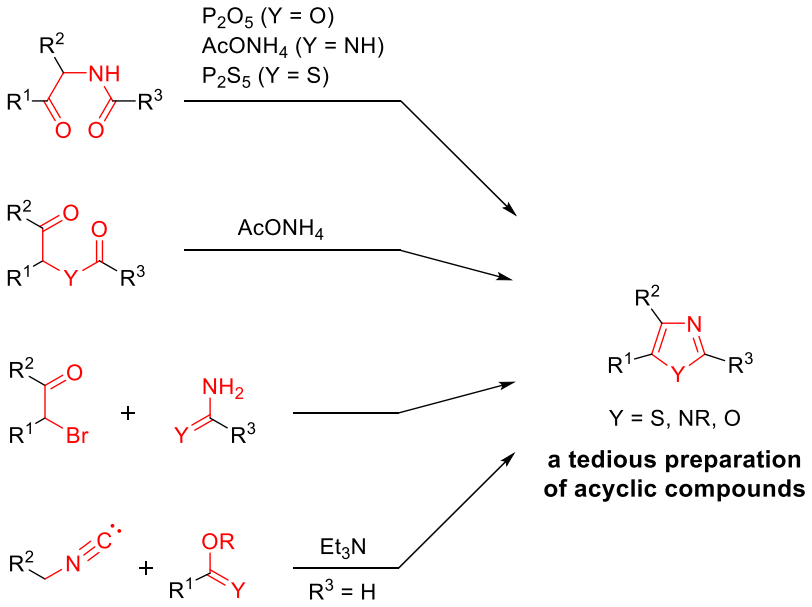
Figure 2–2. Application of the multiply substituted azoles

多置換アゾールを合成する手法として，(1)官能基化された鎖状化合物の環化反応，(2)アゾール環の修飾の二つが挙げられる。

(1)　官能基化された鎖状化合物の環化反応

アゾールの合成戦略として，鎖状化合物の脱水縮合が知られている（Scheme 2–1)[29]。一分子の鎖状化合物からアゾール環を合成する反応として，P_2O_5 や酢酸アンモニウム，または P_2S_5 などを用いた鎖状アミドの脱水縮合，酢酸アンモニウムを用いた鎖状ケトンの脱水縮合が挙げられる。また，二分子の鎖状化合物からアゾールを合成する反応として，ブロモケトンとアミドの脱水縮合，イソニトリルとエステル誘導体の環化反応が挙げられる。本戦略は，置換基を望みの位置に導入できる利点があるものの，多くの置換基をもつ複雑な鎖状化合物の合成に工程数を要する欠点がある。

Scheme 2–1.　Construction of an Azole Ring

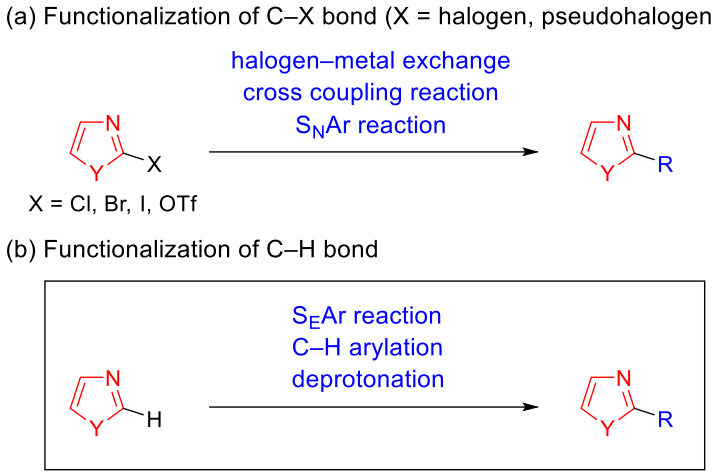


(2)　アゾール環の修飾

多置換アゾールのもう一つの合成戦略として，アゾール環へ置換基を直接導入する手法が挙げられる。本戦略は，鎖状化合物の脱水縮合（Scheme 2–1)と比較し，市販のアゾールを出発化合物として利用できる点が優れている。一般に，アゾールに置換基を導入する際，(a) C–X 結合（X＝ ハロゲン，擬ハロゲン)を足

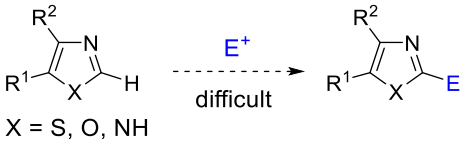
がかりに官能基を導入するが[30]，(b) C–H 結合を直接官能基化する反応と比較し，ハロゲンを失うため，原子効率が低い (Scheme 2–2)[31]。したがって，本研究では，原子効率に優れたアゾール修飾法として，(b) C–H 結合を直接官能基化する反応に着目した。

Scheme 2–2. The Concept of Direct Functionalization of Azoles



(b) アゾールの C–H 結合を修飾する手法の一つに，芳香族求電子置換反応 (S_EAr)が挙げられる。しかし，アゾールは，電子不足芳香環に位置づけられるため，芳香族求電子置換反応を用いた求電子剤の導入は有効ではない (Scheme 2–3)[29c]。

Scheme 2–3. Electrophilic Aromatic Substitution (S_EAr) of Azoles

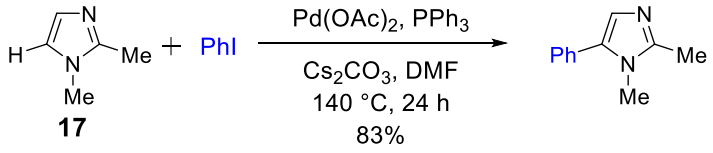


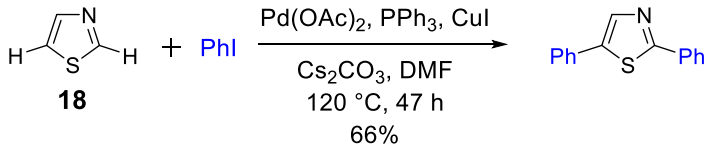
近年，遷移金属触媒を利用した，C–H アリール化の発展によって，アゾールへ直接芳香環を導入することが可能となった (Scheme 2–4)。1997 年，野村，三浦らは，イミダゾール **17**，チアゾール(**18**)，ベンゾオキサゾール(**19**)を基質として，触媒量の酢酸パラジウムとトリフェニルホスフィン存在下，それぞれの基質の C–H 結合を切断し，フェニル基を導入している (Scheme 2–4a)[32]。また，森らは，チアゾール **20** に $PdCl_2$(dppb)と酢酸銀を作用させ，ホモカップリング体 **21**

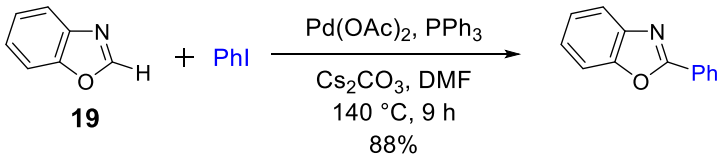
を収率 83%で得ている (Scheme 2–4b)[33]。伊丹らは，ベンゾオキサゾール(**19**)に対し，フェノール誘導体 **22** とニッケル触媒を作用させると，ナフチル基が導入できることを明らかにした (Scheme 2–4c)[34]。C–H アリール化は，C–H 結合を切断し，芳香環を直接導入できるため，原子効率に優れているが，導入可能な置換基が限られる点が欠点である。その他，遷移金属触媒を用いた C–H アリール化については，Fu，Lautens，Fagnou，Catellani，You らにより優れた総説が報告されている[35]。

Scheme 2–4. Transition Metal-Catalyzed C–H Arylation

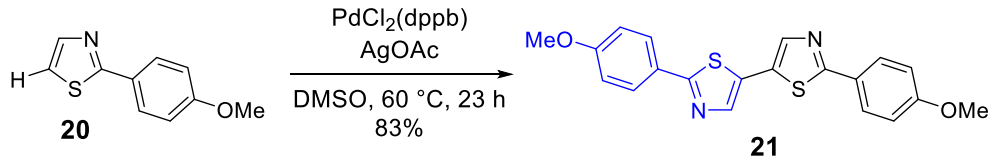
(a) Transition metal-catalyzed C–H arylation (Nomura)



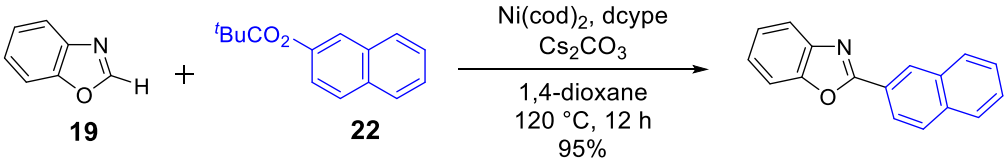




(b) Palladium catalyzed C–H homocoupling of the thiazole (Mori)



(c) Nickel catalyzed C–H/C–O coupling of azoles (Itami)

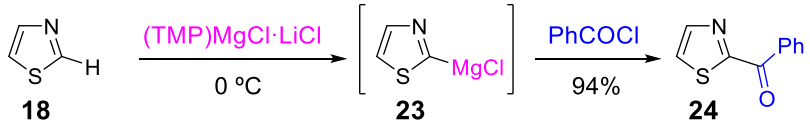


芳香環だけでなく，幅広い置換基を導入する手法として，脱プロトン反応を経由した求電子剤の導入が挙げられる (Scheme 2–5)。Knochel らは，チアゾール(**18**)

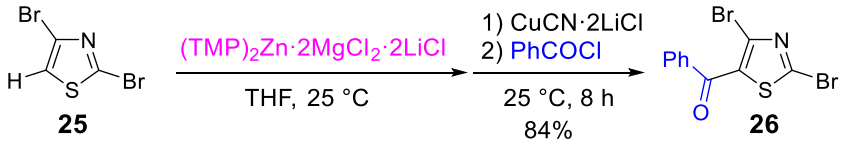
を基質とし，マグネシウムアミド塩基として(TMP)MgCl·LiCl を作用させ，発生させた有機マグネシウム反応剤 **23** を，塩化ベンゾイルで処理し，2-ベンゾイルチアゾール(**24**)を収率 94%で合成している (Scheme 2–5a)[36]。また，ジブロモチアゾール **25** に，亜鉛アミド塩基として，$(TMP)_2Zn·2MgCl_2·2LiCl$ を作用させ，塩化ベンゾイルと反応させることで，5-ベンゾイルチアゾール **26** を収率 84%で得ている (Scheme 2–5b)[37]。塩基として温和な亜鉛アミド塩基を利用することで，後の変換に有用な足がかりとなるブロモ基を残したまま，C–H 結合の官能基化が可能となった。また, Mongin らは, ベンゾチアゾール(**27**)に, 塩化亜鉛 TMEDA と LiTMP の混合物を作用させることで，ヨウ素化体 **28** を収率 67%で得ている (Scheme 2–5c)[38]。以上のように，脱プロトン的な官能基化は，アゾール環へ幅広い求電子剤を位置選択的に導入できる。したがって，著者は，脱プロトン反応を経由するアゾールの修飾に着目した。なお, マグネシウムアミドおよび亜鉛アミド塩基を利用した C–H 結合の修飾については, Knochel, 根東, Mulvey, Mongin, 内山らの優れた報告および総説が知られている [10d,39]。

Scheme 2–5. Deprotonation and Electrophilic Trapping of Azoles

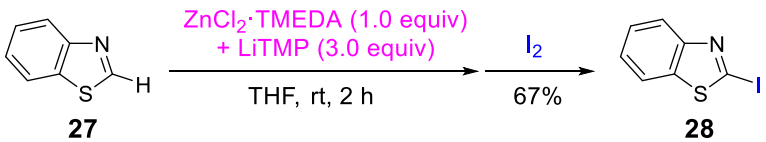
(a) Deprotonation with magnesium amide base (Knochel)



(b) Deprotozincation with zinc amide base (Knochel)



(c) In situ transmetalation (Mongin)



2-2-2　短寿命有機リチウム

一般に，脱プロトン反応によって発生する活性種として，有機リチウム，有機マグネシウム反応剤，有機亜鉛反応剤が挙げられる (Figure 2–3)[40]。有機リチウムは，有機マグネシウム反応剤，有機亜鉛反応剤と比較し，反応性が高く，様々な化学結合を容易に構築できるため，優れた合成前駆体である[10a–c,41]。その反面，望まない異性化反応や分解反応を引き起こすことがある。

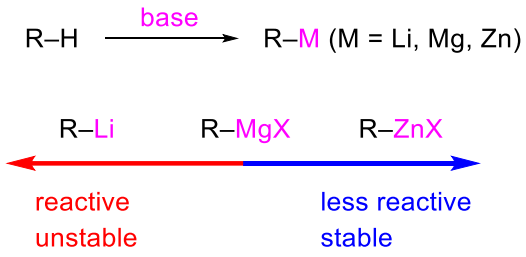
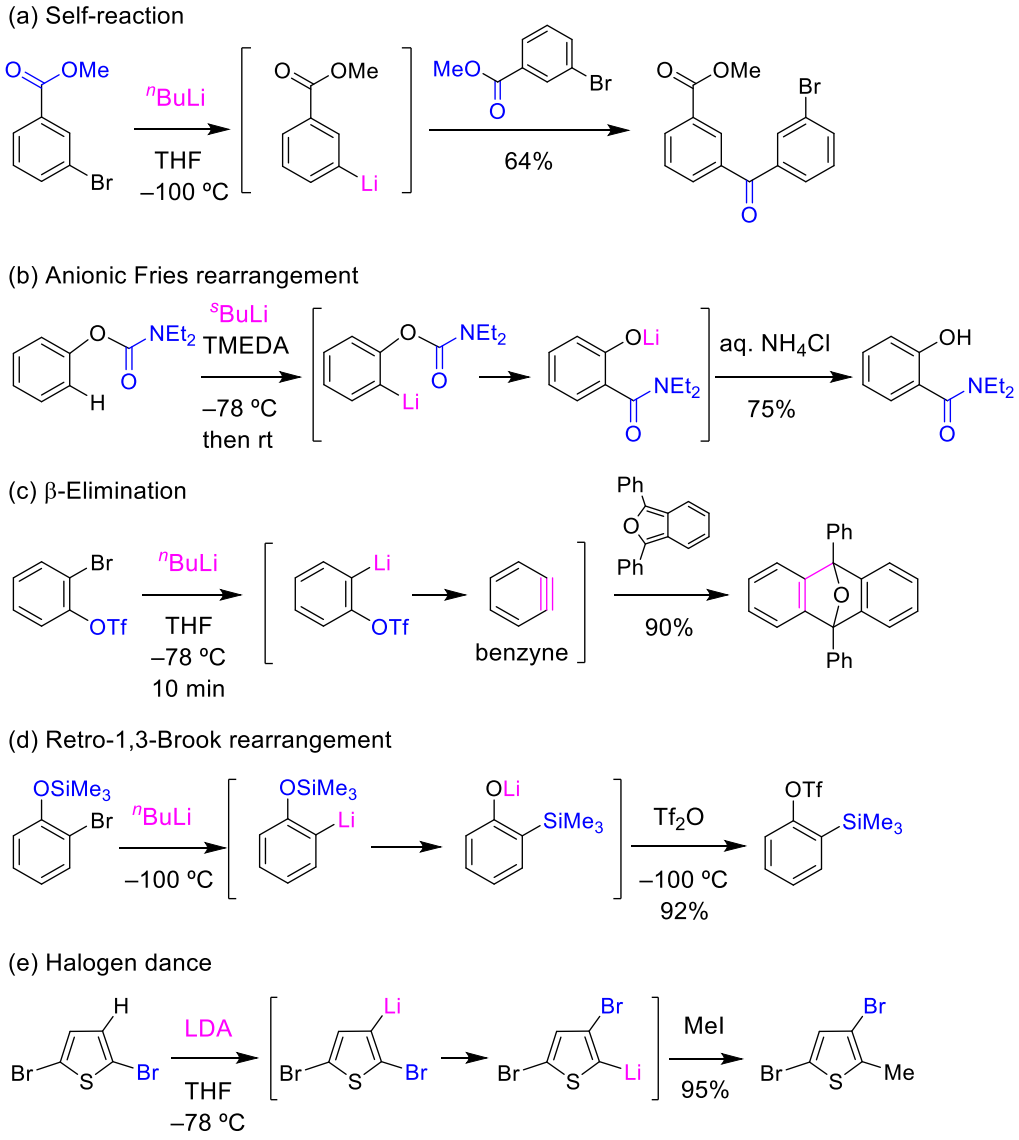


Figure 2–3. Organometallic species generated through deprotonation

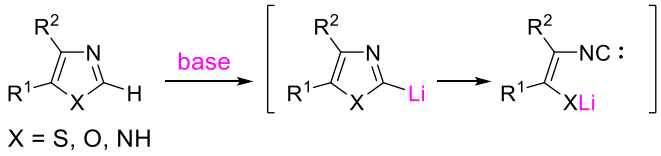
以下，短寿命有機リチウムの反応を分類した (Scheme 2–6)。すなわち，(a) 自己反応，(b) Fries 転位，(c) β 脱離，(d) Brook 転位，(e) ハロゲンダンスが挙げられる[42]。

Scheme 2–6. Representative Reactions of Reactive Organolithiums



上記の反応は，有機リチウムの高い反応性に起因するため，–78 °C 以下の低温や，反応性の低い有機マグネシウム反応剤や有機亜鉛反応剤の利用により，抑制できる場合がある[2c,43]。なお，短寿命有機リチウムの反応およびその抑制方法の詳細は，著者らが総説[15h]に記載した。さらに，アゾール由来の有機リチウムも同様に，官能基許容性が低く，開環反応や分解反応が進行することが報告されている (Scheme 2–7)[44]。

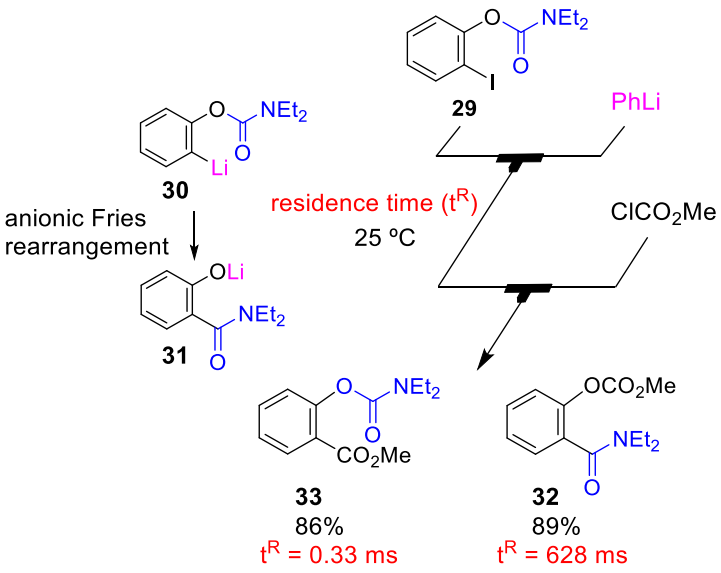
Scheme 2–7. A Ring Opening Reaction of Azolyllithiums



以上の報告より，従来，利用が困難であったアゾール由来の短寿命有機リチウムの官能基許容性を向上させ，副反応を抑制できれば，アゾール環へ幅広い置換基を直接的に導入できると考えた。

短寿命有機リチウムの官能基許容性を向上させる手法の一つに，直径がマイクロメートルオーダーの微細な流路を利用し，反応時間をミリ秒単位で精密に制御する，フローマイクロリアクターを用いたフロー合成が知られている[4e,45]。吉田らは，カルバミン酸エステル **29** にフェニルリチウムを作用させると，短寿命有機リチウム **30** がフェノキシド **31** へ Fries 転位し，滞留時間 628 ms 後にクロロギ酸メチルで処理すると，アミド **32** を収率 89%で得たことを報告した (Scheme 2–8)[46]。一方，滞留時間を 0.33 ms とすると，Fries 転位が進行する前の短寿命有機リチウム **30** 由来の生成物 **33** を収率 86%で得ている。現在，フローマイクロリアクターは，短寿命有機リチウムを利用する優れた手法であるが[47]，

Scheme 2–8. Selective Trapping of the Two Organolithiums in Anionic Fries Rearrangement

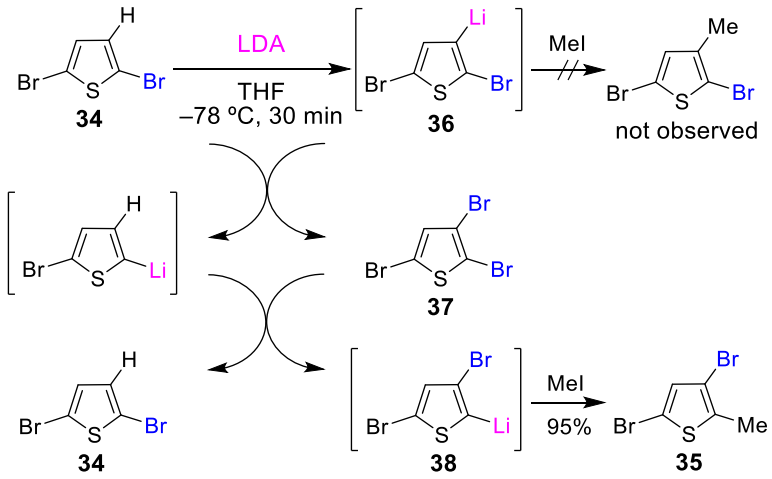


有機リチウムの発生法として，脱プロトン反応[48]よりも，ハロゲン–リチウム交換の報告が多い[15h,45]。したがって，本研究では，実験操作が簡便なバッチ反応において，脱プロトン反応によって発生した短寿命有機リチウムの利用をめざした。

2-2-3　ハロゲンダンス

合成化学上有用な短寿命有機リチウムの反応として，ハロゲンダンスがあげられる[15] (詳細は，第一章，1–3)。加納らは，ジブロモチオフェン **34** に LDA を作用させ，ヨウ化メチルで処理すると，3,5-ジブロモチオフェン(**35**)が収率 95% で生成したと報告している (Scheme 2–9)[42e]。この結果は，発生した有機リチウム **36** がチオフェン **34** とハロゲン–リチウム交換し，トリブロモ体 **37** が発生した後，二回目のハロゲン–リチウム交換によって，熱力学的に最安定な有機リチウム **38** が生成したためと考えられる。

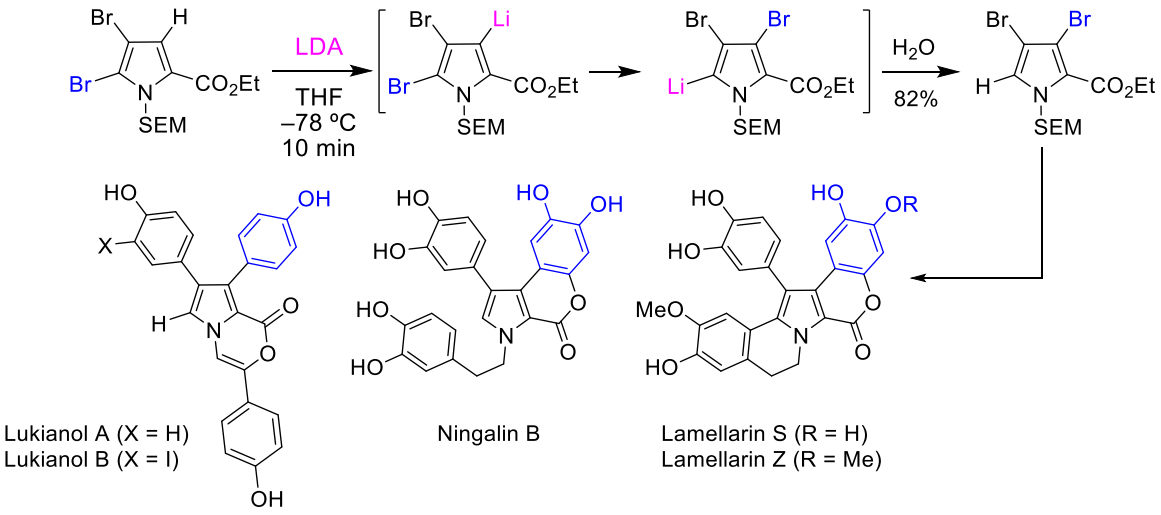
Scheme 2–9.　Halogen Dance of 2,5-Dibromothiophene



当研究室では，ブロモ基の移動に伴い置換様式を変換できるハロゲンダンスを利用し，チオフェン，フランの位置選択的な官能基化に成功している[19e,f,26c,d,49]。また，ピロールのハロゲンダンスを利用し，ラメラリン類の網羅的合成[50]にも成功している (Scheme 2–10)。最近では，ピロールのハロゲンダンスを利用した脂質異常症治療薬として知られるアトルバスタチンの形式合成[51]，ピロールのハロゲンダンスの抑制を鍵としたラメラリン U とラメラリン A3[52]，ディクティオデンドリン B[53]の全合成も報告している。ハロゲンダンスは，後の変換が容易なブ

ロモ基を残したまま，複数の有機リチウムを経由できるため，置換様式が異なる複数の構造異性体を自在に合成できる可能性がある。しかし，反応速度が非常に速く，今まで熱力学的に最安定な有機リチウム一種類しか利用されてこなかった[15,42e]。そこで，著者は，ブロモアゾールのハロゲンダンス前後で生成する短寿命有機リチウムをそれぞれ選択的に利用できれば，複数の構造異性体を同一の出発化合物から合成できると考えた。

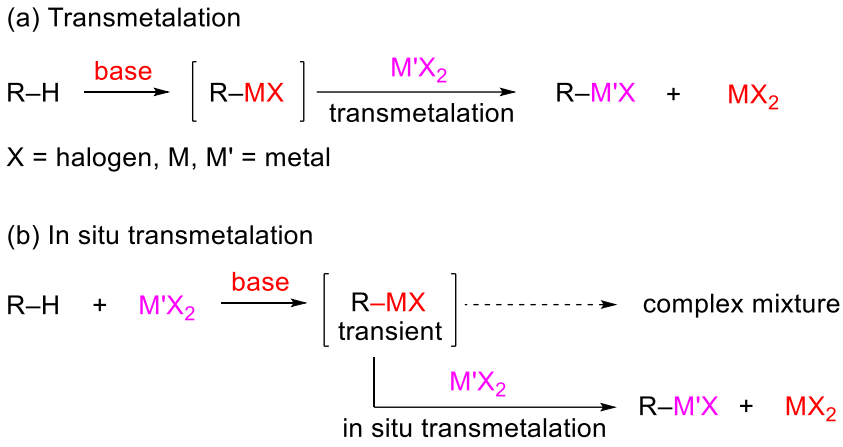
Scheme 2–10. Total Syntheses of Lamellarins and Their Congeners



2-2-4 In situ トランスメタル化

短寿命有機リチウムを利用する手法として，in situ トランスメタル化が挙げられる (Scheme 2–11)。通常，トランスメタル化は，脱プロトン的に発生させた有機金属 R–MX に対して，金属塩 $M'X_2$ を後から加えることで，金属原子の交換が進行し，熱力学的に安定な有機金属 R–M'X が生成する反応である (Scheme 2–11a)。一方，in situ トランスメタル化は，あらかじめ金属塩 $M'X_2$ を加えておくことで，発生した有機金属 R–MX を反応系中でただちに金属交換し，より安定な有機金属 R–M'X へ変換する反応である[54] (Scheme 2–11b)。通常のトランスメタル化とは異なり，あらかじめ金属塩 $M'X_2$ を加えておき，短寿命有機金属 R–MX をただちに金属交換するため，初めに発生した短寿命有機金属 R–MX 由来の副反応[15h]を防ぐことができる。本反応は，短寿命有機金属 R–MX の望まない

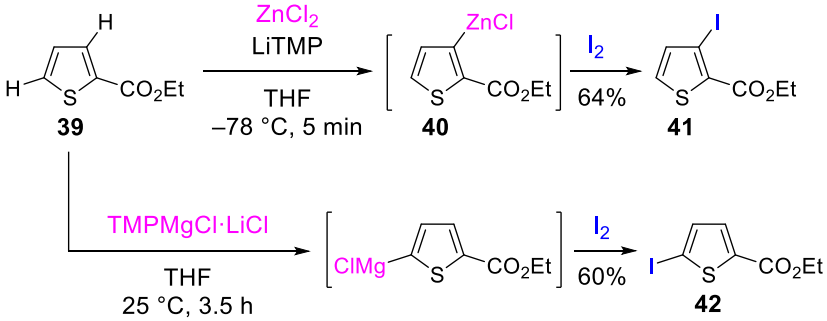
Scheme 2–11. The Concept of In Situ Transmetalation



分解反応を抑制できることに加えて，脱プロトン反応が不利な場合でも化学平衡を生成物に傾け，基質 R–H の脱プロトン反応を促進できる利点がある。

Knochel らは，チオフェン **39** に塩化亜鉛を共存させた状態で，リチウムアミド塩基として LiTMP を作用させると，有機亜鉛反応剤 **40** が発生し，ヨウ素で処理することで，チオフェン **41** を収率 64%で合成している (Scheme 2–12)[55]。一方，マグネシウムアミド塩基として TMPMgCl·LiCl を作用させると，ヨウ素化体 **42** を収率 60%で得ている。

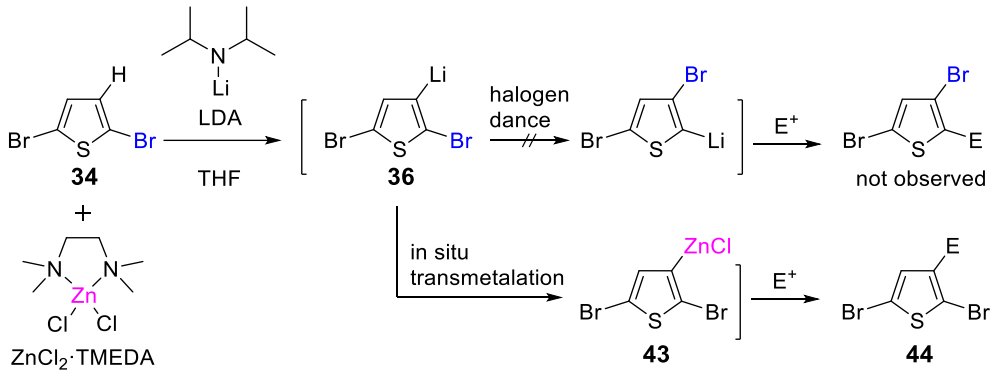
Scheme 2–12. Selective Formation of Two Organometallic Species by In Situ Transmetalation and Deprotonation with TMPMgCl·LiCl



当研究室の林は，チオフェン **34** を基質とし，塩化亜鉛 TMEDA[56]を共存させた状態で，LDA を作用させると，発生したチエニルリチウム **36** をただちに有機亜鉛反応剤 **43** へ誘導し，チオフェン **44** を得ている (Scheme 2–13)[57]。本反応に

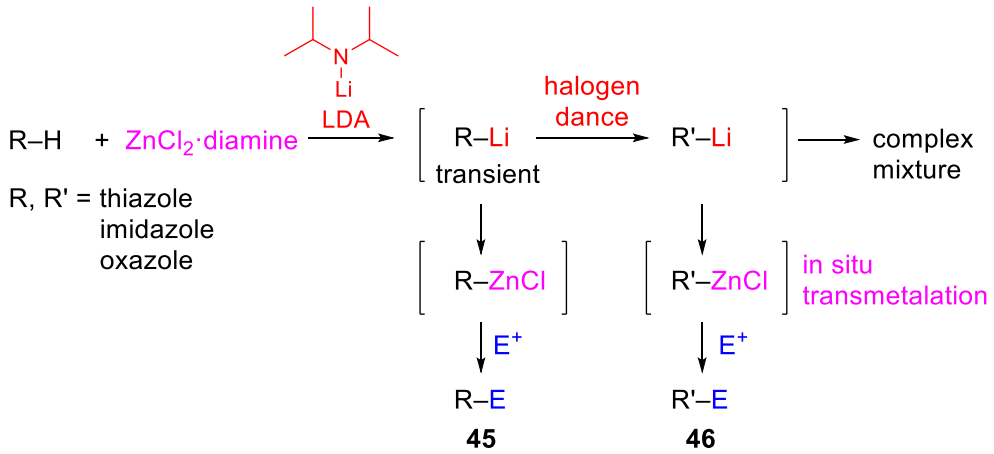
より，ハロゲンダンスにおける熱力学的に不安定な有機リチウム **36** の利用[58]に初めて成功した。林は，塩化亜鉛にジアミンを配位させることで，塩化亜鉛とLDA の望まないトランスメタル化を抑制できたと報告している。また，当研究室の平井は，同様の条件を用いて，フランから発生させた短寿命有機リチウムの選択的な捕捉に成功している[59]。

Scheme 2–13. Selective Trapping of the Transient Thienyllithium



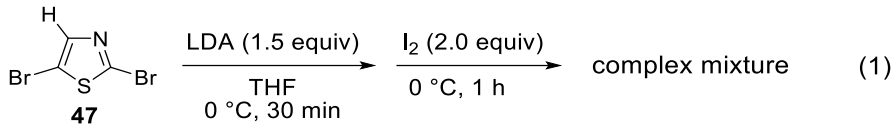
以上の研究背景から，アゾールのハロゲンダンスにおける複数の短寿命有機リチウムに対して，in situ トランスメタル化を利用し，複数の構造異性体 **45** と **46** の合成をめざした (Scheme 2–14)。今回，チアゾール，イミダゾール，オキサゾールを基質とし，in situ トランスメタル化の最適条件を検討した。

Scheme 2–14. This Work: Syntheses of Multiple Bromoazoles by Using Halogen Dance Reaction and In Situ Transmetalation



2–3　チアゾリルリチウムの選択的捕捉

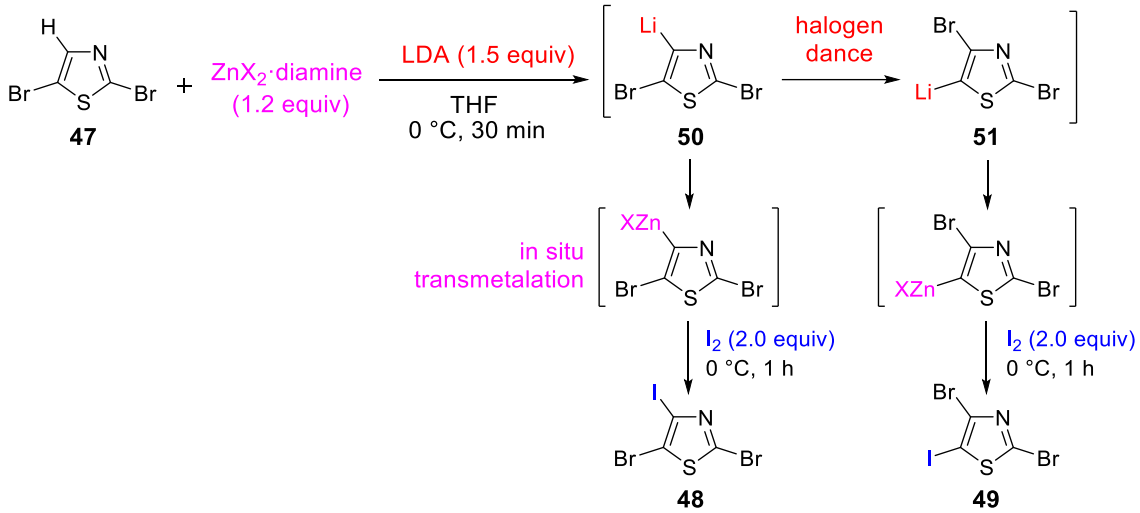
まず，後の変換が容易なブロモ基を二つもつ 2,5-ジブロモチアゾール(**47**)を基質とし，脱プロトン的リチオ化を経由し，多置換チアゾールの合成をめざした (Eq. 1)。チアゾール **47** に，塩基として LDA を 0 °C で作用させ，ヨウ素で処理した結果，原料は消失したものの，ヨウ素化体は全く得られず，複雑な混合物の生成を得た。この結果から，ジブロモチアゾール **47** 由来の有機リチウムが不安定であるとわかった。



そこで，in situ トランスメタル化によって，発生した短寿命チアゾリルリチウムの分解反応を抑制することを考えた。Knochel らの報告[55]を参考に，ジブロモチアゾール **47** に塩化亜鉛を共存させた状態で，LDA を作用させ，ヨウ素で処理した (Table 2–1)。その結果，4 位ヨウ素化体 **48** を収率 13%，5 位ヨウ素化体 **49** を収率 57%で得た (entry 1)。なお，4 位ヨウ素化体 **48** と 5 位ヨウ素化体 **49** は，水素核をもたないため，^{1}H NMR では定量できず，カラムクロマトグラフィーでも分離できないため，それぞれの収率は，定量 ^{13}C NMR (逆ゲート付きプロトンデカップリング法[60])を用いて計算した。得られた二種類のヨウ素化体 **48** と **49** の構造は，X 線結晶構造解析によって決定した[61]。次に，ハロゲン化亜鉛ジアミンによる in situ トランスメタル化を検討した (Figure 2–4)[62]。まず，塩化亜鉛 TMEDA を利用すると，4 位ヨウ素化体 **48** を収率 89%で選択的に得た (entry 2)。この結果から，塩化亜鉛に TMEDA が配位すると，トランスメタル化が速くなり，有機リチウム **50** 由来の 4 位ヨウ素化体 **48** のみが得られたと考えられる。一方，臭化亜鉛 TMEDA やヨウ化亜鉛 TMEDA を利用すると，有機リチウム **51** 由来の 5 位ヨウ素化体 **49** が主生成物として確認された (entries 3 and 4)。この結果より，塩化亜鉛 TMEDA は，臭化亜鉛 TMEDA やヨウ化亜鉛 TMEDA よりもトランスメタル化が速いことがわかった。次に，5 位ヨウ素化体 **49** の合成に最適なハロゲン化亜鉛ジアミンを検討した。塩化亜鉛ジアミンとして，TMEDA のエチレン架橋をシクロヘキサンに代えた塩化亜鉛 TMCDA を利用すると，4 位ヨウ素化体 **48** を収率 44%，5 位ヨウ素化体 **49** を収率 30%で得た (entry 5)。ま

た，TMEDA のメチル基をエチル基に代えた塩化亜鉛 TEEDA を用いた場合，5 位ヨウ素化体 **49** の選択性が向上した (entry 6)。この結果から，かさ高いジアミン配位子をもつ塩化亜鉛は，トランスメタル化の速度が低下することが

Table 2–1. Effects of ZnX_2·diamine on the In Situ Zincation of Thiazolyllithiums[a]



entry	ZnX_2·diamine	**48** (%)[b]	**49** (%)[b]
1[c]	$ZnCl_2$	13	57
2	$ZnCl_2$·TMEDA	89[d] (91[d,f])	–[e]
3	$ZnBr_2$·TMEDA	23	61
4[g]	ZnI_2·TMEDA	4	65
5	$ZnCl_2$·TMCDA	44	30
6	$ZnCl_2$·TEEDA	13	54
7	$ZnCl_2$·BuMeEDA	12	71
8	$ZnCl_2$·TMPDA	–[e]	72[d] (87[d,h])
9	$ZnCl_2$·DMP	16	69
10	$ZnBr_2$·TMEDA	–[e]	39
11[g]	ZnI_2·TMEDA	5	78

[a]Reaction conditions: 2,5-dibromothiazole (**47**; 1.0 equiv, 0.30 mmol), ZnX_2·diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), 0 °C, 30 min, then iodine (2.0 equiv, 0.60 mmol), 0 °C, 1 h. [b]The yield was determined by a quantitative ^{13}C NMR technique. [c]Recovery of 3% of **47**. [d]Isolated yield. [e]Not observed in the ^{13}C NMR spectrum of the crude product. [f]The reaction was performed using 10 mmol of 2,5-dibromothiazole (**47**). [g]The products involved a minute amount (< 10%) of an inseparable byproduct. [h]The reaction was performed using 7.5 mmol of 2,5-dibromothiazole (**47**).

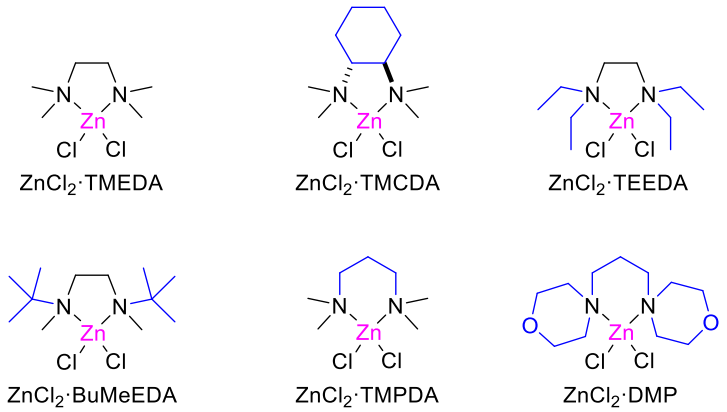


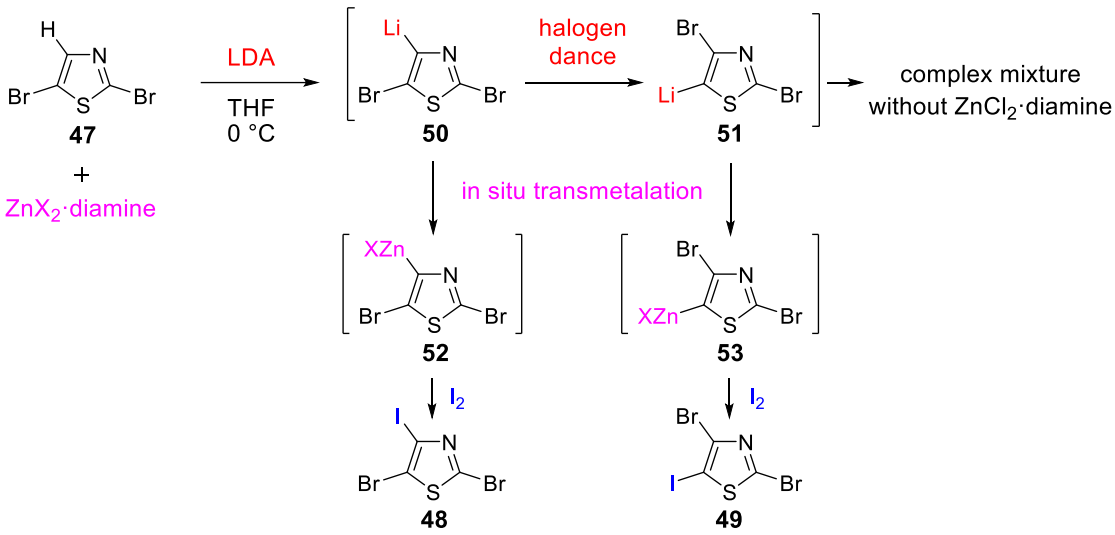
Figure 2–4. Structures of zinc halide diamine complexes

わかった。よりかさ高いエチレンジアミンをもつ塩化亜鉛 BuMeEDA を加えると，4 位ヨウ素化体 **48** が収率 12%で観察されたものの，5 位ヨウ素化体 **49** を収率 71%で得た (entry 7)。検討の結果，TMEDA より架橋炭素が一つだけ多い TMPDA をもつ塩化亜鉛 TMPDA を利用すると，5 位ヨウ素化体 **49** を収率 72%で選択的に得た (entry 8)。また，モルホリンをもつジアミン配位子として DMP を選択すると，4 位ヨウ素化体 **48** と 5 位ヨウ素化体 **49** の混合物(1:4)が生成した (entry 9)。なお，臭化亜鉛 TMPDA を用いた場合，収率は低下したものの，塩化亜鉛 TMPDA と同様に，5 位ヨウ素化体 **49** を選択的に得た (entry 10)。一方，ヨウ化亜鉛 TMPDA を用いると，5 位ヨウ素化体 **49** と分離不能な副生成物の混合物が生成した (entry 11)。二種類のヨウ素化体 **48** および **49** を選択的に合成するそれぞれの最適条件は，グラムスケール合成にも適用できた (entries 2 and 8)。

短寿命チアゾリルリチウムの in situ トランスメタル化における，ハロゲン化亜鉛ジアミンの効果を考察する (Scheme 2–15)。塩化亜鉛 TMEDA を用いると，ヨウ素化体 **48** を選択的に与えたことから，はじめに発生した有機リチウム **50** をただちに in situ トランスメタル化し，有機亜鉛反応剤 **52** を生成させるためには，配位子として TMEDA が必要であるとわかった。この結果は，TMEDA が塩化亜鉛に配位することで，塩化亜鉛同士の会合状態が解離し，有機リチウムのトランスメタル化が速くなったためと考えた。また，ジアミン配位子をかさ高くすることで，5 位ヨウ素化体 **49** の選択性が向上したことから，かさ高いジアミン配位子によって，有機リチウム **50** の捕捉速度が遅くなり，相対的にハロゲンダンスが優先したため，有機リチウム **51** を in situ トランスメタル化できたと考えた。すなわち，塩化亜鉛 TMPDA は，はじめに発生した有機リチウム **50** を捕捉

しない一方で，ハロゲンダンス後の有機リチウム **51** の分解反応を抑制し，有機亜鉛反応剤 **53** を与える，最適なかさ高さをもつことが明らかとなった。

Scheme 2–15. Rationale for the Selective Trapping of Transient Thiazolyllithiums



なお，発生した有機リチウム **50** と **51** の熱力学的な安定性を比較するため，DFT 計算によって p*K*a を算出したところ（詳細は，第二章，2-8-6），チアゾール **47** の 4 位プロトンの p*K*a は 33.7，チアゾール **25** の 5 位プロトンの p*K*a は 26.3 であった (Figure 2–5)。この結果から，チアゾール **47** に由来する有機リチウム **50** が，ハロゲンダンスによって熱力学的に最安定なチアゾール **25** 由来のチアゾリルリチウム **51** へと変換されることがわかった。

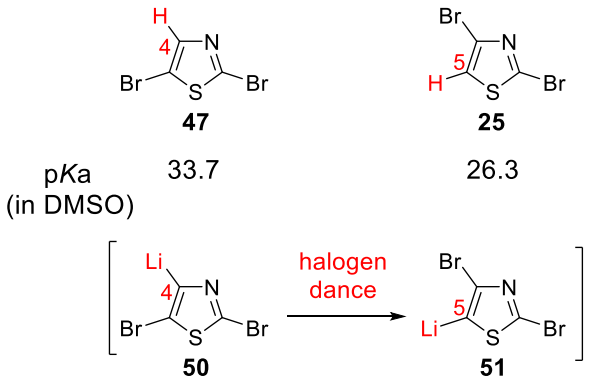
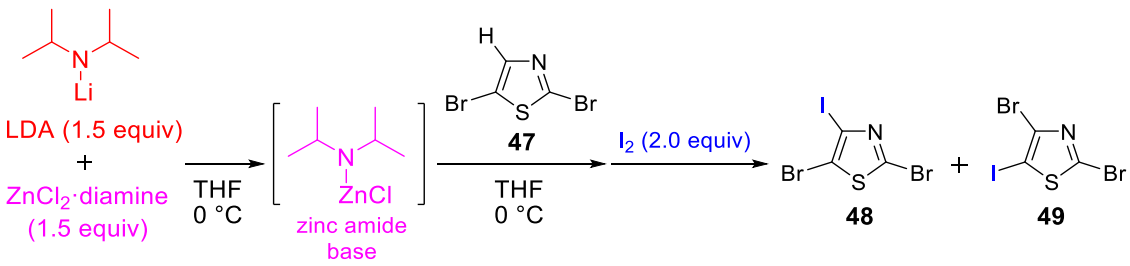


Figure 2–5. The p*K*a values of dibromothiazoles

次に，LDA による脱プロトンによって発生した有機リチウム **50** が，ハロゲンダンスしていることを確かめた (Table 2–2)。あらかじめ，LDA と塩化亜鉛ジアミンから発生させた亜鉛アミド塩基に，ジブロモチアゾール **47** を作用させ，ヨウ素で処理した。その結果，塩化亜鉛 TMEDA，塩化亜鉛 TMPDA のどちらを利用した場合も，原料を回収した (entries 1 and 2)。この結果から，チアゾール **47** は LDA によって脱プロトンされており，チアゾリルリチウム **50** が発生した後に，ハロゲンダンスが進行するとわかった。なお，少量のヨウ素化体が得られた結果から，亜鉛アミド塩基を発生させた際，未反応の LDA と塩化亜鉛ジアミンが反応系中に残存していたことが考えられる。

Table 2–2. Deprotonation of Dibromothiazole with Zinc Amide Base



entry	$ZnCl_2$·diamine	**47** (%)[a]	**48** (%)[b]	**49** (%)[b]
1	$ZnCl_2$·TMPDA	59	trace	trace
2	$ZnCl_2$·TMEDA	62	trace	trace

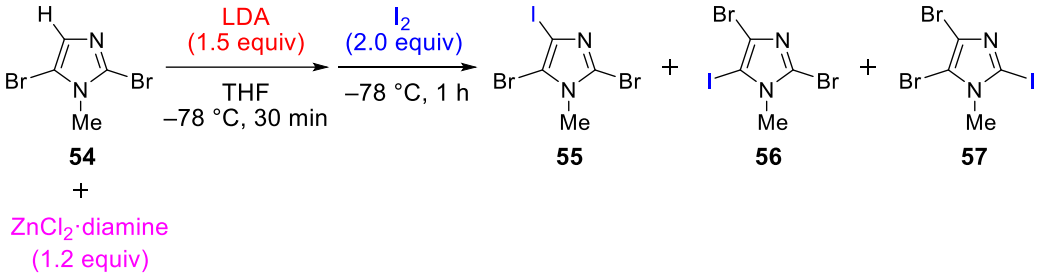
[a]The yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [b]A minute amount (< 5%) of thiazole **48** and **49** were determined by ^{13}C NMR after purification of a crude product by column chromatography.

本節では，ハロゲンダンスにおける二種類の短寿命チアゾリルリチウムを，塩化亜鉛ジアミンによって選択的に in situ トランスメタル化し，二種類の構造異性体を合成した。また，ジアミン配位子の選択によって，トランスメタル化の速度を精密に制御できるという新たな知見を得た。なお，DFT 計算によって，チアゾールのハロゲンダンスが熱力学的に安定な有機リチウムが生成する方向に進行することが確認できた。

2-4　イミダゾリルリチウムの選択的捕捉

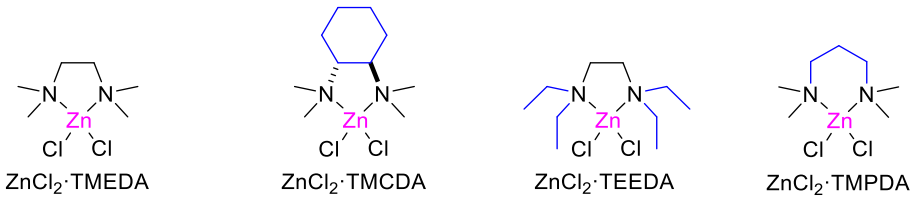
次に，2,5-ジブロモイミダゾール **54** を基質とし，ハロゲンダンスで発生する複数のイミダゾリルリチウムの選択的捕捉を検討した (Table 2–3)。まず，イミダゾール **54** に塩化亜鉛を共存させた状態で，LDA を作用させ，ヨウ素で処理した結果，三種類のヨウ素化体 **55**–**57** を得た (entry 1)。それぞれの構造は，X 線結晶構造解析によって決定した[63]。次に，塩化亜鉛 TMEDA を用いたところ，−78 °C では選択性が発現しなかったものの，0 °C では，はじめに発生する有機リチウム由来のヨウ素化体 **55** を収率 58%で選択的に得た (entries 2 and 3)。一方で，塩化亜鉛 TMCDA を利用すると，ハロゲンダンス後のヨウ素体 **56** を収率 64%で得た (entry 4)。なお，塩化亜鉛 TEEDA や塩化亜鉛 TMPDA を用いた場合は，ヨウ素化体 **56** と **57** の混合物が生成した (entries 5 and 6)。検討の結果，塩化亜鉛を利用しない条件によって，ヨウ素化体 **57** を収率 67%で選択的に得た (entry 7)。以上の結果から，イミダゾールは，チアゾールとは異なり，ハロゲンダンスによって三種類の構造異性体が合成可能であるとわかった。

Table 2–3. Effects of $ZnCl_2$·diamine on the In Situ Zincation of Imidazolyllithiums[a]



entry	$ZnCl_2$·diamine	**55** (%)[b]	**56** (%)[b]	**57** (%)[b]
1[c]	$ZnCl_2$	17	2	3
2	$ZnCl_2$·TMEDA	30	37	16
3[d]	$ZnCl_2$·TMEDA	49 (58[e])	4	–[f]
4	$ZnCl_2$·TMCDA	–[f]	50 (59[e], 64[e,g])	24
5	$ZnCl_2$·TEEDA	–[f]	49	36
6	$ZnCl_2$·TMPDA	–[f]	38	49
7	none	–[f]	18	73 (67[e])

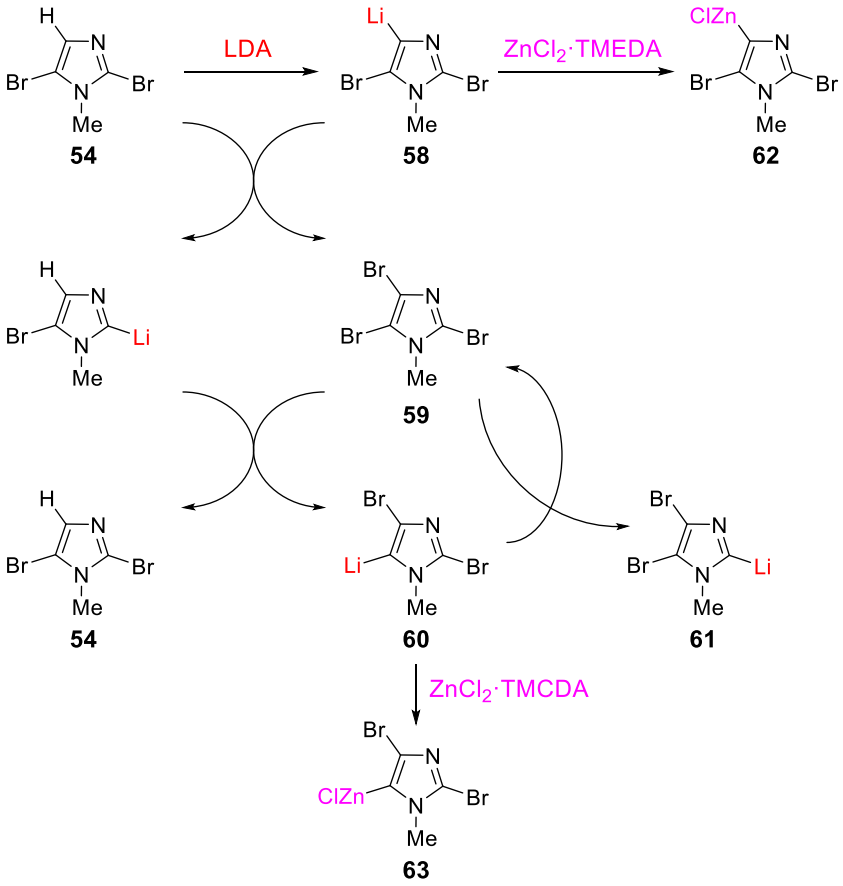
[a]Reaction conditions: 2,5-dibromo-1-methyl-1*H*-imidazole (**54**; 1.0 equiv, 0.30 mmol), $ZnCl_2$·diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), −78 °C, 30 min, then iodine (2.0 equiv, 0.60 mmol), −78 °C, 1 h. [b]The yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c]Recovery of 51% of **54**. [d]The reaction was performed at 0 °C. [e]Isolated yield. [f]Not observed in the crude product. [g]The reaction was performed using 1.0 mmol of 2,5-dibromo-1-methyl-1*H*-imidazole (**54**).



検討結果から，ハロゲンダンスの反応機構を推定した (Scheme 2–16)。まず，脱プロトン的に発生したイミダゾリルリチウム **58** が，イミダゾール **54** とハロゲン–リチウム交換し，トリブロモイミダゾール **59** を与える。続く二回目のハロゲン–リチウム交換によって，イミダゾリルリチウム **60** が生成する。イミダゾリルリチウム **60** は，トリブロモ体 **59** を触媒として，イミダゾリルリチウム **61** へ異性化する。想定した反応経路では，イミダゾリルリチウム **58** が，イミダゾリルリチウム **60**，イミダゾリルリチウム **61** へ逐次的に変換される。ジアミン

配位子としてTMEDAを用いると有機亜鉛反応剤**62**が，適度にかさ高いTMCDAを用いると有機亜鉛反応剤**63**が，塩化亜鉛ジアミンを利用しない場合はイミダゾリルリチウム**61**が選択的に生成し，ヨウ素化によってヨウ素化体**55**と**56**，および**57**へ変換されたと考えた。

Scheme 2–16. Plausible pathway of Halogen Dance Reaction of Imidazolyllithiums



逐次的にハロゲンダンスが進行する反応経路が実現可能かどうかを明らかにするため，有機リチウム**60**が**61**に異性化するか確かめた (Scheme 2–17)。ヨウ素化体**56**および**57**を出発化合物とし，触媒としてトリブロモイミダゾール**59** (13 mol%)を共存させた状態で，1 当量の ^{n}BuLi を–78 °C で 30 分間作用させ，ヨウ素で反応を停止させた。その結果，いずれのヨウ素化体を基質とした場合も，ヨウ素化体**56**と**57**の混合物を得た。この結果から，有機リチウム**60**と**61**の間には化学平衡があり，Scheme 2–16 で示したような逐次的なハロゲンダンスが実現可能であるとわかった。しかし，ヨウ素化体**56**を出発化合物とした際に，ヨウ素化体**57**の収率は 36%であり，最適化した反応条件 (Table 2–3, entry 7)に

おいて，ヨウ素化体 **57** が収率 73%で得られた実験結果とは一致しなかった。したがって, 直線型の反応経路 (Figure 2–6)だけではなく, 分岐型の反応経路 (Figure 2–7)も想定される。チアゾールと同様に，DFT 計算によって有機リチウムの

Scheme 2–17. Isomerization of 2,4- and 4,5-dibromoimidazolyllithiums

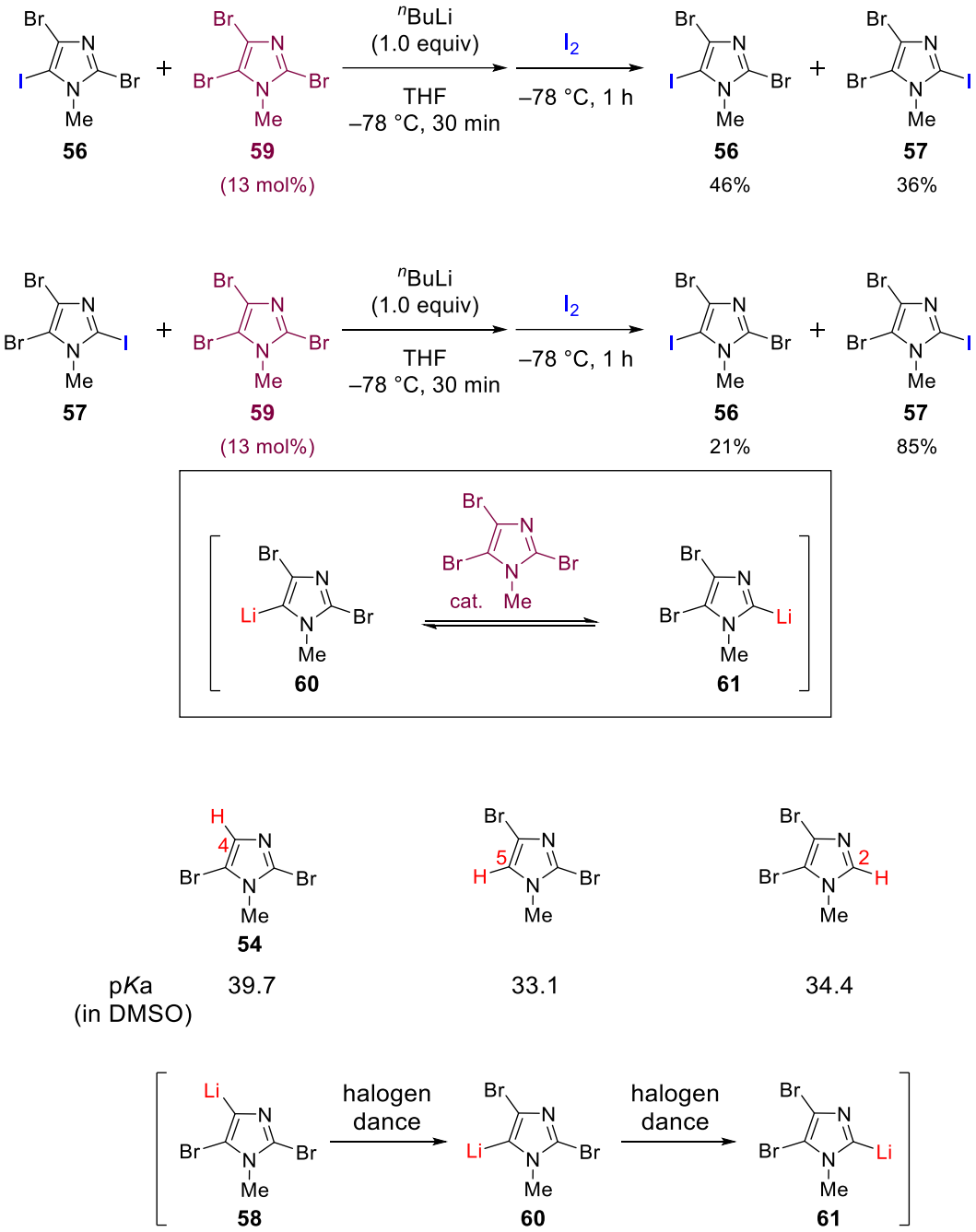


Figure 2–6. The calculated p*K*a values of dibromoimidazoles

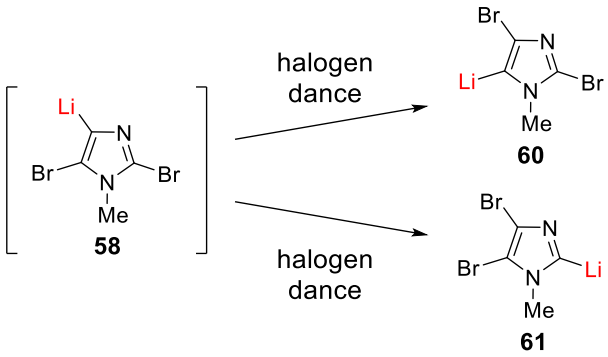


Figure 2–7. Pausible pathway based on the calculated p*K*a values

熱力学的安定性を比較すると，2,5-ジブロモイミダゾール **54** の 4 位プロトンの p*K*a が 39.7，2,4-ジブロモイミダゾールの 5 位プロトンの p*K*a が 33.1，4,5-ジブロモイミダゾリルリチウムの 2 位プロトンの p*K*a が 34.4 であった (Figure 2–6)。したがって，DFT 計算からは，イミダゾリルリチウム **60** からイミダゾリルリチウム **61** へ異性化する直線型の反応経路は，熱力学的な安定性の差が小さいため支持されず，分岐型の反応経路を支持する結果を得た。しかし，著者は，イミダゾリルリチウム **61** の熱力学的安定性を，p*K*a の計算値が過小評価している可能性を考えた。すなわち，イミダゾリルリチウム **61** は，二量体を形成し，計算値よりも，熱力学的に安定化されている（p*K*a が 34.4 よりも小さい）可能性がある (Figure 2–8)。なお，エネルギー図は，一回目のハロゲンダンスでイミダゾリルリチウム **58** が発生した後，二量体 **64** を形成することで，二度目のハロゲンダンスが進行した可能性を示している。後に Table 2–4, entry 8 で示すように，2-ブロモイミダゾール **65** が，ハロゲンダンスにより 5-ブロモ-2-ヨードイミダゾール **66** へ定量的に変換された結果は，直線型の反応経路 (Figure 2–6)が二量体の形成を駆動力として進行したためと考えられる。なお，イミダゾールとチアゾールの塩基性を比較すると，イミダゾールの 3 位窒素原子が，チアゾールの 3 位窒素原子よりも塩基性が高いことが，DFT 計算および文献値 [29c,64]から明らかになっている。したがって，イミダゾールの方が，チアゾールよりも塩基性が高く，二量体の形成が有利であるため，イミダゾールを基質とした場合に，有機リチウム **61** 由来のヨウ素化体 **57** を含めた，三種類の構造異性体が合成できたと考えられる。以上のような，実験および計算化学的な結果から，現在は，直線型の反応経路 (Figure 2–6)と分岐型の反応経路 (Figure 2–7)，いずれの経路でもハロゲンダンスが進行すると考えている。

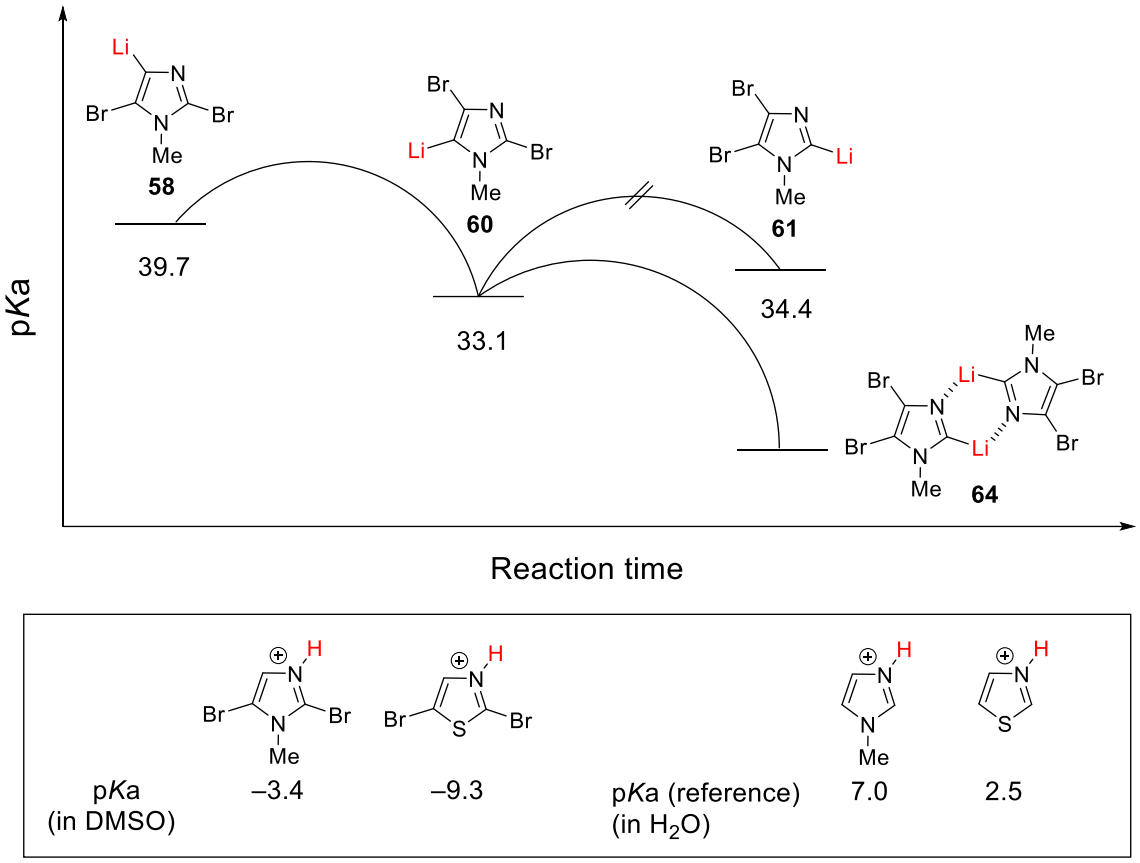
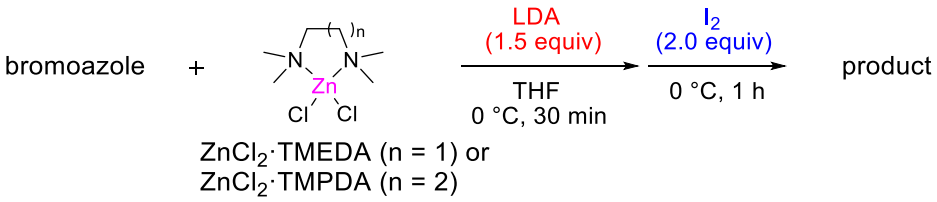


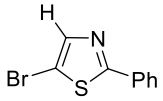
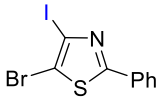
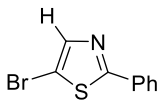
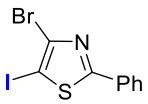
Figure 2–8. Plausible mechanism of double halogen dance of 2,5-dibromoimidazole

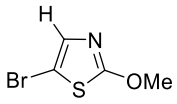
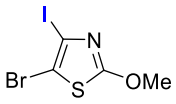
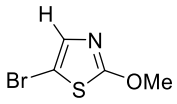
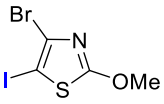
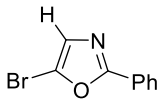
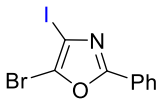
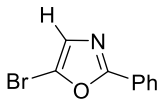
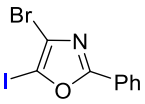
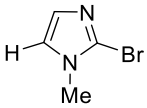
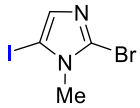
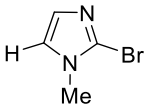
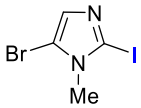
2-5　基質および求電子剤の一般性

開発した手法が様々なブロモアゾールへ適用可能か調べた。ブロモアゾールを基質とし，塩化亜鉛 TMEDA および塩化亜鉛 TMPDA を適切に選択し，二種類の構造異性体を選択的に合成した (Table 2–4)。まず，ブロモフェニルチアゾール **67** を基質とした場合，塩化亜鉛 TMEDA を共存させた状態で LDA を作用させ，ヨウ素を加えると，ヨウ素化体 **68** を収率 91%で得た (entry 1)。一方，塩化亜鉛 TMPDA を利用すると，ハロゲンダンスが進行し，ヨウ素化体 **69** を収率 91%で合成した (entry 2)。ブロモメトキシチアゾール **70** を基質とすると，塩化亜鉛 TMEDA を 0 °C，塩化亜鉛 TMPDA を−78 °C で利用することで，ヨウ素体 **71** と **72** をそれぞれ収率 83%および収率 78%で選択的に得た (entries 3 and 4)。ブロモフェニルオキサゾール **73** を基質とした場合も同様に，ヨウ素化体 **74** と **75** を収率 85%と収率 91%で合成した (entries 5 and 6)[65]。ブロモイミダゾール **65** を基質とし，塩化亜鉛 TMEDA を−78 °C で用いると，ヨウ素化体 **76** を収率 71%で得た (entry 7)。一方，塩化亜鉛を用いないと，ハロゲンダンスが進行し，ヨウ素化体 **66** を収率 80%で合成した (entry 8)。検討結果から，はじめに発生する短寿命アゾリルリチウムを選択的に捕捉するためには，塩化亜鉛 TMEDA が最適であるとわかった。また，モノブロモイミダゾール **65** を基質とした場合，

Table 2–4.　Selective In Situ Transmetalation Followed by Iodination[a]



entry	bromoazole	$ZnCl_2$·diamine	product	yield (%)[b]
1	 **67**	$ZnCl_2$·TMEDA	 **68**	91
2	 **67**	$ZnCl_2$·TMPDA	 **69**	91

3	 **70**	$ZnCl_2$·TMEDA	 **71**	83
4[c]	 **70**	$ZnCl_2$·TMPDA	 **72**	78
5	 **73**	$ZnCl_2$·TMEDA	 **74**	85
6[c]	 **73**	$ZnCl_2$·TMPDA	 **75**	91
7[c]	 **65**	$ZnCl_2$·TMEDA	 **76**	71
8[c]	 **65**	none	 **66**	80

[a]Reaction conditions: bromoazole (1.0 equiv, 0.30 mmol), $ZnCl_2$·diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), 0 °C, 30 min, then iodine (2.0 equiv, 0.60 mmol), 0 °C, 1 h. [b]Isolated yield. [c]Reaction was performed at −78 °C.

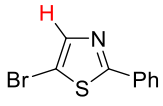
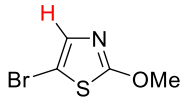
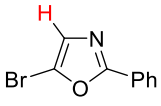
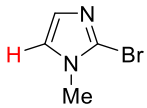
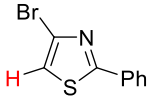
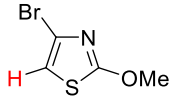
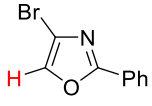
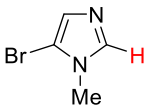
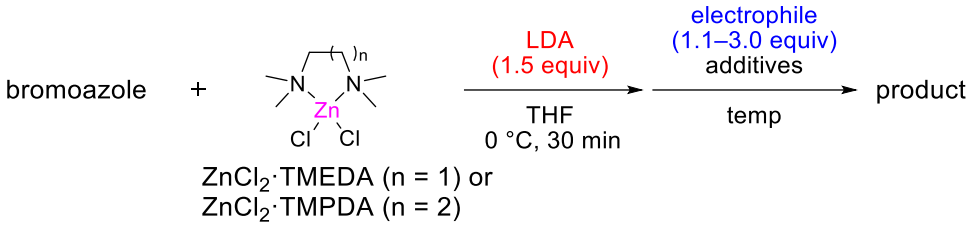
	 **67**	 **70**	 **73**	 **65**
p*K*a (in DMSO)	36.8	36.8	36.9	37.3
				
p*K*a (in DMSO) (Δp*K*a)	28.6 (–8.2)	29.8 (–7.0)	30.4 (–6.5)	37.4 (+0.1)

Figure 2–9. The p*K*a values of the thiazoles, oxazole, and imidazole

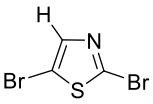
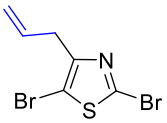
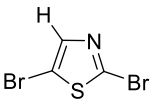
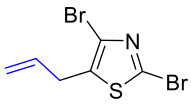
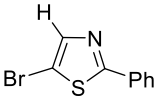
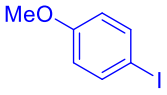
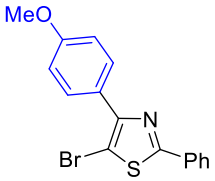
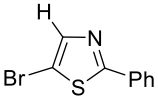
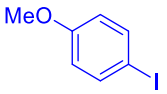
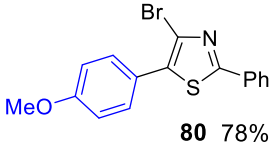
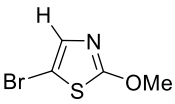
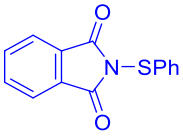
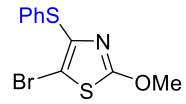
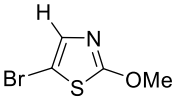
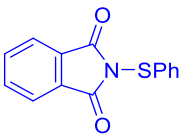
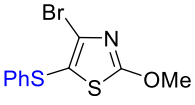
塩化亜鉛 TMPDA を用いると，ヨウ素化体 **66** ではなくヨウ素化体 **76** が主生成物として生成した結果から，イミダゾール **65** のハロゲンダンスの反応速度が遅いことがわかった。実際，DFT 計算によって対応する有機リチウムの共役酸の p*K*a を算出したところ，ハロゲンダンスの駆動力(ハロゲンダンス前後の有機リチウムの共役酸の p*K*a の差)が，他のアゾールと比較して小さいことが確認された (Figure 2–9)。したがって，Figure 2–8 で説明したように，イミダゾール **65** のハロゲンダンスも，二量体の形成を駆動力として進行した可能性が考えられる。

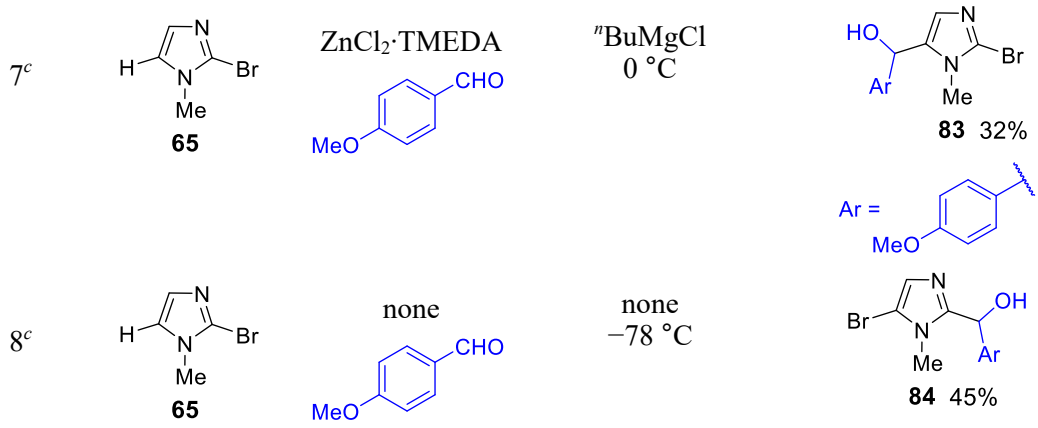
次に，ヨウ素以外の求電子剤を導入した (Table 2–5)。ジブロモチアゾール **47** を基質とし，塩化亜鉛 TMEDA を用いた場合，発生した有機亜鉛反応剤は，CuCN·2LiCl によるトランスメタル化[66]を経由すると，ヨウ化アリルと反応でき，アリル化体 **77** を収率 87%で得た (entry 1)。一方，塩化亜鉛 TMPDA を用いた場合も，アリル化が進行し，アリル体 **77** と構造異性体の関係にあるアリル化体 **78** を収率 65%で合成した (entry 2)。なお，CuCN·2LiCl を添加しない条件では，塩化亜鉛 TMEDA および塩化亜鉛 TMPDA のどちらを利用した場合も，チアゾール **47** のみを回収した。ブロモフェニルチアゾール **67** と塩化亜鉛 TMEDA から発生させた有機亜鉛反応剤は, 還流条件でもハロゲンダンスは進行せず, 根岸カップリング[67]によりチアゾール **79** へ収率 65%で変換された (entry 3)。また，塩化亜鉛 TMPDA を用いると，構造異性体 **80** が収率 78%で合成できた (entry 4)。ブロモメトキシチアゾール **70** を基質とした場合, 酢酸銅(II)を触媒とするフェニルチオ化[68]が進行し，中程度の収率ではあるものの，フェニルチオ体 **81** と **82** を選択的に得ることができた (entries 5 and 6)。モノブロモイミダゾール **65** と塩化亜鉛 TMEDA から発生させた有機亜鉛反応剤は，*p*-アニスアルデヒドとは反応しなかった。そこで，添加剤として *n*BuMgCl[69]を 2 当量加えたところ，イミダゾール **65** が 40%回収されたものの，*p*-アニスアルデヒドへの求核付加が進行し，付加体 **83** を収率 32%で得た (entry 7)。一方，塩化亜鉛を加えずに発生させたイミダゾール **65** 由来の有機リチウムを，*p*-アニスアルデヒドと反応させると，ハロゲンダンス後の付加体 **84** を収率 45%で合成できた (entry 8)。

Table 2–5. Selective In Situ Transmetalation Followed by Electrophilic Trapping[a]



$ZnCl_2$·TMEDA (n = 1) or
$ZnCl_2$·TMPDA (n = 2)

entry	bromoazole	$ZnCl_2$·diamine electrophile	additives temp	product yield (%)[b]
1	 **47**	$ZnCl_2$·TMEDA 	CuCN·2LiCl rt	 **77** 87%
2	 **47**	$ZnCl_2$·TMPDA 	CuCN·2LiCl rt	 **78** 65%
3	 **67**	$ZnCl_2$·TMEDA 	$Pd_2(dba)_3$ 3 mol% $P(4\text{-}CF_3C_6H_4)_3$ 11 mol% reflux	 **79** 65%
4[c]	 **67**	$ZnCl_2$·TMPDA 	$Pd_2(dba)_3$ 3 mol% $P(4\text{-}CF_3C_6H_4)_3$ 11 mol% reflux	 **80** 78%
5	 **70**	$ZnCl_2$·TMEDA 	$Cu(OAc)_2$ 7 mol% rt	 **81** 47%
6[c]	 **70**	$ZnCl_2$·TMPDA 	$Cu(OAc)_2$ 7 mol% rt	 **82** 27%

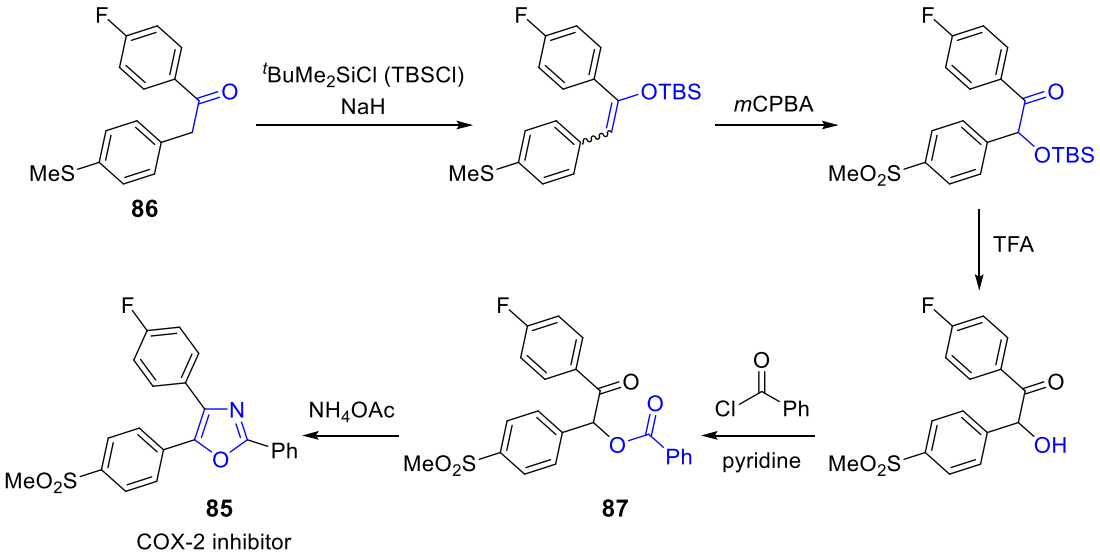


[a]Reaction conditions: bromoazole (1.0 equiv, 0.30 mmol), $ZnCl_2$·diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), 0 °C, 30 min, then electrophile (1.1–3.0 equiv). [b]Isolated yield. [c]Reaction temperature: −78 °C.

2-6　非ステロイド系抗炎症薬の短段階合成

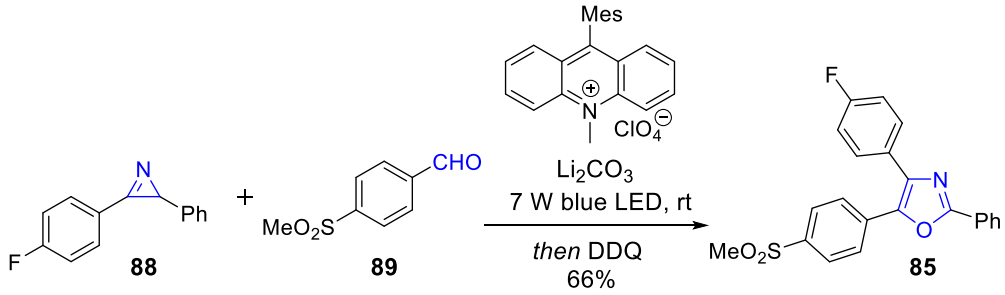
第二章で開発した手法を用いて，非ステロイド抗炎症薬とその構造異性体の合成を達成した。まず，COX-2 阻害剤として知られるオキサゾール **85**[70]の合成に取り組んだ。Norman らは，鎖状ケトン **86** を基質とし，鎖状ジカルボニル化合物 **87** の脱水縮合を経由して，オキサゾール **85** を合成している (Scheme 2–18)[71]。しかし，鎖状ケトン **86** は，フルオロベンゼンから一工程で導かれるため，本合成法は，合計六工程を要する点が問題であった。

Scheme 2–18.　The Strategy for the Synthesis of COX-2 Inhibitor



Xiao らは，2*H*-アジリン **88** を基質とし，アルデヒド **89** を作用させ，光触媒反応を用いて，オキサゾール **85** を収率 66%で合成している (Scheme 2–19)[72]。本反応は，迅速にオキサゾール **85** を合成できるが，原料のアジリン **88** の調製が必要な点，オキサゾール **85** へ導入可能な置換基の一般性が乏しく，その誘導体の合成が困難な点が問題である。

Scheme 2–19. Synthesis of COX-2 Inhibitor Using Photoredox Catalysis



今回，オキサゾール **85** の合成前駆体として，オキサゾール **90** を選択した (Figure 2–10)。オキサゾール **90** は，今回開発した手法を用いれば，市販のブロモオキサゾール **73** から容易に合成できるため，合計二段階でオキサゾール **85** が合成できると考えた。また，オキサゾール **85** の構造異性体 **91** も同様に，ブロモオキサゾール **73** から合成したオキサゾール **92** を用いれば，合成できると考えた。本合成経路は，他の合成経路と比較して工程数が少ない点，誘導体の網羅的合成ができる点で優れている。

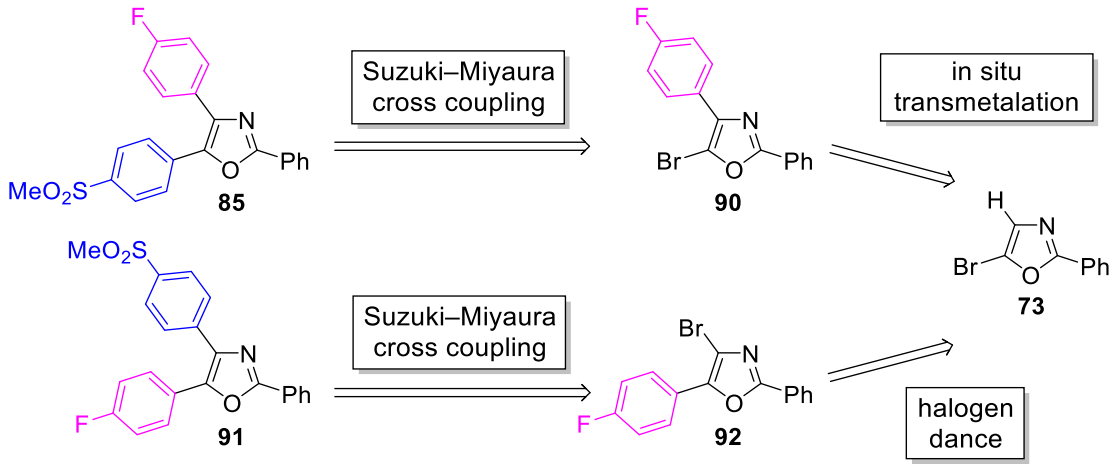
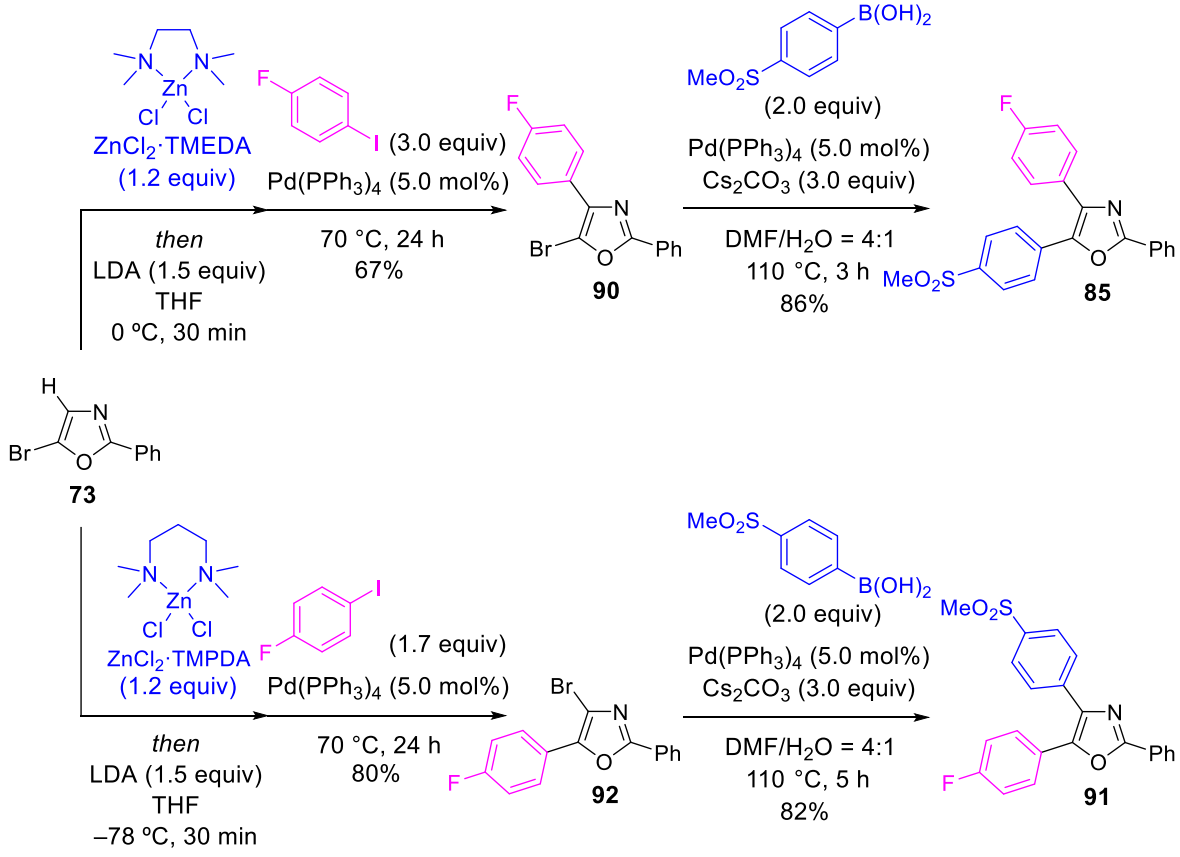


Figure 2–10. This work: selective synthesis of COX-2 inhibitor and the constitutional isomer

前節の Table 2–4 では，塩化亜鉛 TMEDA および塩化亜鉛 TMPDA を用いると，オキサゾール **73** から二種類の構造異性体 **74** と **75** が選択的に合成できることが明らかとなった。したがって，塩化亜鉛 TMEDA と塩化亜鉛 TMPDA を用いて発生させた有機亜鉛反応剤をそれぞれ利用し，オキサゾール **85** と **91** の合成をめざした (Scheme 2–20)。検討の結果，オキサゾール **73** に塩化亜鉛 TMEDA を共存させた状態で，LDA を作用させ，$Pd(PPh_3)_4$ を 5.0 mol%，1-フルオロ-4-ヨードベンゼンを 3.0 当量加え，70 °C で加熱すると，オキサゾール **90** を収率 67% で合成できた。さらに，オキサゾール **73** に塩化亜鉛 TMPDA を共存させた状態で，LDA を−78 °C で作用させ，$Pd(PPh_3)_4$ を 5.0 mol%，1-フルオロ-4-ヨードベンゼンを 1.7 当量加え，70 °C で加熱すると，オキサゾール **92** を収率 80%で合成できた。オキサゾール **92** の合成では，オキサゾール **90** と比較し，1-フルオロ 4-ヨードベンゼンの当量を半分に減らしても，根岸カップリングが円滑に進行することがわかった。合成したそれぞれの構造異性体 **90** と **92** に対して，4-(メチルスルホニル)フェニルボロン酸，$Pd(PPh_3)_4$，炭酸セシウムを加え，DMF と蒸留水

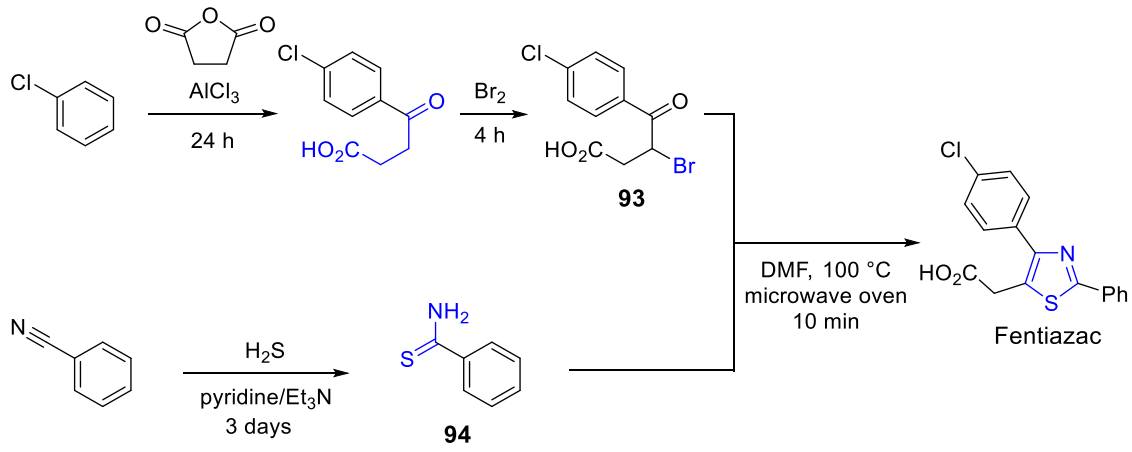
Scheme 2–20. Synthesis of COX-2 Inhibitor and the Isomer by Using In Situ Transmetalation



の混合溶媒(4:1)中，110 °C で加熱すると，鈴木–宮浦カップリング[1a,73]が進行し，目的の COX-2 阻害剤 **85** とその構造異性体 **91** をそれぞれ収率 86%と 82%で得た。なお，構造異性体 **91** の合成において，反応温度を 110 °C から，75 °C に低下させると，目的物は全く得られず，オキサゾール **92** を定量的に回収した。塩化亜鉛ジアミンとして，塩化亜鉛 TMEDA，塩化亜鉛 TMPDA を適切に選択し，COX-2 阻害剤 **85** およびその構造異性体 **91** を選択的に合成できた。本合成法により，従来六工程を経て合成されていた COX-2 阻害剤 **85** の合成経路を 2 工程にまで簡略化でき，同一の出発化合物から構造異性体 **91** の合成も達成できた。それぞれの構造は，X 線結晶構造解析によって決定した[74]。

次に，非ステロイド性抗炎症薬として知られるフェンチアザック[75]に着目した。Högberg らは，鎖状ケトンの脱水縮合を経由し，フェンチアザックを合成している (Scheme 2–21)[76]。すなわち，二工程で調製した鎖状ケトン **93** と一工程で調製したチオアミド **94** をマイクロウェーブで 100 °C に加熱し，フェンチアザックを合成している。本手法は合計四工程を要する点，反応時間が長い点が問題であった。

Scheme 2–21. The Synthesis of Fentiazac by Using Cyclization Strategy



今回，酸処理によって容易にフェンチアザックへ変換可能なフェンチアザック *tert*-ブチルエステル(**95**)とその構造異性体 **96** を合成した (Figure 2–11)。フェニルチアゾール **67** から誘導したチアゾール **97** を根岸カップリングにより変換し，フェンチアザック誘導体 **95** を得る合成経路を立案した。また，チアゾール **98** を調製すれば，構造異性体 **96** も合成可能になると考えた。

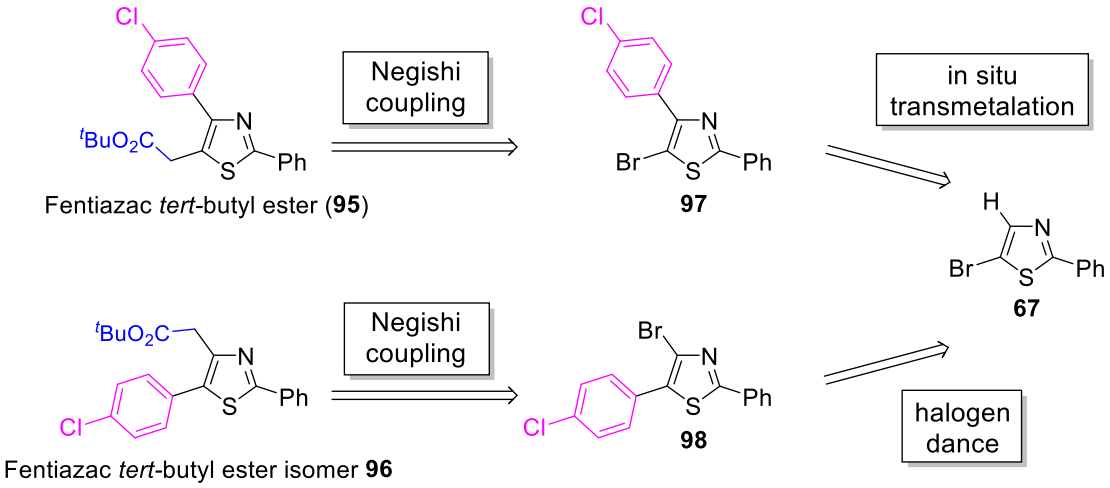
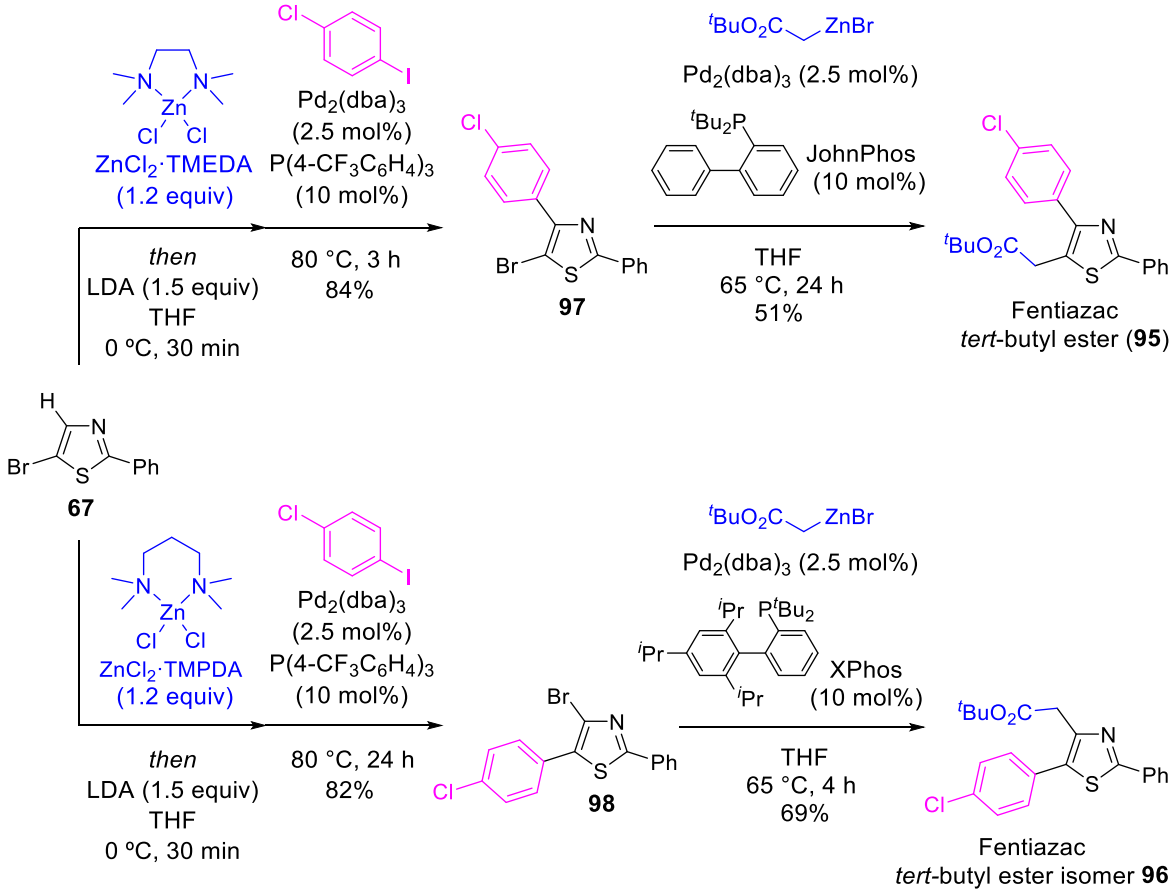


Figure 2–11. Selective synthesis of Fentiazac *tert*-butyl ester and the isomer

まず，チアゾール **67** にクロロフェニル基を導入した (Scheme 2–22)。チアゾール **67** に塩化亜鉛 TMEDA を共存させた状態で，LDA を作用させ，$Pd_2(dba)_3$ を

Scheme 2–22. Synthesis of Fentiazac *tert*-Butyl Ester and the Isomer by Using In Situ Transmetalation



2.5 mol%，P(4-$CF_3C_6H_4$)$_3$ を 10 mol%，1-クロロ-4-ヨードベンゼンを 3.0 当量加え，80 °C で加熱すると，チアゾール **97** を収率 84%で合成できた。また，塩化亜鉛 TMPDA を用いると，チアゾール **97** の構造異性体 **98** を収率 82%で得た。合成したチアゾール **97** に対して，Reformatsky 反応剤，$Pd_2(dba)_3$，JohnPhos を加え，THF 中，65 °C で 24 時間加熱すると，根岸カップリングが進行し，フェンチアザック *tert*-ブチルエステル(**95**)を収率 51%で得た。なお，第二章の内容を含む論文では，配位子として DavePhos を用いると，フェンチアザック *tert*-ブチルエステル(**95**)の収率が大幅に向上した。さらに，チアゾール **95** に対して TFA を作用させると，*tert*-ブチルエステルの脱保護が進行し，フェンチアザックの短段階合成を達成している。また，チアゾール **98** に，Reformatsky 反応剤，$Pd_2(dba)_3$，XPhos を加え，THF 中，65 °C で 4 時間加熱すると，フェンチアザック誘導体の構造異性体 **96** を収率 69%で得た。Pd 触媒として $Pd(PPh_3)_4$ を用いた場合や，ホスフィン配位子として JohnPhos を用いた場合は，どちらも目的物は全く得られず，チアゾール **98** を定量的に回収した。なお，第二章の内容を含む論文内では，Pd 触媒と XPhos の当量を増やすことで構造異性体 **96** の収率が向上し，TFA を用いた *tert*-ブチルエステルの脱保護によって，フェンチアザック異性体の合成を達成している。以上より，チアゾール **67** を出発化合物とし，フェンチアザック *tert*-ブチルエステル(**95**)およびその構造異性体 **96** が合成できた。本合成法により，合成経路および反応時間を短縮でき，構造異性体の網羅的合成も可能となった。

2-7　結言

第二章では，リチウムから亜鉛への金属交換を利用し，アゾールの分解反応を抑制し，ハロゲンダンスを達成した。塩化亜鉛 TMEDA および塩化亜鉛 TMPDA の選択的な in situ トランスメタル化を利用し，ブロモ基の置換様式が異なる複数の構造異性体を選択的に合成した。また，発生させた有機亜鉛反応剤は合成的に利用可能であり，様々な求電子剤を位置選択的に導入できるとわかった。

また，アゾールの母核がハロゲンダンスに与える影響が明らかとなった(Figure 2–12)。すなわち，チアゾール (Y＝S)，イミダゾール (Y＝NMe)，オキサゾール (Y＝O)は，ブロモ基が 5 位から 4 位へ移動するハロゲンダンスがただちに進行した。この結果は，いずれのアゾールにおいても発生する二種類の有機リチウム **99** と **100** の p*K*a の差が 5.0 以上であり，熱力学的な安定性に大きな差が

あったためと考えられる。なお，イミダゾールについては，ブロモ基の 2 位から 5 位への移動（5 位リチオ化体 **100** から 2 位リチオ化体 **101** へのハロゲンダンス）が進行したが，結果に反して発生する二種類の有機リチウムの p*K*a の差は 0.1 以下であった。著者は，アゾールの中で最も 3 位窒素原子の塩基性が高いイミダゾール由来の有機リチウム **101** のみが二量体を有利に形成しやすく，p*K*a の計算値以上に，2 位リチオ化体 **101** が熱力学的に安定化された可能性を考えた。

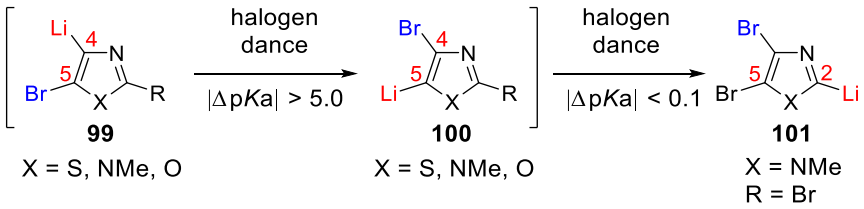


Figure 2–12. Summary of azolyllithiums in a halogen dance

合成したブロモアレーンはさらなる化学変換が可能であり，オキサゾール骨格を有する非ステロイド系の COX-2 阻害剤，チアゾール骨格を有するフェンチアザック誘導体，さらにそれぞれの構造異性体を合成できた。本合成法により，ハロゲンダンスを用いてブロモ基を移動させ，構造異性体の関係にある様々なブロモアレーンを合成する合成戦略の有用性を実証できた。また，通常はフローマイクロリアクターなど特殊な反応装置を用いる必要がある短寿命有機リチウムを，実験操作が容易なバッチ反応器で利用でき，多置換アゾールの簡便な合成が可能となった。

2-8 Experimental Section

2-8-1 General

Analytical thin layer chromatography (TLC) was performed on Merck 60 F_{254} aluminum sheets precoated with a 0.25 mm thickness of silica gel. Melting points (Mp) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wavenumbers (cm^{-1}). ^{1}H NMR (400 MHz) and $^{13}C\{^{1}H\}$ NMR (100 MHz) spectra were obtained on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm) and coupling constants are given in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet,

q = quartet, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^{1}H\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, DMSO-d_6: δ 39.52 ppm). High-resolution mass spectroscopy (HRMS) was performed on a JEOL JMS-T100LP AccuTOF LC-Plus [electrospray ionization (ESI)] with a JEOL MS-5414DART attachment.

2-8-2 Materials

Unless otherwise stated, all reactions were conducted in a flame-dried glassware under an inert atmosphere of nitrogen. All workup and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel 60N (45–75 μm, Wako Pure Chemical Industries, Ltd.). Anhydrous THF (>99.5%, water content: <10 ppm) and anhydrous CH_2Cl_2 (>99.5%, water content: <1 ppm) were purchased from Kanto Chemical Co., Inc. and further dried by passing through a solvent purification system (Glass Contour) prior to use. Distilled water was purchased from Nacalai tesque, Inc. (Product number: 49506-64). LDA (2.0 M in THF/heptane/ethylbenzene) was purchased from Sigma-Aldrich Co. (Product number: 361798). ^{n}BuMgCl (2.0 M in THF) was purchased from Sigma-Aldrich Co. (Product number: 291005).

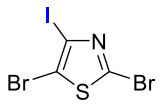
2-8-3 Decomposition of Thiazolyllithium (Equation 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromothiazole (**47**) (72.4 mg, 0.298 mmol, 1.0 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with iodine (161.5 mg, 0.636 mmol, 2.1 equiv). After stirring at 0 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product (82.9 mg), whose signals in the ^{13}C NMR spectrum were not identical to those of 2,5-dibromothiazole (**47**), 4-iodothiazole **48**, and 5-iodothiazole **49**.

2-8-4 Effects of ZnX_2·diamine on the In Situ Zincation of Thiazolyllithiums (Table 2–1)

General Procedure A

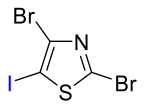
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromothiazole (**47**) (0.300 mmol, 1.0 equiv), $ZnCl_2$·diamine (0.360 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with iodine (0.600 mmol, 2.0 equiv). After stirring at 0 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide a mixture of **48** and **49**. The ratio of **48** and **49** was calculated by ^{13}C NMR spectroscopy using the inverse-gated ^{1}H decoupling sequence (the calculated signals of **48** and **49** were observed at 137.3 ppm and 74.7 ppm, respectively. scans = 1024, relaxation time = 10 s). The relative values of integration for the peaks observed at 137.3 ppm and 74.7 ppm were obtained using a mixture of **48** (11.4 mg, 30.9 μmol, value of integration = 1.01) and **49** (11.7 mg, 31.7 μmol, value of integration = 1.00).



48

2,5-Dibromo-4-iodothiazole (48) (Table 2–1, entry 2)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a colorless solid (98.4 mg, 0.267 mmol, 89%) from 2,5-dibromothiazole (**47**) (73.1 mg, 0.301 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (91.2 mg, 0.361 mmol, 1.2 equiv), and iodine (153.7 mg, 0.606 mmol, 2.0 equiv) according to the general procedure A. R_f = 0.33 (hexane/diethyl ether = 50:1); Mp 42–43 ºC; IR (ATR, cm^{-1}): 1440, 1391, 1010, 991; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 137.3, 116.1, 100.1; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_3H^{79}Br_2INS$, 367.7241; found, 367.7246.



49

2,4-Dibromo-5-iodothiazole (49) (Table 2–1, entry 8)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 100:1) to provide the title compound as a colorless solid (79.9 mg, 0.217 mmol, 72%) from 2,5-dibromothiazole (**47**) (72.5 mg, 0.298 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (95.9 mg, 0.360 mmol, 1.2 equiv), and iodine (154.6 mg, 0.609 mmol, 2.0 equiv) according to the general procedure A. R_f = 0.33 (hexane/diethyl ether = 50:1); Mp 88–90 ºC; IR (ATR, cm^{-1}): 1445, 1189, 1010, 816; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 140.3, 134.0, 74.7; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_3H^{79}Br_2INS$, 367.7241; found, 367.7241.

Control Experiments

Reaction with a premixed $ZnCl_2$·TMEDA and LDA

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with $ZnCl_2$·TMEDA (113.5 mg, 0.450 mmol, 1.5 equiv) and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the reaction mixture. After stirring at 0 ºC for 30 min, the reaction mixture was treated with 2,5-dibromothiazole (**47**) (72.0 mg, 0.296 mmol, 1.0 equiv). After stirring at 0 ºC for 30 min, the reaction mixture was treated with iodine (161.8 mg, 0.638 mmol, 2.2 equiv). After stirring at 0 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The recovery yield of 2,5-dibromothiazole (**47**) was determined to be 59% by ^1H NMR analysis using 1,1,2,2-tetrachloroethane (32.8 mg, 0.195 mmol) as an internal standard by comparing relative values of integration for the peak observed at 7.52 ppm (1 proton for **47**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction with a premixed $ZnCl_2$·TMPDA and LDA

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with $ZnCl_2$·TMPDA (119.5 mg, 0.448 mmol, 1.5 equiv) and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the reaction mixture. After stirring at 0 ºC for 30 min, the reaction mixture was treated with 2,5-dibromothiazole (**47**) (73.2 mg, 0.301 mmol, 1.0 equiv). After stirring at 0 ºC for 30 min, the reaction mixture was treated with iodine (152.7 mg, 0.602 mmol, 2.0 equiv). After stirring at 0 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The recovery yield of 2,5-dibromothiazole (**47**) was determined to be 62% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (35.7 mg, 0.213 mmol) as an internal standard by comparing relative values of integration for the peak observed at 7.52 ppm (1 proton for **47**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

2-8-5 Preparation of ZnX_2·diamine Complexes

$ZnCl_2$·TMEDA

General procedure for the preparation of ZnX_2·diamine: $ZnCl_2$·TMEDA

A 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum was charged with $ZnCl_2$ (13.62 g, 99.8 mmol, 1.0 equiv). The flask was evacuated, flame-dried, left to cool under vacuum, and flushed with argon. To the flask was added ethanol (100 mL) via a syringe. TMEDA (18.0 mL, 120 mmol, 1.2 equiv) was added dropwise to the resulting solution. The white precipitate was formed with a slight evolution of heat. The resulting suspension was stirred at 25 ºC for 1 h, at which time the precipitate was collected by filtration, and washed with hexane to give a crude solid, which was recrystallized from THF to provide the title compound as colorless needles (19.12 g, 75.6 mmol, 76%), whose ^{1}H NMR spectrum was identical to that reported in the literature.[39b] Mp 164−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73

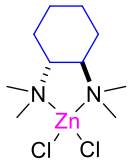
(s, 4H), 2.62 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 57.0, 47.9; Anal. Calcd. for $C_6H_{16}N_2Cl_2Zn$: C, 28.54; H, 6.39; N, 11.09. Found: C, 28.53; H, 6.42; N, 10.92.

$ZnBr_2$·TMEDA

The title compound was prepared in 79% yield (8.104 g, 23.7 mmol) as colorless needles from $ZnBr_2$ (6.750 g, 29.9 mmol, 1.0 equiv), ethanol (30 mL), and TMEDA (5.4 mL, 36 mmol, 1.2 equiv) according to the general procedure. Mp 174−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (s, 4H), 2.64 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 56.9, 48.4; Anal. Calcd. for $C_6H_{16}N_2Br_2Zn$: C, 21.11; H, 4.72; N, 8.21. Found: C, 21.11; H, 4.71; N, 8.15.

ZnI_2·TMEDA

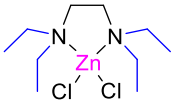
The title compound was prepared in 60% yield (6.189 g, 14.2 mmol) as a colorless solid from ZnI_2 (7.532 g, 23.6 mmol, 1.0 equiv), ethanol (24.0 mL), and TMEDA (4.3 mL, 28 mmol, 1.2 equiv) according to the general procedure. Mp 196−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (br, 4H), 2.68 (br, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 56.8, 49.8; Anal. Calcd. for $C_6H_{16}N_2I_2Zn$: C, 16.55; H, 3.70; N, 6.43. Found: C, 16.54; H, 3.34; N, 6.43.



$ZnCl_2$·TMCDA

$ZnCl_2$·TMCDA

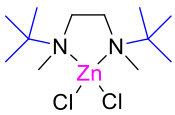
The title compound was obtained in 71% yield (4.389 g, 14.3 mmol) as a colorless solid from $ZnCl_2$ (2.730 g, 20.0 mmol, 1.0 equiv), ethanol (20.0 mL), and TMCDA[77] (4.6 mL, 24 mmol, 1.2 equiv) according to the general procedure. Mp >250 °C; IR (ATR, cm^{-1}): 2932, 1461, 1014; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 6H), 2.60−2.53 (m, 2H), 2.40 (s, 6H), 2.06−1.98 (m, 2H), 1.91−1.79 (m, 2H), 1.36−1.08 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 64.6, 46.5, 40.3, 24.2, 22.2; Anal. Calcd. for $C_{10}H_{22}N_2Cl_2Zn$: C, 39.18; H, 7.23; N, 9.14. Found: C, 39.06; H, 7.24; N, 9.05.



$ZnCl_2$·TEEDA

$ZnCl_2$·TEEDA

The title compound was prepared in 78% yield (12.07 g, 39.1 mmol) as a colorless solid from $ZnCl_2$ (6.826 g, 50.1 mmol, 1.0 equiv), ethanol (50.0 mL), TEEDA (13.0 mL, 60.7 mmol, 1.2 equiv) according to the general procedure. Mp 126−128 °C; IR (ATR, cm^{-1}): 2987, 2972, 1471, 1453, 1383, 1126, 1021, 754, 724; ^1H NMR (400 MHz, $CDCl_3$): δ 3.20−3.09 (m, 4H), 2.85−2.74 (m, 8H), 1.16 (t, 12 H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 50.6, 46.1, 8.7; Anal. Calcd. for $C_{10}H_{24}N_2Cl_2Zn$: C, 38.92; H, 7.84; N, 9.08. Found: C, 38.66; H, 8.00; N, 8.99.



$ZnCl_2$·BuMeEDA

$ZnCl_2$·BuMeEDA

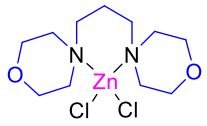
The title compound was obtained in 70% yield (4.676 g, 13.9 mmol) as a colorless solid from $ZnCl_2$ (2.707 g, 19.9 mmol, 1.0 equiv), ethanol (20.0 mL), and BuMeEDA[78] (5.8 mL, 24 mmol, 1.2 equiv) according to the general procedure. The ^1H and ^{13}C NMR spectra were identical to those reported in the literature.[79] Mp 228−230 °C; IR (ATR, cm^{-1}): 2978, 1481, 1192, 894; ^1H NMR (400 MHz, $CDCl_3$): δ 3.44 (d, 2H, J = 9.0 Hz), 2.55 (s, 6H), 2.37 (d, 2H, J = 9.0 Hz), 1.42 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 59.9, 47.9, 38.9, 25.9; Anal. Calcd. for $C_{12}H_{28}N_2Cl_2Zn$: C, 42.81; H, 8.38; N, 8.32. Found: C, 42.42; H, 8.24; N, 8.16.

$ZnCl_2$·TMPDA

$ZnCl_2$·TMPDA

The title compound was obtained in 83% yield (11.11 g, 41.7 mmol) as a colorless solid from $ZnCl_2$ (6.857 g, 50.3 mmol, 1.0 equiv), ethanol (50.0 mL), and TMPDA (10.0 mL, 59.9 mmol, 1.2 equiv) according to the general procedure. Mp 221−223 °C; IR (ATR,

cm^{-1}): 1478, 1459, 1036, 1005, 959, 816; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86−2.82 (m, 4H), 2.58 (s, 12H), 1.94−1.86 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 60.7, 47.5, 22.1; Anal. Calcd. for $C_7H_{18}N_2Cl_2Zn$: C, 31.55; H, 6.81; N, 10.51. Found: C, 31.50; H, 6.78; N, 10.39.



$ZnCl_2$·DMP

$ZnCl_2$·DMP

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum was charged with 1,3-dibromopropane (5.563 g, 27.6 mmol, 1.0 equiv), morpholine (4.782 g, 54.9 mmol, 2.0 equiv), sodium hydroxide (2.363 g, 59.1 mmol, 2.1 equiv), and water (16 mL). After stirring at 25 ºC for 42 h, the reaction mixture was treated with sodium hydroxide (4.365 g). The aqueous layer was extracted with $CHCl_3$ (15.0 mL) ten times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product as a mixture of DMP and morpholine, which was used for the next reaction without further purification. The title compound was prepared in 53% yield (4.40 g, 12.6 mmol) as a colorless solid from $ZnCl_2$ (3.261 g, 23.9 mmol), ethanol (24.0 mL), and the crude DMP (6.084 g, 28.6 mmol, 1.2 equiv) according to the general procedure. Mp 242−243 °C; IR (ATR, cm^{-1}): 1110, 967, 876, 619; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (td, 4H, J = 12.2 Hz, 1.8 Hz), 3.81 (d, 4H, J = 12.8 Hz), 3.48 (d, 4H, J = 11.6 Hz), 3.00–2.92 (m, 4H), 2.45 (ddd, 4H, J = 12.0 Hz, 11.6 Hz, 3.2 Hz), 1.99 (tt, 2H, J = 6.0 Hz, 5.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 63.7, 60.2, 56.4, 19.2; Anal. Calcd. for $C_{11}H_{22}N_2O_2Cl_2Zn$: C, 37.69; H, 6.33; N, 7.99. Found: C, 37.44; H, 6.21; N, 7.79.

$ZnBr_2$·TMPDA

The title compound was obtained in 69% yield (4.885 g, 13.7 mmol) as a colorless solid from $ZnBr_2$ (4.510 g, 20.0 mmol, 1.0 equiv), ethanol (20.0 mL), and TMPDA (4.0 mL, 24 mmol, 1.2 equiv) according to the general procedure. Mp >250 °C; IR (ATR, cm^{-1}): 2959, 1461, 1034, 1001; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88−2.82 (m, 4H), 2.58 (s, 12H),

1.94−1.89 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 60.4, 47.8, 22.1; Anal. Calcd. for $C_7H_{18}N_2Br_2Zn$: C, 23.66; H, 5.10; N, 7.88. Found: C, 23.60; H, 4.99; N, 7.79.

ZnI_2·TMPDA

The title compound was obtained in 95% yield (8.542 g, 19.0 mmol) as a colorless solid from ZnI_2 (6.384 g, 20.0 mmol, 1.0 equiv), ethanol (20.0 mL), and TMPDA (4.0 mL, 24 mmol, 1.2 equiv) according to the general procedure. Mp >250 °C; IR (ATR, cm^{-1}): 1474, 1456, 1000; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92−2.87 (m, 4H), 2.59 (s, 12H), 1.97−1.92 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 60.0, 48.4, 22.4; Anal. Calcd. for $C_7H_{18}N_2I_2Zn$: C, 18.71; H, 4.04; N, 6.23. Found: C, 18.73; H, 3.88; N, 6.14.

2-8-6 The p*K*a Values of Dibromothiazoles (Figure 2–5)

All calculation studies on equilibrium geometry at ground state were performed on density functional theory by Spartan version 18 (Wavefunction, Inc). The standard reaction Gibbs free energies (Δ*G*°) of deprotonation were calculated using B3LYP/6-311+G** level of theory in polar solvent at 298 K and 1 atm (Eq. 2).

Based on p*K*a table by Evans[80], the obtained Δ*G*° values were converted into p*K*a values by the calibration curve shown in Figure S1.

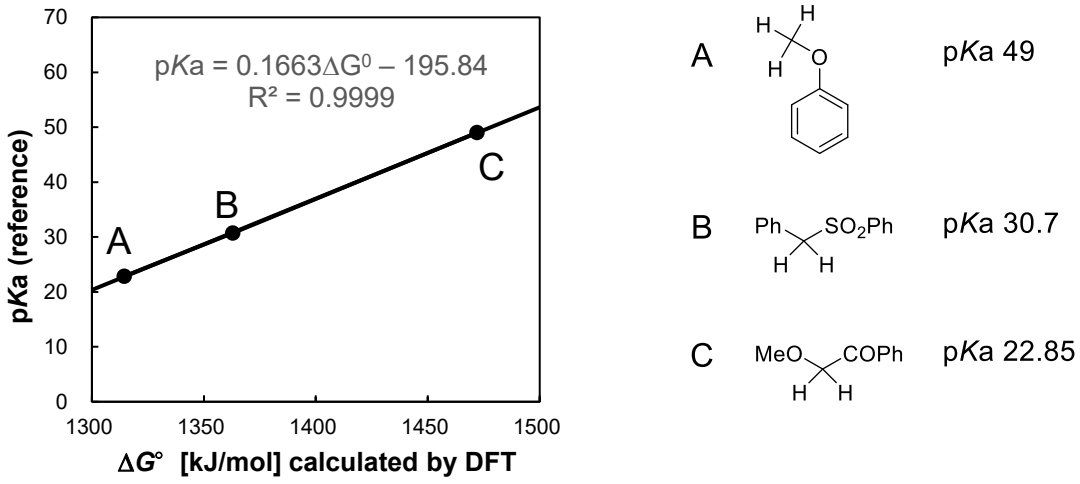
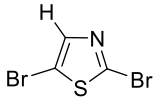
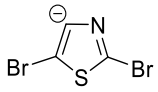
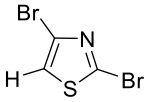
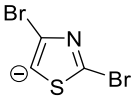
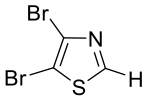
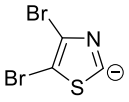
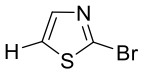
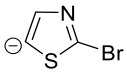
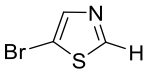
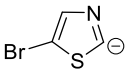
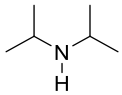
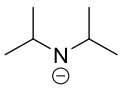
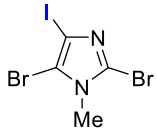


Figure S1. The calibration of Δ*G*° values into p*K*a value

The calculated p*K*a values (in DMSO) of thiazole **47** and **25** were as follows.

R–H	R^- (anion)	$\Delta G°$ [kJ/mol]	p*K*a (in DMSO)
 **47**		1380.5	33.7
 **25**		1335.5	26.3
		1346.8	28.1
		1362.8	30.8
		1362.7	30.8
		1443.7	44.3

2-8-7 Effects of $ZnCl_2$·diamine on the In Situ Zincation of Imidazolyllithiums (Table 2–3)



55

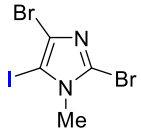
2,5-Dibromo-4-iodo-1-methyl-1*H*-imidazole (55) (Table 2–3, entry 3)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless solid (63.2 mg, 0.173 mmol, 58%) from 2,5-dibromo-1-methyl-1*H*-imidazole (**54**) (72.0 mg, 0.300 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.2 mg, 0.357 mmol, 1.2 equiv), and iodine (153.5 mg, 0.605 mmol, 2.0 equiv) according to the general procedure A (see Chapter 2, 2-8-4). R_f = 0.41

(hexane/diethyl ether = 1:1); Mp 106–108 ºC; IR (ATR, cm^{-1}): 1476, 1403, 1185, 958; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 119.8, 112.7, 85.1, 35.4; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_4H_4{}^{79}Br_2IN_2$, 364.7786; found, 364.7769.

General Procedure B

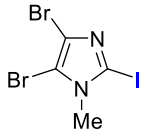
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromo-1-methyl-1*H*-imidazole (**54**) (0.300 mmol, 1.0 equiv), $ZnCl_2$·diamine (0.360 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 30 min, the reaction mixture was treated with iodine (0.600 mmol, 2.0 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography.



56

2,4-Dibromo-5-iodo-1-methyl-1*H*-imidazole (56) (Table 2–3, entry 4)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless solid (229.3 mg, 0.627 mmol, 64%) from 2,5-dibromo-1-methyl-1*H*-imidazole (**54**) (234.5 mg, 0.977 mmol, 1.0 equiv), $ZnCl_2$·TMCDA (368.8 mg, 1.20 mmol, 1.2 equiv), anhydrous THF (10 mL), LDA (2.0 M, 0.75 mL, 1.5 mmol, 1.5 equiv), and iodine (508.1 mg, 2.00 mmol, 2.1 equiv) according to the general procedure B. R_f = 0.47 (hexane/diethyl ether = 1:1); Mp 99–101 ºC; IR (ATR, cm^{-1}): 2926, 1472, 1213, 962; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 124.1, 119.6, 76.0, 37.4; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_4H_4{}^{79}Br_2IN_2$, 364.7786; found, 364.7801.



57

4,5-Dibromo-2-iodo-1-methyl-1*H*-imidazole (57) (Table 2–3, entry 7)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless solid (74.5 mg, 0.204 mmol, 67%) from 2,5-dibromo-1-methyl-1*H*-imidazole (**54**) (73.2 mg, 0.305 mmol, 1.0 equiv) and iodine (160.0 mg, 0.630 mmol, 2.1 equiv) according to the general procedure B. R_f = 0.58 (hexane/diethyl ether = 1:1); Mp 138–139 ºC; IR (ATR, cm^{-1}): 2916, 1382, 1219, 970; ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 118.3, 106.4, 88.0, 37.2; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_4H_4{}^{79}Br_2IN_2$, 364.7786; found, 364.7803.

Control Experiment (Scheme 2–17)

Isomerization of 2,4-dibromoimidazolyllithium

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,4-dibromo-5-iodo-1-methyl-1*H*-imidazole (**56**) (36.5 mg, 0.0998 mmol, 1.0 equiv), 2,4,5-tribromo-1-methyl-1*H*-imidazole (**59**) (4.0 mg, 0.013 mmol, 13 mol%), which was prepared according to the procedure described in Chapter 5, 5-8-6, and anhydrous THF (1.0 mL). The solution was cooled to –78 °C. *n*BuLi (1.51 M, 70 μL, 0.11 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at –78 °C for 30 min, the reaction mixture was treated with iodine (56.0 mg, 0.221 mmol, 2.2 equiv). After stirring at –78 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,4-dibromo-5-iodo-1-methyl-1*H*-imidazole (**56**) and 4,5-dibromo-2-iodo-1-methyl-1*H*-imidazole (**57**) were determined to be 46% and 36% by ^1H NMR analysis using 1,1,2,2-tetrachloroethane (31.1 mg, 0.185 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 3.67 ppm

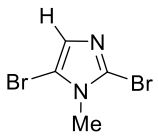
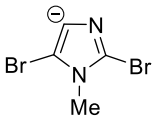
(3 protons for **56**) and 3.65 ppm (3 proton for **57**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

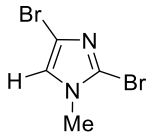
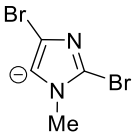
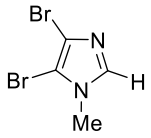
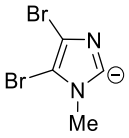
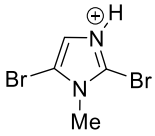
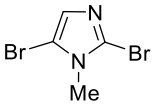
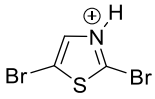
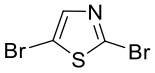
Isomerization of 4,5-dibromoimidazolyllithium

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 4,5-dibromo-2-iodo-1-methyl-1*H*-imidazole (**57**) (38.3 mg, 0.105 mmol, 1.0 equiv), 2,4,5-tribromo-1-methyl-1*H*-imidazole (**59**) (4.3 mg, 0.013 mmol, 13 mol%), which was prepared according to the procedure described in Chapter 5, 5-8-6, and anhydrous THF (1.0 mL). The solution was cooled to –78 °C. ^{n}BuLi (1.51 M, 70 μL, 0.11 mmol, 1.0 equiv) was added to the Schlenk tube. After stirring at –78 °C for 30 min, the reaction mixture was treated with iodine (61.8 mg, 0.243 mmol, 2.3 equiv). After stirring at –78 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,4-dibromo-5-iodo-1-methyl-1*H*-imidazole (**56**) and 4,5-dibromo-2-iodo-1-methyl-1*H*-imidazole (**57**) were determined to be 21% and 85% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (30.8 mg, 0.184 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 3.67 ppm (3 protons for **56**) and 3.65 ppm (3 proton for **57**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

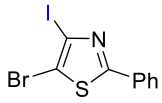
2-8-8 The Calculation of p*K*a Values (Figure 2–6 and 2–8)

The p*K*a values of azoles were calculated as the procedure described in Chapter 2, 2-8-6.

R–H	R^{-}	Δ*G*° [kJ/mol]	p*K*a (in DMSO)
 **38**		1416.6	39.7

		1376.8	33.1
		1384.2	34.4
		1157.0	−3.4
		1121.5	−9.3

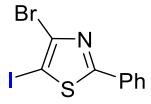
2-8-9 Selective In Situ Transmetalation Followed by Iodination (Table 2–4)



68

5-Bromo-4-iodo-2-phenylthiazole (68) (Table 2–4, entry 1)

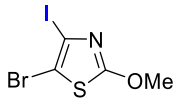
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a colorless solid (99.0 mg, 0.270 mmol, 91%) from 5-bromo-2-phenylthiazole (**67**) (71.6 mg, 0.298 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (91.2 mg, 0.361 mmol, 1.2 equiv), and iodine (152.3 mg, 0.600 mmol, 2.0 equiv) according to the general procedure A (see Chapter 2, 2-8-4). R_f = 0.16 (hexane/diethyl ether = 50:1); Mp 72–74 ºC; IR (ATR, cm^{-1}): 1739, 1460, 1438, 760; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89–7.81 (m, 2H), 7.49–7.40 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 132.3, 131.0, 129.2, 126.3, 113.4, 103.0; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_9H_6{}^{81}BrINS$, 367.8429; found, 367.8421.



69

4-Bromo-5-iodo-2-phenylthiazole (69) (Table 2–4, entry 2)

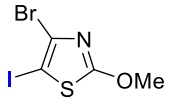
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide the title compound as a colorless solid (99.6 mg, 0.272 mmol, 91%) from 5-bromo-2-phenylthiazole (**67**) (71.7 mg, 0.299 mmol, 1.0 equiv), $ZnCl_2 \cdot$TMPDA (96.3 mg, 0.361 mmol, 1.2 equiv), and iodine (160.6 mg, 0.633 mmol, 2.3 equiv) according to the general procedure A (see Chapter 2, 2-8-4). The ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[81] R_f = 0.16 (hexane/diethyl ether = 20:1); Mp 93–95 ºC; IR (ATR, cm^{-1}): 1462, 1250, 984, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.83 (m, 2H), 7.50–7.41 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.5, 135.8, 132.2, 131.1, 129.2, 126.2, 71.8; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_9H_6{}^{79}BrINS$, 365.8449; found, 365.8465.



71

5-Bromo-4-iodo-2-methoxythiazole (71) (Table 2–4, entry 3)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a colorless solid (79.2 mg, 0.248 mmol, 83%) from 5-bromo-2-methoxythiazole (**70**) (58.3 mg, 0.300 mmol, 1.0 equiv), $ZnCl_2 \cdot$TMEDA (91.2 mg, 0.361 mmol, 1.2 equiv), and iodine (159.5 mg, 0.628 mmol, 2.1 equiv) according to the general procedure A (see Chapter 2, 2-8-4). R_f = 0.32 (hexane/diethyl ether = 50:1); Mp 44–46 ºC; IR (ATR, cm^{-1}): 1520, 1415, 1253, 817; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.1, 103.8, 94.5, 58.7; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_4H_4{}^{81}BrINOS$, 321.8221; found, 321.8235.

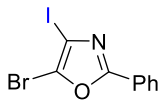


72

4-Bromo-5-iodo-2-methoxythiazole (72) (Table 2–4, entry 4)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether

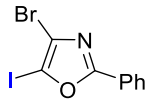
= 50:1) to provide the title compound as a colorless solid (73.9 mg, 0.231 mmol, 78%) from 5-bromo-2-methoxythiazole (**70**) (57.5 mg, 0.296 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (96.3 mg, 0.361 mmol, 1.2 equiv), and iodine (158.8 mg, 0.626 mmol, 2.1 equiv) according to the general procedure B (see Chapter 2, 2-8-7). R_f = 0.20 (hexane/diethyl ether = 50:1); Mp 54–56 ºC; IR (ATR, cm^{-1}): 1520, 1415, 1258, 1217, 836; ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.0, 128.0, 61.3, 59.0; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_4H_4{}^{81}BrINOS$, 321.8221; found, 321.8213.



74

5-Bromo-4-iodo-2-phenyloxazole (74) (Table 2–4, entry 5)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide the title compound as a pale yellow solid (91.0 mg, 0.260 mmol, 85%) from 5-bromo-2-phenyloxazole (**73**) (68.6 mg, 0.306 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.1 mg, 0.357 mmol, 1.2 equiv), and iodine (152.0 mg, 0.599 mmol, 2.0 equiv) according to the general procedure A (see Chapter 2, 2-8-4). R_f = 0.42 (hexane/diethyl ether = 20:1); Mp 83–85 ºC; IR (ATR, cm^{-1}): 1446, 1451, 1190, 1012, 990; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00–7.96 (m, 2H), 7.49–7.44 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 131.4, 129.0, 127.6, 126.3, 125.9, 87.3; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_9H_6{}^{79}BrINO$, 349.8677; found, 349.8668.

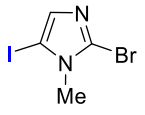


75

4-Bromo-5-iodo-2-phenyloxazole (75) (Table 2–4, entry 6)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless solid (94.9 mg, 0.271 mmol, 91%) from 5-bromo-2-phenyloxazole (**73**) (66.6 mg, 0.297 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (96.7 mg, 0.363 mmol, 1.2 equiv), and iodine (157.0 mg, 0.619 mmol, 2.1 equiv) according to the general procedure B (see Chapter 2, 2-8-7). R_f = 0.29 (hexane/diethyl ether = 30:1); Mp 97–98 ºC; IR (ATR, cm^{-1}): 2922, 1512, 990, 703; ^1H NMR (400 MHz,

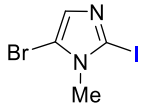
$CDCl_3$): δ 8.02–7.97 (m, 2H), 7.50–7.43 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.5, 131.5, 129.0, 127.5, 126.4, 126.0, 89.2; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_9H_6{}^{81}BrINO$, 351.8657; found, 351.8665.



76

2-Bromo-5-iodo-1-methyl-1*H*-imidazole (76) (Table 2–4, entry 7)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless solid (61.5 mg, 0.214 mmol, 71%) from 2-bromo-1-methyl-1*H*-imidazole (**65**) (48.8 mg, 0.303 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.4 mg, 0.358 mmol, 1.2 equiv), and iodine (156.4 mg, 0.616 mmol, 2.0 equiv) according to the general procedure B (see Chapter 2, 2-8-7). R_f = 0.19 (hexane/diethyl ether = 10:1); Mp 163–164 ºC; IR (ATR, cm^{-1}): 2924, 1400, 1244, 816; ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H), 3.63 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 137.3, 120.2, 71.6, 35.8; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_4H_5{}^{79}BrIN_2$, 286.8681; found, 286.8687.



66

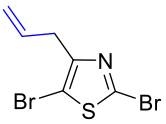
5-Bromo-2-iodo-1-methyl-1*H*-imidazole (66) (Table 2–4, entry 8)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless solid (69.8 mg, 0.243 mmol, 80%) from 2-bromo-1-methyl-1*H*-imidazole (**65**) (49.1 mg, 0.305 mmol, 1.0 equiv), and iodine (157.8 mg, 0.622 mmol, 2.0 equiv) according to the general procedure B (see Chapter 2, 2-8-7). R_f = 0.12 (hexane/diethyl ether = 10:1); Mp 116–118 ºC; IR (ATR, cm^{-1}): 1443, 1251, 1136, 921; ^1H NMR (400 MHz, $CDCl_3$): δ 7.07 (s, 1H), 3.62 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 132.5, 105.2, 89.6, 35.7; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_4H_5{}^{79}BrIN_2$, 286.8681; found, 286.8688.

2-8-10 Selective In Situ Transmetalation Followed by Electrophilic Trapping (Table 2–5)

Preparation of a THF solution of CuCN·2LiCl

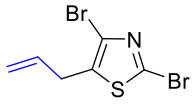
A THF solution of CuCN·2LiCl was prepared according to the procedure described in the previous report.[82] Commercially available LiCl (4.074 g, 96.1 mmol) was heated with a heat gun under vacuum for 15 min in a Schlenk tube. After cooling to room temperature, anhydrous CuCN (4.299 g, 48.0 mmol) and THF (48 mL) was added to the Schlenk tube. The reaction mixture was stirred at room temperature for 3 h to provide a THF solution of CuCN·2LiCl, which was used as a 1.0 M solution in the following experiments.



77

2,5-Dibromo-4-(2-propenyl)-thiazole (77) (Table 2–5, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromothiazole (**47**) (72.3 mg, 0.298 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (91.1 mg, 0.361 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with CuCN·2LiCl (1.0 M in THF, 0.45 mL, 0.45 mmol, 1.5 equiv) and allyl iodide (40 µL, 0.44 mmol, 1.5 equiv). The resulting mixture was warmed to 25 ºC for 2 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a colorless oil (73.4 mg, 0.259 mmol, 87%); R_f = 0.19 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 1261, 1097, 1020, 799; ^1H NMR (400 MHz, $CDCl_3$): δ 5.99–5.82 (m, 1H), 5.21–5.09 (m, 2H), 3.48 (dd, 2H, J = 6.4, 0.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.0, 134.7, 133.4, 117.4, 106.5, 34.0; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_6H_6{}^{79}Br^{81}BrNS$, 283.8567; found, 283.8575.



78

2,4-Dibromo-5-(2-propenyl)-thiazole (78) (Table 2–5, entry 2)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromothiazole (**47**) (72.4 mg, 0.298 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (96.6 mg, 0.362 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with copper(I) cyanide di(lithium chloride) complex (1.0 M, 0.45 mL, 0.45 mmol, 1.5 equiv) and allyl iodide (30 µL, 0.330 mmol, 1.1 equiv). The resulting mixture was warmed to 25 ºC for 3 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a pale yellow oil (55.1 mg, 0.195 mmol, 65%); R_f = 0.17 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 1507, 1409, 1192, 1019; ^1H NMR (400 MHz, $CDCl_3$): δ 5.98–5.82 (m, 1H), 5.22–5.10 (m, 2H), 3.48 (ddd, 2H, J = 6.4, 1.4, 1.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.6, 134.0, 133.4, 122.6, 118.4, 32.1; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_6H_6{}^{79}Br_2NS$, 281.8588; found, 281.8578.

Control Experiments

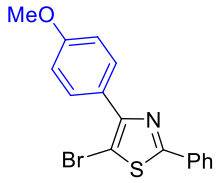
Reaction with allyl iodide without CuCN·2LiCl (Table 2–5, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromothiazole (**47**) (72.4 mg, 0.298 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.6 mg, 0.359 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with allyl iodide (41 µL, 0.45 mmol, 1.5 equiv). The resulting mixture was warmed to 25 ºC for 3 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the

aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The recovery yield of 2,5-dibromothiazole (**47**) was determined to be 66% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (43.3 mg, 0.258 mmol) as an internal standard by comparing relative values of integration for the peak observed at 7.52 ppm (1 proton for **47**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. None of allylated thiazole **77** was observed in the ^{1}H NMR spectrum.

Reaction with allyl iodide without CuCN·2LiCl (Table 2–5, entry 2)

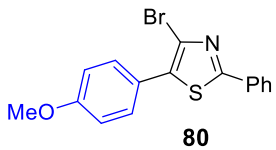
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromothiazole (**47**) (73.8 mg, 0.304 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (96.5 mg, 0.362 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with allyl iodide (30 μL, 0.330 mmol, 1.1 equiv). The resulting mixture was warmed to 25 ºC for 3 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The filtrate was concentrated under reduced pressure to give a crude product. The recovery yield of 2,4-dibromothiazole was determined to be 69% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (36.6 mg, 0.218 mmol) as an internal standard by comparing relative values of integration for the peak observed at 7.21 ppm (1 proton for 2,4-dibromothiazole) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. None of allylated thiazole **78** was observed in the ^{1}H NMR spectrum.



79

5-Bromo-4-(4-methoxyphenyl)-2-phenylthiazole (79) (Table 2–5, entry 3)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-2-phenylthiazole (**67**) (71.9 mg, 0.299 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.7 mg, 0.359 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, to the reaction mixture was added a THF solution (1.0 mL) of $Pd_2(dba)_3$ (7.5 mg, 8.2 μmol, 2.7 mol%) and tris[4-(trifluoromethyl)phenyl]phosphine (15.1 mg, 32.4 μmol, 10.8 mol%). After addition of 1-iodo-4-methoxybenzene (211.1 mg, 0.902 mmol, 3.0 equiv), the reaction mixture was stirred at 80 ºC for 21 h. The reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide the title compound as a pale yellow solid (67.2 mg, 0.194 mmol, 65%); R_f = 0.32 (hexane/diethyl ether = 20:1); Mp 94–95 ºC; IR (ATR, cm^{-1}): 1610, 1480, 1252, 1177; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 2H, J = 9.2 Hz), 7.94–7.91 (m, 2H), 7.47–7.43 (m, 3H), 7.00 (d, 2H, J = 9.2 Hz), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.0, 159.8, 153.0, 133.2, 130.5, 130.1, 129.1, 126.3, 126.2, 113.8, 102.1, 55.4; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}{}^{79}BrNOS$, 345.9901; found, 345.9896.

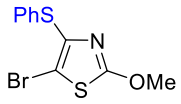


80

4-Bromo-5-(4-methoxyphenyl)-2-phenylthiazole (80) (Table 2–5, entry 4)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-2-phenylthiazole (**67**)

(71.8 mg, 0.299 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (96.3 mg, 0.361 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, to the reaction mixture was added a THF solution (1.0 mL) of $Pd_2(dba)_3$ (7.5 mg, 8.2 µmol, 2.7 mol%) and tris[4-(trifluoromethyl)phenyl]phosphine (16.1 mg, 34.5 µmol, 11.5 mol%). After addition of 1-iodo-4-methoxybenzene (215.7 mg, 0.922 mmol, 3.1 equiv), the reaction mixture was stirred at 80 ºC for 3 h. The reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide the title compound as a pale yellow solid (80.6 mg, 0.233 mmol, 78%); R_f = 0.34 (hexane/diethyl ether = 20:1); Mp 94–96 ºC; IR (ATR, cm^{-1}): 1530, 1419, 1247, 740; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95–7.91 (m, 2H), 7.63 (d, 2H, *J* = 8.8 Hz), 7.47–7.43 (m, 3H), 6.99 (d, 2H, *J* = 8.8 Hz), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.0, 160.1, 133.2, 132.8, 130.6, 129.1, 126.2, 122.5, 122.4, 114.3, 114.2, 55.5; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}{}^{81}BrNOS$, 347.9881; found, 347.9895.

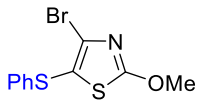


81

5-Bromo-2-methoxy-4-(phenylthio)thiazole (81) (Table 2–5, entry 5)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-2-methoxythiazole (**70**) (57.6 mg, 0.297 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (91.5 mg, 0.362 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was transferred to a mixture of *N*-phenylthiophthalimide (229.3 mg, 0.898 mmol, 3.0 equiv) and copper(II) acetate monohydrate (3.8 mg, 21 µmol, 7.0 mol%) in anhydrous THF (0.5 mL). After stirring at 25 ºC for 24 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic

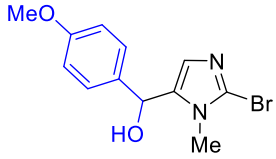
extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a red oil (42.5 mg, 0.141 mmol, 47%); R_f = 0.22 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 1530, 1419, 1247, 740; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.18 (m, 5H), 4.03 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.0, 140.0, 134.5, 129.3, 129.1, 126.8, 104.8, 58.5; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_9{}^{81}BrNOS_2$, 303.9289; found, 303.9284.



82

4-Bromo-2-methoxy-5-(phenylthio)thiazole (82) (Table 2–5, entry 6)

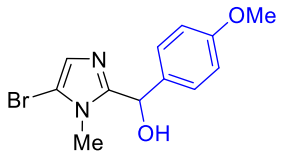
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-2-methoxythiazole (**70**) (57.6 mg, 0.297 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (95.5 mg, 0.358 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 30 min, the reaction mixture was transferred to a mixture of *N*-phenylthiophthalimide (229.9 mg, 0.901 mmol, 3.0 equiv) and copper(II) acetate monohydrate (2.7 mg, 15 μmol, 5.0 mol%) in anhydrous THF (0.5 mL). After stirring at 25 ºC for 24 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 100:1) to provide the title compound as a yellow oil (24.6 mg, 81.4 μmol, 27%); R_f = 0.22 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 1512, 1410, 1249, 1225; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.19 (m, 5H), 4.10 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.3, 135.8, 130.2, 129.4, 127.8, 127.0, 115.2, 58.9; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_9{}^{81}BrNOS_2$, 303.9289; found, 303.9276.



83

(2-Bromo-1-methyl-1*H*-imidazol-5-yl)(4-methoxyphenyl)methanol (83) (Table 2–5, entry 7)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-bromo-1-methyl-1*H*-imidazole (**65**) (48.8 mg, 0.303 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.2 mg, 0.357 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with ^{n}BuMgCl (2.0 M, 0.30 mL, 2.0 equiv). After stirring at 0 ºC for 10 min, the reaction mixture was treated with 4-methoxybenzaldehyde (110 µL, 0.905 mmol, 3.0 equiv). After stirring at 25 ºC for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) to provide the title compound as a colorless solid (29.2 mg, 98.3 µmol, 32%); R_f = 0.15 (hexane/ethyl acetate = 1:1); Mp 134–135 ºC; IR (ATR, cm^{-1}): 3216, 2925, 1512, 1248; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 2H, J = 8.8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 6.64 (s, 1H), 5.79 (d, 1H, J = 4.4 Hz), 3.83 (s, 3H), 3.54 (s, 3H), 2.34 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.3, 137.0, 132.6, 128.4, 127.7, 121.6, 113.9, 67.3, 55.4, 33.0; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{14}{}^{79}BrN_2O_2$, 297.0239; found, 297.0232.



84

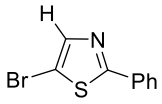
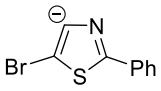
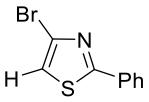
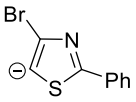
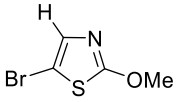
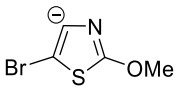
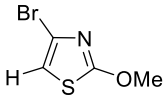
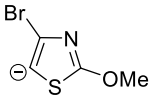
(5-Bromo-1-methyl-1*H*-imidazol-2-yl)(4-methoxyphenyl)methanol (84) (Table 2–5, entry 8)

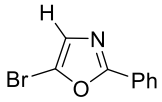
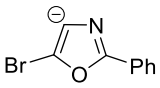
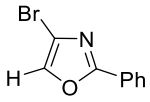
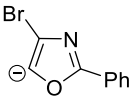
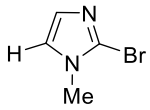
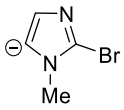
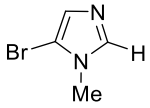
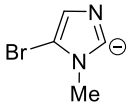
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-bromo-1-methyl-1*H*-imidazole (**65**) (48.9 mg, 0.304 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). The solution was

cooled to −78 ºC. LDA (2.0 M, 0.23 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 30 min, the reaction mixture was treated with 4-methoxybenzaldehyde (110 μL, 0.905 mmol, 3.0 equiv). After stirring at −78 ºC for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) to provide the title compound as a colorless solid (40.3 mg, 0.136 mmol, 45%); R_f = 0.13 (hexane/ethyl acetate = 1:1); Mp 147–149 ºC; IR (ATR, cm^{-1}): 3242, 1511, 1247, 787; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, 2H, *J* = 8.6 Hz), 7.00 (s, 1H), 6.89 (d, 2H, *J* = 8.6 Hz), 5.78 (s, 1H), 3.80 (s, 4H), 3.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.4, 150.1, 132.3, 127.8, 126.9, 114.1, 105.2, 69.5, 55.4, 31.8; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{14}{}^{79}BrN_2O_2$, 297.0239; found, 297.0226.

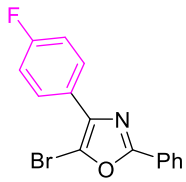
2-8-11 The p*K*a Values of the Thiazoles, Oxazole, and Imidazole (Figure 2–9)

The p*K*a values of azoles were calculated as the procedure described in Chapter 2, 2-8-6.

R–H	R^- (anion)	ΔG [kJ/mol]	p*K*a (in DMSO)
 **67**		1398.7	36.8
		1349.3	28.6
 **70**		1398.9	36.8
		1357.1	29.8

 **73**		1399.8	36.9
		1360.5	30.4
 **65**		1401.8	37.3
		1402.6	37.4

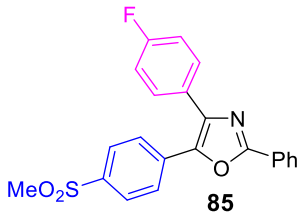
2-8-12 Divergent Syntheses of Biologically Active Azoles (Schemes 2–20 and 2–22)


90

5-Bromo-4-(4-fluorophenyl)-2-phenyloxazole (90)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-phenyl-5-bromooxazole (**73**) (447.0 mg, 2.00 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (606.8 mg, 2.40 mmol, 1.20 equiv), and anhydrous THF (20.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 1.5 mL, 3.0 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 1 h, the reaction mixture was treated with $Pd(PPh_3)_4$ (116.2 mg, 0.101 mmol, 5.0 mol%) and 1-fluoro-4-iodobenzene (700 μL, 6.00 mmol, 3.0 equiv). After stirring at 70 ºC for 24 h, the reaction mixture was treated with saturated aqueous ammonium chloride (14 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with water (60 mL), dried over sodium

sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 100:1) to provide the title compound as a colorless solid (427.4 mg, 1.34 mmol, 67%); R_f = 0.24 (hexane/diethyl ether = 100:1); Mp 107–109 ºC; IR (ATR, cm^{-1}): 1501, 1232, 973, 840, 705; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09–8.06 (m, 2H), 8.03 (dd, 2H, J = 9.0 Hz, 5.4 Hz), 7.51–7.47 (m, 3H), 7.16 (dd, 2H, J = 9.0 Hz, 9.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.8 (d, $^1J_{C–F}$ = 247.3 Hz), 162.3, 137.6, 131.0, 129.0, 128.6 (d, $^3J_{C–F}$ = 7.6 Hz), 126.7, 126.4, 116.4, 115.7 (d, $^2J_{C–F}$ = 21.1 Hz) (one aromatic carbon signal is missing due to overlapping); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 162.1 (d, $^1J_{C–F}$ = 244.3 Hz), 161.6, 136.7, 131.4, 129.3, 128.3 (d, $^3J_{C–F}$ = 7.7 Hz), 126.1 (d, $^4J_{C–F}$ = 2.9 Hz), 126.0, 125.8, 117.6, 115.9 (d, $^2J_{C–F}$ = 21.1 Hz); HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}{}^{79}BrFNO$, 317.9930; found, 317.9936.

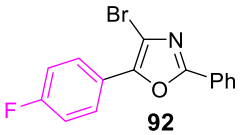


85

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (85)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-4-(4-fluorophenyl)-2-phenyloxazole (**74**) (474.4 mg, 1.49 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (87.8 mg, 76.0 μmol, 5.1 mol%), 4-(methylsulfonyl)phenylboronic acid (606.6 mg, 3.03 mmol, 2.0 equiv), cesium carbonate (687.3 mg, 2.11 mmol, 1.4 equiv), DMF (12.5 mL), and distilled water (3.0 mL). After stirring at 110 ºC for 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (20 mL) three times. The combined organic extracts were washed with water (200 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (CH_2Cl_2/hexane = 5:1). The obtained product was washed with hexane (20 mL) to provide the title compound as a yellow pale solid (502.0 mg, 1.28 mmol, 86%), whose ^1H NMR and ^{13}C NMR spectra were identical to those reported in the literature.[72] R_f = 0.19 (CH_2Cl_2/hexane = 5:1); Mp 203–204 ºC; IR (ATR, cm^{-1}): 1510, 1315, 1151, 777; ^1H

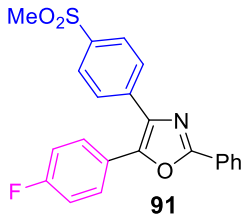
NMR (400 MHz, $CDCl_3$): δ 8.19–8.14 (m, 2H), 7.95 (d, 2H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.4 Hz), 7.68 (dd, 2H, J = 8.6 Hz, 5.4 Hz), 7.54–7.49 (m, 3H), 7.16 (dd, 2H, J = 8.8 Hz, 8.4 Hz), 3.10 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.2 (d, $^1J_{C–F}$ = 248.2 Hz), 161.3, 143.5, 139.8, 138.8, 134.0, 131.2, 130.4 (d, $^3J_{C–F}$ = 7.7 Hz), 129.1, 128.1, 126.8, 126.6, 116.2 (d, $^2J_{C–F}$ = 22.1 Hz), 44.6 (twoaromatic carbon signal is missing due to overlapping); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 162.4 (d, $^1J_{C–F}$ = 245.3 Hz), 160.3, 143.6, 140.5, 137.6, 132.7, 131.3, 130.3 (d, $^3J_{C–F}$ = 8.9 Hz), 129.3, 127.9 (d, $^4J_{C–F}$ = 2.8 Hz), 127.8, 126.7, 126.4, 126.2, 116.0 (d, $^2J_{C–F}$ = 21.1 Hz), 43.4; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{17}FNO_3S$, 394.0913; found, 394.0909.



92

4-Bromo-5-(4-fluorophenyl)-2-phenyloxazole (92)

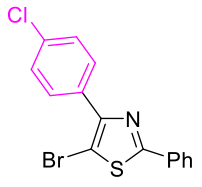
A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-phenyl-5-bromooxazole (**73**) (447.8 mg, 2.00 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (641.5 mg, 2.41 mmol, 1.20 equiv), and anhydrous THF (20.0 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 1.5 mL, 3.0 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 30 min, the reaction mixture was treated with $Pd(PPh_3)_4$ (114.0 mg, 98.7 μmol, 4.9 mol%) and 1-fluoro-4-iodobenzene (400 μL, 3.42 mmol, 1.7 equiv). After stirring at 70 ºC for 24 h, the reaction mixture was treated with saturated aqueous ammonium chloride (14 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with water (60 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 100:1) to provide the title compound as a colorless solid (71.0 mg, 0.193 mmol, 62%); R_f = 0.24 (hexane/diethyl ether = 100:1); Mp 106–107 ºC; IR (ATR, cm^{-1}): 1499, 1238, 976, 835, 710; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11–8.05 (m, 2H), 7.99 (dd, 2H, J = 8.6 Hz, 5.0 Hz), 7.51–7.46 (m, 3H), 7.18 (dd, 2H, J = 8.8 Hz, 8.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.8 (d, $^1J_{C–F}$ = 248.2 Hz), 160.1, 145.5, 131.1, 129.0, 127.5 (d, $^3J_{C–F}$ = 8.6 Hz), 126.4, 126.3, 123.4 (d, $^4J_{C–F}$ = 2.9 Hz), 116.1 (d, $^2J_{C–F}$ = 22.1 Hz), 112.5; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}{}^{79}BrFNO$, 317.9930; found, 319.9922.



91

5-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (91)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-4-(4-fluorophenyl)-2-phenyloxazole (**90**) (477.8 mg, 1.50 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (86.4 mg, 7.48 μmol, 5.0 mol%), 4-(methylsulfonyl)phenylboronic acid (600.4 mg, 3.00 mmol, 2.0 equiv), cesium carbonate (693.0 mg, 2.13 mmol, 1.4 equiv), DMF (12.5mL), and distilled water (3.0 mL). After stirring at 110 ºC for 5 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (40 mL) three times. The combined organic extracts were washed with water (200 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (CH_2Cl_2) to provide the title compound as a yellow pale solid (485.5 mg, 1.23 mmol, 82%); R_f = 0.21 (CH_2Cl_2/hexane = 5:1); Mp 168–170 ºC; IR (ATR, cm^{-1}): 1510, 1314, 1150, 777; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16–8.11 (m, 2H), 7.97 (d, 2H, J = 8.8 Hz), 7.94 (d, 2H, J = 8.8 Hz), 7.65 (dd, 2H, J = 9.0 Hz, 5.4 Hz), 7.53–7.49 (m, 3H), 7.15 (dd, 2H, J = 8.8 Hz, 8.4 Hz), 3.09 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.3 (d, $^1J_{C–F}$ = 249.1 Hz), 160.8, 146.4, 139.9, 138.1, 134.7, 130.9, 129.2 (d, $^3J_{C–F}$ = 8.6 Hz), 129.0, 128.6, 127.9, 126.9, 126.6, 124.6 (d, $^4J_{C–F}$ = 2.9 Hz), 116.4 (d, $^2J_{C–F}$ = 22.1 Hz), 44.6; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{17}FNO_3S$, 394.0913; found, 394.0896.

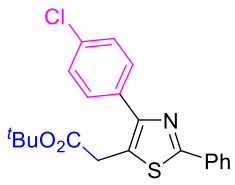


97

5-Bromo-4-(4-chlorophenyl)-2-phenylthiazole (97)

A flame-dried 20-mL round-bottomed flask equipped with a Teflon-coated magnetic

stirring bar and a rubber septum under nitrogen was charged with 5-bromo-2-phenylthiazole (**67**) (72.4 mg, 0.30 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.3 mg, 0.358 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 4.6 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, to the reaction mixture was added a THF solution (1.0 mL) of $Pd_2(dba)_3$ (7.3 mg, 8.0 μmol, 2.6 mol%) and tris[4-(trifluoromethyl)phenyl]phosphine (14.4 mg, 30.9 μmol, 10 mol%). After addition of 1-iodo-4-chlorobenzene (215.8 mg, 0.905 mmol, 3.0 equiv), the reaction mixture was stirred at 80 ºC for 3 h. The reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (3 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 100:1) to provide the title compound as a colorless solid (89.0 mg, 0.254 mmol, 84%); R_f = 0.14 (hexane/diethyl ether = 100:1); Mp 128–130 ºC; IR (ATR, cm^{-1}): 1477, 1092, 827, 760; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 2H, J = 8.4 Hz), 7.94–7.90 (m, 2H), 7.48–7.42 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.5, 152.1, 134.6, 133.0, 132.1, 130.7, 130.1, 129.2, 128.7, 126.4, 103.8; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}{}^{81}Br^{35}ClNS$, 351.9385; found, 351.9384.

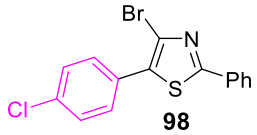


Fentiazac
tert-butyl ester (**95**)

Fentiazac *tert*-butyl ester (95)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-4-(4-chlorophenyl)-2-phenylthiazole (**97**) (35.0 mg, 0.100 mmol, 1.0 equiv), $Pd_2(dba)_3$ (2.4 mg, 2.6 μmol, 2.6 mol%), JohnPhos (5.3 mg, 17.8 μmol, 18 mol%). The separately prepared *tert*-butyl 2-bromozincacetate[83] (0.075 M, 2.0 mL, 0.15 mmol, 1.5 equiv) was added to the solution via a syringe. After stirring at 65 ºC for 24 h, the reaction mixture was treated with saturated aqueous ammonium chloride (3 mL). After being partitioned, the aqueous layer

was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with water (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 30:1) to provide the title compound as a pale yellow solid (19.5 mg, 50.5 μmol, 51%); Mp 93–95 ºC; IR (ATR, cm^{-1}): 1732, 1484, 1149, 763; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.95 (m, 2H), 7.66 (d, 2H, J = 8.4 Hz), 7.47–7.41 (m, 5H), 3.82 (s, 2H), 1.49 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.3, 166.3, 152.7, 134.2, 133.6, 133.3, 130.3, 130.2, 129.0, 128.8, 126.6, 125.6, 82.4, 34.6, 28.1; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{21}{}^{35}ClNO_2S$, 386.0982; found, 386.0969.

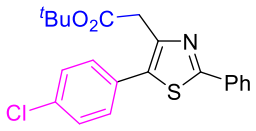


98

4-Bromo-5-(4-chlorophenyl)-2-phenylthiazole (98)

A flame-dried 20-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromo-2-phenylthiazole (**67**) (71.3 mg, 2.97 mmol, 1.0 equiv), $ZnCl_2$·TMPDA (96.2 mg, 0.361 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.23 mL, 4.6 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, to the reaction mixture was added a THF solution (1.0 mL) of $Pd_2(dba)_3$ (7.2 mg, 7.9 μmol, 2.6 mol%) and tris[4-(trifluoromethyl)phenyl]phosphine (14.3 mg, 30.7 μmol, 10 mol%). After addition of 1-iodo-4-chlorobenzene (216.7 mg, 0.909 mmol, 3.1 equiv), the reaction mixture was stirred at 80 ºC for 24 h. The reaction mixture was treated with saturated aqueous ammonium chloride (3 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (3 mL) three times. The combined organic extracts were washed with water (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 100:1) to provide the title compound as a pale yellow solid (85.6 mg, 0.244 mmol, 82%); R_f = 0.19 (hexane/diethyl ether = 20:1); Mp 119–120 ºC; IR (ATR, cm^{-1}): 1473, 1093, 823, 762; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.92 (m, 2H), 7.64 (d, 2H, J = 8.8 Hz), 7.48–7.42 (m, 5H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.9, 135.0, 132.5, 131.9, 130.9, 130.4,

129.15, 129.10, 128.7, 126.3, 123.4; HRMS (DART$^+$) *m/z*: [M+H]$^+$ calcd. for $C_{15}H_{10}{}^{81}Br^{35}ClNS$, 351.9385; found, 351.9389.



Fentiazac *tert*-butyl ester isomer **96**

Fentiazac *tert*-butyl ester isomer (96)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 4-bromo-5-(4-chlorophenyl)-2-phenylthiazole (**92**) (35.2 mg, 0.100 mmol, 1.0 equiv), $Pd_2(dba)_3$ (5.0 mg, 5.5 μmol, 5.5 mol%), XPhos (9.5 mg, 19.9 μmol, 20 mol%). The separately prepared *tert*-butyl 2-bromozincacetate[84] (0.035 M, 4.3 mL, 0.15 mmol, 1.5 equiv) was added to the solution via a syringe. The solution was heated to 65 ºC. After stirring at 65 ºC for 4 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (3 mL) three times. The combined organic extracts were washed with water (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 30:1) to provide the title compound as a pale yellow solid (26.6 mg, 0.0689 mmol, 69%); Mp 93–94 ºC; IR (ATR, cm^{-1}): 1732, 1486, 1146, 762; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.92 (m, 2H), 7.48–7.39 (m, 7H), 3.76 (s, 2H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.9, 165.9, 146.2, 134.5, 133.7, 133.5, 130.6, 130.2, 130.1, 129.1, 129.0, 126.5, 81.5, 37.2, 28.2; HRMS (DART$^+$) *m/z*: [M+H]$^+$ calcd. for $C_{21}H_{21}{}^{35}ClNO_2S$, 386.0982; found, 386.0984.

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(62) Deposition Numbers 2073487 (for $ZnCl_2$·TMEDA), 2073489 (for $ZnBr_2$·TMEDA), 2073507 (for ZnI_2·TMEDA), 2073576 (for $ZnCl_2$·TEEDA), 2073871 (for $ZnCl_2$·TMPDA), and 2073647 (for $ZnCl_2$·DMP) contain the supplementary crystallographic data for this paper. These data are provided free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(63) Deposition Numbers 2072650 (for **55**), 2076120 (for **56**), and 2072658 (for **57**) contain the supplementary crystallographic data for this paper. These data are provided free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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第三章

ブロモアレーンの形式ハロゲンダンス

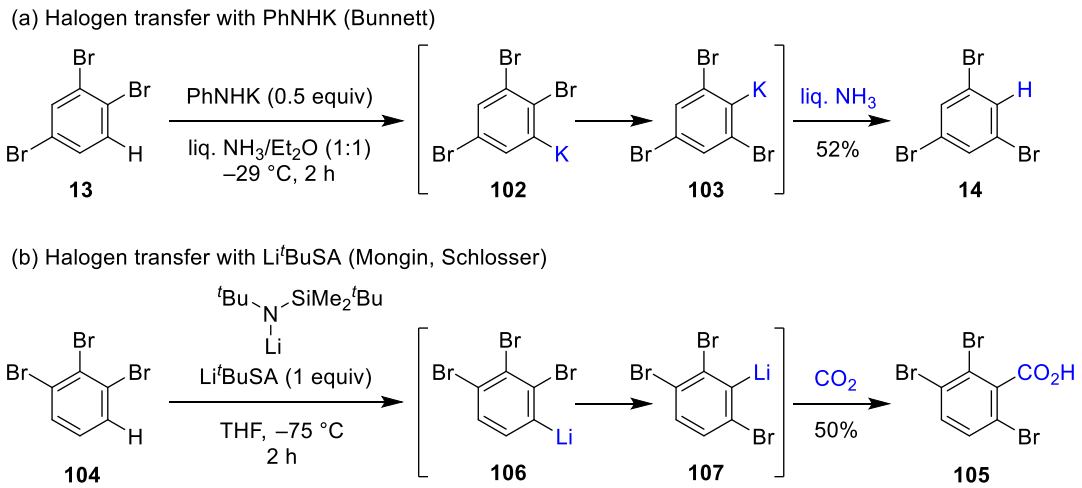
3-1　緒言

第二章では，反応系中でただちに有機リチウムを有機亜鉛反応剤へ金属交換する in situ トランスメタル化を精密に制御し，短寿命アゾリルリチウムのハロゲンダンスを実現させた。第三章では，報告例が少ないベンゼンのハロゲンダンスに着目した。第二章と同様，ベンゼン由来の短寿命有機リチウムは不安定で，望まないベンザインの形成が問題であった。有機リチウムを経由したハロゲンダンスが困難であったため，本章では，有機リチウムを有機亜鉛反応剤へ in situ トランスメタル化することで，ベンゼンのハロゲンダンスをめざした。第二章と同様に in situ トランスメタル化によって有機亜鉛反応剤を発生させた後，臭素化によってハロゲンダンスの鍵中間体を生成させ，続く位置選択的な臭素–マグネシウム交換，求電子剤の導入によって段階的な形式ハロゲンダンスを達成した。形式ハロゲンダンスによって，ブロモベンゼンだけでなく，幅広いヘテロ芳香環に適用可能な一般性が高いハロゲンダンスの反応条件を確立した。

3-2　形式ハロゲンダンス

第一章，第二章で述べたように，従来，ブロモチオフェン [17,19] やブロモピリジン [20] のハロゲンダンスは数多く報告されてきた。一方，ブロモベンゼンやその他のヘテロ芳香環のハロゲンダンスの例 [10c,25a,84] は限られていた。例えば，Bunnett らは，トリブロモベンゼンのハロゲンダンスを報告している (Scheme 3–1a)[16]。トリブロモベンゼン **13** に対して，PhNHK を液体アンモニア，ジエチルエーテル溶媒中で作用させ，1,3,5-トリブロモベンゼン(**14**)を収率 52%で得ている。

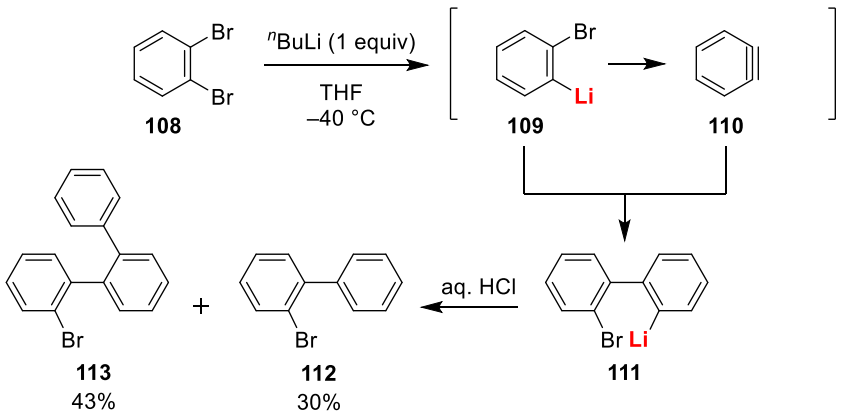
Scheme 3–1. Halogen Dance of Bromobenzenes Under Classical Conditions



本反応は，有機カリウム **102** が有機カリウム **103** へハロゲンダンスし，液体アンモニアによってプロトン化されることで進行したと考えられる。しかし，Bunnett の手法では，プロトン以外の求電子剤は検討されていない点が問題であった。また，Mongin と Schlosser は，ハロゲンダンスに有効な塩基として，リチウム *tert*-ブチル(*tert*-ブチルジメチルシリル)アミド (Li^{t}BuSA)を報告している (Scheme 3–1b)[85]。トリブロモベンゼン **104** に Li^{t}BuSA を作用させ，二酸化炭素を作用させることで，安息香酸誘導体 **105** を収率 50%で得ている。本反応は，発生した有機リチウム **106** のハロゲンダンスによって，有機リチウム **107** が生成し進行したと考えらえる。しかし，トリブロモベンゼン **104** のハロゲンダンス以外に，Li^{t}BuSA が適用された例は報告されておらず，一般性が高いベンゼンのハロゲンダンスの反応条件は未開発であった。

以上のように，ハロゲンダンスの基質として利用できるブロモアレーンが限られている研究背景を受け，より一般性が高いハロゲンダンスの反応条件の開発をめざした。ベンゼンのハロゲンダンスの一般性が低い理由として，ハロゲンダンスにおける反応中間体の有機リチウムがアラインを形成し分解することが考えられる。Chen らは，1,2-ジブロモベンゼン(**108**)に ^{n}BuLi を作用させ，発生させたブロモアリールリチウム **109** が非常に不安定で，ただちに LiBr の脱離を伴ってベンザイン(**110**)が形成されると報告している (Scheme 3–2)[4a]。発生したベンザイン(**110**)は，求電子性が高く，ブロモアリールリチウム **109** と反応し，ビアリールリチウム **111** を与えた後，酸性条件の後処理によって，2-ブロモビフェニル(**112**)とテルフェニル **113** をそれぞれ収率 30%と 43%で得ている。その他のブロモアリールリチウムのアライン形成，またフローマイクロリアクターや

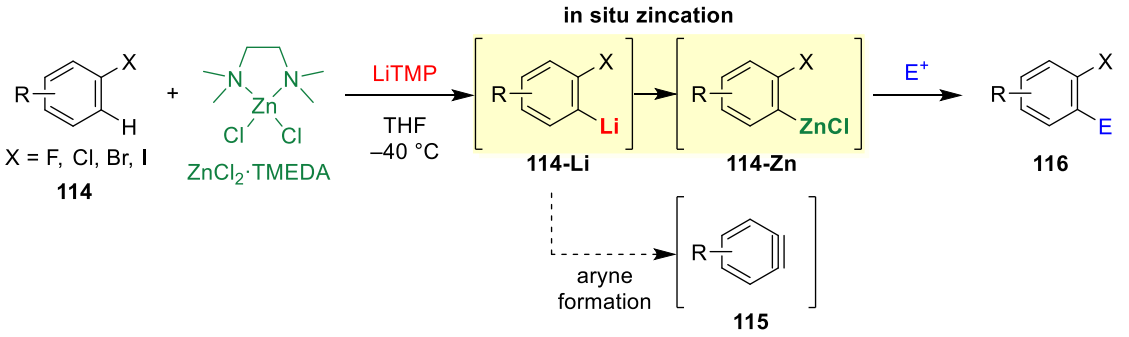
Scheme 3–2. Aryne Formation of the Short-Lived Bromoaryllithium



有機マグネシウム，有機亜鉛反応剤を利用したアライン形成の抑制方法については，著者らが総説 [15h] を執筆している。

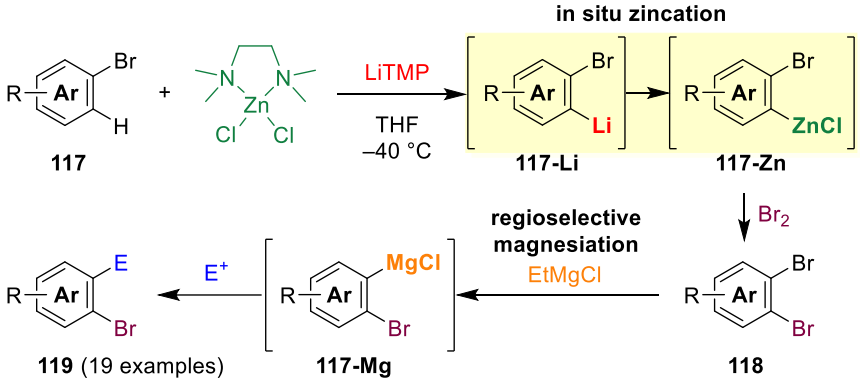
ハロゲンダンスの反応機構として，発生したブロモアリールリチウムがフラスコ内で連続的かつ分子間の臭素–リチウム交換を繰り返すことが知られている [15]。著者は，短寿命ブロモアリールリチウムの望まないアライン形成や分解反応 [4c,4e,15h] を抑制できれば，ベンゼンのハロゲンダンスが達成できると考えた。最近，当研究室の馮は，短寿命ブロモアリールリチウム **114-Li** を in situ トランスメタル化 [54b,55,86] によって選択的に捕捉し，アライン形成の抑制に成功している (Scheme 3–3)[87]。第二章で開発した手法と同様に，ハロベンゼン **114** と塩化亜鉛 TMEDA の混合物に対して，LiTMP を作用させると，発生した短寿命有機リチウム **114-Li** はベンザイン **115** を形成せず，ただちに有機亜鉛反応剤 **114-Zn** へと変換され，求電子剤による捕捉によってハロベンゼン **116** を得ている。

Scheme 3–3. Trapping of Haloaryllithium by In Situ Transmetalationin a Batch Reactor



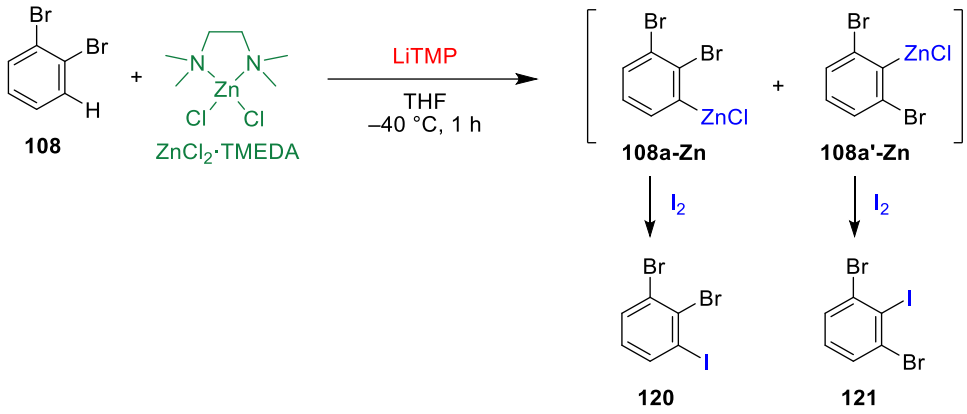
本研究では，in situ トランスメタル化を利用し，アライン形成を抑制したベンゼンのハロゲンダンスを考案した (Scheme 3–4)。まず，ブロモベンゼン **117** から発生させた有機リチウム **117-Li** の in situ トランスメタル化によって有機亜鉛反応剤 **117-Zn** を発生させた後，臭素化によってハロゲンダンスの鍵中間体 [15] と考えられている臭素化体 **118** を得た。さらに，EtMgCl を用いた位置選択的な臭素–マグネシウム交換，求電子剤による捕捉を経て，官能基化されたブロモアレーン **119** へ変換した。ブロモアレーン **118** のハロゲン–金属交換において，適度な安定性と反応性をあわせもつ有機マグネシウム **117-Mg** に着目し，幅広い求電子剤の導入に成功した。二工程を通じて，ブロモアレーン **117** から，ブロモ基の置換位置が変化したブロモアレーン **119** を段階的な形式ハロゲンダンスを経て合成できるようになった。

Scheme 3–4. This Work: Stepwise Halogen Dance Through In Situ Zincation Without Aryne Formation



まず，当研究室の馮が最近報告した塩化亜鉛 TMEDA と LiTMP の組み合わせを用いたジブロモベンゼン **108** の in situ トランスメタル化[87]について，反応条件を再検討した (Table 3–1)。ジブロモベンゼン **108** から発生させた **108-Zn** の臭素化は，鍵中間体を与えるが，構造異性体の関係にある **120** と **121** に対応する二種類の有機金属 **108a-Zn** と **108a'-Zn** を区別するため，臭素化の代わりにヨウ素化を実施した。ジブロモベンゼン **108** と塩化亜鉛 TMEDA の THF 溶液に 1.8 当量の LiTMP を加えた。反応温度を−40 °C とし，LiTMP を 1 時間作用させた後，ヨウ素で処理した結果，ヨウ素化体 **120** を収率 92%で得た (entry 1)。反応温度を検討したところ，−78 °C と 0 °C は，原料のジブロモベンゼン **108** の回収量が増加した (entries 2 and 3)。塩化亜鉛 TMEDA を利用しない条件では，複雑な混合物が生成した (entry 4)。一方で，塩化亜鉛を用いた場合，二種類のヨウ素化体 **120** と **121** を得た (entry 5)[88]。これらの結果から，塩化亜鉛 TMEDA が一段階目の脱プロトン反応に有効であるとわかった。リチウムアミド塩基として LDA を作用させると，原料の 1,2-ジブロモベンゼン(**108**)を 39%回収した (entry 6)。また，塩基として，(TMP)ZnCl·LiCl[89]，$(TMP)_2Zn·2MgCl_2·2LiCl$[37]，(TMP)MgCl·LiCl[36]を用いると，完全に原料を回収した (entries 7–9)。以上の結果から，塩化亜鉛 TMEDA と LiTMP の組み合わせが，対応する有機亜鉛反応剤 **108a-Zn** を発生させるために不可欠であるとわかった。

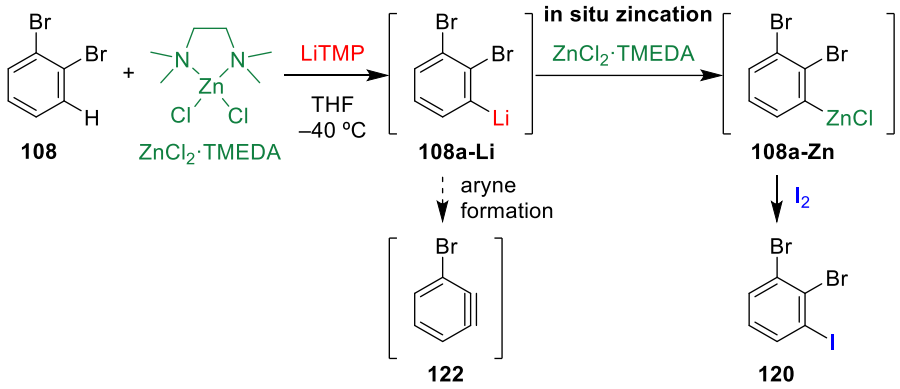
Table 3–1. Optimization for In Situ Zincation of 1,2-Dibromobenzene[a]



entry	deviations	**108** (%)[b]	**120** (%)[b]	**121** (%)[b]
1	none	4	92 (88[c])	–[d]
2	−78 °C	19	77	–[d]
3	0 °C	13	79	–[d]
4	without $ZnCl_2$·TMEDA	–[d]	–[d]	–[d]
5	$ZnCl_2$ instead of $ZnCl_2$·TMEDA	13	25	12
6	LDA instead of LiTMP	39	31	–[d]
7	(TMP)ZnCl·LiCl instead of LiTMP and $ZnCl_2$·TMEDA	87	–[d]	–[d]
8	$(TMP)_2Zn·2MgCl_2·2LiCl$ instead of LiTMP and $ZnCl_2$·TMEDA	92	–[d]	–[d]
9	(TMP)MgCl·LiCl instead of LiTMP	98	–[d]	–[d]

[a]Reaction conditions: 1,2-dibromobenzene (**108**; 1.0 equiv, 0.30 mmol), $ZnCl_2$·TMEDA (1.0 equiv), THF (3.0 mL), then LiTMP (1.8 equiv), −40 °C, 1 h, then iodine (2 equiv), −40 °C, 1 h. [b]Yield determined by ^1H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield. [d]Not detected.

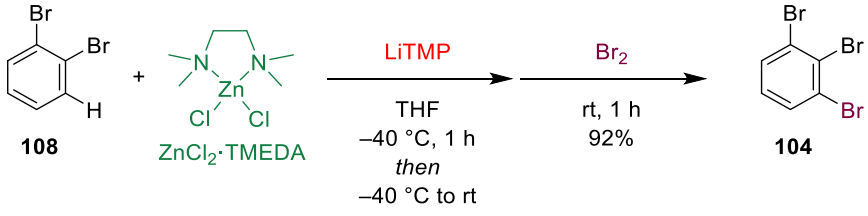
Scheme 3–5. Effects of the Zinc Chloride Diamine to Prevent the Aryne Formation



塩化亜鉛 TMEDA と LiTMP を用いた場合，円滑に脱プロトン反応が進行した結果から，反応機構を推定した (Scheme 3–5)。まず，ジブロモベンゼン **108** は，LiTMP による脱プロトン的リチオ化によって，有機リチウム **108a-Li** へ変換される。発生した有機リチウム **108a-Li** は，塩化亜鉛 TMEDA によって in situ トランスメタル化され，対応する有機亜鉛反応剤 **108a-Zn** に導かれる。有機リチウム **108a-Li** と塩化亜鉛の反応が，塩化亜鉛 TMEDA との反応よりも遅い実験結果 (Table 3–1, entry 5)は，第二章の実験結果 (Table 2–1, entry 1)と一致している。塩化亜鉛 TMEDA を用いなかった場合 (Table 3–1, entry 4)，短寿命な有機リチウム **108a-Li** は，アライン **122** の形成によって分解した [15h] と考えている。有機亜鉛反応剤 **108a-Zn** は，ヨウ素と反応すると，ヨードベンゼン **120** を与える。

馮が報告した反応条件によって発生させた有機亜鉛反応剤 **108a-Zn** は，ヨウ素化だけではなく，臭素化も可能であった (Scheme 3–6)。ヨウ素の代わりに臭素を作用させたところ，ジブロモベンゼン **108** の臭素化が進行し，収率 92%で 1,2,3-トリブロモベンゼン(**104**)が得られた。

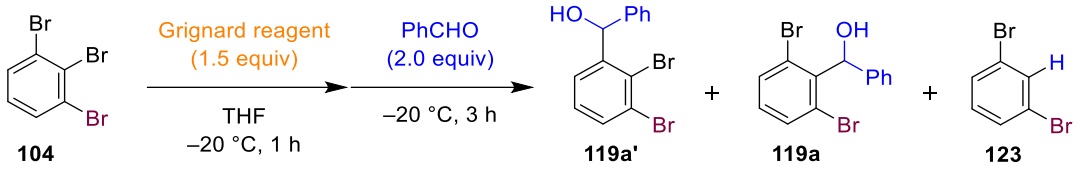
Scheme 3–6. Bromination of 1,2-Dibromobenzene by Using In Situ Transmetalation



3-3　ブロモアレーンの基質一般性

ベンゼンの形式ハロゲンダンスを達成するために, トリブロモベンゼン **104** のもつ三つの臭素原子のうち，最もかさ高い位置の 2 位の臭素原子を選択的に臭素–マグネシウム交換させる Grignard 反応剤を検討した (Table 3–2)。トリブロモベンゼン **104** に対して，Grignard 反応剤を 1.5 当量作用させ，ベンズアルデヒドを–20 °C で 3 時間反応させた。まず，臭素–マグネシウム交換に一般的に利用されることが多い, ^{i}PrMgCl·LiCl[39a] を用いたところ, 目的の付加体 **119a** を収率 54% で得たが，望まない異性体 **119a'** も収率 8%で生成した (entry 1)。この結果は，かさ高いイソプロピル基の立体障害によって，立体的にすいた位置の臭素原子における臭素–マグネシウム交換が進行しやすかったためと考えられる。異性体 **119a'** の収率を低下させるため，イソプロピル基よりも炭素原子が一つ少ないエチル基をもつ EtMgCl を用いたところ，目的の付加体 **119a** を収率 71%で選択的に得た (entry 2)。一方で, さらに炭素原子を減らした MeMgBr を用いたところ，原料を定量的に回収した (entry 3)。なお，Me_3SiCH_2MgCl·LiCl を用いた場合も同様に原料を回収した (entry 4)。また，イソプロピル基のような枝分かれ構造をもたない直鎖の ^{n}BuMgCl を作用させると，ベンズヒドロール **119a** の収率は 62% だった (entry 5)。なお，イソプロピル基よりも炭素数が一つ多い ^{t}BuMgCl を用いた場合は，原料を定量的に回収した (entry 6)。以上の結果から，適度にかさ高い EtMgCl が選択的な臭素–マグネシウム交換に最適であるとわかった。ジブロモベンゼン **108** の in situ トランスメタル化を用いた臭素化，および生成したトリブロモベンゼン **104** の EtMgCl による選択的な臭素–マグネシウム交換を実施し，二段階の形式ハロゲンダンスを達成した。

Table 3–2. Screening of Grignard Reagents for Selective Bromine–Magnesium Exchange[a]



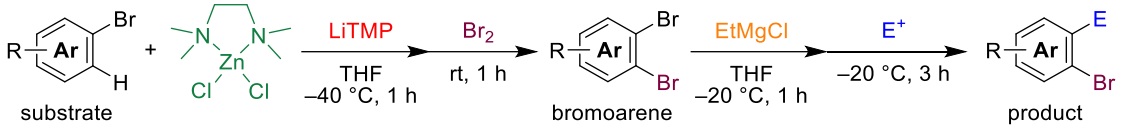
entry	Grignard reagent	**108** (%)[b]	**119a'** (%)[b]	**119a** (%)[b]	**123** (%)[b]	**ratio**[c]
1	^{i}PrMgCl·LiCl	17	8	54	8	7
2	EtMgCl	9	4	71	15	18
3	MeMgBr	92	–[d]	–[d]	–[d]	–[d]
4	Me_3SiCH_2MgCl·LiCl	quant	–[d]	–[d]	–[d]	–[d]
5	^{n}BuMgCl	–[d]	4	62	28	16
6	^{t}BuMgCl	76	–[d]	–[d]	–[d]	–[d]

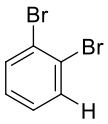
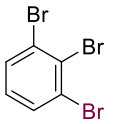
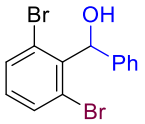
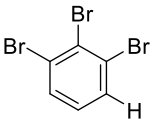
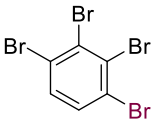
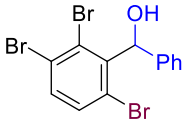
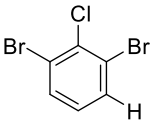
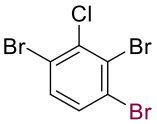
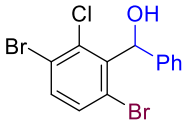
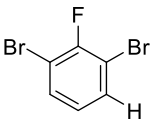
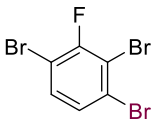
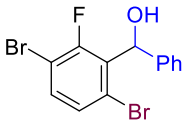
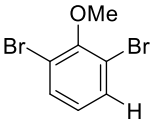
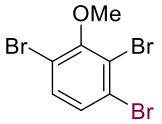
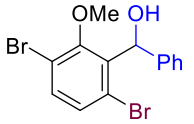
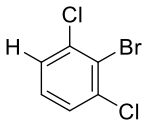
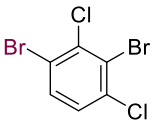
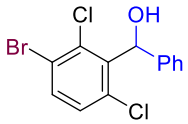
[a]Reaction conditions: 1,2,3-tribromobenzene (**104**; 1.0 equiv, 0.15 mmol), THF (1.5 mL), then Grignard reagent (1.5 equiv, 0.23 mmol), –20 °C, 1 h, then PhCHO (2.0 equiv, 0.30 mmol), –20 °C, 3 h. [b]The yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c]Ratio for the yield of **119a** and **119a'**. [d]Not detected.

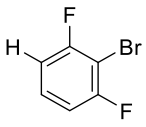
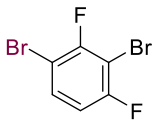
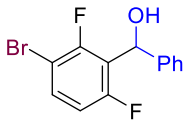
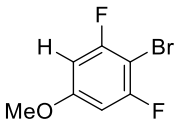
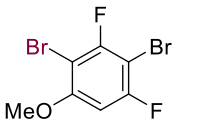
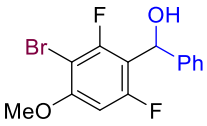
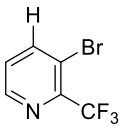
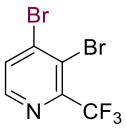
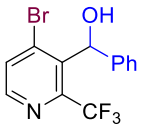
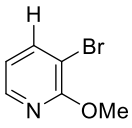
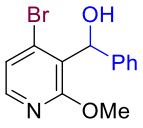
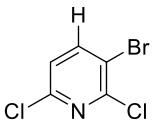
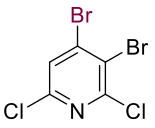
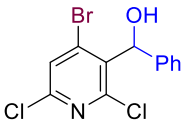
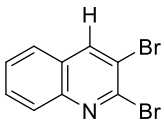
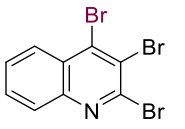
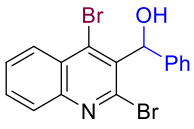
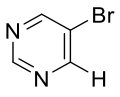
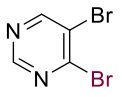
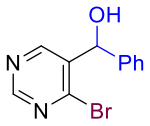
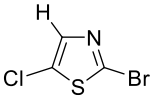
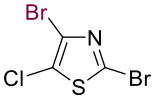
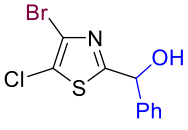
開発した形式ハロゲンダンスの基質一般性を調べた (Table 3–3)。まず，Table 3–1，Table 3–2 で示したように，一段階目の 1,2-ジブロモベンゼン(**108**)の臭素化は収率 92%で進行し，二段階目の選択的臭素–マグネシウム交換およびベンズアルデヒドによる捕捉が収率 69%で進行した (entry 1)。トリハロベンゼン **104** や **117c–d** を出発化合物とすると，臭素化が収率 85–95%で進行し，続く位置選択的な臭素–マグネシウム交換，ベンズアルデヒドとの反応により，対応するベンズヒドロール **119b–d** を収率 52%–85%で得た (entries 2–4)。また，同じ反応条件を用いると，ジブロモアニソール **117e** は，トリブロモアニソール **118e** を経由し，ベンズヒドロール **119e** へ収率 62%で導かれた (entry 5)。さらに，ブロモベンゼン **117f–h** の臭素化は，収率 64%–86%で進行し，ベンズヒドロール **119f–h** が収率 71%–86%で得られた (entries 6–8)。本反応では，臭素原子の形式的な 1,3-転移反応が達成された。ブロモベンゼンに加えて，ブロモヘテロアレーンの臭素原子の移動も実施可能であった。最適条件を用いて，2-(トリフルオロメチル)ピリジン **117i** をジブロモピリジン **118i** と付加体 **119i** へそれぞれ収率 71%と 62%で変換できた (entry 9)。メトキシピリジン **117j** とジクロロピリジン **117k** の臭素化は円滑に進行したが，EtMgCl を用いたマグネシオ化において，C3 位と C4 位が反

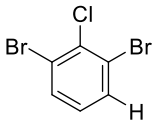
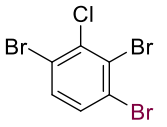
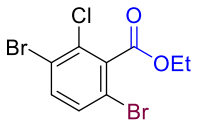
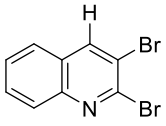
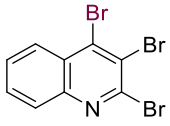
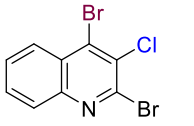
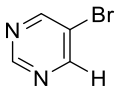
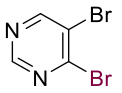
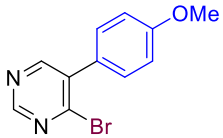
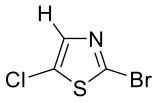
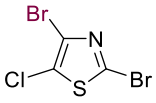
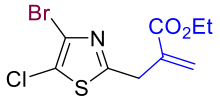
応したピリジンの混合物を得た (C3/C4 = 2.9:1 for **117j**, 2.1:1 for **117k**)。メタル化の反応剤を検討した結果，PhLi を用いると，3-ピリジンメタノール **119j** を収率 29%で選択的に与えた (entry 10)。また，ジクロロピリジン **117k** に対して，^{n}BuLi を作用させると，3-ピリジンメタノール **119k** が収率 28%で選択的に得られた (entry 11)。これらの結果から，発生した有機リチウムがハロゲンダンスによって，熱力学的により安定な 3-ピリジルリチウム[90]へ異性化すると考えた。ジブロモキノリン **117l** のハロゲン移動反応は，トリブロモキノリン **118l** と 3-キノリンメタノール **119l** をそれぞれ収率 91%と 64%で与えた (entry 12)。ピリミジン **117m**[91] とチアゾール **117n** は，ジブロモアレーン **118m** と **118n**，付加体 **119m** と **119n** にそれぞれ収率 41%と 81%，76%と 53%で変換された (entries 13 and 14)。チアゾール **117n** のハロゲン移動反応は，一般的にチアゾールの C2 位でのハロゲンダンスで必要とされているシリル基[44b]を用いることなく，円滑に進行した。また，ベンゼン **117c**，キノリン **117l**，ピリミジン **117m**，チアゾール **117n** から発生させたアリールマグネシウムは，アシル化，塩素化[92]，根岸カップリング反応[67]，アリル化[82,93]が進行し，それぞれ目的のブロモアレーン **119o–r** を収率 49%–75%[94]で得た (entries 15–18)。以上のように，段階的ハロゲンダンスが，様々なブロモアレーンの合成を可能とする堅牢な手法であるとわかった。

Table 3–3. Range of Bromoarenes Applicable to the Stepwise Halogen Transfer[a]



entry	substrate	bromoarene	product
1	 **108**	 **104** 92%	 **119a** 69% (84%[d])
2	 **104**	 **118b** 88%	 **119b** 58%
3	 **117c**	 **118c** 85%	 **119c** 52%[e]
4	 **117d**	 **118d** 95%	 **119d** 85%
5	 **117e**	 **118e** 94%	 **119e** 62%[e,f]
6	 **117f**	 **118f** 86%	 **119f** 79%

7	 **117g**	 **118g** 64%	 **119g** 86%
8	 **117h**	 **118h** 67%[g]	 **119h** 71%[e]
9	 **117i**	 **118i** 71%	 **119i** 62%[f]
10	 **117j**	 **118j** 94%	 **119j** 29%[h]
11	 **117k**	 **118k** 82%	 **119k** 28%[i]
12	 **117l**	 **118l** 91%	 **119l** 64%
13	 **117m**	 **118m** 41%	 **119m** 76%
14	 **117n**	 **118n** 81%[g]	 **119n** 53%[f]

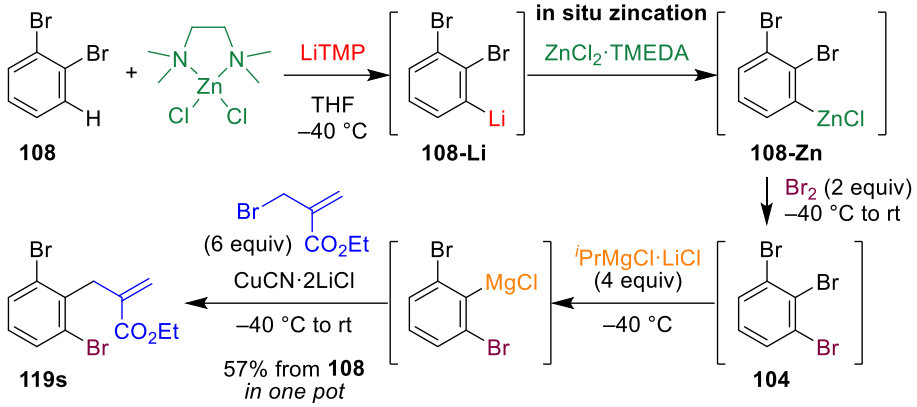
15	 **117c**	 **118c** 85%	 **119o** 75%[j]
16	 **117l**	 **118l** 91%	 **119p** 72%[k]
17	 **117m**	 **118m** 41%	 **119q** 49%[l]
18	 **117n**	 **118n** 81%[g]	 **119r** 49%[m]

[a]Reaction conditions: substrate (1.0 equiv, 3.0 mmol), $ZnCl_2$·TMEDA (1.0 equiv), THF (30 mL), then LiTMP (1.8 equiv), –40 °C, 1 h, then bromine (2 equiv), rt, 1 h. [b]Isolated yield. [c]Reaction conditions: bromoarene (1.0 equiv, 0.15 mmol), THF (1.5 mL), then EtMgCl (1.5 equiv), −20 °C, 1 h, then PhCHO (2 equiv), −20 °C, 3 h. [d]Reaction using 3.0 mmol of 1,2,3-tribromobenzene (**104**). [e]Reaction temperature was −40 °C instead of −20 °C. [f]Reaction time was 5 h instead of 3 h. [g]Reaction with LDA (2.0 equiv) instead of LiTMP. [h]Reaction conditions: 2-methoxypyridine (**117j**; 1.0 equiv, 0.15 mmol), THF (1.5 mL), then PhLi (1.2 equiv), −78 °C, 50 min, then PhCHO (2 equiv), −78 °C , 3 h. [i]Reaction conditions: 2,6-dichloropyridine (**117k**; 1.0 equiv, 0.15 mmol), THF (1.5 mL), then ^{n}BuLi (1.2 equiv), −78 °C, 50 min, then PhCHO (2 equiv), −78 °C to rt, 1 h. [j]Reaction with ethyl cyanoformate (2 equiv), −40 °C, 3 h. [k]Reaction with trichloroacetyl chloride (2 equiv), −20 °C, 5 h. [l]Reaction with $Pd(PPh_3)_4$ (11 mol%), 4-iodoanisole (2 equiv), 60 °C, 4 h. [m]Reaction with CuCN·2LiCl (1.5 equiv), ethyl 2-(bromomethyl)acrylate (2 equiv), rt, 3 h.

3-4　ワンポット形式ハロゲンダンス

最後に，段階的ハロゲンダンスをワンポットで実施した (Scheme 3–7)。まず，Scheme 3–6 と同様に，ジブロモベンゼン **108** の脱プロトンを経る臭素化によって，トリブロモベンゼン **104** を与えた。その後，反応を停止させずに，4 当量の ^{i}PrMgCl·LiCl[39a,95]を−40 °C で 1 時間作用させ，CuCN·2LiCl と 6 当量の 2-(ブロモメチル)アクリル酸エチル[96]を加えると，アリル化 [82,93] が進行し，2-フェニルアクリル酸エチル **119s** を収率 57%で得た。

Scheme 3–7. One-Pot Halogen Dance of 1,2-Dibromobenzene



3-5　結言

第二章と同様に，リチウムから亜鉛への金属交換を利用し，段階的ハロゲンダンスの開発に成功した。一段階目の臭素化には安定な有機亜鉛反応剤を用い，二段階目の求電子剤の導入には反応性の高い有機マグネシウムを用いた。開発した反応は，ブロモベンゼンに加えて，ブロモヘテロアレーンにも適用することができ，ブロモアレーンの基質一般性を大幅に向上させた。段階的ハロゲンダンスのワンポット化も実施可能であり，ブロモ基の移動を伴った直接的な官能基化に成功した。今まで報告されたいずれのハロゲンダンスよりも基質一般性が高い反応条件の開発に成功した。

3-6　Experimental Section

3-6-1　General

Analytical thin layer chromatography (TLC) was performed on Wako 70 F_{254} glass sheets precoated with a 0.25 mm thickness of silica gel. Melting points (Mp) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wavenumbers (cm^{-1}). ^{1}H NMR (400 MHz), $^{13}C\{^{1}H\}$ NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, DMSO-d_5: δ 2.50 ppm) and coupling constants are given in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^{1}H\}$

NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, CD_3CN: δ 118.26 ppm). Chemical shifts for ^{19}F NMR are reported in ppm from $CFCl_3$ with the solvent resonance as the internal standard ($C_6H_5CF_3$ in $CDCl_3$: δ –62.61 ppm[97]). High-resolution mass spectroscopy (HRMS) was performed on a JEOL JMS-T100LP AccuTOF LC-Plus [electrospray ionization (ESI)] with a JEOL MS-5414DART attachment, and [electron ionization (EI)] with a JEOL JMS-700 MStation.

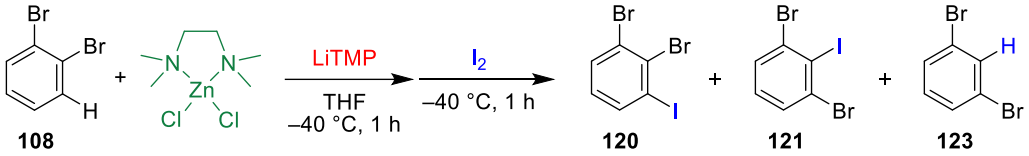
3-6-2 Materials

All workup and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel® 60N (63–212 μm, FUJIFILM Wako Pure Chemical Co., Ltd.) or high-efficiency irregular silica (25–40 μm, Santai Science Inc.). Anhydrous THF (>99.5%, water content: <30 ppm) was purchased from Kanto Chemical Co., Inc. and further dried by passing through a solvent purification system (Glass Contour) prior to use. LDA (2.0 M in THF/heptane/ethylbenzene), ^{i}PrMgCl·LiCl (1.3 M in THF), $(TMP)_2Zn·2MgCl_2·2LiCl$ (12 wt% in THF/toluene), and TMPMgCl·LiCl (1.0 M in THF/toluene) were purchased from Sigma-Aldrich Co. and used as received. EtMgCl (2.0 M in THF) was purchased from Tokyo Chemical Industry Co., Ltd. and used as received. ^{n}BuLi (1.6 M in hexane) was purchased from Kanto Chemical Co. and used as received. Substrates **108** (Product Number: D0168), **104** (Product Number: T3329), **117e** (Product Number: D1943), **117f** (Product Number: B0983), **117g** (Product Number: D1943), **117h** (Product Number: B3392), and **117k** (Product Number: B4935) were purchased from Tokyo Chemical Industry Co., Ltd. and used as received. Substrates **117c** (Product Number: BD215130), **117d** (Product Number: BD231692), **117i** (Product Number: BD212864), **117j** (Product Number: BD3459), and **117n** (Product Number: BD157684) were purchased from BLD Pharmatech Ltd. and used as received. Substrate **117m** (Product Number: 036376) was purchased from Oakwood Pharmacy Ltd. and used as received. Substrate **117l** was prepared according to the procedure described in Chapter 3, 3-6-4. Freshly prepared $Pd(PPh_3)_4$ [98] and $ZnCl_2·TMEDA$ [99] were used in the following experiments. Trimethylsilyl chloride (Me_3SiCl) was purchased from Tokyo Chemical Industry Co., Ltd. and distilled over CaH_2.

3-6-3 Optimization for In Situ Zincation of 1,2-Dibromobenzene (Table 3–1)

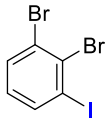
Preparation of a THF solution of LiTMP

A THF solution of LiTMP was prepared according to the procedure described in our previous report.[100] A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with TMPH (0.60 mL, 3.5 mmol) and THF (2.4 mL). To a THF solution of TMPH was added ^{n}BuLi (1.52 M in hexane, 2.30 mL, 3.5 mmol) dropwise at –78 °C. The resulting solution was stirred at 0 °C for 30 min to provide a THF solution of LiTMP, which was used as a 0.66 M solution in the following experiments.



entry[a]	deviations	**108** (%)[b]	**120** (%)[b]	**121** (%)[b]	**123** (%)[b]
1	none	4	92 (88[c])	–[d]	–[d]
2	–78 °C	19	77	–[d]	–[d]
3	0 °C	13	79	–[d]	–[d]
4	without $ZnCl_2$·TMEDA	–[d]	–[d]	–[d]	–[d]
5	$ZnCl_2$ instead of $ZnCl_2$·TMEDA	13	25	12	6
6	LDA instead of LiTMP	39	31	–[d]	3
7	TMPZnCl·LiCl instead of $ZnCl_2$·TMEDA/LiTMP	87	–[d]	–[d]	–[d]
8	$(TMP)_2Zn·2MgCl_2·2LiCl$ instead of $ZnCl_2$·TMEDA/LiTMP	92	–[d]	–[d]	–[d]
9	TMPMgCl·LiCl instead of LiTMP	98	–[d]	–[d]	–[d]

[a]Reaction conditions: 1,2-dibromobenzene (**108**; 1.0 equiv, 0.29–0.31 mmol), $ZnCl_2$·TMEDA (1.0 equiv, 0.30 mmol), THF (3.0 mL), then LiTMP (1.7–2.0 equiv, 0.53 mmol), –40 °C, 1 h, then iodine (2 equiv, 0.6 mmol), –40 °C, 1 h. [b]The yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield. [d]Not detected.



120

1,2-Dibromo-3-iodobenzene (120) (Table 3–1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (71.6 mg, 0.304 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (78.7 mg, 0.312 mmol, 1.0 equiv), and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (178.4 mg, 0.703 mmol, 2.3 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (96.1 mg, 0.266 mmol, 88%), whose ^{1}H and ^{13}C NMR data were identical with those reported in the literature.[101] R_f = 0.69 (hexane); Mp 74–75 °C; IR (ATR, cm^{-1}): 1546, 1420, 1386, 768; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, 1H, J = 7.7, 1.2 Hz), 7.60 (dd, 1H, J = 8.0, 1.2 Hz), 6.84 (dd, 1H, J = 8.0, 7.7 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.3, 133.5, 132.0, 129.7, 124.6, 102.3.

Reaction at –78 °C (Table 3–1, entry 2)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (70.2 mg, 0.298 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (75.8 mg, 0.300 mmol, 1.0 equiv), and anhydrous THF (3.0 mL). The solution was cooled to –78 °C. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at –78 °C for 1 h, the reaction mixture was treated with iodine (187.6 mg, 0.739 mmol, 2.5 equiv). After stirring at –78 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium

thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 1,2-dibromobenzene (**108**), 1,2-dibromo-3-iodobenzene (**120**), 1,3-dibromo-2-iodobenzene (**121**), and 1,3-dibromobenzene (**123**) were determined to be 19%, 77%, 0%, and 0% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (36.9 mg, 0.220 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 7.17 ppm (2 protons for **108**), 7.82 ppm (1 proton for **120**, whose chemical shift was identical with those reported in the literature[101]), 7.56 ppm (2 protons for **121**, whose chemical shift was identical with those reported in the literature[102]), and 7.44 ppm (2 protons for **123**, whose chemical shift was identical with those reported in the literature[103]) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction at 0 °C (Table 3–1, entry 3)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (67.9 mg, 0.288 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (76.7 mg, 0.304 mmol, 1.1 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 °C. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at 0 °C for 1 h, the reaction mixture was treated with iodine (175.2 mg, 0.690 mmol, 2.4 equiv). After stirring at 0 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

Reaction in the absence of $ZnCl_2$·TMEDA (Table 3–1, entry 4)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (67.3 mg, 0.285 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.9 equiv) was added to the Schlenk tube.

After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (160.1 mg, 0.631 mmol, 2.2 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

Reaction with $ZnCl_2$ instead of $ZnCl_2$·TMEDA (Table 3–1, entry 5)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with $ZnCl_2$ (41.3 mg, 0.303 mmol, 0.99 equiv). The Schlenk tube was heated with a heat gun under vacuum for 5 min. After cooling to room temperature, the Schlenk tube was charged with 1,2-dibromobenzene (**108**) (73.0 mg, 0.309 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (161.6 mg, 0.637 mmol, 2.1 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

Reaction with LDA instead of LiTMP (Table 3–1, entry 6)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (72.2 mg, 0.306 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (75.7 mg, 0.300 mmol, 0.98 equiv), and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. LDA (2.0 M, 0.30 mL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (166.2 mg, 0.655 mmol, 2.1 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The

combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

Preparation of TMPZnCl·LiCl

A THF solution of TMPZnCl·LiCl was prepared according to the procedure described in the previous report.[89] A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with $ZnCl_2$ (1.069 g, 7.84 mmol, 1.1 equiv). The Schlenk tube was heated with a heat gun under vacuum for 5 min. After cooling to room temperature, the Schlenk tube was charged with anhydrous THF (8.0 mL). The resulting solution was transferred to a THF solution of LiTMP (0.66 M, 10.5 mL, 6.9 mmol, 1.0 equiv) via cannula at room temperature. The resulting solution was stirred at room temperature for 1 h to provide a THF solution of TMPZnCl·LiCl (0.23 M).[83]

Reaction with TMPZnCl·LiCl instead of $ZnCl_2$·TMEDA and LiTMP (Table 3–1, entry 7)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (73.4 mg, 0.311 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. TMPZnCl·LiCl (0.23 M, 2.6 mL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (164.5 mg, 0.648 mmol, 2.1 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

Reaction with $(TMP)_2Zn·2MgCl_2·2LiCl$ instead of $ZnCl_2$·TMEDA and LiTMP (Table 3–1, entry 8)

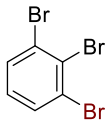
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (72.3

mg, 0.306 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (12 wt%, 1.8 mL, 0.61 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (163.7 mg, 0.645 mmol, 2.1 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

Reaction with TMPMgCl·LiCl instead of LiTMP (Table 3–1, entry 9)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (72.7 mg, 0.308 mmol, 1.0 equiv), $ZnCl_2{\cdot}TMEDA$ (76.5 mg, 0.303 mmol, 0.98 equiv), and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. TMPMgCl·LiCl (1.0 M, 0.60 mL, 0.60 mmol, 1.9 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (167.3 mg, 0.659 mmol, 2.1 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

3-6-4 Range of Bromoarenes Applicable to the Stepwise Halogen Transfer (Scheme 3–6, Table 3–2 and 3–3)



104

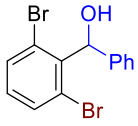
1,2,3-Tribromobenzene (104) (Scheme 3–6 and Table 3–3, entry 1)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (709.8 mg, 3.01 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (757.9 mg, 3.00 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (873.0 mg, 2.77 mmol, 92%), whose ^{1}H and ^{13}C NMR data were identical with those reported in the literature.[104] R_f = 0.63 (hexane); Mp 77–79 °C; IR (ATR, cm^{-1}): 1551, 1424, 1394, 769; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, J = 7.8 Hz), 7.03 (t, 1H, J = 7.8 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 132.6, 129.3, 127.7, 126.3; HRMS (EI) *m/z*: $[M]^+$ calcd. for $C_6H_3{}^{79}Br_2{}^{81}Br$, 313.7764; found, 313.7764.

Screening of Grignard reagents (Table 3–2)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,3-tribromobenzene (**104**) (47.2 mg, 0.150 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. Grignard reagent (0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.0 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product The yields of 1,2,3-tribromobenzene (**104**), (2,3-dibromophenyl)phenylmethanol (**119a'**), (2,6-dibromophenyl)phenylmethanol (**119a**), and 1,3-dibromobenzene (**123**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (32.4 mg, 0.193 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 7.03 ppm (1 proton for **104**), 6.23 ppm (1

proton for **119a'**, whose chemical shift was identical with those reported in the literature[87]), 6.65 ppm (1 proton for **119a**), and 7.44 ppm (2 protons for **123**, whose chemical shift was identical with those reported in the literature[103]) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.



119a

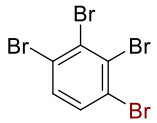
(2,6-Dibromophenyl)phenylmethanol (119a) (Table 3–3, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,3-tribromobenzene (**104**) (46.5 mg, 0.148 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.1 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless oil (34.7 mg, 0.101 mmol, 69%); R_f = 0.23 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1740, 1430, 1019, 801, 734, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, J = 8.2 Hz), 7.36–7.26 (m, 5H), 7.07 (t, 1H, J = 8.2 Hz), 6.65 (d, 1H, J = 11.0 Hz), 3.52 (d, 1H, J = 11.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.5, 140.2, 133.6, 130.4, 128.4, 127.3, 125.7, 125.1, 76.4; HRMS (DART$^+$) *m/z*: $[M–OH]^+$ calcd. for $C_{13}H_9{}^{81}Br_2$, 326.9030; found, 326.9033.

Reaction run on a 3 mmol scale

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,3-tribromobenzene (**104**) (944.4 mg, 3.00 mmol, 1.0 equiv) and anhydrous THF (30 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 2.30 mL, 4.6 mmol, 1.5 equiv) was added to the Schlenk tube.

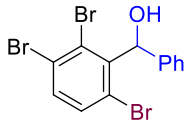
After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (610 μL, 5.98 mmol, 2.0 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide (2,6-dibromophenyl)phenylmethanol (**119a**) as a colorless oil (857.9 mg, 2.51 mmol, 84%).



118b

1,2,3,4-Tetrabromobenzene (118b) (Table 3–3, entry 2)

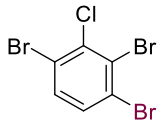
A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,3-tribromobenzene (**104**) (948.9 mg, 3.01 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (753.5 mg, 2.98 mmol, 0.99 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (1.042 g, 2.65 mmol, 88%), whose ^1H and ^{13}C NMR data were identical with those reported in the literature.[105] R_f = 0.70 (hexane); Mp 51–52 °C; IR (ATR, cm^{-1}): 1410, 1330, 1162, 805; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 132.9, 129.2, 124.9; HRMS (EI) *m/z*: $[M]^+$ calcd. for $C_6H_2{}^{79}Br^{81}Br_3$, 395.6829; found, 395.6847.



119b

Phenyl(2,3,6-tribromophenyl)methanol (119b) (Table 3–3, entry 2)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,3,4-tetrabromobenzene (**118b**) (58.7 mg, 0.149 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 µL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 µL, 0.30 mmol, 2.0 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 91:9) to provide the title compound as a colorless oil (36.3 mg, 0.0862 mmol, 58%); R_f = 0.27 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1424, 1155, 1055, 1024, 810, 756, 736, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 1H, J = 8.6 Hz), 7.47 (d, 1H, J = 8.6 Hz), 7.37–7.23 (m, 5H), 6.73 (d, 1H, J = 10.8 Hz), 3.59 (d, 1H, J = 10.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN): δ 144.5, 142.3, 135.2, 134.9, 129.0, 128.3, 127.8, 127.2, 126.4, 124.7, 76.8; HRMS (DART$^+$) *m/z*: $[M–OH]^+$ calcd. for $C_{13}H_8{}^{79}Br^{81}Br_2$, 404.8135; found, 404.8150.

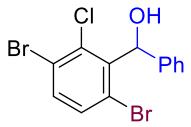


118c

1,2,4-Tribromo-3-chlorobenzene (118c) (Table 3–3, entry 3)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,3-dibromo-2-chlorobenzene (**117c**) (814.5 mg, 3.01 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (752.6 mg, 2.98 mmol, 0.99 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C

for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (891.3 mg, 2.55 mmol, 85%); R_f = 0.60 (hexane); Mp 51–52 °C; IR (ATR, cm^{-1}): 1415, 1340, 1167, 804; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 1H, J = 8.6 Hz), 7.40 (d, 1H, J = 8.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.6, 132.9, 132.1, 126.9, 125.4, 122.3; HRMS (EI) *m/z*: $[M]^+$ calcd. for $C_6H_2{}^{79}Br_2{}^{81}Br^{37}Cl$, 349.7352; found, 349.7343.

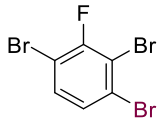


119c

(3,6-Dibromo-2-chlorophenyl)(phenyl)methanol (119c) (Table 3-3, entry 3)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,4-tribromo-3-chlorobenzene (**118c**) (51.9 mg, 0.149 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.1 equiv). After stirring at –40 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 91:9) to provide the title compound as a colorless oil (29.1 mg, 0.0773 mmol, 52%); R_f = 0.28 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1428, 1162, 1069, 1025, 808, 742, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 1H, J = 8.8 Hz), 7.44 (d, 1H, J = 8.8 Hz), 7.37–7.25 (m, 5H), 6.69 (d, 1H, 11.0 Hz), 3.44 (d, 1H, 11.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.3, 141.0, 135.5,

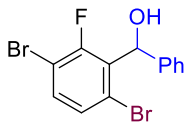
134.0, 133.2, 128.6, 127.5, 125.4, 124.3, 124.0, 75.6; HRMS (DART$^+$) *m/z*: [M–OH]$^+$ calcd. for $C_{13}H_8{}^{79}Br^{81}Br^{35}Cl$, 358.8661; found, 358.8677.



118d

1,2,4-Tribromo-3-fluorobenzene (118d) (Table 3–3, entry 4)

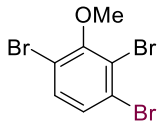
A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,3-dibromo-2-fluorobenzene (**117d**) (764.3 mg, 3.01 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (754.0 mg, 2.99 mmol, 0.99 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (952.1 mg, 2.86 mmol, 95%); R_f = 0.63 (hexane); Mp <33 °C; IR (ATR, cm^{-1}): 1441, 1397, 1172, 1075, 875, 801, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, 1H, *J* = 8.5, 6.4 Hz), 7.33 (dd, 1H, *J* = 8.5, 1.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.7 (d, $^1J_{C–F}$ = 248.2 Hz), 132.7, 129.5 (d, $^3J_{C–F}$ = 3.8 Hz), 125.2, 114.2 (d, $^2J_{C–F}$ = 23.0 Hz), 108.7 (d, $^2J_{C–F}$ = 23.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): –89.8; HRMS (EI) *m/z*: [M]$^+$ calcd. for $C_6H_2{}^{79}Br_2{}^{81}BrF$, 331.7670; found, 331.7661.



119d

(3,6-Dibromo-2-fluorophenyl)(phenyl)methanol (119d) (Table 3–3, entry 4)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,4-tribromo-3-fluorobenzene (**118d**) (53.0 mg, 0.159 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 1.9 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 9:1) to provide the title compound as a colorless oil (48.7 mg, 0.135 mmol, 85%); R_f = 0.29 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1449, 1145, 1041, 1025, 891, 803, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.25 (m, 7H), 6.40 (dd, 1H, J = 9.4, 1.4 Hz), 2.94 (dd, 1H, J = 9.4, 3.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.1 (d, $^1J_{C–F}$ = 251.1 Hz), 141.2, 133.6, 132.1 (d, $^2J_{C–F}$ = 14.3 Hz), 129.9 (d, $^3J_{C–F}$ = 3.8 Hz), 128.7, 127.9, 125.6, 122.6 (d, $^3J_{C–F}$ = 4.7 Hz), 109.7 (d, $^2J_{C–F}$ = 22.0 Hz), 73.6; ^{19}F NMR (376 MHz, $CDCl_3$): –104.7; HRMS (DART$^+$) *m/z*: $[M–OH]^+$ calcd. for $C_{13}H_8{}^{79}Br^{81}BrF$, 342.8956; found, 342.8973.

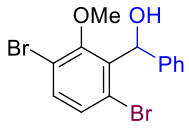


118e

1,2,4-Tribromo-3-methoxybenzene (118e) (Table 3–3, entry 5)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,3-dibromo-2-methoxybenzene (**117e**) (777.2 mg, 2.92 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (758.2 mg, 3.00 mmol, 1.1 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.1 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted

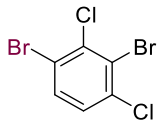
with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (842.8 mg, 2.76 mmol, 94%); R_f = 0.57 (hexane); Mp <25 °C; IR (ATR, cm^{-1}): 1454, 1421, 1367, 1000, 801; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H, *J* = 8.6 Hz), 7.29 (d, 1H, *J* = 8.6 Hz), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.7, 132.8, 129.9, 125.0, 122.2, 117.0, 60.6; HRMS (EI) *m/z*: $[M]^+$ calcd. for $C_7H_5{}^{79}Br_2{}^{81}BrO$, 343.7870; found, 343.7882.



119e

(3,6-Dibromo-2-methoxyphenyl)(phenyl)methanol (119e) (Table 3–3, entry 5)

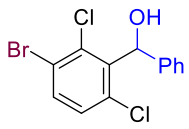
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,4-tribromo-3-methoxybenzene (**118e**) (42.9 mg, 0.140 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. EtMgCl (2.0 M, 120 µL, 0.24 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 µL, 0.30 mmol, 2.1 equiv). After stirring at –40 °C for 5 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 91:9) to provide the title compound as a colorless solid (32.5 mg, 0.0874 mmol, 62%); R_f = 0.32 (hexane/diethyl ether = 10:1); Mp 58–60 °C; IR (ATR, cm^{-1}): 1454, 1389, 1040, 1026, 995, 802, 744, 700; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H, *J* = 8.4 Hz), 7.37–7.33 (m, 4H), 7.31 (d, 1H, *J* = 8.4 Hz), 7.29–7.24 (m, 1H), 6.32 (d, 1H, *J* = 11.8 Hz), 4.00 (d, 1H, *J* = 11.8 Hz), 3.27 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.6, 143.6, 139.4, 134.0, 130.0, 128.5, 127.4, 125.2, 123.1, 117.0, 74.5, 61.6; HRMS ($DART^+$) *m/z*: $[M–OH]^+$ calcd. for $C_{14}H_{11}{}^{79}Br_2O$, 352.9177; found, 352.9193.



118f

1,3-Dibromo-2,4-dichlorobenzene (118f) (Table 3–3, entry 6)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-bromo-1,3-dichlorobenzene (**117f**) (674.2 mg, 2.98 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (771.9 mg, 3.06 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (779.0 mg, 2.56 mmol, 86%); R_f = 0.60 (hexane); Mp 44–46 °C; IR (ATR, cm^{-1}): 1420, 1346, 1172, 807; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, 1H, J = 8.8 Hz), 7.26 (d, 1H, J = 8.8 Hz); ^1H NMR (400 MHz, DMSO-d_6): δ 7.85 (d, 1H, J = 8.8 Hz), 7.59 (d, 1H, J = 8.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.8, 135.5, 132.5, 128.8, 124.8, 121.6; HRMS (EI) *m/z*: $[M]^+$ calcd. for $C_6H_2{}^{79}Br^{81}Br^{35}Cl_2$, 303.7878; found, 303.7878.

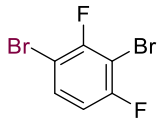


119f

(3-Bromo-2,6-dichlorophenyl)(phenyl)methanol (119f) (Table 3–3, entry 6)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,3-dibromo-2,4-dichlorobenzene (**118f**) (47.3 mg, 0.155 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.5 equiv) was added to the

Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 1.9 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 20:1 to 3:2) to provide the title compound as a colorless oil (40.8 mg, 0.123 mmol, 79%); R_f = 0.52 (hexane/diethyl ether = 3:2); IR (ATR, cm^{-1}): 1433, 1164, 1094, 1025, 745, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 1H, *J* = 8.8 Hz), 7.37–7.26 (m, 5H), 7.24 (d, 1H, *J* = 8.8 Hz), 6.69 (d, 1H, *J* = 11.0 Hz), 3.39 (d, 1H, *J* = 11.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.0, 140.0, 135.5, 134.3, 133.7, 130.0, 128.5, 127.5, 125.4, 123.3, 73.4; HRMS ($DART^+$) *m/z*: $[M–OH]^+$ calcd. for $C_{13}H_8{}^{81}Br^{35}Cl_2$, 314.9166; found, 314.9179.

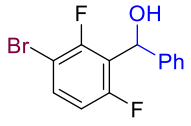


118g

1,3-Dibromo-2,4-difluorobenzene (118g) (Table 3–3, entry 7)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-bromo-1,3-difluorobenzene (**117g**) (577.0 mg, 2.99 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (761.1 mg, 3.01 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless oil (522.4 mg, 1.92 mmol, 64%); R_f = 0.50 (hexane); IR (ATR, cm^{-1}): 1466, 1449, 1431, 1416, 1007, 806, 699; ^1H NMR (400 MHz,

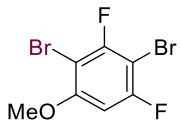
$CDCl_3$): δ 7.50 (ddd, 1H, J = 8.9, 7.4, 5.2 Hz), 6.90 (ddd, 1H, J = 8.9, 7.6, 2.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.4 (d, $^1J_{C-F}$ = 249.2 Hz), 156.6 (d, $^1J_{C-F}$ = 246.2 Hz), 132.1 (d, $^3J_{C-F}$ = 8.6 Hz), 112.9 (d, $^2J_{C-F}$ = 24.0 Hz), 104.6 (dd, $^2J_{C-F}$ = 22.1 Hz, $^3J_{C-F}$ = 3.9 Hz), 99.4 (dd, $^2J_{C-F}$ = 25.9, 24.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): –95.4, –105.1; HRMS (EI) *m/z*: $[M]^+$ calcd. for $C_6H_2{}^{79}Br^{81}BrF_2$, 271.8471; found, 271.8465.



119g

(3-Bromo-2,6-difluorophenyl)(phenyl)methanol (119g) (Table 3–3, entry 7)

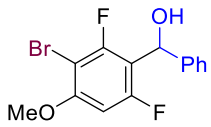
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,3-dibromo-2,4-difluorobenzene (**118g**) (41.1 mg, 0.151 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.0 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 20:1 to 3:2) to provide the title compound as a colorless solid (38.7 mg, 0.129 mmol, 86%); R_f = 0.41 (hexane/diethyl ether = 3:2); Mp 49–50 °C; IR (ATR, cm^{-1}): 1614, 1470, 1271, 1219, 1174, 1005, 808, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.44 (m, 1H), 7.42–7.33 (m, 4H), 7.32–7.27 (m, 1H), 6.85 (ddd, 1H, J = 9.4, 8.8, 1.7 Hz), 6.25 (s, 1H), 2.70 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.9 (dd, $^1J_{C-F}$ = 248.2 Hz, $^3J_{C-F}$ = 6.7 Hz), 157.1 (dd, $^1J_{C-F}$ = 247.7 Hz, $^3J_{C-F}$ = 8.1 Hz), 141.5, 132.8 (d, $^3J_{C-F}$ = 8.6 Hz), 128.7, 128.0, 125.6, 121.1 (dd, $^2J_{C-F}$ = 17.3, 17.2 Hz), 113.2 (dd, $^2J_{C-F}$ = 24.0 Hz, $^4J_{C-F}$ = 3.9 Hz), 104.7 (dd, $^2J_{C-F}$ = 22.0 Hz, $^4J_{C-F}$ = 3.8 Hz), 68.0; ^{19}F NMR (376 MHz, $CDCl_3$): –106.2, –114.7; HRMS ($DART^+$) *m/z*: $[M–OH]^+$ calcd. for $C_{13}H_8{}^{81}BrF_2$, 282.9757; found, 282.9768.



118h

2,4-Dibromo-1,3-difluoro-5-methoxybenzene (118h) (Table 3–3, entry 8)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-bromo-1,3-difluoro-5-methoxybenzene (**117h**) (668.4 mg, 3.00 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (757.4 mg, 3.00 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LDA (2.0 M, 3.0 mL, 6.0 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane) to provide the title compound as a colorless solid (604.3 mg, 2.00 mmol, 67%); R_f = 0.24 (hexane); Mp 78–79 °C; IR (ATR, cm^{-1}): 1605, 1581, 1474, 1440, 1422, 1369, 1199, 1103, 1081, 1046, 817, 695; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (dd, 1H, J = 9.8, 1.8 Hz), 3.90 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.5 (dd, $^1J_{C–F}$ = 245.3 Hz, $^3J_{C–F}$ = 6.7 Hz), 157.2 (dd, $^1J_{C–F}$ = 243.4 Hz, $^3J_{C–F}$ = 7.6 Hz), 156.9 (dd, $^3J_{C–F}$ = 11.5, 5.7 Hz), 96.5 (dd, $^2J_{C–F}$ = 27.8 Hz, $^4J_{C–F}$ = 2.9 Hz), 95.3 (dd, $^2J_{C–F}$ = 25.0 Hz, $^4J_{C–F}$ = 3.8 Hz), 89.5 (dd, $^2J_{C–F}$ = 26.9, 25.8 Hz), 57.1; ^{19}F NMR (376 MHz, $CDCl_3$): –95.6, –104.8; HRMS (EI) *m/z*: $[M]^+$ calcd. for $C_7H_4{}^{79}Br_2F_2O$, 299.8597; found, 299.8601.

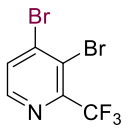


119h

(3-Bromo-2,6-difluoro-4-methoxyphenyl)(phenyl)methanol (119h) (Table 3–3, entry 8)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,4-dibromo-1,3-difluoro-5-

methoxybenzene (**118h**) (45.2 mg, 0.150 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.0 equiv). After stirring at –40 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 9:1 to 3:2) to provide the title compound as a colorless oil (34.9 mg, 0.106 mmol, 71%); R_f = 0.30 (hexane/diethyl ether = 3:2); IR (ATR, cm^{-1}): 1625, 1196, 1158, 1092, 684; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.27 (m, 5H), 6.52 (dd, 1H, J = 11.8, 1.8 Hz), 6.20 (d, 1H, J = 8.4 Hz), 3.89 (s, 3H), 2.60 (ddd, 1H, J = 8.4, 1.8, 1.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.4 (dd, $^1J_{C–F}$ = 246.3 Hz, $^3J_{C–F}$ = 10.5 Hz), 158.0 (dd, $^1J_{C–F}$ = 245.3 Hz, $^3J_{C–F}$ = 10.5 Hz), 157.2 (dd, $^3J_{C–F}$ = 12.5, 6.7 Hz), 142.1, 128.6, 127.8, 125.6, 112.9 (dd, $^2J_{C–F}$ = 19.2, 18.2 Hz), 96.5 (dd, $^2J_{C–F}$ = 27.8 Hz, $^4J_{C–F}$ = 2.8 Hz), 95.2 (dd, $^2J_{C–F}$ = 24.4 Hz, $^4J_{C–F}$ = 3.9 Hz), 67.7, 56.9; ^{19}F NMR (376 MHz, $CDCl_3$): –106.0, –113.9; HRMS (DART$^+$) *m/z*: $[M–OH]^+$ calcd. for $C_{14}H_{10}{}^{79}BrF_2O$, 310.9883; found, 310.9891.

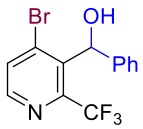


118i

3,4-Dibromo-2-(trifluoromethyl)pyridine (118i) (Table 3–3, entry 9)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-(trifluoromethyl)pyridine (**117i**) (662.7 mg, 2.93 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (756.6 mg, 3.00 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.1 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous

layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1) to provide the title compound as a colorless solid (637.1 mg, 2.09 mmol, 71%); R_f = 0.24 (hexane/diethyl ether = 49:1); Mp 39–40 °C; IR (ATR, cm^{-1}): 1306, 1205, 1142, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, 1H, J = 5.0 Hz), 7.79 (d, 1H, J = 5.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.9 (q, $^2J_{C-F}$ = 33.9 Hz), 147.1, 139.2, 131.5, 121.8, 120.8 (q, $^1J_{C-F}$ = 274.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): –66.2; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_6H_3{}^{79}Br_2F_3N$, 303.8584; found, 303.8581.

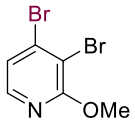


119i

(4-Bromo-2-(trifluoromethyl)pyridin-3-yl)(phenyl)methanol (119i) (Table 3–3, entry 9)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3,4-dibromo-2-(trifluoromethyl)pyridine (**118i**) (42.5 mg, 0.139 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.2 equiv). After stirring at –20 °C for 5 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 9:1 to 3:2) to provide the title compound as a colorless solid (28.7 mg, 0.0864 mmol, 62%); R_f = 0.30 (hexane/diethyl ether = 3:2); Mp 136–138 °C; IR (ATR, cm^{-1}): 1310, 1176, 1129, 739, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, 1H, J = 5.2 Hz), 7.76 (d, 1H, J = 5.2 Hz), 7.38–7.27 (m, 3H), 7.24–7.19 (m, 2H), 6.47 (d, 1H, J = 9.6 Hz), 3.20 (d, 1H, J = 9.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.5, 147.8 (q, $^2J_{C-F}$ = 32.9 Hz), 140.6, 137.0, 136.0, 133.3, 128.6, 127.7, 125.8, 121.6 (q, $^1J_{C-F}$ = 262.3 Hz), 71.0; ^{19}F NMR (376 MHz, $CDCl_3$): –64.3; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{10}{}^{79}BrF_3NO$, 331.9898;

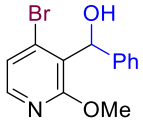
found, 331.9899.



118j

3,4-Dibromo-2-methoxypyridine (118j) (Table 3–3, entry 10)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-methoxypyridine (**117j**) (560.9 mg, 2.98 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (758.0 mg, 3.00 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1) to provide the title compound as a colorless solid (745.8 mg, 2.79 mmol, 94%), whose ^1H and ^{13}C NMR data were identical with those reported in the literature.[106] R_f = 0.33 (hexane/diethyl ether = 49:1); Mp 81–83 °C; IR (ATR, cm^{-1}): 1562, 1462, 1377, 1045, 1011; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1H, J = 5.6 Hz), 7.14 (d, 1H, J = 5.6 Hz), 4.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.3, 145.0, 136.5, 121.8, 110.3, 55.1; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_6H_6{}^{79}Br^{81}BrNO$, 267.8796; found, 267.8805.

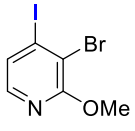


119j

(4-Bromo-2-methoxypyridin-3-yl)(phenyl)methanol (119j) (Table 3–3, entry 10)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3,4-dibromo-2-methoxypyridine

(**118j**) (40.5 mg, 0.152 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –78 °C. A separate flame-dried 20 mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with iodobenzene (36.9 mg, 0.181 mmol, 1.2 equiv) and anhydrous THF (1.0 mL). After the solution of iodobenzene was cooled to –78 °C, ^{n}BuLi (1.56 M, 125 μL, 0.195 mmol, 1.3 equiv) was added to the Schlenk tube. The resulting mixture was stirred at –78 °C for 30 min, at which time the resulting solution was transferred to the THF solution of 3,4-dibromo-2-methoxypyridine (**118j**) via cannula. The reaction mixture was stirred at –78 °C for 50 min. To the solution was added benzaldehyde (31 μL, 0.30 mmol, 2.0 equiv). After the resulting mixture was stirred at –78 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 9:1 to 7:3) to provide the title compound as a colorless oil (13.0 mg, 0.0442 mmol, 29%); R_f = 0.25 (hexane/diethyl ether = 7:3); IR (ATR, cm^{-1}): 1563, 1460, 1386, 1224, 1020, 737, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, 1H, J = 5.4 Hz), 7.36–7.24 (m, 5H), 7.18 (d, 1H, J = 5.4 Hz), 6.29 (d, 1H, J = 11.8 Hz), 4.09 (d, 1H, J = 11.8 Hz), 3.90 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.9, 146.0, 142.2, 134.4, 128.4, 127.5, 125.6, 125.5, 122.2, 73.4, 54.3; HRMS (DART^{+}) *m/z*: [M+H]$^{+}$ calcd. for $C_{13}H_{13}{}^{81}BrNO_2$, 296.0109; found, 296.0122.

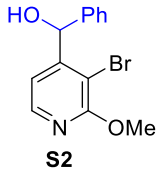


S1

3-Bromo-4-iodo-2-methoxypyridine (S1) (Table 3–3, entry 10)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-methoxypyridine (**117j**) (271.1 mg, 1.44 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (389.8 mg, 1.54 mmol, 1.1 equiv), and anhydrous THF (15 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 4.0 mL, 2.6 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with iodine (763.8 mg, 3.01 mmol, 2.1 equiv) at room

temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous ammonium chloride (10 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (8 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/diethyl ether = 19:1) to provide the title compound as a colorless solid (433.3 mg, 1.38 mmol, 96%). R_f = 0.20 (hexane); Mp 130–132 °C; IR (ATR, cm^{-1}): 1563, 1459, 1367, 1040, 1004, 812; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, 1H, J = 5.0 Hz), 7.35 (d, 1H, J = 5.0 Hz), 3.98 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.5, 145.2, 128.2, 115.4, 114.5, 55.2; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_6H_6{}^{81}BrINO$, 315.8657; found, 315.8664.



S2

(3-Bromo-2-methoxypyridin-4-yl)(phenyl)methanol (S2) (Table 3–3, entry 10)

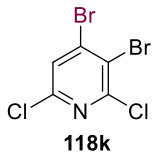
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-4-iodo-2-methoxypyridine (**S1**) (49.4 mg, 0.157 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. ^{i}PrMgCl·LiCl (1.3 M, 175 μL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 1.9 equiv). After stirring at –40 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to provide the title compound as a colorless oil (28.6 mg, 0.0972 mmol, 62%); R_f = 0.28 (hexane/ethyl acetate = 3:1); IR (ATR, cm^{-1}): 1590, 1468, 1383, 1038, 1017, 701; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, 1H, J = 5.0 Hz), 7.43–7.38 (m, 2H), 7.37–7.27 (m, 3H), 7.23 (d, 1H, J = 5.0 Hz), 6.16 (d, 1H, J = 4.0 Hz), 4.00 (s, 3H), 2.42 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 153.7, 145.4, 141.0, 128.8, 128.4, 127.3, 116.0, 106.9, 74.4, 54.8;

HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{13}{}^{81}BrNO_2$, 296.0109; found, 296.0120.

Control Experiment

Reaction of 3,4-dibromo-2-methoxypyridine (118j) with EtMgCl

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3,4-dibromo-2-methoxypyridine (**118j**) (40.2 mg, 0.151 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.0 equiv). After stirring at –40 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of (4-bromo-2-methoxypyridin-3-yl)(phenyl)methanol (**119j**) and (3-bromo-2-methoxypyridin-4-yl)(phenyl)methanol (**S2**) were determined to be 57% and 20% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (25.9 mg, 0.154 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 6.29 ppm (1 proton for **119j**) and 6.16 ppm (1 proton for **S2**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

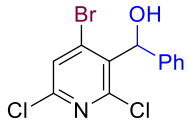


118k

3,4-Dibromo-2,6-dichloropyridine (118k) (Table 3–3, entry 11)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2,6-dichloropyridine (**117k**) (683.1 mg, 3.01 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (760.0 mg, 3.01 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous

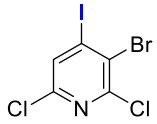
ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/diethyl ether = 99:1) to provide the title compound as a colorless solid (752.1 mg, 2.46 mmol, 82%); R_f = 0.33 (hexane); Mp 78–79 °C; IR (ATR, cm^{-1}): 1526, 1516, 1294, 1134, 772; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.3, 148.8, 139.0, 127.5, 122.7; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_5H_2{}^{81}Br_2{}^{35}Cl_2N$, 307.7890; found, 307.7902.



119k

(4-Bromo-2,6-dichloropyridin-3-yl)(phenyl)methanol (119k) (Table 3–3, entry 11)

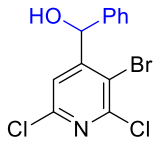
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3,4-dibromo-2,6-dichloropyridine (**118k**) (46.2 mg, 0.151 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –78 °C. ^{n}BuLi (1.56 M, 120 µL, 0.19 mmol, 1.2 equiv) was added to the Schlenk tube. After stirring at –78 °C for 50 min, the reaction mixture was treated with benzaldehyde (31 µL, 0.30 mmol, 2.0 equiv). The reaction mixture was allowed to warm to room temperature with stirring over 1 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1) to provide the title compound as a colorless oil (14.2 mg, 0.0426 mmol, 28%); R_f = 0.31 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 1547, 1525, 1271, 874, 714; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.39–7.27 (m, 5H), 6.59 (d, 1H, J = 10.2 Hz), 3.19 (d, 1H, J = 10.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.6, 149.7, 139.9, 137.4, 135.1, 128.7, 128.2, 127.9, 125.4, 73.2; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_9{}^{81}Br{}^{35}Cl_2NO$, 333.9224; found, 333.9239.



S3

3-Bromo-2,6-dichloro-4-iodopyridine (S3) (Table 3–3, entry 11)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2,6-dichloropyridine (**117k**) (340.3 mg, 1.50 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (379.0 mg, 1.50 mmol, 1.0 equiv), and anhydrous THF (15 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 4.0 mL, 2.6 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with iodine (764.6 mg, 3.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous ammonium chloride (10 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (8 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/diethyl ether = 49:1) to provide the title compound as a colorless solid (282.5 mg, 0.801 mmol, 53%). R_f = 0.28 (hexane/diethyl ether = 49:1); Mp 118–120 °C; IR (ATR, cm^{-1}): 1523, 1504, 1371, 1287, 1140, 746; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.3, 148.7, 133.9, 127.2, 116.4; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_5H_2{}^{81}Br^{35}Cl^{37}ClIN$, 355.7742; found, 355.7758.



S4

(3-Bromo-2,6-dichloropyridin-4-yl)(phenyl)methanol (S4) (Table 3–3, entry 11)

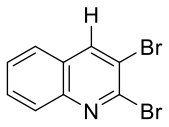
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2,6-dichloro-4-iodopyridine (**S3**) (53.8 mg, 0.153 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. ^{i}PrMgCl·LiCl (1.3 M, 175 μL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated

with benzaldehyde (31 μL, 0.30 mmol, 2.0 equiv). After stirring at –40 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 5:1 to 3:2) to provide the title compound as a colorless solid (29.4 mg, 0.0883 mmol, 58%); R_f = 0.26 (hexane/diethyl ether = 3:2); Mp 92–94 °C; IR (ATR, cm^{-1}): 1560, 1526, 1336, 1316, 1218, 1133, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.41–7.32 (m, 5H), 6.04 (d, 1H, J = 3.2 Hz), 2.46–2.41 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.3, 150.8, 149.4, 139.5, 129.1, 127.7, 122.1, 118.6, 75.1 (one aromatic carbon signal is missing due to overlapping); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN): δ 159.9, 150.9, 149.7, 141.2, 129.5, 129.2, 128.9, 123.2, 119.2, 75.1; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_9{}^{81}Br^{35}Cl^{37}ClNO$, 335.9195; found, 335.9209.

Control Experiment (Table 3–3, entry 11)

Reaction of 3,4-dibromo-2,6-dichloropyridine (118k) with EtMgCl

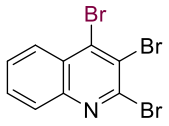
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3,4-dibromo-2,6-dichloropyridine (**118k**) (44.9 mg, 0.147 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.0 equiv). After stirring at –40 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of (4-bromo-2,6-dichloropyridin-3-yl)(phenyl)methanol (**118k**) and (3-bromo-2,6-dichloropyridin-4-yl)(phenyl)methanol (**S4**) were determined to be 49% and 23% by ^1H NMR analysis using 1,1,2,2-tetrachloroethane (40.2 mg, 0.240 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 6.59 ppm (1 proton for **118k**) and 6.04 ppm (1 proton for **S4**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.



117l

2,3-Dibromoquinoline (117l) (Table 3–3, entry 12)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromoquinoline (1.032 g, 4.96 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (1.269 g, 5.03 mmol, 1.0 equiv), and anhydrous THF (33 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 14 mL, 9.2 mmol, 2.2 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (520 μL, 10.1 mmol, 2.4 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to provide the title compound as a colorless solid (1.225 g, 4.27 mmol, 86%), whose ^1H and ^{13}C NMR data were identical with those reported in the literature.[107] R_f = 0.31 (hexane/ethyl acetate = 20:1); Mp 97–99 °C; IR (ATR, cm^{-1}): 1485, 1360, 1115, 950, 754; ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.03 (d, 1H, J = 9.2 Hz), 7.78–7.72 (m, 2H), 7.61 (ddd, 1H, J = 8.0, 7.0, 1.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 146.8, 142.9, 140.5, 131.0, 128.8, 128.2, 128.1, 126.8, 119.8; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_9H_6{}^{79}Br_2N$, 285.8867; found, 285.8876.

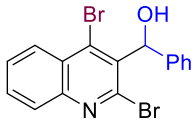


118l

2,3,4-Tribromoquinoline (118l) (Table 3–3, entry 12)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromoquinoline (**117l**) (855.1 mg, 2.98 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (758.7 mg, 3.00 mmol, 1.0 equiv), and

anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a colorless solid (991.5 mg, 2.71 mmol, 91%), whose ^{1}H and ^{13}C NMR data were identical with those reported in the literature. R_f = 0.23 (hexane/diethyl ether = 50:1); Mp 121–122 °C; IR (ATR, cm^{-1}): 1531, 1475, 1274, 1174, 758; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 8.8 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.81–7.76 (m, 1H), 7.71–7.65 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.5, 142.6, 137.4, 131.4, 129.3, 129.2, 128.2, 128.1, 124.1; HRMS (DART^{+}) *m/z*: [M+H]$^{+}$ calcd. for $C_9H_5{}^{81}Br_3N$, 369.7911; found, 369.7916.

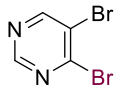


119l

(2,4-Dibromoquinolin-3-yl)(phenyl)methanol (119l) (Table 3–3, entry 12)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3,4-tribromoquinoline (**118l**) (52.8 mg, 0.144 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 μL, 0.30 mmol, 2.1 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1 to 2:1) to provide the title compound as a

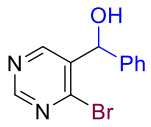
colorless solid (36.4 mg, 0.0926 mmol, 64%); R_f = 0.43 (hexane/diethyl ether = 2:1); Mp 147–148 °C; IR (ATR, cm^{-1}): 1552, 1477, 1053, 759, 720; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, 1H, *J* = 8.3 Hz), 8.06 (d, 1H, *J* = 8.3 Hz), 7.81 (ddd, 1H, *J* = 8.7, 8.3, 1.3 Hz), 7.72 (ddd, 1H, *J* = 8.7, 8.3, 1.3 Hz), 7.38–7.27 (m, 5H), 6.92 (d, 1H, *J* = 11.0 Hz), 3.64 (d, 1H, *J* = 11.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.6, 141.9, 140.9, 137.6, 134.9, 131.7, 129.01, 128.99, 128.6, 127.9, 127.6, 127.5, 125.6, 76.0; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{12}{}^{79}Br^{81}BrNO$, 393.9265; found, 393.9280.



118m

4,5-Dibromopyrimidine (118m) (Table 3–3, entry 13)

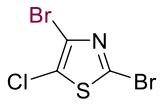
A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 5-bromopyrimidine (**117m**) (477.1 mg, 3.00 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (760.2 mg, 3.01 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 8.0 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 μL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 97:3 to 19:1) to provide the title compound as a pale yellow solid (294.5 mg, 1.24 mmol, 41%); R_f = 0.32 (hexane/diethyl ether = 10:1); Mp <36 °C; IR (ATR, cm^{-1}): 1613, 1468, 1390, 1181; ^1H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.77 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.9, 156.3, 154.1, 124.4; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_4H_3{}^{81}Br_2N_2$, 240.8622; found, 240.8629.



119m

(4-Bromopyrimidin-5-yl)(phenyl)methanol (119m) (Table 3–3, entry 13)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 4,5-dibromopyrimidine (**118m**) (36.0 mg, 0.151 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 µL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 µL, 0.30 mmol, 2.0 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 17:3 to 3:7) to provide the title compound as a colorless oil (30.6 mg, 0.115 mmol, 76%); R_f = 0.34 (hexane/diethyl ether = 3:7); IR (ATR, cm^{-1}): 1537, 1417, 1385, 752, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 8.79 (s, 1H), 7.43–7.30 (m, 5H), 6.06 (d, 1H, J = 3.2 Hz), 2.93 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.6, 156.4, 152.8, 140.4, 138.0, 129.1, 128.9, 127.3, 73.1; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{10}{}^{79}BrN_2O$, 264.9977; found, 264.9990.

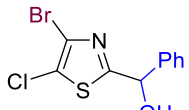


118n

2,4-Dibromo-5-chlorothiazole (118n) (Table 3–3, entry 14)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-bromo-5-chlorothiazole (**117n**) (603.8 mg, 3.04 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (758.3 mg, 3.00 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to –40 °C. LDA (2.0 M, 3.0 mL, 6.0 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the resulting mixture was treated with bromine (310 µL, 6.01 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated

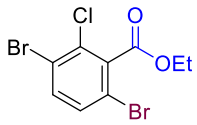
with saturated aqueous sodium thiosulfate (20 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/diethyl ether = 97:3) to provide the title compound as a colorless solid (686.5 mg, 2.48 mmol, 81%); R_f = 0.27 (hexane); Mp 29–30 °C; IR (ATR, cm^{-1}): 1471, 1406, 1205, 1038, 1014, 826; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 133.1, 125.2, 124.3; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_3H^{81}Br_2{}^{37}ClNS$, 281.7815; found, 281.7826.



119n

(4-Bromo-5-chlorothiazol-2-yl)(phenyl)methanol (119n) (Table 3–3, entry 14)

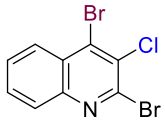
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,4-dibromo-5-chlorothiazole (**118n**) (42.6 mg, 0.151 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 µL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with benzaldehyde (31 µL, 0.30 mmol, 2.0 equiv). After stirring at –20 °C for 5 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to provide the title compound as a colorless solid (24.6 mg, 0.0807 mmol, 53%); R_f = 0.26 (hexane/ethyl acetate = 10:1); Mp 92–94 °C; IR (ATR, cm^{-1}): 1488, 1454, 1218, 1153, 1046, 856, 705; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.34 (m, 5H), 5.96 (d, 1H, J = 3.6 Hz), 3.05–2.98 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.5, 140.1, 129.2, 129.1, 126.7, 124.8, 124.3, 74.2; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_8{}^{81}Br{}^{37}ClNOS$, 307.9149; found, 307.9158.



119o

Ethyl 3,6-dibromo-2-chlorobenzoate (119o) (Table 3–3, entry 15)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2,4-tribromo-3-chlorobenzene (**118c**) (52.6 mg, 0.151 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –40 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with ethyl cyanoformate (29 μL, 0.30 mmol, 2.0 equiv). After stirring at –40 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 24:1 to 23:2) to provide the title compound as a colorless solid (38.6 mg, 0.113 mmol, 75%); R_f = 0.65 (hexane/diethyl ether = 10:1); Mp 40–41 °C; IR (ATR, cm^{-1}): 1737, 1433, 1379, 1265, 1248, 1175, 1153, 1066, 811; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, 1H, J = 8.8 Hz), 7.35 (d, 1H, J = 8.8 Hz), 4.47 (q, 2H, J = 7.3 Hz), 1.42 (t, 3H, J = 7.3 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 137.4, 134.9, 132.3, 131.9, 122.5, 118.5, 62.8, 14.2; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_9H_8{}^{79}Br_2{}^{35}ClO_2$, 340.8580; found, 340.8591.

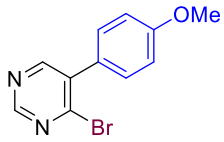


119p

2,4-Dibromo-3-chloroquinoline (119p) (Table 3–3, entry 16)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3,4-tribromoquinoline (**118l**) (56.3 mg, 0.154 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with trichloroacetyl

chloride (34 μL, 0.30 mmol, 1.9 equiv). After stirring at –20 °C for 5 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 14:1) to provide the title compound as a colorless solid (35.7 mg, 0.111 mmol, 72%); R_f = 0.41 (hexane/diethyl ether = 14:1); Mp 121–122 °C; IR (ATR, cm^{-1}): 1553, 1538, 1477, 1345, 1281, 1181, 758; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (dd, 1H, *J* = 8.1, 1.3 Hz), 8.05 (dd, 1H, *J* = 8.1, 1.4 Hz), 7.77 (ddd, 1H, *J* = 8.4, 8.1, 1.4 Hz), 7.70 (ddd, 1H, *J* = 8.4, 8.1, 1.3 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 146.1, 140.8, 134.3, 131.3, 131.0, 129.3, 129.2, 128.0, 127.6; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_9H_5{}^{79}Br_2{}^{35}ClN$, 319.8477; found, 319.8493.

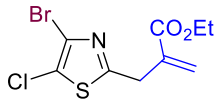


119q

4-Bromo-5-(4-methoxyphenyl)pyrimidine (119q) (Table 3–3, entry 17)

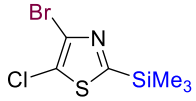
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 4,5-dibromopyrimidine (**118m**) (37.2 mg, 0.156 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with $ZnCl_2$·TMEDA (45.9 mg, 0.182 mmol, 1.2 equiv). The reaction mixture was allowed to warm to room temperature with stirring over 1 h, at which time the reaction mixture was treated with $Pd(PPh_3)_4$ (20.3 mg, 17.7 μmol, 11 mol%) and 4-iodoanisole (73.9 mg, 0.316 mmol, 2.0 equiv). After stirring at 60 °C for 4 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 4:1 to 1:1) to provide the title compound as a colorless solid (20.2 mg, 0.0762 mmol, 49%); R_f = 0.48 (hexane/diethyl ether = 1:1); Mp 89–90 °C; IR (ATR,

cm^{-1}): 1523, 1515, 1393, 1249, 826, 756, 673; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (s, 1H), 8.56 (s, 1H), 7.39 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.4, 157.3, 156.9, 153.0, 137.7, 130.7, 127.2, 114.3, 55.5; HRMS (DART^{+}) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{10}{}^{79}BrN_2O$, 264.9977; found, 264.9988.



119r

Ethyl 2-((4-bromo-5-chlorothiazol-2-yl)methyl)acrylate (119r) (Table 3–3, entry 18)
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,4-dibromo-5-chlorothiazole (**118n**) (41.4 mg, 0.149 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with CuCN·2LiCl (1.0 M, 225 μL, 0.23 mmol, 1.5 equiv) and ethyl 2-(bromomethyl)acrylate (41 μL, 0.30 mmol, 2.0 equiv). The reaction mixture was allowed to warm to room temperature with stirring over 3 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound as a colorless oil (22.5 mg, 0.0724 mmol, 49%); R_f = 0.27 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1715, 1486, 1211, 1176, 1161, 1045, 850, 649; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.39 (s, 1H), 5.84 (d, 1H, J = 1.0 Hz), 4.23 (q, 2H, J = 7.1 Hz), 3.93 (d, 2H, J = 1.0 Hz), 1.30 (t, 3H, J = 7.1 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.5, 165.9, 136.0, 129.3, 124.5, 123.0, 61.5, 37.0, 14.3; HRMS (DART^{+}) *m/z*: $[M+H]^+$ calcd. for $C_9H_{10}{}^{81}Br^{37}ClNO_2S$, 313.9254; found, 313.9257.

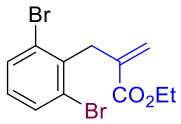


S5

4-Bromo-5-chloro-2-(trimethylsilyl)thiazole (S5) (Table 3–3, entry 18)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,4-dibromo-5-chlorothiazole (**118n**) (40.9 mg, 0.147 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to –20 °C. EtMgCl (2.0 M, 120 µL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at –20 °C for 1 h, the reaction mixture was treated with Me_3SiCl (38 µL, 0.30 mmol, 2.0 equiv). After stirring at –20 °C for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1 to 24:1) to provide the title compound as a colorless oil (13.9 mg, 0.0514 mmol, 35%); R_f = 0.40 (hexane/diethyl ether = 30:1); IR (ATR, cm^{-1}): 1455, 1371, 1253, 1208, 1041, 998, 844, 826; ^1H NMR (400 MHz, $CDCl_3$): δ 0.39 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.8, 128.6, 126.2, –1.2; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_6H_{10}{}^{79}Br^{35}ClNSSi$, 269.9175; found, 269.9181.

3-6-5 One-Pot Halogen Dance of 1,2-Dibromobenzene (Scheme 3–7)



119s

Ethyl 2-(2,6-dibromobenzyl)acrylate (119s)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (70.3 mg, 0.298 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (76.6 mg, 0.303 mmol, 1.0 equiv), and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with bromine (31 µL, 0.60 mmol, 2.0 equiv) at room

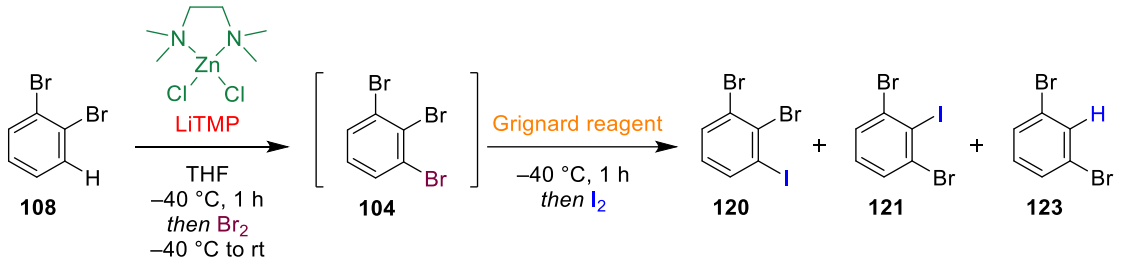
temperature. After stirring at room temperature for 1 h, the solution was cooled to –40 °C. ^{i}PrMgCl (1.3 M, 930 μL, 1.2 mmol, 4.1 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with CuCN·2LiCl (1.0 M, 450 μL, 0.45 mmol, 1.5 equiv) and ethyl 2-(bromomethyl)acrylate (250 μL, 1.81 mmol, 6.1 equiv). The reaction mixture was allowed to warm to room temperature with stirring over 3 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (3 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/diethyl ether = 93:7) to provide the title compound as a colorless oil (59.6 mg, 0.171 mmol, 57%); R_f = 0.48 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1715, 1430, 1280, 1255, 1134, 773, 713; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 2H, J = 7.8 Hz), 6.99 (t, 1H, J = 7.8 Hz), 6.22–6.19 (m, 1H), 4.98–4.94 (m, 1H), 4.29 (q, 2H, J = 7.2 Hz), 4.02 (dd, 2H, J = 2.0, 1.6 Hz), 1.35 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.7, 138.0, 136.4, 132.4, 129.4, 126.2, 124.6, 61.1, 38.7, 14.4; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_{12}H_{13}{}^{79}Br_2O_2$, 346.9282; found, 346.9274.

Control Experiments

Optimization of Grignard reagents

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1,2-dibromobenzene (**108**) (70.8 mg, 0.300 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (75.5 mg, 0.299 mmol, 1.0 equiv), and anhydrous THF (3.0 mL). The solution was cooled to –40 °C. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with bromine (31 μL, 0.60 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the solution was cooled to –40 °C. ^{i}PrMgCl·LiCl (1.3 M, 930 μL, 1.2 mmol, 4.0 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with iodine (493.4 mg, 1.94 mmol, 6.5 equiv). After stirring at –40 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered.

The filtrate was concentrated under reduced pressure to give a crude product. The yields were calculated according to the procedure described in Table 3–1, entry 2.

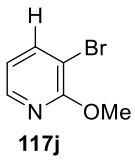
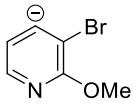
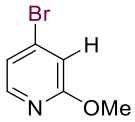
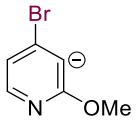


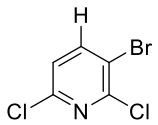
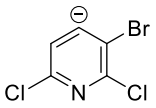
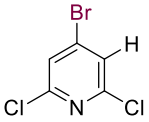
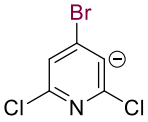
entry[a]	Grignard reagent	**108** (%)[b]	**104** (%)[b]	**120** (%)[b]	**121** (%)[b]	**123** (%)[b]
1	^{i}PrMgCl·LiCl (2.0 equiv)[c]	10	29	5	43	13
2	^{i}PrMgCl·LiCl (4.0 equiv)	10	–[d]	13	66	12
3	MeMgBr (4.0 equiv)	4	83	–[d]	9	–[d]
4	Me_3SiCH_2MgCl·LiCl (4.0 equiv)	12	80	–[d]	–[d]	–[d]
5	EtMgCl (4.0 equiv)	12	48	2	44	–[d]
6	^{n}BuMgCl (4.0 equiv)	16	79	–[d]	–[d]	–[d]
7	^{t}BuMgCl (4.0 equiv)	9	86	–[d]	–[d]	–[d]

[a]Reaction conditions: 1,2-dibromobenzene (**108**; 1.0 equiv, 0.30 mmol), $ZnCl_2$·TMEDA (1.0 equiv, 0.30 mmol), THF (3.0 mL), then LiTMP (1.8 equiv, 0.54 mmol), –40 °C, 1 h, then bromine (2.0 equiv, 0.60 mmol), rt, 1 h, then Grignard reagent, –40 °C, 1 h, then iodine (6.0–6.5 equiv, 1.8–2.0 mmol), –40 °C, 1 h. [b]The yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c]Reaction with iodine (3.0 equiv, 0.90 mmol). [d]Not detected.

3-6-6 Calculation of p*K*a Values

The calculated p*K*a values in DMSO were as follows (see Chapter 2, 2-8-6).

R–H	R$^-$ (anion)	$\Delta G°$ [kJ/mol]	p*K*a (in DMSO)
 **117j**		1400.4	37.0
		1385.4	34.5

 **117k**		1367.5	31.6
		1359.4	30.2

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(88) The yield of 1,3-dibromobenzene was 6%. See Chapter 3, 3-6-3.
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(90) The p*K*a values of 3-bromo-2-methoxypyridine (**117j**) at the C4 position and 4-bromo-2-methoxypyridine at the C3 position in DMSO were calculated to be 37.0 and 34.5, respectively. The p*K*a values of 3-bromo-2,6-dichloropyridine (**117k**) at the C4 position and 4-bromo-2,6-dichloropyridine at the C3 position in DMSO were calculated to be 31.6 and 30.2. See Chapter 3, 3-6-6.
(91) There is the only one report on the halogen dance reaction of pyrimidine: Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *Tetrahedron* **1994**, *50*, 10299.
(92) Reaction with NCS provided an inseparable mixture of 2,4-dibromo-3-chloroquinoline (**119p**) and 2,4-dibromoquinoline in 88% and 8% NMR yields, respectively. In addition, reaction with 1,1,1,2,2,2-hexachloroethane also provided an inseparable mixture of 2,4-dibromo-3-chloroquinoline (**119p**) and 2,4-dibromoquinoline in 74% and 26% NMR yields, respectively.
(93) Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
(94) Regioselective silylation of thiazole **117n** was also performed using TMSCl to provide 4-bromo-5-chloro-2-(trimethylsilyl)thiazole in 81% NMR yield. The product was volatile and obtained in 35% isolated yield. See Chapter 3, 3-6-4.
(95) Although the bromine–magnesium exchange using ^{i}PrMgCl·LiCl (4 equiv) was completed, the reaction with EtMgCl (4 equiv) resulted in the recovery of tribromobenzene **104** in 48% yield. Moreover, ^{i}PrMgCl·LiCl (2 equiv) also gave tribromobenzene **104** in 29% yield. See Chapter 3, 3-6-5.
(96) Reaction with ethyl 2-(bromomethyl)acrylate (3 equiv) decreased the yield of allylated benzene **119s**.
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第四章

リチウムアリールトリフルオロボラート触媒によるハロゲンダンス

4-1　緒言

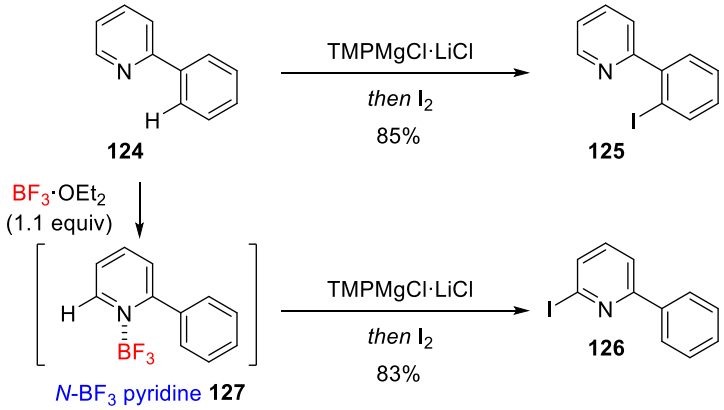
第二章，第三章では，リチウムから亜鉛への金属交換を鍵とし，望まない分解反応やアライン形成を抑制しながら，ブロモアレーンのハロゲンダンスを実施し，基質一般性を大幅に向上させた。第四章では，リチウムからホウ素への金属交換が，ハロゲンの移動反応を触媒的に加速させることを見出した。すなわち，触媒量の三フッ化ホウ素を用いると，ハロゲンダンスが劇的かつ特異的に加速されるとわかった。反応機構を詳細に調べた結果，有機リチウムと三フッ化ホウ素が反応し発生した，リチウムアリールトリフルオロボラートがブロモ基の受け渡しを触媒することがわかった。DFT 計算によって，リチウム–フッ素相互作用が連続する分子間ハロゲン–金属交換の活性化エネルギーが低下させ，ハロゲンダンスを加速させたことを明らかにした。

4-2　ルイス酸の検討

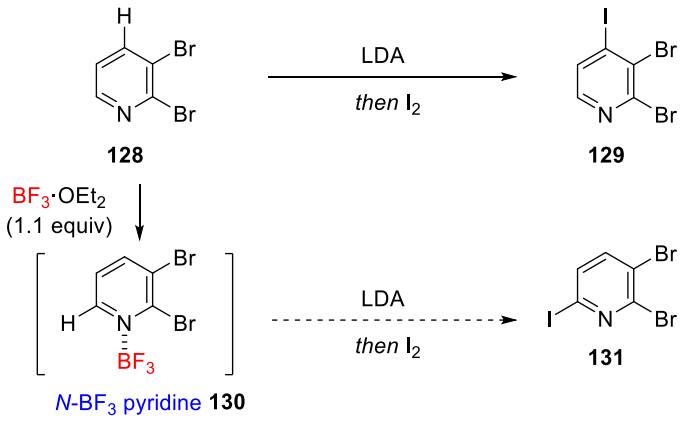
研究を始めた当初，ハロゲンダンスにおける触媒の開発[20a,108]ではなく，化学量論量のルイス酸を用いた脱プロトン反応の位置性制御[109]の研究をしていた (Scheme 4–1)。Knochel は，古典的な化学選択的脱プロトンとして知られる D*o*M 反応[10,110]に対して，三フッ化ホウ素とピリジンの組み合わせが，脱プロトンの位置を変化させるために有効であると報告している (Scheme 4–1a)[111]。フェニルピリジン **124** に TMPMgCl·LiCl を作用させると，脱プロトンが進行し，ヨウ素化によって，ヨードベンゼン **125** を収率 85%で得ている。一方，化学量論量の三フッ化ホウ素ジエチルエーテル錯体 BF_3·OEt_2 を加えると，ヨードピリジン **126** が収率 83%で生成している。この結果は，*N*-BF_3 ピリジン **127**[112]が形成され，ピリジン窒素の隣接位で脱プロトンが促進したためと考えられる。著者は，この研究を参考に，後の化学変換の起点となるブロモ基をもつジブロモピリジン **128** の脱プロトンの位置を変化させることを試みた (Scheme 4–1b)。すなわち，2,3-ジブロモピリジン(**128**)に LDA を作用させると，最も酸性度の高い C4 位のプロトンが脱プロトンされ，ヨウ素化によって 4-ヨードピリジン **129** が得られると考えた。一方で，化学量論量の BF_3·OEt_2 を加えると，*N*-BF_3 ピリジン **130** を与え，脱プロトンが C6 位で進行し，6-ヨードピリジン **131** が得られると期待した。

Scheme 4–1. *N*-BF_3 Pyridine: Switching of Deprotonation Site

(a) Switching deprotonation site of 2-phenylpyridine (Knochel)

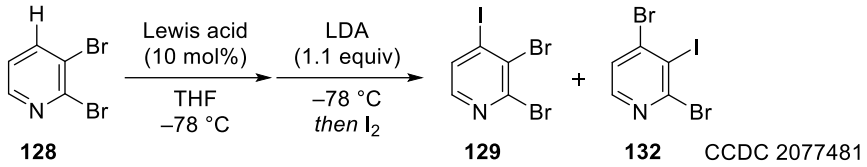


(b) Attempt to switch deprotonation site of 2,3-dibromopyridine (initial idea)



まず，BF_3·OEt_2 が脱プロトン反応に与える影響を調べた (Table 4–1)。ジブロモピリジン **128** の THF 溶液に LDA を–78 °C で 1 時間作用させ，ヨウ素で反応を停止させた。その結果，ヨードピリジン **129** と **132** をそれぞれ収率 77%と 8%で得た (entry 1)。この結果から，ピリジン **128** の脱プロトンは C4 位で進行し，その後，低収率ではあるもののハロゲンダンスが進行し，ヨードピリジン **132** が生成するとわかった。生成物の比は，Mongin らの LiTMP と$(TMP)_2Zn$ を用いた報告[20d]と同じであった。次に，1 当量の BF_3·OEt_2 を用いたところ，ヨードピリジン **129** は生成せず，ピリジン **128** を定量的に回収した (entry 2)。なお，当初想定していた脱プロトンの位置が変化した生成物 **131** は得られなかった。一方，BF_3·OEt_2 を 10 mol%加えると，予想外にも，3-ヨードピリジン **132** を収率 76%で得た (entry 3)。以上の結果から，化学量論量の BF_3·OEt_2 は脱プロトンの位置を変化させなかったが，触媒量の BF_3·OEt_2 がハロゲンダンスを劇的に加速させ

Table 4–1. Screening of Lewis Acids[a]



128 **129** **132** CCDC 2077481

entry	Lewis acid	amount	**128** (%)[b]	**129** (%)[b]	**132** (%)[b]
1	none	none	–[c]	77	8
2	$BF_3{\cdot}OEt_2$	1.0 equiv	77	–[c]	–[c]
3	$BF_3{\cdot}OEt_2$	10 mol%	8	–[c]	quant (76[d])
4	BCl_3	10 mol%	91	–[c]	–[c]
5	BBr_3	10 mol%	79	–[c]	–[c]
6	BEt_3	10 mol%	9	68	19
7	$B(C_6F_5)_3$	10 mol%	24	48	12
8	$B(O^iPr)_3$	10 mol%	12	27	26
9	AlF_3	10 mol%	–[c]	77	8
10	ZnF_2	10 mol%	–[c]	75	10
11	$TiCl_4$	10 mol%	22	25	32
12	$Sc(OTf)_3$	10 mol%	33	28	25

[a]Reaction conditions: 2,3-dibromopyridine (**128**; 1.0 equiv, 3.0 mmol), Lewis acid, THF (30 mL), −78 °C, 10 min, then LDA (1.1 equiv, 3.3 mmol), −78 °C, 1 h, then iodine (2.0 equiv, 6.0 mmol), −78 °C, 1 h. [b]Yields determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c]Not detected. [d]Isolated yield.

るとわかった。その他のルイス酸を検討したところ，BCl_3 や BBr_3 を用いた場合は，ジブロモピリジン **128** を定量的に回収した (entries 4 and 5)。同様に，BEt_3 や $B(C_6F_5)_3$，または $B(O^iPr)_3$ を用いた場合は，3-ヨードピリジン **132** を収率 12–26% で得た (entries 6–8)。ホウ素原子をもたないルイス酸を検討したところ，AlF_3 や ZnF_2 は，3-ヨードピリジン **132** の収率を向上させなかった (entries 9 and 10)。また，$TiCl_4$ や $Sc(OTf)_3$ は，3-ヨードピリジン **132** をそれぞれ収率 32%と 25%で与えた (entries 11 and 12)。以上より，予想外にも，触媒量の $BF_3{\cdot}OEt_2$ が特異的かつ劇的にハロゲンダンスを加速させることがわかった。得られた予想外の結果を説明するために，*N*-BF_3 ピリジン **130** が生成した可能性を確かめた。

4-3　触媒活性種の同定

まず，^{1}H NMR 実験によって，*N*-BF_3 錯体が生成した可能性を確かめた (Figure 4–1)。ジブロモピリジン **128** の THF-d_8 溶液に 0.5 当量の BF_3·OEt_2 を加え，^{1}H NMR を測定した (Figure 4–1a)。しかし，20 °C において，ジエチルエーテル (3.38 ppm と 1.11 ppm)以外の新たなシグナルは観測されず，*N*-BF_3 ピリジン **130** のシグナルは検出されなかった。低温 NMR を測定したが，−100 °C においても

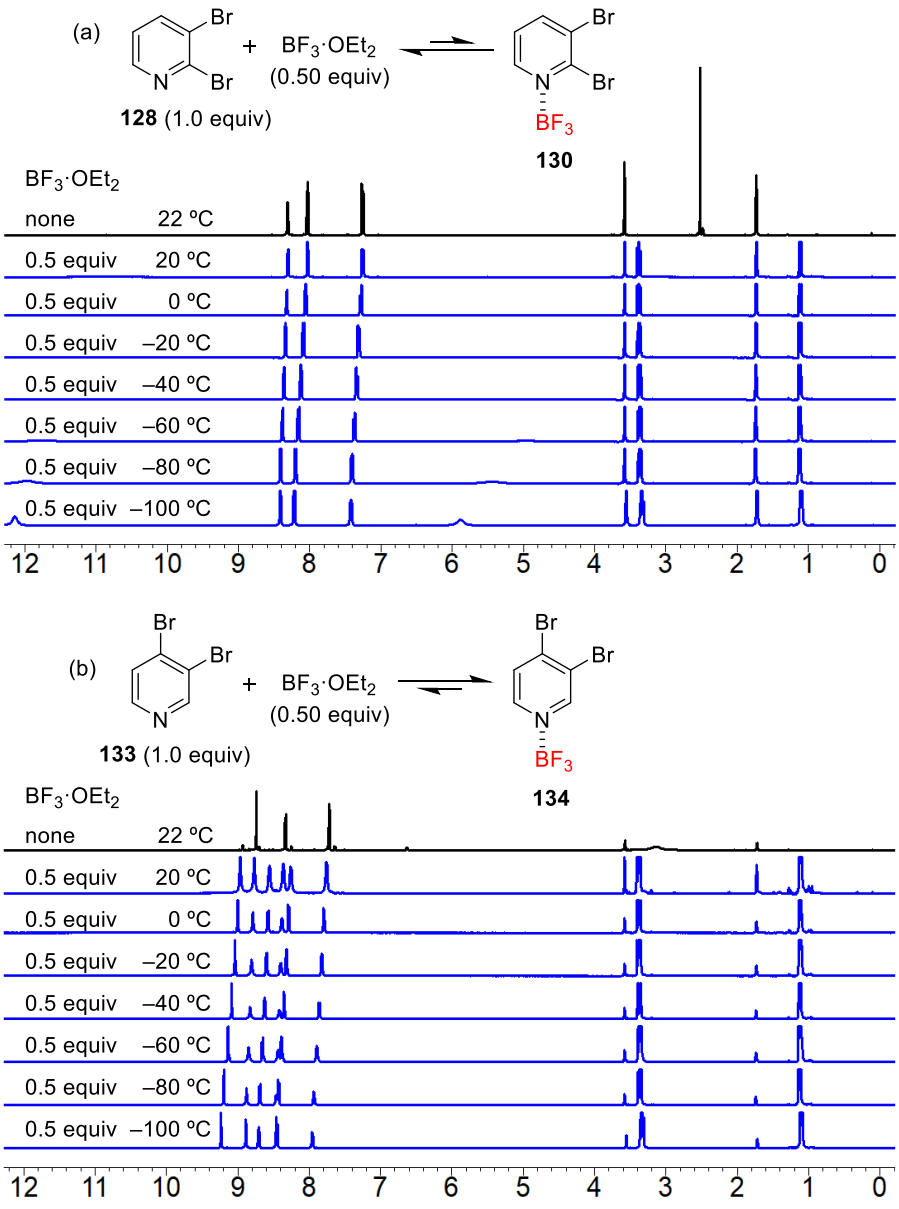
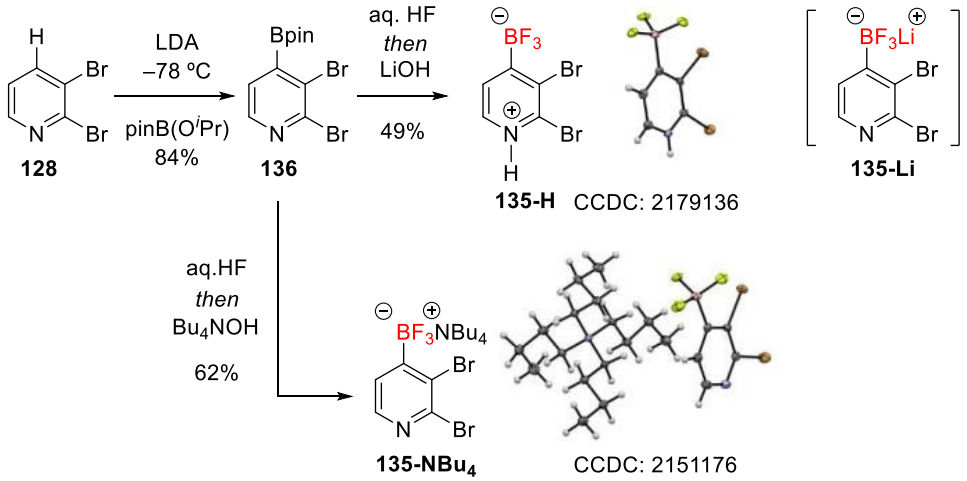


Figure 4–1. (a) ^{1}H NMR (400 MHz, THF-d_8) spectra of a mixture of 2,3-dibromopyridine (**128**; 1.0 equiv) and BF_3·OEt_2 (0.5 equiv). (b) ^{1}H NMR (400 MHz, THF-d_8) spectra of a mixture of 3,4-dibromopyridine (**133**; 1.0 equiv) and BF_3·OEt_2 (0.5 equiv).

N-BF_3 ピリジン **130** のシグナルは観測されなかった[113]。Knochel らが報告した *N*-BF_3 ピリジン **127** を与えるフェニルピリジン **124**[111] とは対照的に，2,3-ジブロモピリジン(**128**)は，C2 位のブロモ基の立体障害および電子求引効果によって三フッ化ホウ素との配位が阻害されたと考えられる[114]。C2 位のブロモ基の効果を確かめるため，対照実験として 3,4-ジブロモピリジン(**133**)を用いて同様の条件で ^{1}H NMR を測定した (Figure 4–1b)。その結果，−100 °C から 20 °C の温度領域でピリジン **133** よりも高周波数（低磁場）側に移動した，*N*-BF_3 錯体 **134** に帰属可能な新たなシグナルを検出した[115]。この結果は，平衡定数の計算値から予測される結果と一致している（詳細は，第四章，4-7-5)。

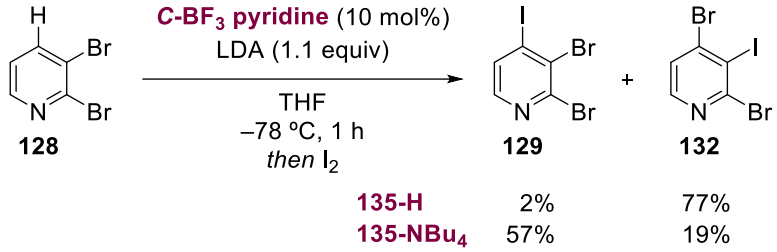
N-BF_3 ピリジンの形成が不利とわかったので，真の触媒として *C*-BF_3 ピリジン **135-Li** を提案し，その合成および触媒活性評価を試みた (Scheme 4–2)。ジブロモピリジン **128** に LDA を作用させ，pinBO^{i}Pr[116]で反応を停止させると，対応するボロン酸ピナコールエステル **136** が収率 84%で得られた。リチウムアリールトリフルオロボラートの合成法として唯一知られている Batey らの報告[117]に従って，ピナコールエステル **136** にフッ化水素酸を作用させ，水酸化リチウムで処理した。しかし，Batey らのフェニルボロン酸ピナコールエステルの報告とは異なり，リチウム塩ではなくプロトン付加体 **135-H** を収率 49%で得た。この結果は，ベンゼンよりも塩基性が高いピリジンが，プロトン付加体を形成しやすかったためと考えられる。ピリジンボロン酸ピナコールエステル **136** は，フッ化水素酸を作用させた後，Bu_4NOH で処理し，シリカゲルカラムクロマトグラフィーで精製すると，テトラブチルアンモニウム塩 **135-NBu$_4$** を収率 62%で与えた。

Scheme 4–2. Synthesis of Trifluoroborates 135-H and 135-NBu$_4$



脱プロトン的リチオ化によってリチウムアリールトリフルオロボラート **135-Li** へ変換可能な触媒前駆体 **135-H** を合成できたので，アリールトリフルオロボラート **135-H** と **135-NBu4** の触媒活性を評価した (Scheme 4–3)。その結果，プロトン付加体 **135-H** がハロゲンダンスを触媒し, 3-ヨードピリジン **132** を収率 77% で与えた。この結果から，当初想定していた *N*-BF_3 ピリジンではなく，リチウムアリールトリフルオロボラート，すなわち *C*-BF_3 ピリジン **135-Li** が，真の触媒となることがわかった。なお，テトラブチルアンモニウム塩 **135-NBu4** は，低い触媒活性を示した。

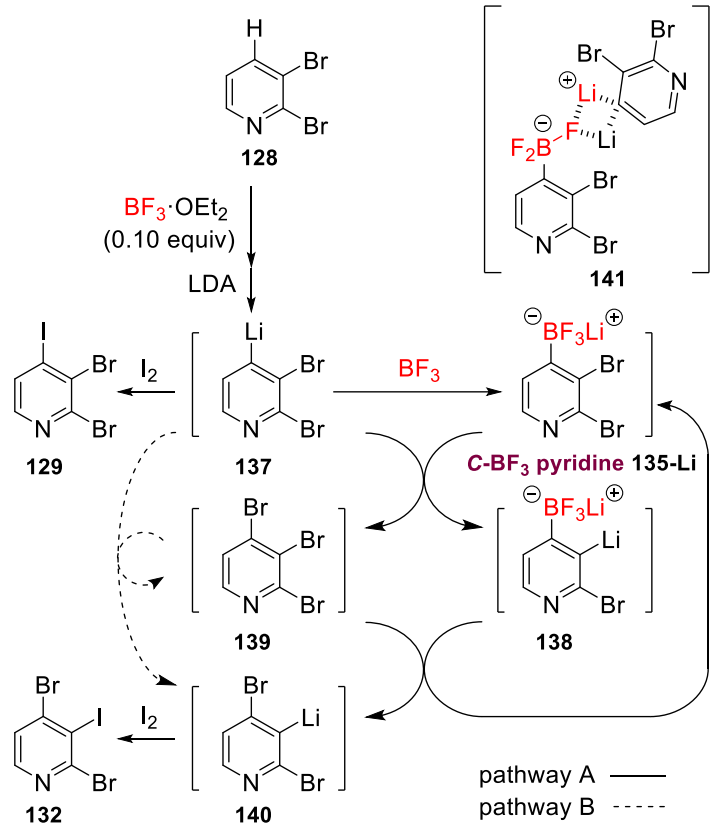
Scheme 4–3. Trifluoroborate-Catalyzed Halogen Dance



4-4　DFT 計算を用いた反応機構の解明

実験結果に基づいた推定反応機構を示す (Scheme 4–4, pathway A)。リチウムアリールトリフルオロボラート **135-Li** は, 二回の分子間臭素–リチウム交換を触媒する。まず，2,3-ジブロモピリジン(**128**)の脱プロトン的リチオ化によって，ピリジルリチウム **137** が発生し，ただちに BF_3·OEt_2 と反応し，リチウムアリールトリフルオロボラート **135-Li** を与える。生成した触媒量の **135-Li** は，別分子のピリジルリチウム **137** と臭素–リチウム交換し，ピリジルリチウム **138** とトリブロモピリジン **139** を生成する。ピリジルリチウム **138** とトリブロモピリジン **139** の二回目の臭素–リチウム交換によって，触媒 **135-Li** の再生を伴いながら，熱力学的に最も安定な[118]ピリジルリチウム **140** が得られる。アリールトリフルオロボラートのカウンターカチオンの効果 (Scheme 4–3)から，ピリジルリチウム **137** と **135-Li** の臭素–リチウム交換が錯体 **141** を経由し進行していると考えられる。ジブロモピリジン **128** のハロゲンダンスは，Quéguiner らによって報告されている [20a] が，今回開発した反応とは反応機構が異なっている (Scheme 4–4, pathway B)。すなわち，ピリジルリチウム **137** の臭素化によって発生したトリブロモピリジン **139** がピリジルリチウム **137** から **140** への異性化を触媒している。

Scheme 4–4. Plausible Pathway for Halogen Dance



反応経路の DFT 計算を実施し，触媒 **135-Li** が触媒活性を示した理由を調べた (Figure 4–1)。DFT 計算に関する全ての計算結果は，共同研究者の東京大学大学院薬学研究科の平野圭一教授（現金沢大学医薬保健研究域薬学系）と内山真伸教授らによって行われた。計算は，M062*X*/6-31+G*と Lanl2DZ(Br)+PCM(THF)に基づいている。まず，ピリジルリチウム **137** がリチウムアリールトリフルオロボラート **135-Li** と配位し，錯体 **CP1A** を与える。原系 **SMA** からの臭素–リチウム交換が遷移状態 **TS1A** を経由し，+23.0 kcal mol^{-1} の活性化エネルギーで化合物 **138** と **139** の錯体 **CP2A** を生成する。本触媒系の活性化エネルギーは，従来報告された pathway B の **SMB** から **TS1B** への臭素–リチウム交換よりも，3.7 kcal mol^{-1} 小さいとわかった。また，遷移状態 **TS1A** における F–Li と Br–Li の原子間距離は，それぞれの原子の van der Waals 半径[119] (Li, 1.82 Å; F, 1.35 Å; Br, 1.85 Å)の和よりも短かった。この結果から，F–Li 相互作用[120]によって，熱力学的に不安定なピリジルリチウム **138** が生成したと考えられる。F–Li 相互作用による臭素–リチウム交換の加速効果は，テトラブチルアンモニウム塩 **135-NBu4** がほとんど触

媒活性を示さなかった実験結果 (Scheme 4–3)と一致している[121]。錯体 **CP2A** から **CP3A** への再結合(+0.7 kcal mol^{-1})のあと，二度目の臭素–リチウム交換が **TS2** (+4.3 kcal mol^{-1})を経由し，**CP4A** を与えた後，3-リチオピリジン **140** が生成し，触媒 **135-Li** が再生される (**PDA**)。これらの結果から，本反応は熱力学的に最も安定なピリジルリチウム **140** の生成を駆動力として進行しているとわかった。また，F–Li 相互作用によって，**TS1A** と **TS2A** が安定化されていることも明らかになった。今回，通常クロスカップリング反応[122]や光レドックス反応[123]，芳香族求電子置換反応[124]，その他の有用な化学変換[125]に化学量論量の反応剤として利用されてきたトリフルオロボラートを，ブロモ基の受け渡しを加速させる有機触媒として利用した初めての例である。

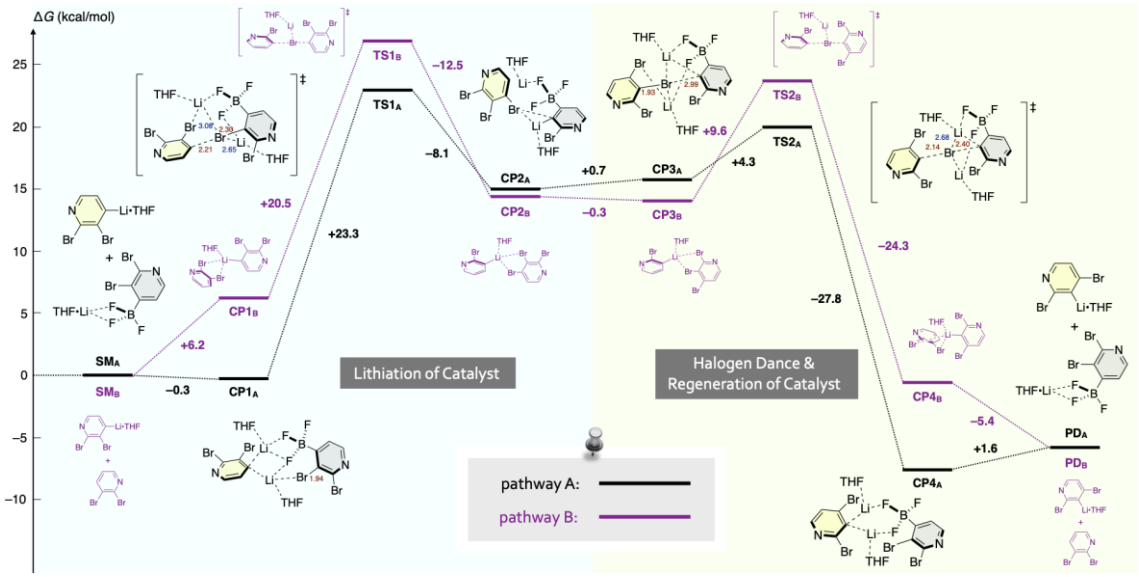


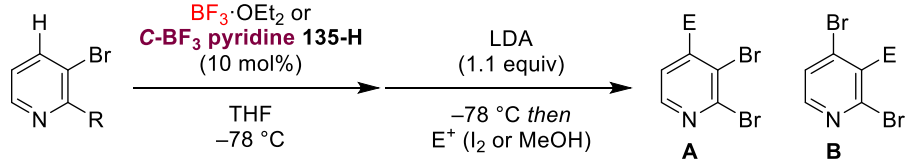
Figure 4–1. DFT calculations of the halogen dance catalyzed by lithium aryltrifluoroborate based on the level of M062*X*/6-31+G* and LanI2DZ(Br)+PCM(THF). Distances between atoms (Å) are as follows: red, C–Br; blue, Li–Br.

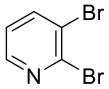
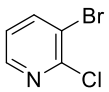
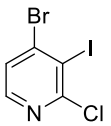
4-5　ピリジン誘導体の基質一般性

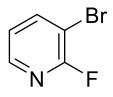
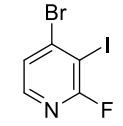
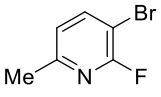
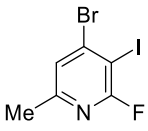
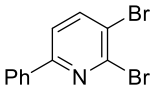
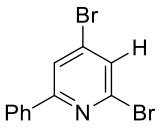
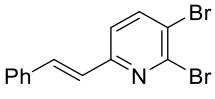
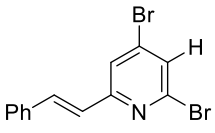
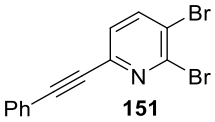
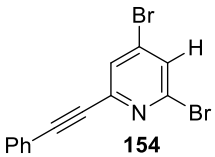
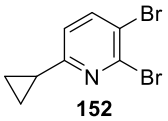
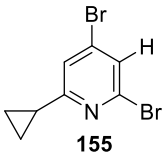
触媒 **135-Li** は，様々なブロモピリジンのハロゲンダンスを触媒した (Table 4–2)。ジブロモピリジン **128** (entry1)と同様に，3-ブロモ-2-クロロピリジン(**142**)と BF_3·OEt_2 (10 mol%)の THF 溶液に LDA (1.1 当量)を–78 °C で 4 時間作用させたところ，3-ヨードピリジン **143** が収率 62%で生成し，原料 **142** を 20%回収した (entry 2)。残った 2-クロロピリジン **142** を完全に消費させるために LDA (1.5 当量)を作用させたが，望みの 3-ヨードピリジン **143** の収率が 15%に低下した。こ

の結果は，LDA と $BF_3{\cdot}OEt_2$ の反応が進行し，触媒生成の過程が阻害されたためと考えられる。一方で，触媒前駆体 **135-H** を用いると，LDA (1.5 当量)を作用させた場合にピリジン **142** を消費でき，3-ヨードピリジン **143** を収率 70%で得た。したがって，触媒前駆体 **135-H** は，$BF_3{\cdot}OEt_2$ よりも優れた触媒として機能することがわかった。アリールトリフルオロボラート **135-H** は，2-フルオロピリジン **144** も完全に消費でき，3-ヨードピリジン **145** を収率 84%で与えた (entry 3)。最適化した条件は，2-フルオロ-6-ピコリン **146** に適用でき，3-ヨード-6-ピコリン **147** が収率 74%で生成した (entry 4)。次に，C6 位に置換基をもつピリジンのハロゲンダンスを実施した。6-フェニルピリジン **148** と触媒前駆体 **135-H** を用いた反応では，メタノールで反応を停止させると，2,4-ブロモピリジン **149** を収率 89%で得た (entry 5)[126]。触媒前駆体 **135-H** は，6-スチリルピリジン **150**，6-フェニルエチニルピリジン **151**，6-シクロプロピルピリジン **152** のハロゲンダンスを促進させ，対応する 2,4-ジブロモピリジン **153**–**155** を与えた (entries 6–8)。この結果から，*C*-BF_3 ピリジンがハロゲン原子の受け渡しを加速させる触媒[127]として優れていることが明らかとなった。

Table 4–2. Range of Bromopyridines Synthesized by Lithium Aryltrifluoroborate-Catalyzed Halogen Dance



entry	substrate	product	catalyst	yield (%)[b] (**A**:**B**)
1	 **128**	 **132** ($E^+ = I_2$)	none	77:9
			$BF_3{\cdot}OEt_2$	–[c]:100 (76[d])
			135-H	2:77
2	 **142**	 **143** ($E^+ = I_2$)	none	90:4
			$BF_3{\cdot}OEt_2$[e]	–[c]:62
			$BF_3{\cdot}OEt_2$[f]	70:15
			135-H[f]	2:82 (70[d])

3	 **144**	 **145** ($E^+ = I_2$)	none	22:74
			$BF_3{\cdot}OEt_2$	3:70
			135-H[g]	6:93 (84[d])
4	 **146**	 **147** ($E^+ = I_2$)	none	–[c]:45
			$BF_3{\cdot}OEt_2$	11:50
			135-H[f]	–[c]:79 (74[d])
5	 **148**	 **149** (E^+ = MeOH)	none	50:46
			$BF_3{\cdot}OEt_2$	70:28
			135-H[j]	–[c]:90 (89[d])
6	 **150**	 **153** (E^+ = MeOH)	none	62:37
			$BF_3{\cdot}OEt_2$	54:24
			135-H[j]	6:91 (82[d])
7	 **151**	 **154** (E^+ = MeOH)	none	6:43
			$BF_3{\cdot}OEt_2$	16:53
			135-H[j]	–[c]:61 (46[d])
8	 **152**	 **155** (E^+ = MeOH)	none	55:41
			$BF_3{\cdot}OEt_2$	62:28
			135-H[k]	8:82 (71[d])

[a]Reaction conditions are as follows: bromopyridine (1.0 equiv, 3.0 mmol), catalyst (10 mol%), THF (30 mL), then LDA (1.1 equiv, 3.3 mmol), –78 °C, 1 h, then iodine (2.0 equiv, 6.0 mmol), –78 °C, 1 h. [b]Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c]Not observed. [d]Isolated yield. [e]The reaction was performed with LDA (1.1 equiv) for 4 h. [f]The reaction was performed with LDA (1.5 equiv) for 4 h. [g]The reaction was performed with LDA (1.5 equiv) for 1 h. [h]The reaction was performed using 0.30 mmol pyridine. [i]Reaction conditions are as follows: bromopyridine (1.0 equiv, 0.15 mmol), catalyst (10 mol%), THF (1.5 mL), then LDA (1.1 equiv, 0.17 mmol), −78 °C, 1 h, then MeOH (2.0 mL), −78 °C, 5 min. [j]The reaction was performed with LDA (1.5 equiv, 0.23 mmol) for 3 h. [k]The reaction was performed with LDA (1.5 equiv, 0.23 mmol) for 5 h.

4-6　結言

第二章と第三章で用いたリチウムから亜鉛への金属交換とは異なり，リチウムからホウ素への金属交換によって発生したリチウムアリールトリフルオロボラートが，ブロモ基の転位が遅いブロモピリジンのハロゲンダンスを劇的に加速させる有機触媒として機能することを新たに見出した。DFT 計算によって，F–Li 相互作用が連続的な分子間臭素–リチウム交換を促進するとわかった。触媒前駆体 **135-H** は，LDA との共存性の面で $BF_3{\cdot}OEt_2$ よりも優れており，幅広い基質に対して高い触媒活性を示した。本研究によって，有機トリフルオロボラートが有機触媒として利用できる新たな概念を提示できた。触媒の構造活性相関に関する研究によって，より幅広い置換様式をもつブロモアレーンの供給が期待される。

4-7　Experimental Section

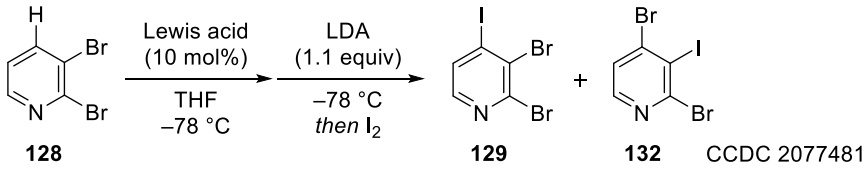
4-7-1　General

Analytical thin layer chromatography (TLC) was performed on Wako 70 F_{254} glass sheets precoated with a 0.25 mm thickness of silica gel. Melting points (Mp) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wavenumbers (cm^{-1}). ^{1}H NMR (400 MHz), $^{13}C\{^{1}H\}$ NMR (100 MHz), ^{19}F NMR (376 MHz), ^{11}B NMR (128 MHz) spectra were obtained on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, THF-d_7: δ 1.72 ppm, DMSO-d_5: δ 2.50 ppm) and coupling constants are given in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^{1}H\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, DMSO-d_6: δ 39.52 ppm). Chemical shifts for ^{19}F NMR are reported in ppm from $CFCl_3$ with the solvent resonance as the external standard ($C_6H_5CF_3$ in $CDCl_3$: −62.61 ppm[97]). Chemical shifts for ^{11}B NMR are reported in ppm from $BF_3{\cdot}OEt_2$ with the solvent resonance as the external standard ($BF_3{\cdot}OEt_2$ in $CDCl_3$: 0.00 ppm). High-resolution mass spectroscopy (HRMS) was performed on a JEOL JMS-T100LP AccuTOF LC-Plus [electrospray ionization (ESI)] with a JEOL MS-5414DART attachment.

4-7-2 Materials

All workup and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel® 60N (63–212 μm, Wako Pure Chemical Industries, Ltd.) or high-efficiency irregular silica (25–40 μm, Santai Science Inc.). Anhydrous THF (>99.5%, water content: <30 ppm) was purchased from FUJIFILM Wako Pure Chemical Co. and further dried by passing through a solvent purification system (Glass Contour) prior to use. Distilled water was purchased from Nacalai tesque, Inc. (Product number: 49506-64). LDA (2.0 M in THF/heptane/ethylbenzene) was purchased from Sigma-Aldrich Co. (Product number: 361798) and used as received. $BF_3 \cdot OEt_2$ (45–49 wt% as BF_3) was purchased from Nacalai tesque, Inc. (Product number: 05306-02) and used as received. Freshly prepared $Pd(PPh_3)_4$[98] and $ZnCl_2 \cdot TMEDA$[99] were used in the following experiments.

4-7-3 Screening of Lewis Acids (Table 4–1)



128 **129** **132** CCDC 2077481

Reaction without Lewis acid (Table 4–1, entry 1)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (708.0 mg, 2.99 mmol, 1.0 equiv) and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.578 g, 6.22 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromo-4-iodopyridine (**129**) and 2,4-dibromo-3-iodopyridine (**132**) were

determined to be 77% and 9% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (95.9 mg, 0.571 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 7.91 ppm (1 proton for **129**, whose ^{1}H NMR data were consistent with those reported in the literature[20d]) and 8.12 ppm (1 proton for **132**, whose ^{1}H NMR data were consistent with those reported in the literature[20d]) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction with stoichiometric BF_3·OEt_2 (Table 4–1, entry 2)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (716.9 mg, 3.02 mmol, 1.0 equiv), BF_3·OEt_2 (380 μL, 3.03 mmol, 1.0 equiv), and anhydrous THF (30 mL). The solution was cooled to −78 ºC and stirred at –78 °C for 10 min. LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.552 g, 6.12 mmol, 2.0 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yield of 2,3-dibromopyridine (**128**) was determined to be 77% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (84.7 mg, 0.505 mmol) as an internal standard by comparing relative values of integration for the peak observed at 8.33 ppm (1 proton for **128**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

2,4-Dibromo-3-iodopyridine (132) (Table 4–1, entry 3)

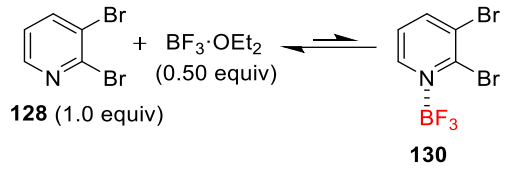
A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (712.5 mg, 3.01 mmol, 1.0 equiv), BF_3·OEt_2 (38 μL, 0.30 mmol, 0.10 equiv), and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.544 g, 6.08 mmol, 2.0 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous

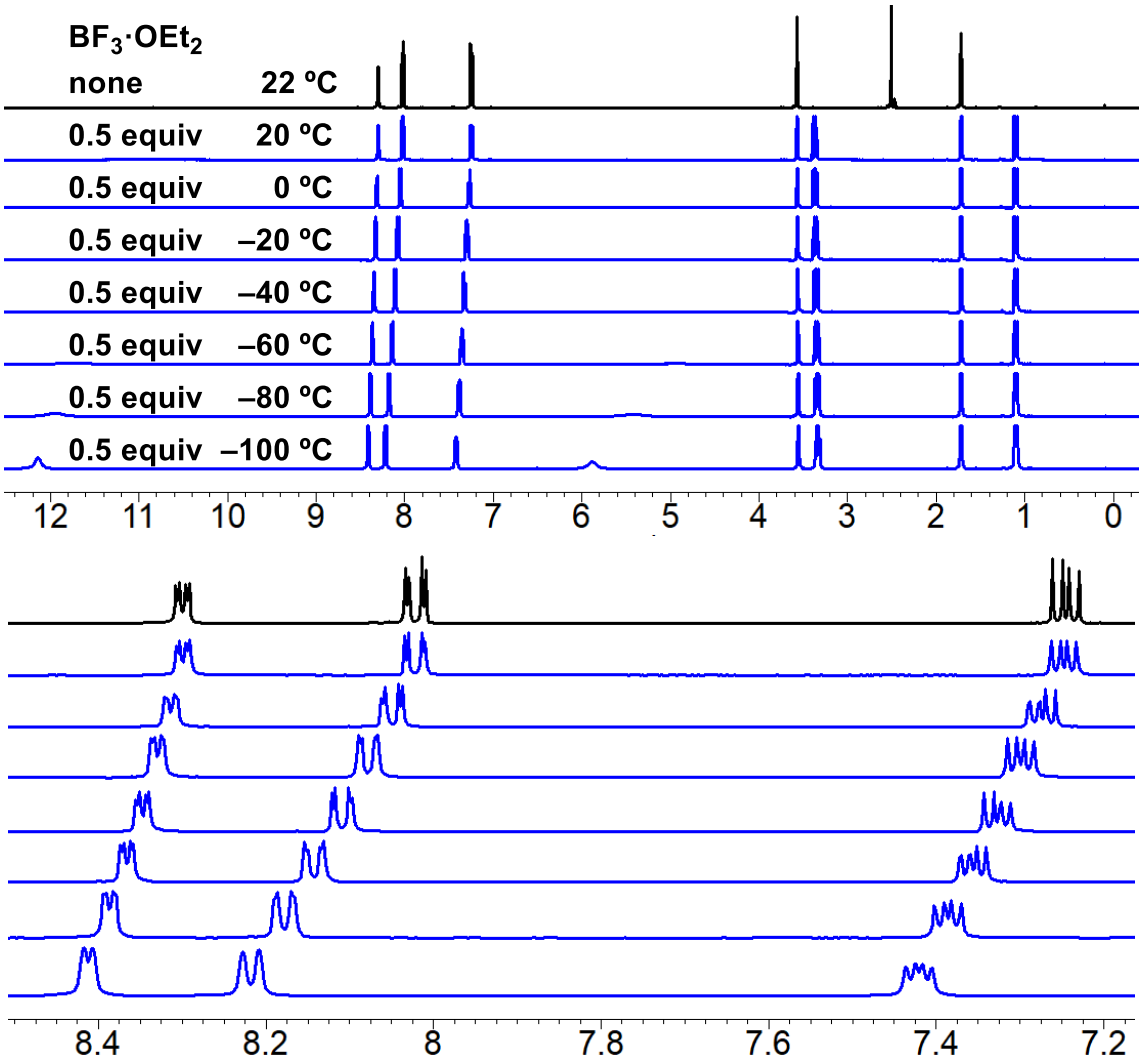
layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a colorless solid (827.7 mg, 2.28 mmol, 76%), whose ^{1}H NMR and ^{13}C NMR data were consistent with those reported in the literature.[20d] R_f = 0.40 (hexane/diethyl ether = 50:1); Mp 90–92 ºC; IR (ATR, cm^{-1}): 2924, 1528, 1406, 1320, 1180; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 1H, *J* = 5.0 Hz), 7.49 (d, 1H, *J* = 5.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.9, 148.9, 142.3, 126.7, 108.3; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_5H_3{}^{79}Br_2IN$, 361.7677; found, 361.7690.

Reaction with Lewis acids (Table 4–1, entries 4–12)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (712.4 mg, 3.01 mmol, 1.0 equiv), Lewis acid (0.30 mmol, 0.10 equiv), and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.547 g, 6.10 mmol, 2.0 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromopyridine (**128**), 2,3-dibromo-4-iodopyridine (**129**), and 2,4-dibromo-3-iodopyridine (**132**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 8.34 ppm (1 proton for **128**), 7.91 ppm (1 proton for **129**), and 8.13 ppm (1 proton for **132**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

4-7-4 ^{1}H NMR Experiments (Figure 4–1)

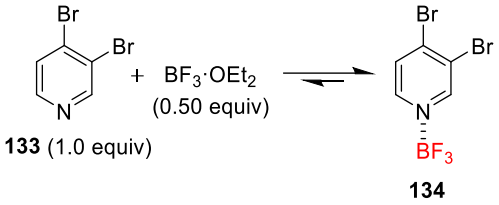


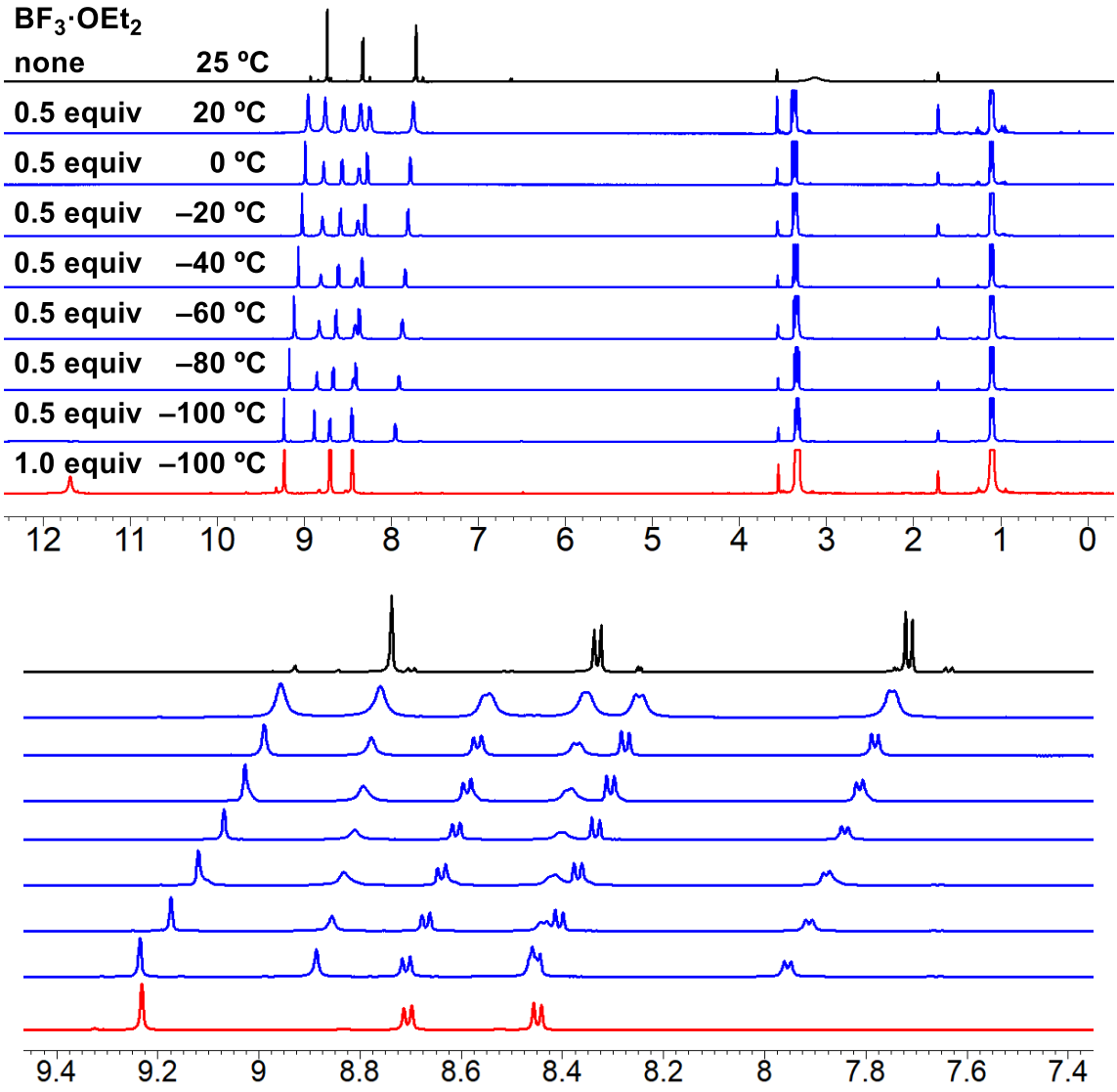


Reaction of 2,3-dibromopyridine (128) and BF_3·OEt_2

A 50-mL vial equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2,3-dibromopyridine (**128**) (18.1 mg, 0.0764 mmol, 1.0 equiv), BF_3·OEt_2 (4.7 µL, 0.037 mmol, 0.5 equiv), and THF-d_8 (750 µL). After stirring at 25 ºC for 10 min, the reaction mixture was analyzed by variable temperature ^{1}H NMR spectroscopy. The signals of 2,3-dibromopyridine (**128**) were observed at 8.30 ppm (1 proton), 8.02 ppm (1 proton), and 7.25 ppm (1 proton) at 20 °C. New signals assigned as

2,3-dibromopyridine·BF_3 complex (**130**) were not detected.





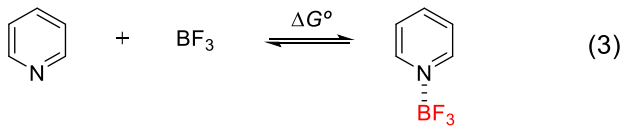
Reaction of 3,4-dibromopyridine (133) and BF_3·OEt_2

A 50-mL vial equipped with a Teflon-coated magnetic stirring bar and a rubber septum

was charged with 3,4-dibromopyridine (**133**) (17.1 mg, 0.0721 mmol, 1.0 equiv), $BF_3 \cdot OEt_2$ (4.7 μL, 0.037 mmol, 0.5 equiv), and THF-d_8 (750 μL). After stirring at 25 ºC for 10 min, the reaction mixture was analyzed by variable temperature ^1H NMR spectroscopy. The signals of 3,4-dibromopyridine (**133**) and new signals assigned as 3,4-dibromopyridine·BF_3 complex **134** were observed at 8.96 ppm (1 proton for **133**), 8.76 ppm (1 proton for **133**), 8.54 ppm (1 proton, for **134**), 8.35 ppm (1 proton for **134**), 8.26 ppm (1 proton, for **133**), and 7.75 ppm (1 proton for **134**) at 20 °C.

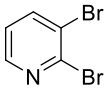
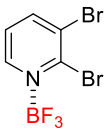
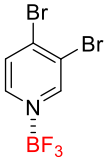
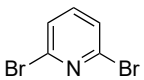
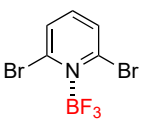
4-7-5 Calculation of Equilibrium Constant of the Complexation of Pyridine and BF_3

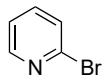
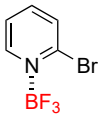
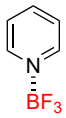
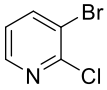
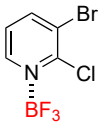
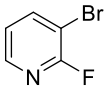
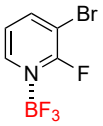
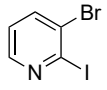
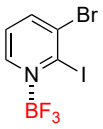
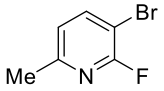
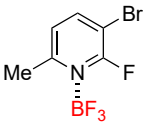
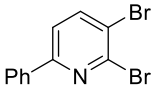
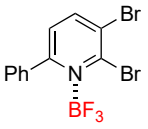
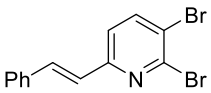
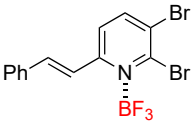
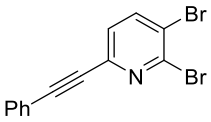
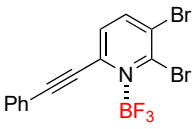
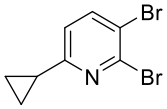
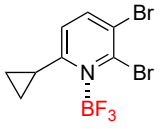
All calculation studies on equilibrium geometry at ground state were performed on density functional theory by Spartan version 18 (Wavefunction, Inc.). The standard reaction Gibbs free energies ($\Delta G°$) of the coordination were calculated using B3LYP/6-311+G** level of theory in polar solvent at 298 K and 1 atm [Eq. (3)].



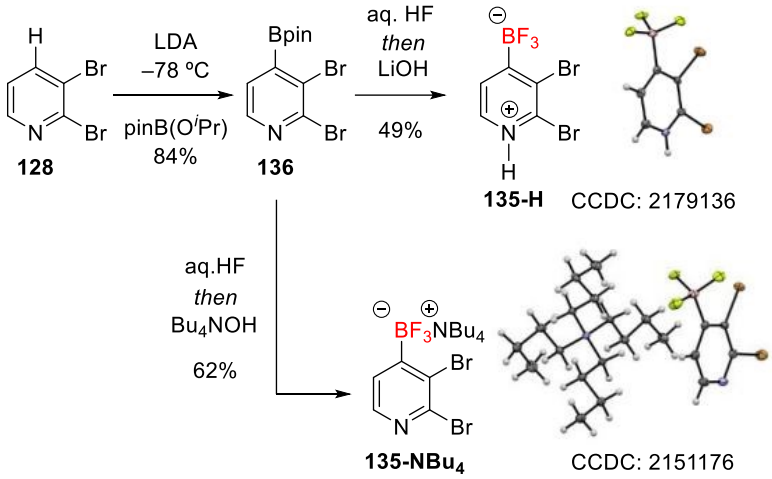
(3)

The calculated equilibrium constant (K values in DMF) of pyridine and BF_3 were as follows.

pyridine	pyridine·BF_3 complex	$\Delta G°$ (kJ/mol)	pK (in DMF)	K/K_1
		−72.0	−12.6 (K_1)	1.00
		-1.09×10^2	−19.1	3.07×10^6
		−18.3	−3.21	3.82×10^{-10}

		−84.8	−14.9	1.70×10^{2}
		-1.28×10^{2}	−22.5	7.08×10^{9}
		−75.3	−13.2	3.67
		−68.9	−12.1	0.279
		−70.0	−12.3	0.445
		−56.4	−9.89	1.85×10^{-3}
		−27.9	−4.88	1.81×10^{-8}
		−35.2	−6.17	3.55×10^{-7}
		−35.6	−6.24	4.14×10^{-7}
		−25.1	−4.40	5.96×10^{-9}

4-7-6 Synthesis of Trifluoroborates 135-H and 135-NBu4 (Scheme 4–2)



2,3-Dibromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (136)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (1.182 g, 4.99 mmol, 1.0 equiv) and anhydrous THF (25 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 3.30 mL, 6.6 mmol, 1.3 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with 4,4,5,5-tetramethyl-2-(1-methylethoxy)-1,3,2-dioxaborolane (2.00 mL, 9.80 mmol, 2.0 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with MeOH (20 mL). After stirring at −78 ºC for 5 min, to the reaction mixture was added aqueous HCl (1 M, 10 mL) and brine (10 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1 to 3:1, gradient) to provide the title compound as a colorless solid (1.526 g, 4.21 mmol, 84%): R_f = 0.57 (hexane/ethyl acetate = 1:1); Mp 92–94 ºC; IR (ATR, cm^{-1}): 1361, 1335, 1140, 856; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, 1H, J = 4.4 Hz), 7.35 (d, 1H, J = 4.4 Hz), 1.38 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.2, 144.8, 128.3, 127.8, 85.4, 24.8 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom); HRMS (DART$^+$) *m/z*: [M+H]$^+$ calcd. for $C_{11}H_{15}{}^{11}B^{79}Br^{81}BrNO_2$, 363.9542; found, 363.9554.

2,3-Dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (135-H)

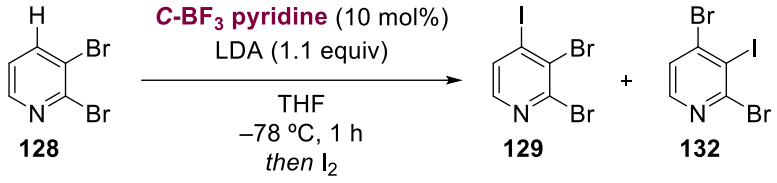
A 200-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2,3-dibromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**136**) (2.888 g, 7.96 mmol, 1.0 equiv) and MeOH (16 mL). After stirring at 25 ºC for 5 min, the reaction mixture was treated with hydrofluoric acid (4.4 M, 5.45 mL, 24 mmol, 3.0 equiv). After stirring at 25 ºC for 1 h, the reaction mixture was concentrated under reduced pressure to give a crude product, which was washed with $CHCl_3$ (50 mL). The crude product was treated with aqueous LiOH (0.78 M, 20 mL). The aqueous layer was extracted with ethyl acetate (50 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the title compound as a colorless solid (1.180 g, 3.87 mmol, 49%); R_f = 0.30 (ethyl acetate); Mp >250 ºC; IR (ATR, cm^{-1}): 1648, 1340, 1174, 995; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (d, 1H, J = 4.4 Hz), 7.34 (d, 1H, J = 4.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 146.5, 143.7, 128.0, 127.3 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom); ^{19}F NMR (376 MHz, DMSO-d_6): δ −140.7; ^{11}B NMR (128 MHz, DMSO-d_6): δ 3.26 (q, $^1J_{B–F}$ = 5.5 Hz); HRMS (ESI$^-$/TOF) *m/z*: [M−H]$^-$ calcd. for $C_5H_2{}^{11}B^{79}Br_2{}^{19}F_3N$, 301.8599; found, 301.8612.

Tetrabutylammonium trifluoro(2,3-dibromo-4-pyridinyl)borate (135-NBu$_4$)

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2,3-dibromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**136**) (498 mg, 1.37 mmol, 1.0 equiv) and MeOH (3.4 mL). After stirring at 25 ºC for 5 min, the reaction mixture was treated with hydrofluoric acid (4.4 M, 1.18 mL, 5.2 mmol, 3.8 equiv). After stirring at 0 ºC for 1 min, the reaction mixture was warmed to 25 ºC for 1 h, at which time the reaction mixture was treated with aqueous tetrabutylammonium hydroxide (1.5 M, 1.12 mL, 1.7 mmol, 1.2 equiv). After stirring at 25 ºC for 1 h, the reaction mixture was diluted with CH_2Cl_2 (2 mL). After being partitioned, the aqueous the aqueous layer was extracted with CH_2Cl_2 (2 mL) three times. The combined organic extracts were washed with water (5 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (CH_2Cl_2 to ethyl acetate, gradient) and recrystallization (hexane/EtOH = 5:2) to provide the title compound as a

colorless solid (464.1 mg, 0.850 mmol, 62%); R_f = 0.32 (ethyl acetate); Mp 73–74 ºC; IR (ATR, cm^{-1}): 2964, 1331, 1161, 1024; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, 1H, *J* = 4.4 Hz), 7.51 (d, 1H, *J* = 4.4 Hz), 3.20–3.11 (m, 8H), 1.64–1.53 (m, 8H), 1.40 (qt, 8H, *J* = 7.4 Hz, 7.4 Hz), 0.99 (t, 12H, *J* = 7.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 146.4, 144.4, 128.4, 128.1, 58.8, 24.0, 19.8, 13.7 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom); ^{19}F NMR (376 MHz, $CDCl_3$): δ −142.7; ^{11}B NMR (128 MHz, $CDCl_3$): δ 3.23; Anal. calcd. for $C_{21}H_{38}BBr_2F_3N_2$: C, 46.18; H, 7.01; N, 5.13, found: C, 46.11; H, 7.10; N, 5.13.

4-7-7 Trifluoroborate-Catalyzed Halogen Dance (Scheme 4–3)



Reaction with precatalyst 135-H

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (711.7 mg, 3.00 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (93.2 mg, 0.30 mmol, 10 mol%), and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.574 g, 6.20 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromo-4-iodopyridine (**129**) and 2,4-dibromo-3-iodopyridine (**132**) were determined to be 2% and 77% by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.91 ppm (1 proton for **129**) and 8.13 ppm (1 proton for **132**) with that of 1,1,2,2-

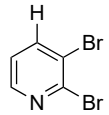
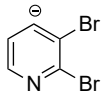
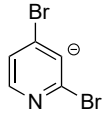
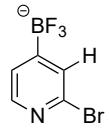
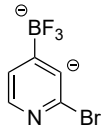
tetrachloroethane observed at 5.96 ppm.

Reaction with catalyst 135-NBu$_4$

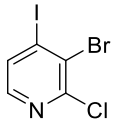
A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (707.5 mg, 2.99 mmol, 1.0 equiv), tetrabutylammonium trifluoro(2,3-dibromo-4-pyridinyl)borate (**135-NBu$_4$**) (163.4 mg, 0.30 mmol, 0.10 equiv), and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.567 g, 6.17 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromo-4-iodopyridine (**129**) and 2,4-dibromo-3-iodopyridine (**132**) were determined to be 57% and 19% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.91 ppm (1 proton for **129**) and 8.13 ppm (1 proton for **132**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

4-7-8 Calculation of p*K*a Values

The calculated p*K*a values in DMSO were as follows (see Chapter 2, 2-8-6).

R–H	R^- (anion)	$\Delta G°$ [kJ/mol]	p*K*a (in DMSO)
 **5**		1382.1	34.0
		1367.5	31.6
		1441.0	43.8

4-7-9 Range of Bromopyridines Synthesized by Lithium Aryltrifluoroborate-Catalyzed Halogen Dance (Table 4–2)


S6

3-Bromo-2-chloro-4-iodopyridine (S6) (Table 4–2, entry 2)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-chloropyridine (**142**) (58.2 mg, 0.302 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (90.8 mg, 0.360 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.225 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 1 h, the reaction mixture was treated with iodine (159.4 mg, 0.628 mmol, 2.1 equiv). After stirring at 0 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column

chromatography (hexane/diethyl ether = 49:1) to provide the title compound as a colorless solid (88.6 mg, 0.278 mmol, 92%); R_f = 0.38 (hexane/diethyl ether = 5:1); Mp 130–131 ºC; IR (ATR, cm^{-1}): 1543, 1341, 1189, 827; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 1H, J = 5.0 Hz), 7.72 (d, 1H, J = 5.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.6, 147.3, 134.1, 128.6, 115.0; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_5H_3{}^{79}Br^{35}ClIN$, 317.8182; found, 317.8187.

143

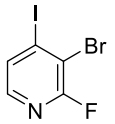
CCDC 2195350

4-Bromo-2-chloro-3-iodopyridine (143) (Table 4–2, entry 2)

The yields of 3-bromo-2-chloro-4-iodopyridine (**S6**) and 4-bromo-2-chloro-3-iodopyridine (**143**) were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.94 ppm (1 proton for **S6**) and 8.14 ppm (1 proton for **143**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-chloropyridine (**142**) (572.7 mg, 2.98 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (92.7 mg, 0.304 mmol, 10 mol%), and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 2.25 mL, 4.5 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 4 h, the reaction mixture was treated with iodine (1.604 g, 6.32 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1) to provide the title compound as a colorless solid (662.3 mg, 2.08 mmol, 70%), whose ^1H NMR and ^{13}C NMR spectra were consistent with those reported in the literature.[128] R_f = 0.38 (hexane/diethyl ether = 5:1); Mp 88–89 ºC; IR (ATR, cm^{-1}): 1537, 1414, 1333, 1189; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, 1H,

J = 5.0 Hz), 7.46 (d, 1H, J = 5.0 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 156.6, 148.6, 143.1, 126.5, 104.0; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_5H_3{}^{81}Br^{35}ClIN$, 319.8162; found, 319.8168.



S7

3-Bromo-2-fluoro-4-iodopyridine (S7) (Table 4–2, entry 3)

A flame-dried 500-mL two-necked flask equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under nitrogen was charged with 3-bromo-2-fluoropyridine (**144**) (1.769 g, 10.0 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (3.022 g, 12.0 mmol, 1.2 equiv), and anhydrous THF (100 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 7.50 mL, 15.0 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 30 min, the reaction mixture was treated with iodine (5.161 g, 20.3 mmol, 2.0 equiv). After stirring at 0 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (40 mL) and saturated aqueous ammonium chloride (40 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (50 mL) three times. The combined organic extracts were washed with water (100 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 99:1) and recrystallization (hexane) to provide the title compound as a colorless solid (1.965 g, 6.51 mmol, 65%); R_f = 0.48 (hexane/diethyl ether = 5:1); Mp 100–101 ºC; IR (ATR, cm^{-1}): 1562, 1447, 1377, 878; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, 1H, J = 5.0 Hz), 7.66 (d, 1H, J = 5.0 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 159.2 (d, $^{1}J_{C–F}$ = 237.7 Hz), 145.8 (d, $^{3}J_{C–F}$ = 14.3 Hz), 133.0 (d, $^{4}J_{C–F}$ = 4.8 Hz), 116.5, 114.2 (d, $^{2}J_{C–F}$ = 38.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.3; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_5H_3{}^{79}BrFIN$, 301.8478; found, 301.8483.

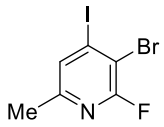
145

CCDC 2151209

4-Bromo-2-fluoro-3-iodopyridine (145) (Table 4–2, entry 3)

The yields of 3-bromo-2-fluoro-4-iodopyridine (**S7**) and 4-bromo-2-fluoro-3-iodopyridine (**145**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.82 ppm (1 proton for **S7**) and 7.99 ppm (1 proton for **145**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

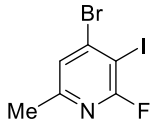
A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-fluoropyridine (**144**) (522.0 mg, 2.97 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (90.9 mg, 0.298 mmol, 10 mol%), and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 2.25 mL, 4.5 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.611 g, 6.35 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1) to provide the title compound as a colorless solid (756.1 mg, 2.51 mmol, 84%), whose ^{1}H NMR and ^{13}C NMR spectra were consistent with those reported in the literature.[129] R_f = 0.48 (hexane/diethyl ether = 5:1); Mp 74–76 ºC; IR (ATR, cm^{-1}): 1562, 1433, 1378, 828; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 1H, J = 5.6 Hz), 7.43 (d, 1H, J = 5.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.3 (d, $^{1}J_{C–F}$ = 235.8 Hz), 147.2 (d, $^{3}J_{C–F}$ = 16.3 Hz), 144.1, 125.9 (d, $^{4}J_{C–F}$ = 4.8 Hz), 85.6 (d, $^{2}J_{C–F}$ = 45.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −46.4; HRMS (DART^{+}) *m/z*: [M+H]$^{+}$ calcd. for $C_5H_3{}^{81}BrFIN$, 303.8457; found, 303.8450.



S8

3-Bromo-2-fluoro-4-iodo-6-methylpyridine (S8) (Table 4–2, entry 4)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-fluoro-6-methylpyridine (**146**) (57.6 mg, 0.303 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (91.3 mg, 0.362 mmol, 1.2 equiv), and anhydrous THF (3.0 mL). The solution was cooled to 0 ºC. LDA (2.0 M, 0.225 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 ºC for 1 h, the reaction mixture was treated with iodine (157.4 mg, 0.620 mmol, 2.0 equiv). After stirring at 0 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1 to 19:1, gradient) to provide the title compound as a colorless solid (81.1 mg, 0.257 mmol, 85%); R_f = 0.52 (hexane/diethyl ether = 5:1); Mp 102–103 ºC; IR (ATR, cm^{-1}): 1570, 1433, 1364, 800; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.1 (d, $^1J_{C–F}$ = 236.7 Hz), 156.4 (d, $^3J_{C–F}$ = 14.3 Hz), 132.3 (d, $^4J_{C–F}$ = 4.8 Hz), 116.5, 110.1 (d, $^2J_{C–F}$ = 39.3 Hz), 23.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.2; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_6H_5{}^{79}BrFIN$, 315.8634; found, 315.8649.



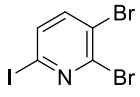
147

4-Bromo-2-fluoro-3-iodo-6-methylpyridine (147) (Table 4–2, entry 4)

The yields of 3-bromo-2-fluoro-4-iodo-6-methylpyridine (**S8**) and 4-bromo-2-fluoro-3-iodo-6-methylpyridine (**147**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.54 ppm (1 proton for **S8**) and 7.31 ppm (1 proton for **147**) with

that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The signals of 3-bromo-2-fluoro-4-iodo-6-methylpyridine (**S8**) were identical with the spectrum obtained by the following procedure.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-fluoro-6-methylpyridine (**146**) (57.2 mg, 0.301 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (9.8 mg, 0.032 mmol, 11 mol%), and anhydrous THF (3.0 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.225 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 4 h, the reaction mixture was treated with iodine (157.5 mg, 0.621 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1 to 19:1, gradient) to provide the title compound as a colorless solid (70.1 mg, 0.222 mmol, 74%); R_f = 0.51 (hexane/diethyl ether = 5:1); Mp 83–84 ºC; IR (ATR, cm^{-1}): 1573, 1523, 1358, 821; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 1H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.4 (d, $^1J_{C–F}$ = 234.8 Hz), 157.9 (d, $^3J_{C–F}$ = 14.4 Hz), 143.8 (d, $^3J_{C–F}$ = 2.9 Hz), 125.3 (d, $^4J_{C–F}$ = 4.8 Hz), 80.8 (d, $^2J_{C–F}$ = 45.0 Hz), 23.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ −47.4; HRMS (DART$^+$) *m/z*: [M+H]$^+$ calcd. for $C_6H_5{}^{81}BrFIN$, 317.8614; found, 317.8627.



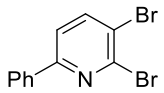
S9

2,3-Dibromo-6-iodopyridine (S9)

A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-amino-6-bromopyridine (3.459 g, 20.0 mmol, 1.0 equiv) and DMF (11.7 mL). The solution was cooled to 0 ºC. NBS (3.561 g, 20.0 mmol, 1.0 equiv) was added to the flask for 4 min. After stirring at 25 ºC for 3.5 h, the reaction mixture was poured into saturated aqueous sodium thiosulfate (100 mL), at which time a colorless solid was precipitated. The solid was collected by filtration and dried under

reduced pressure to give a crude 2-amino-5,6-dibromopyridine (**S10**) as a colorless solid (5.134 g), which was used for the next step without further purification.

A 300-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a reflux tube was charged with 2-amino-5,6-dibromopyridine (**S10**) (2.833 g, 11.2 mmol, 1.0 equiv), copper(I) iodide (3.221 g, 16.9 mmol, 1.5 equiv), CH_2I_2 (25.00 g, 93.3 mmol, 8.3 equiv), isoamyl nitrite (6.00 mL, 45.1 mmol, 4.0 equiv), and anhydrous THF (22.5 mL). The flask was placed in a preheated oil bath and heated at 60 °C for 1 h. After cooling to room temperature, the resulting mixture was treated with saturated aqueous sodium thiosulfate (50 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (20 mL) three times. The combined organic extracts were washed with brine (100 mL), and dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 100:0 to 2:1, gradient) and recrystallization (hexane/$CHCl_3$ = 20:1) to provide the title compound as a colorless solid (2.499 g, 6.89 mmol, 61%); R_f = 0.57 (hexane/diethyl ether = 5:1); Mp 71–72 ºC; IR (ATR, cm^{-1}): 1527, 1388, 1316, 1002; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H, J = 7.6 Hz), 7.49 (d, 1H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.1, 142.6, 135.0, 124.4, 112.9; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_5H_3{}^{79}Br^{81}BrIN$, 363.7657; found, 363.7669.

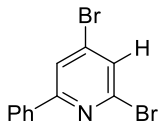


148

2,3-Dibromo-6-phenylpyridine (148) (Table 4–2, entry 5)

A 100-mL round-bottomed equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under nitrogen was charged with 2,3-dibromo-6-iodopyridine (**S9**) (1.087 g, 3.00 mmol, 1.0 equiv), phenylboronic acid (385.6 mg, 3.16 mmol, 1.1 equiv), $Pd(PPh_3)_4$ (177.8 mg, 0.154 mmol, 5 mol%), potassium carbonate (12.53 g, 90.7 mmol, 30 equiv), toluene (12 mL), and distilled water (12 mL). After stirring at 110 ºC for 3 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (15 mL) three times. The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under

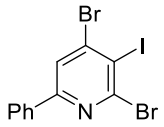
reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 19:1) to provide the title compound as a colorless solid (755.7 mg, 2.41 mmol, 81%); R_f = 0.32 (hexane); Mp 66–68 ºC; IR (ATR, cm^{-1}): 1536, 1414, 1004, 773; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.96 (m, 2H), 7.92 (d, 1H, *J* = 8.4 Hz), 7.57 (d, 1H, *J* = 8.4 Hz), 7.51–7.42 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.8, 143.5, 142.3, 136.8, 130.1, 129.1, 127.0, 121.9, 120.1; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_8{}^{79}Br_2N$, 311.9024; found, 311.9032.



149

2,4-Dibromo-6-phenylpyridine (149) (Table 4–2, entry 5)

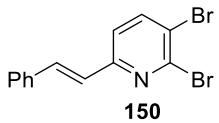
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-phenylpyridine (**148**) (47.1 mg, 0.150 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (5.2 mg, 0.017 mmol, 11 mol%), and anhydrous THF (1.5 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.115 mL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 3 h, the reaction mixture was treated with MeOH (2 mL). After stirring at −78 ºC for 5 min, to the reaction mixture was added saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 100:1) to provide the title compound as a colorless oil (42.1 mg, 0.135 mmol, 89%); R_f = 0.33 (hexane/diethyl ether = 100:1); IR (ATR, cm^{-1}): 1560, 1530, 1364, 751; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.93 (m, 2H), 7.84 (d, 1H, *J* = 1.4 Hz), 7.61 (d, 1H, *J* = 1.4 Hz), 7.51–7.44 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.4, 142.4, 136.6, 134.5, 130.4, 129.1, 128.8, 127.2, 122.6; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_8{}^{79}Br^{81}BrN$, 313.9003; found, 313.9003.



S11

2,4-Dibromo-3-iodo-6-phenylpyridine (S11) (Table 4–2, entry 5)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-phenylpyridine (**148**) (47.1 mg, 0.150 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (4.4 mg, 0.014 mmol, 10 mol%), and anhydrous THF (1.5 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.115 mL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 3 h, the reaction mixture was treated with iodine (79.5 mg, 0.313 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/CH_2Cl_2 = 99:1, gradient) to provide the title compound as a colorless solid (45.5 mg, 0.104 mmol, 69%); R_f = 0.30 (hexane/CH_2Cl_2 = 50:1); Mp 98–99 ºC; IR (ATR, cm^{-1}): 1546, 1321, 1207, 741; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.93 (m, 2H), 7.90 (s, 1H), 7.50–7.45 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.7, 149.5, 142.6, 135.8, 130.6, 129.1, 127.0, 123.0, 105.2; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_7{}^{81}Br_2IN$, 441.7949; found, 441.7969.

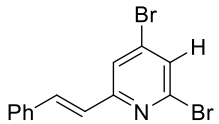


150

2,3-Dibromo-6-[(1*E*)-2-phenylethenyl]pyridine (150) (Table 4–2, entry 6)

A 100-mL round-bottomed equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under nitrogen was charged with 2,3-dibromo-6-iodopyridine (**S9**) (547.0 mg, 1.51 mmol, 1.0 equiv), (*E*)-phenylethenylboronic acid (235.2 mg, 1.59 mmol, 1.1 equiv), $Pd(PPh_3)_4$ (88.9 mg, 0.0769 mmol, 5 mol%), potassium carbonate (6.276 g, 45.4 mmol, 30 equiv), toluene (6.0 mL), and distilled water

(6.0 mL). After stirring at 110 ºC for 4 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (7 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (10 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 49:1 to 7:3, gradient) to provide the title compound as a colorless solid (442.1 mg, 1.30 mmol, 86%); R_f = 0.55 (hexane/CH_2Cl_2 = 7:3); Mp 81–82 ºC; IR (ATR, cm^{-1}): 1561, 1420, 1350, 1145; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, 1H, *J* = 8.2 Hz), 7.64 (d, 1H, *J* = 16.2 Hz), 7.57 (d, 2H, *J* = 7.8 Hz), 7.38 (dd, 2H, *J* = 7.8, 6.9 Hz), 7.33 (t, 1H, *J* = 6.9 Hz), 7.21 (d, 1H, *J* = 8.2 Hz), 7.04 (d, 1H, *J* = 16.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.3, 143.4, 141.9, 136.1, 135.2, 129.1, 129.0, 127.5, 125.5, 121.6, 121.0; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{10}{}^{79}Br^{81}BrN$, 339.9160; found, 339.9172.

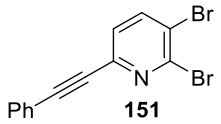


153

2,4-Dibromo-6-[(1*E*)-2-phenylethenyl]pyridine (153) (Table 4–2, entry 6)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-[(1*E*)-2-phenylethenyl]pyridine (**150**) (50.9 mg, 0.150 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (4.8 mg, 0.016 mmol, 10 mol%), and anhydrous THF (1.5 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.115 mL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 3 h, the reaction mixture was treated with MeOH (2 mL). After stirring at −78 ºC for 5 min, to the reaction mixture was added saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the title compound as a colorless solid (41.7 mg, 0.123 mmol, 82%); R_f = 0.30 (hexane/diethyl ether = 50:1); Mp 65–66 ºC; IR (ATR, cm^{-1}): 1556, 1524, 1147, 753; ^1H NMR (400 MHz, $CDCl_3$): δ

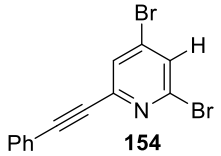
7.68 (d, 1H, J = 16.0 Hz), 7.56 (d, 2H, J = 7.2 Hz), 7.51 (d, 1H, J = 1.6 Hz), 7.47 (br s, 1H), 7.42–7.36 (m, 2H), 7.36–7.31 (m, 1H), 7.00 (d, 1H, J = 16.0 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.9, 142.3, 136.1, 135.9, 134.1, 129.3, 129.0, 128.5, 127.6, 125.2, 124.0; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{10}{}^{79}Br_2N$, 337.9180; found, 337.9195.



151

2,3-Dibromo-6-(2-phenylethynyl)pyridine (151) (Table 4–2, entry 7)

A 100-mL round-bottomed equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under nitrogen was charged with 2,3-dibromo-6-iodopyridine (**S9**) (1.086 g, 2.99 mmol, 1.0 equiv), phenylacetylene (0.365 mL, 3.32 mmol, 1.1 equiv), $Pd(PPh_3)_4$ (176.3 mg, 0.153 mmol, 5 mol%), copper(I) iodide (59.6 mg, 0.313 mmol, 0.10 equiv), and diisopropylamine (20.0 mL). After stirring at 25 ºC for 1 h, the reaction mixture was quenched with saturated hydrochloric acid (1.0 M, 10 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (15 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 97:3 to 7:3, gradient) to provide the title compound as a colorless solid (690.6 mg, 2.05 mmol, 68%); R_f = 0.59 (hexane/CH_2Cl_2 = 7:3); Mp 66–68 ºC; IR (ATR, cm^{-1}): 2222, 1556, 1411, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, 1H, J = 7.8 Hz), 7.61–7.56 (m, 2H), 7.43–7.36 (m, 3H), 7.34 (d, 1H, J = 7.8 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 143.4, 142.1, 141.6, 132.2, 129.6, 128.6, 126.9, 123.1, 121.6, 92.0, 86.9; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_8{}^{79}Br_2N$, 335.9024; found, 335.9030.

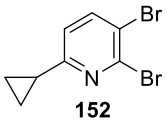


154

2,4-Dibromo-6-(2-phenylethynyl)pyridine (154) (Table 2, entry 7)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-(2-

phenylethynyl)pyridine (**151**) (50.3 mg, 0.149 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (5.4 mg, 0.018 mmol, 12 mol%), and anhydrous THF (1.5 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.115 mL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 5 h, the reaction mixture was treated with MeOH (2 mL). After stirring at −78 ºC for 5 min, to the reaction mixture was added saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 19:1 to 4:1, gradient) to provide the title compound as a colorless solid (23.1 mg, 0.0685 mmol, 46%); R_f = 0.38 (hexane/CH_2Cl_2 = 4:1); Mp 73–74 ºC; IR (ATR, cm^{-1}): 2220, 1553, 1523, 1148, 757; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, 1H, *J* = 2.0 Hz), 7.64 (d, 1H, *J* = 2.0 Hz), 7.61–7.56 (m, 2H), 7.44–7.34 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.6, 142.1, 133.8, 132.4, 130.0, 129.8, 129.3, 128.7, 121.5, 92.4, 86.6; HRMS (DART$^+$) *m/z*: [M+H]$^+$ calcd. for $C_{13}H_8{}^{79}Br^{81}BrN$, 337.9003; found, 337.9015.

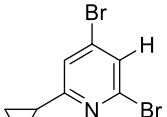


152

2,3-Dibromo-6-cyclopropylpyridine (152) (Table 4–2, entry 8)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-iodopyridine (**S9**) (1.080 g, 2.98 mmol, 1.0 equiv), $PdCl_2$(dppf)·CH_2Cl_2 (493.0 mg, 0.604 mmol, 20 mol%), and anhydrous THF (5.0 mL). The separately prepared cyclopropylzinc bromide[130] (0.27 M,[83] 12.2 mL, 3.3 mmol, 1.1 equiv) was added to the solution via a syringe. After stirring at 50 ºC for 13 h, the reaction mixture was treated with saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (10 mL) three times. The combined organic extracts were washed with water (20 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 20:1 to 10:1, gradient) to provide the title compound as a colorless solid (421.7 mg, 1.52 mmol, 51%); R_f = 0.33 (hexane); Mp 37–38 ºC; IR (ATR, cm^{-1}):

1579, 1538, 1428, 1008; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, 1H, J = 8.0 Hz), 6.95 (d, 1H, J = 8.0 Hz), 1.99–1.92 (m, 1H), 1.04–0.98 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.3, 143.0, 141.2, 121.3, 119.2, 16.8, 10.9; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_8H_8{}^{81}Br_2N$, 279.8983; found, 279.8996.



155

2,4-Dibromo-6-cyclopropylpyridine (155) (Table 4–2, entry 8)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-cyclopropylpyridine (**152**) (41.8 mg, 0.151 mmol, 1.0 equiv), 2,3-dibromo-4-(trifluoro-λ^4-boraneyl)-1λ^4-pyridine (**135-H**) (5.0 mg, 0.016 mmol, 11 mol%), and anhydrous THF (1.5 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 0.115 mL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 5 h, the reaction mixture was treated with MeOH (2 mL). After stirring at −78 ºC for 5 min, to the reaction mixture was added saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 97:3 to 19:1, gradient) to provide the title compound as a colorless oil (29.5 mg, 0.107 mmol, 71%); R_f = 0.30 (hexane); IR (ATR, cm^{-1}): 1565, 1530, 1329, 748; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, 1H, J = 1.4 Hz), 7.24 (d, 1H, J = 1.4 Hz), 1.98–1.90 (m, 1H), 1.07–0.99 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 142.0, 133.5, 127.1, 123.5, 17.2, 11.0; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_8H_8{}^{79}Br^{81}BrN$, 277.9003; found, 277.9010.

4-7-10 Accession Codes

Deposition Numbers 2077481 (for **132**), 2179136 (for **135-H**), 2151176 (for **135-NBu$_4$**), 2195350 (for **143**), and 2151209 (for **145**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_ request/cif, or by emailing data_request@ccdc.cam.ac.uk, or

by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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(113) The broad singlets (12.2 and 5.89 ppm at −100 °C) were observed in the absence of 2,3-dibromopyridine (**128**). In Figure 4–1a, the NMR spectrum of a mixture of 0.5 equiv of $BF_3{\cdot}OEt_2$ and 1.0 equiv of 2,3-dibromopyridine is presented; nevertheless, all the signals of 2,3- dibromopyridine were slightly shifted over the temperature range from −100 to 20 °C. We consider that the displacement of the chemical shifts was attributed to the temperature dependence of the NMR chemical shifts of protons. Coordination of 2,3-dibromopyridine (**128**) to BF_3 was also not observed in $CDCl_3$ and C_6D_6.

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(121) The use of THF was crucial for promoting the halogen dance. When the reaction was performed in Et_2O, 3-iodopyridine **132** was generated in 9% yield, along with 4-iodopyridine **129** (53% yield). The use of toluene resulted in the formation of 3-iodopyridine **132** and 4-iodopyridine **129** in 2% and 34% yields, respectively.

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(126) Electrophilic trapping with iodine provided the corresponding product in 69% isolated yield.
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第五章

KHMDS 触媒による
ハロゲンダンス

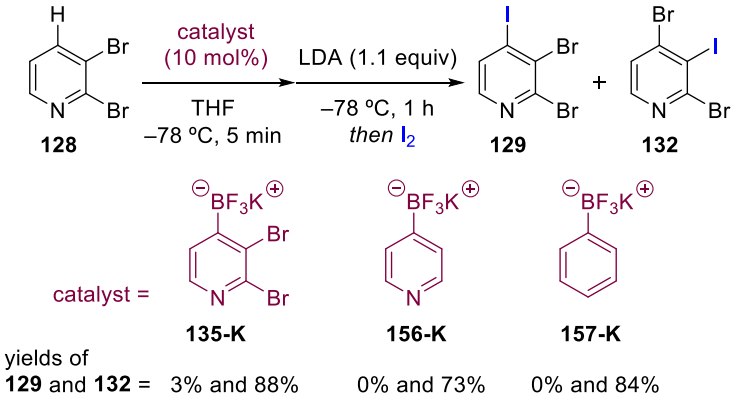
5-1　緒言

第四章では，リチウムからホウ素への金属交換によって発生するリチウムアリールトリフルオロボラートがハロゲンダンスの触媒となることを見出した。第五章では，リチウムからカリウムへの金属交換が，ハロゲンダンスをさらに加速させることがわかった。検討の結果，カリウムアミド塩基として一般的に利用されるKHMDSが，きわめて高い触媒活性を示すことが新たに明らかになった。KHMDSは今まで報告されたいずれの触媒よりも優れた高活性な触媒であり，触媒量を10 mol%としたとき，反応時間を1分にまで短縮できた。KHMDS触媒によるハロゲンダンスは，ピリジンだけでなく，イミダゾール，チオフェン，フラン，ベンゼンなどの幅広いブロモアレーンに適用でき，様々な置換様式をもつブロモアレーンを合成できた。

5-2　カリウムアリールトリフルオロボラートの触媒活性評価

第四章では，リチウムアリールトリフルオロボラートの触媒活性を確かめた。しかし，合成化学的には，リチウム塩よりも安価かつ化学的に安定なカリウムアリールトリフルオロボラート[122–125,131]の利用が一般的である。したがって，まずカリウムアリールトリフルオロボラートの触媒活性を調べた (Scheme 5–1)。ジブロモピリジン **128** の THF 溶液に対して，カリウムアリールトリフルオロボラート **135-K** を 10 mol%加え，LDA を–78 °C で 1 時間作用させ，ヨウ素で反応を停止した。その結果，ハロゲンダンスが進行した 3-ヨードピリジン **132** を収率88%で得た。リチウムをテトラブチルアンモニウムにかえたテトラブチルアンモ

Scheme 5–1　Halogen Dance Reactions Catalyzed with Potassium Aryltrifluoroborates

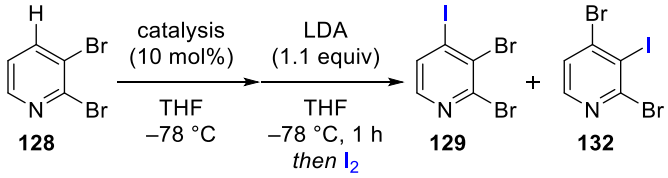


ニウム塩 **135-NBu$_4$**（詳細は，第四章，Scheme 4–3）とは対照的に，リチウムをカリウムにかえたカリウムアリールトリフルオロボラート **135-K** が高い触媒活性を示すことがわかった。また，興味深いことに，臭素原子をもたないカリウム塩 **156-K** も高い触媒活性を示し，3-ヨードピリジン **132** を収率 73%で与えた。さらに，窒素原子をもたないカリウムフェニルトリフルオロボラート(**157-K**)も高活性な触媒となることがわかった。ブロモ基をもたないカリウム塩 **156-K** や **157-K** が高い触媒活性を示した結果から，第四章でブロモ基の受け渡しを加速させたリチウムアリールトリフルオロボラートとは，全く異なる反応機構でハロゲンダンスが進行したことがわかった。

5-3　カリウム塩の触媒活性評価

カリウム塩がハロゲンダンスに与える影響に興味をもち，触媒活性を調べた

Table 5–1. Screening of Halogen Dance Catalysts[a]



entry	catalyst	**128** (%)[b]	**129** (%)[b]	**132** (%)[b]
1	none	–[c]	77	8
2	KO^{t}Bu	–[c]	–[c]	92
3	KOH	–[c]	70	12
4	K_2CO_3	–[c]	74	12
5	KOAc	–[c]	63	21
6	KF	–[c]	66	15
7	KI	–[c]	64	24
8	KHMDS	–[c]	–[c]	94 (86[b])
9	NaHMDS	–[c]	8	64
10	LiHMDS	–[c]	54	15

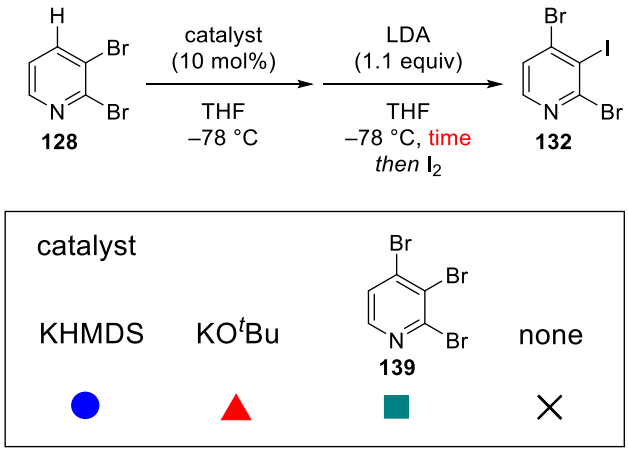
[a]Reaction conditions: 2,3-dibromopyridine (**128**; 1.0 equiv, 3.0 mmol), catalyst (10 mol%, 0.30 mmol), THF (30 mL), then LDA (1.1 equiv, 3.3 mmol), −78 °C, 1 h, then iodine (2.0 equiv, 6.0 mmol), −78 °C, 1 h. [b]Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard. [c]Not observed. [d]Isolated yield.

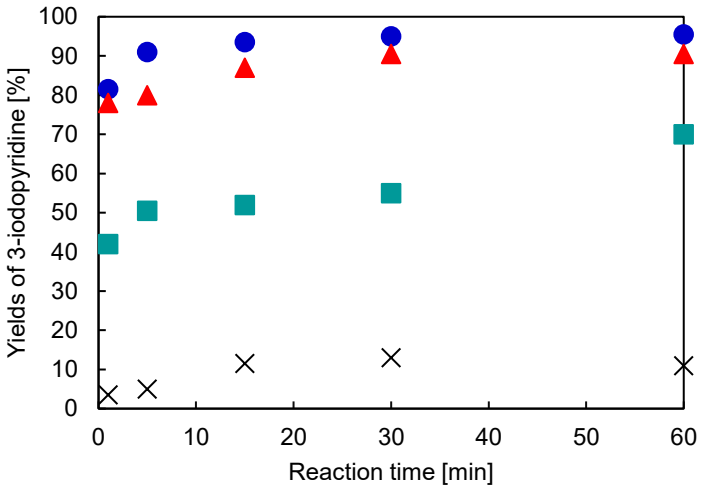
(Table 5–1)。まず，対照実験として，ジブロモピリジン **128** に対して，THF 中で LDA (1.1 当量)を−78 °C で加え，1 時間後にヨウ素で反応を停止させたところ，3-ヨードピリジン **132** を収率 8%で得た (Table 5–1, entry 1 and Table 4–1, entry 1)。ピリジン **128** の遅いハロゲンダンスを加速させるため，カリウム塩の添加効果を調べた。まず，中間体として発生する有機リチウムの反応性を向上させるため，Lochmann–Schlosser 塩基 (^{n}BuLi/KO^{t}Bu)[132]に利用される KO^{t}Bu を触媒量加えた。その結果，10 mol%の KO^{t}Bu がハロゲンダンスを大幅に加速し，3-ヨードピリジン **132** が収率 92%で選択的に得られた (entry 2)。一方で，アルキル基をもたない KOH を用いると，3-ヨードピリジン **132** の収率は 12%だった (entry 3)。弱酸由来のカリウム塩として，K_2CO_3，KOAc，KF を用いた場合も，低収率で 3-ヨードピリジン **132** を得た (entries 3–6)。強酸由来のカリウム塩として KI を用いたが，その触媒活性は低かった (entry 7)。カリウム塩を検討した結果，KO^{t}Bu よりも塩基性が高い KHMDS を用いた場合，3-ヨードピリジン **132** を収率 94%で得た (entry 8)。以上の結果から，強塩基として利用されるカリウム塩として，KHMDS と KO^{t}Bu が高い触媒活性を示すとわかった。また，カウンターカチオンをカリウムから，ナトリウム，リチウムへかえると，3-ヨードピリジン **132** の収率が低下した (entries 9 and 10)。以上の結果から，カリウムイオンが高い触媒活性に必要不可欠であるとわかった。

5-4　KHMDS 触媒を利用したハロゲンダンスの反応速度論的解析

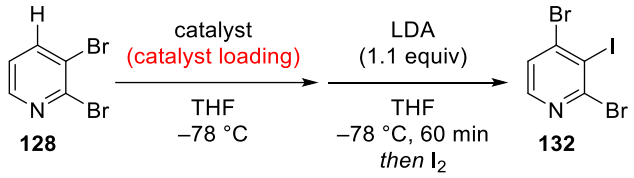
KHMDS の触媒活性を KO^{t}Bu やトリブロモピリジン **139**[20a] と比較するために，反応速度論的解析をおこなった (Figure 5–1)。まず，反応時間に対して 3-ヨードピリジン **132** の収率をプロットした (Figure 5–1a)。KHMDS (10 mol%)を用いた

(a) Yields of 3-iodopyridine vs. reaction time





(b) Yields of 3-iodopyridine vs. catalyst loading



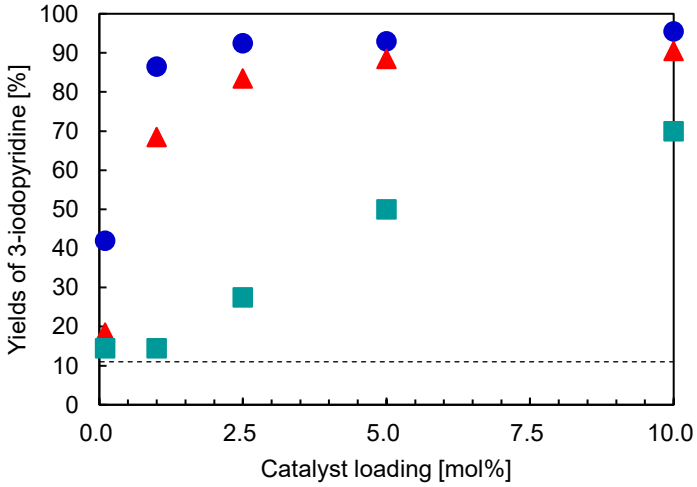


Figure 5–1. Kinetic analysis of KHMDS-catalyzed halogen dance reactions. (a) Plots of the yields of 3-iodopyridine **132** (average of two runs) vs. reaction time upon treatment of 2,3-dibromopyridine (**128**; 1.0 equiv) and a catalyst (10 mol%) in THF with LDA (1.1 equiv), –78 °C, 1–60 min, then iodine (2.0 equiv), –78 °C, 1 h. (b) Plots of the yields of 3-iodopyridine **132** (average of two runs) vs. catalyst loading upon treatment of 2,3-dibromopyridine (**128**; 1.0 equiv) and a catalyst (0.1–10 mol%) in THF with LDA (1.1 equiv), –78 °C, 1 h, then iodine (2.0 equiv), –78 °C, 1 h.

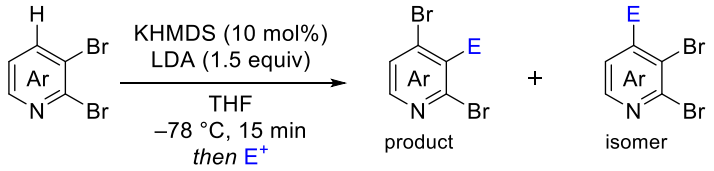
場合，反応時間を 1 分としても，3-ヨードピリジン **132** が収率 82%で得られた。なお, KO^{t}Bu を同様の反応条件で用いると，目的物 **132** が収率 78%で生成した。したがって，KHMDS が KO^{t}Bu よりも高い触媒回転頻度をもつとわかった。さらに，従来報告されていたトリブロモピリジン **139**[20a] (10 mol%)や触媒を用いない条件では，3-ヨードピリジン **132** の収率は大幅に低下した。次に，触媒添加量が収率に与える効果を調べた (Figure 5–1b)。触媒添加量に対して，3-ヨードピリジン **132** の収率をプロットした結果，KHMDS の触媒量を 1.0 mol%，反応時間を 1 時間とした場合でも，3-ヨードピリジン **132** が収率 87%で得られた。また，KO^{t}Bu を同様の反応条件で用いた場合は，KHMDS を用いた場合よりも 3-ヨードピリジン **132** の収率が低下した。さらに，トリブロモピリジン **139** を 1.0 mol%用いると，3-ヨードピリジン **132** の収率は 15%であった。以上の結果から，KHMDS は，KO^{t}Bu やトリブロモピリジンよりも高い触媒活性を示すとわかった。

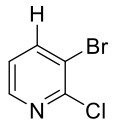
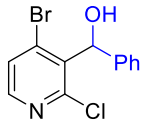
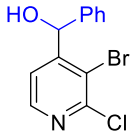
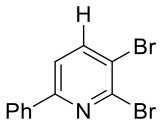
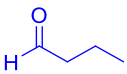
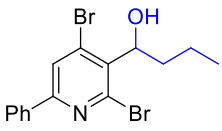
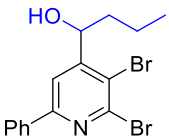
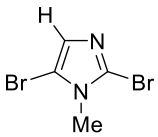
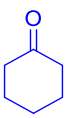
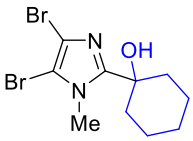
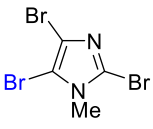
5-5　基質と求電子剤の一般性

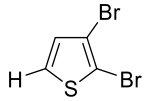
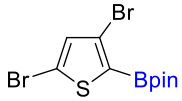
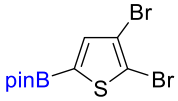
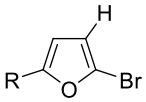
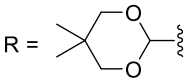
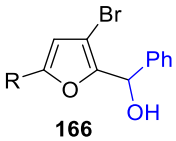
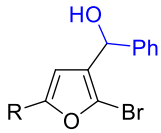
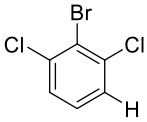
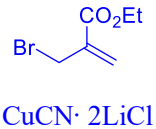
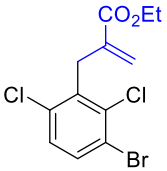
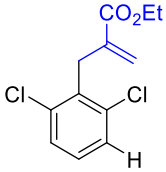
LDA と触媒量の KHMDS の組み合わせを用いて，様々なブロモアレーンのハロゲンダンスを実施した (Table 5–2)。まず，2-クロロ-3-ブロモピリジン (**142**)と KHMDS (10 mol%)の混合物に，LDA (1.5 equiv)を−78 °C で 15 分間作用させ，ベンズアルデヒド (2.0 equiv)と 2 時間反応させた。その結果，付加体 **158** が収率 72%で選択的に得られた (entry 1)。一方で，KHMDS を用いない場合，望まない異性体 **159** が収率 63%で生成した。なお，触媒を加えずに，反応時間を 5 時間としても望まない付加体 **159** が収率 67%で得られたことから，KHMDS が高い触媒活性をもつ優れた触媒であるとわかった。フェニルピリジン **148** も同様に，KHMDS を用いると，ブタナールとの付加体 **160** が収率 66%で選択的に生成した (entry 2)。なお，触媒を加えない場合，付加体 **160** と異性体 **161** がそれぞれ収率 49%と 32%で得られた。KHMDS 触媒を用いたハロゲンダンスは，5 員環ブロモヘテロアレーンにも適用できた。イミダゾール **54** と KHMDS のトルエン溶液に対して，LDA を−78 °C で 15 分間作用させ，シクロヘキサノンと反応させると，付加体 **162** を収率 89%で得た (entry 3)。触媒を用いない場合，シクロヘキサノールの異性体は得られなかったが, ハロゲンダンスの中間体 **59**（詳細は，第二章，Scheme 2–16）が収率 60%で得られた。チオフェン **15** も最適条件を用いると，トルエン溶媒中でもハロゲンダンスが進行し，pinBO^{i}Pr との反応[116]によって，ボロン酸エステル **163** が収率 86%で得られた (entry 4)。KHMDS を用

いない場合は，ボロン酸エステル **163** とその異性体 **164** がそれぞれ収率 55%と 43%で得られた。さらに，ブロモフラン **165** のハロゲンダンス [26d] も，触媒量の KHMDS によって加速された。ブロモフラン **165** と KHMDS (19 mol%)の THF 溶液に LiTMP を 1.5 当量作用させると，原料のブロモフラン **165** が消失し，

Table 5–2. Range of Bromoarenes Synthesized by the KHMDS-Catalyzed Halogen Dance Reaction[a]



entry	substrate	E^+	product (%)[b]	byproduct (%)[b]
1	 **142**		 **158**	 **159**
	with KHMDS		72 (72[c])	3
	without KHMDS		16	63
	without KHMDS[d]		16	67
2[e,f]	 **148**		 **160**	 **161**
	with KHMDS		66 (61[c])	13
	without KHMDS		49	32
3[f,g]	 **54**		 **162**	 **59**
	with KHMDS		89 (80[c])	11
	without KHMDS		23	60

4[h]	 **15**	pinB−O^{i}Pr	 **163**	 **164**
	with KHMDS		86 (57[c])	2
	without KHMDS		55	43
5[f,i]	 **165** 		 **166**	 **167**
	with KHMDS		38[j] (27[c])	4[j]
	without KHMDS		–[j,k]	47[j]
6[l]	 **117f**	 CuCN· 2LiCl	 **168**	 **169**
	with KHMDS		53 (42[c])	4
	without KHMDS		40	29

[a]Reaction conditions: bromobenzene (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 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%) and LiTMP (1.5 equiv, 0.23 mmol) for 1 h. [j]Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [k]Not observed. [l]Reaction conditions: bromobenzene (**117f**; 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 (2.0 equiv, 0.60 mmol), −78 °C to rt, 2 h.

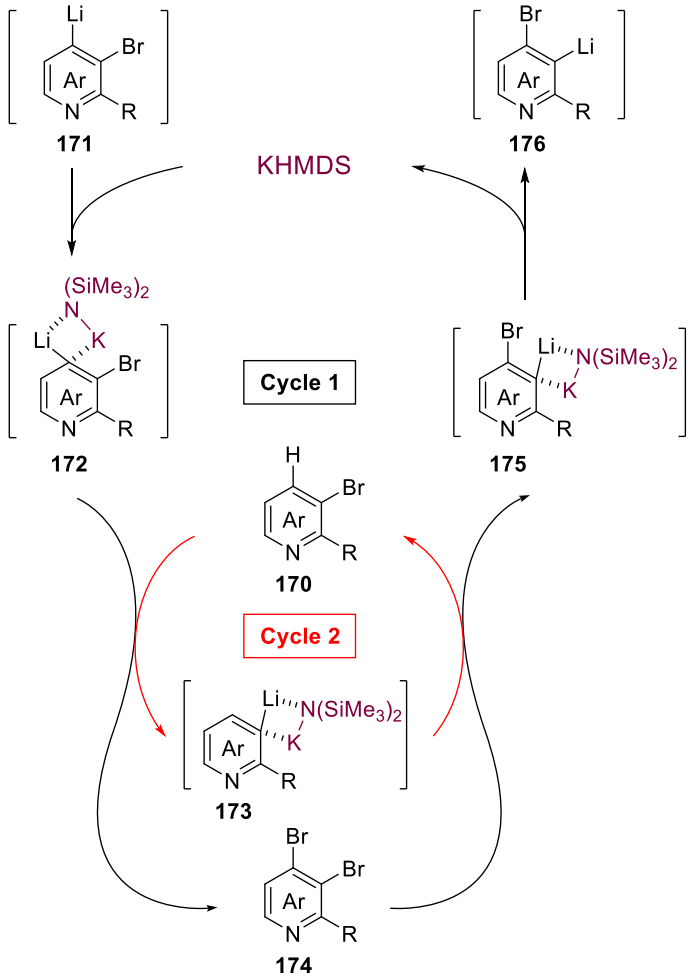
ベンズアルデヒドとの反応によって，付加体 **166** を収率 38%で選択的に得た。我々が以前報告した KO^{t}Bu を化学量論量用いる条件[26c,d]とは，触媒量の KHMDS を用いる点で異なる。KHMDS を用いない場合，異性体 **167** と原料 **165** がそれぞれ収率 47%と 25%で検出された。触媒量の KHMDS によって原料が消費された結果から，KHMDS はハロゲン–金属交換だけでなく，Lochmann–Schlosser 塩基[132]と同様に，脱プロトンも加速させるとわかった。化学量論量の KO^{t}Bu を用いる

通常の Lochmann–Schlosser 塩基と比較し，今回の高速ハロゲンダンスでは，触媒量の KHMDS を利用した。最適条件は，ブロモベンゼンにも適用可能であった。ブロモベンゼン **117f** は，KHMDS を触媒としたハロゲンダンス，銅を用いたアリル化[82,93]が進行し，ブロモ基が移動したアクリル酸エチル **168** が収率 53%で得られた。一方で，KHMDS を加えない場合，アクリル酸エチル **168** とブロモ基が脱離したアクリル酸エチル **169** の分離困難な混合物を得た。望まないアクリル酸エチル **169** は，ハロゲンダンスの中間体として発生した有機リチウム（詳細は，第二章，2-2-3）が，アリル化され生成したと考えている。以上のように，LDA と触媒量の KHMDS の組み合わせが，幅広いブロモアレーンのハロゲンダンス反応を劇的に加速させることが明らかとなった。

5-6　反応機構の推定

高速ハロゲンダンスの反応機構として，KHMDS とブロモピリジン **170** が関与する二元触媒反応[133]を推定した (Scheme 5–2)。まず，ブロモピリジン **170** が LDA によって脱プロトンされ，有機リチウム **171** を与える。有機リチウム **171** に KHMDS が配位すると，Lochmann–Schlosser 塩基のように，Li と K をあわせもつ mixed aggregate[134]とよばれる会合状態をもつ有機金属 **172** を与える。有機金属 **172** は，有機カリウム性をおびているため反応性が高く，ピリジン **170** との臭素–金属交換が速やかに進行し，有機金属 **173** とジブロモピリジン **174** を与える。有機金属 **173** は，ジブロモピリジン **174** との連続的な臭素–リチウム交換により，熱力学的に最も安定な有機金属 **175** を与え，ピリジン **170** が再生する（詳細は，第四章，Scheme 4–4）。有機金属 **175** から KHMDS が脱離し，有機リチウム **176** が生成することで，二元触媒反応の触媒サイクルが完結する。第四章，Figure 4–1 の DFT 計算の結果から，一度目の有機金属 **172** とピリジン **170** の臭素–リチウム交換が律速段階であり，触媒量の KHMDS から発生させた反応性が高い有機金属 **172** が，臭素–リチウム交換を加速させたと考えている。通常，Lochmann–Schlosser 塩基は，化学量論量の KO^{t}Bu を用いて脱プロトン反応を加速させるが，本研究は，触媒量の KHMDS から発生させた mixed aggreagate が臭素–リチウム交換を大幅に加速させた初めての例である。

Scheme 5–2. Plausible Mechanistic Pathway for the Ultrafast Halogen Dance Reaction, Which Proceeds Through a Dual Catalytic Cycle



5-7　結言

第四章では，リチウムからホウ素への金属交換がハロゲンダンスを加速させたが，第五章では，リチウムからカリウムへの金属交換がハロゲンダンスを劇的に加速させた。カリウムアミド塩基として一般的な KHMDS が，KO^{t}Bu やトリブロモピリジンよりも，高い触媒活性を示すことを明らかにした。KHMDS 触媒によるハロゲンダンスは，ブロモピリジンだけでなく，ブロモイミダゾール，ブロモチオフェン，ブロモフラン，ブロモベンゼンなどの幅広いブロモアレーンに適用でき，様々な置換様式をもつブロモアレーンを供給できた。KHMDS 触媒から発生させた反応性が高い mixed aggregate は，二元触媒反応によって連続的な臭素–金属交換を加速させた。通常，有機リチウムと化学量論量の KO^{t}Bu を含む

Schlosser-type の有機金属は脱プロトン反応を加速させるが，今回，有機リチウムと触媒量の KHMDS が脱プロトンだけでなく，臭素–リチウム交換を大幅に加速させることを新たに見出した。

5-8 Experimental Section

References

5-8-1 General

Analytical thin layer chromatography (TLC) was performed on Wako 70 F_{254} glass sheets precoated with a 0.25 mm thickness of silica gel. Melting points (Mp) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wavenumbers (cm^{-1}). ^{1}H NMR (400 MHz), $^{13}C\{^{1}H\}$ NMR (100 MHz), ^{19}F NMR (376 MHz), and ^{11}B NMR (128 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, DMSO-d_5: δ 2.50 ppm) and coupling constants are given in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^{1}H\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (DMSO-d_6: δ 39.52 ppm, $CDCl_3$: δ 77.16 ppm, CD_3CN: δ 118.26 ppm). Chemical shifts for ^{19}F NMR are reported in ppm from $CFCl_3$ with the solvent resonance as the external standard ($C_6H_5CF_3$ in $CDCl_3$: δ −62.61 ppm[97]). Chemical shifts for ^{11}B NMR are reported in ppm from $BF_3{\cdot}OEt_2$ with the solvent resonance as the external standard ($BF_3{\cdot}OEt_2$ in $CDCl_3$: 0.00 ppm). High-resolution mass spectroscopy (HRMS) was performed on a JEOL JMS-T100LP AccuTOF LC-Plus [electrospray ionization (ESI)] with a JEOL MS-5414DART attachment.

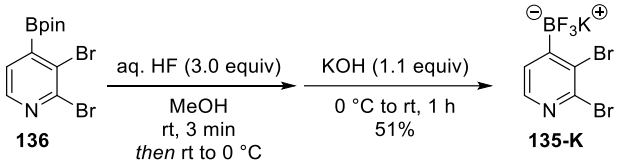
5-8-2 Materials

All workup and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel® 60N (63–212 μm, FUJIFILM Wako Pure Chemical Co., Ltd.) or high-efficiency irregular silica (25–40 μm, Santai Science Inc.). Anhydrous THF (>99.5%, water content: <30 ppm) was purchased from Kanto Chemical Co., Inc. and further dried by passing through

a solvent purification system (Glass Contour) prior to use. ^{n}BuLi (1.6 M in hexane) was purchased from Kanto Chemical Co. and used as received. LDA (2.0 M in THF/heptane/ethylbenzene), ^{i}PrMgCl·LiCl (1.3 M in THF), and KHMDS (0.5 M in toluene), which was used as a 0.50 M solution in the following experiments, were purchased from Sigma-Aldrich Co. and used as received. KO^{t}Bu was purchased from Tokyo Chemical Industry Co., Ltd., stored in a glove box, and used as received. Substrate **128** (Product Number: BD9517), **142** (Product Number: BD9518), and **15** (Product Number: BD9372) were purchased from BLD Pharmatech Ltd. and used as received. Potassium aryltrifluoroborates **156-K** (Product Number: P1684), **157-K** (Product Number: P1582), and substrate **117f** (Product Number: B0982) were purchased from Tokyo Chemical Industry Co., Ltd. and used as received. Substrate **54** (Product Number: 738867) was purchased from Sigma-Aldrich Co. and used as received. Freshly prepared $Pd(PPh_3)_4$[98] and $ZnCl_2$·TMEDA[99] were used in the following experiments.

5-8-3 Halogen Dance Reactions Catalyzed with Potassium Trifluoroborates (Scheme 5–1)

Potassium (2,3-dibromo-4-pyridyl)trifluoroborate (135-K)



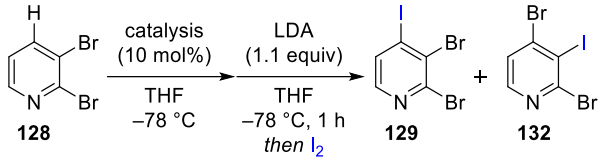
A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2,3-dibromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**136**) (541.4 mg, 1.49 mmol, 1.0 equiv) and MeOH (3.0 mL). After stirring at room temperature for 1 min, the reaction mixture was treated with aqueous hydrofluoric acid (4.4 M, 1.0 mL, 4.4 mmol, 2.9 equiv). After stirring at room temperature for 3 min, the reaction mixture was cooled to 0 ºC. After stirring at 0 ºC for 1 min, the reaction mixture was treated with potassium hydroxide (93.8 mg, 1.67 mmol, 1.1 equiv). After stirring at room temperature for 1 h, the reaction mixture was treated with CH_2Cl_2 (2 mL) and water (10 mL). After being partitioned, the aqueous layer was washed with CH_2Cl_2 (3 mL) ten times. The aqueous layer was treated with potassium hydroxide (190.0 mg, 3.39 mmol, 2.3 equiv). After stirring at room temperature for 1 min, the aqueous layer was extracted with ethyl acetate (8 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was washed with

$CHCl_3$ (50 mL) to provide the title compound as a colorless solid (261.5 mg, 0.763 mmol, 51%); R_f = 0.35 (ethyl acetate); Mp >250 ºC; IR (ATR, cm^{-1}): 1339, 1230, 1173, 1124, 1035, 992, 850; ^1H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, 1H, J = 4.4 Hz), 7.33 (d, 1H, J = 4.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 146.6, 143.8, 128.1, 127.4 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom); ^{19}F NMR (376 MHz, DMSO-d_6): δ −140.8; ^{11}B NMR (128 MHz, DMSO-d_6): δ 1.88 (q, $^1J_{B–F}$ = 41.5 Hz); HRMS (DART$^+$) *m/z*: $[M-K]^-$ calcd. for $C_5H_2{}^{11}B^{79}Br^{81}BrF_3N$, 303.8579; found, 303.8589.

Reaction with catalyst 135-K

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (713.6 mg, 3.01 mmol, 1.0 equiv), potassium (2,3-dibromo-4-pyridyl)trifluoroborate (**135-K**) (106.6 mg, 0.311 mmol, 10 mol%), and anhydrous THF (30 mL). The solution was cooled to −78 ºC. LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.526 g, 6.01 mmol, 2.0 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromo-4-iodopyridine (**129**) and 2,4-dibromo-3-iodopyridine (**132**) were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane (79.4 mg, 0.473 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 7.91 ppm (1 proton for **129**, whose ^1H NMR data were identical with those reported in the literature[20d]) and 8.12 ppm (1 proton for **132**, whose ^1H NMR data were identical with those reported in the literature[20d]) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

5-8-4 Screening of Halogen Dance Catalysts (Table 5–1)



Preparation of a THF solution of KO^{t}Bu (0.10 M)

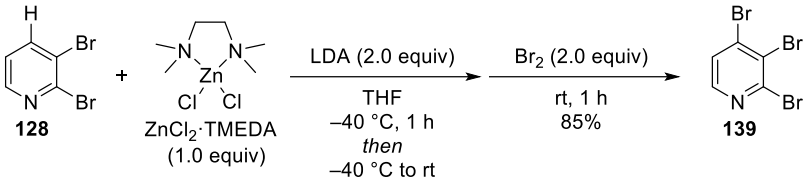
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with KO^{t}Bu (841.5 mg, 7.50 mmol) and anhydrous THF (7.5 mL). The reaction mixture was stirred at room temperature for 1 min to provide a THF solution of KO^{t}Bu (0.10 M).

Reaction with KHMDS (Table 5–1, entry 8)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (711.6 mg, 3.00 mmol, 1.0 equiv) and anhydrous THF (30 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 600 μL, 0.30 mmol, 10 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with iodine (1.560 g, 6.15 mmol, 2.0 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromo-4-iodopyridine (**129**) and 2,4-dibromo-3-iodopyridine (**132**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (92.6 mg, 0.552 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 7.91 ppm (1 proton for **129**, whose ^{1}H NMR data were identical with those reported in the literature[20d]) and 8.12 ppm (1 proton for **132**, whose ^{1}H NMR data were identical with those reported in the literature[20d]) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to provide the title compound as a colorless solid (934.8 mg, 2.58 mmol, 86%), whose ^{1}H and ^{13}C NMR data

were identical with those reported in the literature.[20d] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, 1H, J = 5.2 Hz), 7.49 (d, 1H, J = 5.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.9, 148.9, 142.3, 126.7, 108.3.

5-8-5 Kinetic Analysis of KHMDS-Catalyzed Halogen Dance Reactions (Figure 5–1)



2,3,4-Tribromopyridine (139)

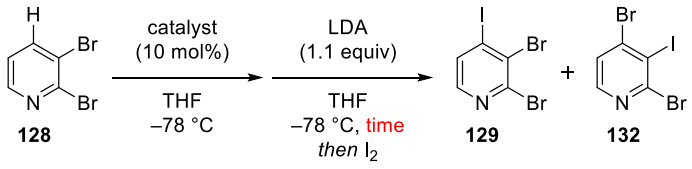
A flame-dried 500-mL two-necked flask equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (2.350 g, 9.92 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (2.498 g, 9.89 mmol, 1.0 equiv), and anhydrous THF (100 mL). The solution was cooled to −40 ºC. LDA (2.0 M, 10.0 mL, 20 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at −40 ºC for 1 h, the resulting mixture was treated with bromine (1.00 mL, 19.4 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (75 mL) and saturated aqueous ammonium chloride (75 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were washed with water (100 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to provide the title compound as a pale yellow solid (2.650 g, 8.39 mmol, 85%), whose ^{1}H and ^{13}C NMR data were identical with those reported in the literature.[135] R_f = 0.53 (hexane/diethyl ether = 10:1); Mp 74–75 ºC; IR (ATR, cm^{-1}): 1536, 1522, 1455, 1417, 1378, 1333, 1189, 820; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, 1H, J = 5.0 Hz), 7.52 (d, 1H, J = 5.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.9, 144.9, 136.9, 127.9, 127.1; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_5H_3{}^{79}Br^{81}Br_2N$, 317.7775; found, 317.7790.

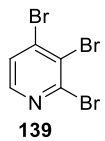
Effects of Reaction Time

Reaction with KHMDS for 1 min (Figure 5–1a)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (714.1 mg, 3.01 mmol, 1.0 equiv) and anhydrous THF (30 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 600 µL, 0.30 mmol, 10 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 min, the reaction mixture was treated with iodine (1.568 g, 6.18 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromo-4-iodopyridine (**129**) and 2,4-dibromo-3-iodopyridine (**132**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (112.0 mg, 0.667 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 7.91 ppm (1 proton for **129**, whose ^{1}H NMR data were identical with those reported in the literature[20d]) and 8.12 ppm (1 proton for **132**, whose ^{1}H NMR data were identical with those reported in the literature[20d]) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

(a) Yields of 3-iodopyridine vs. reaction time[a]



catalyst			
KHMDS	KO^{t}Bu	 **139**	none

catalyst	time	**128** (%)[b]		**129** (%)[b]		**132** (%)[b]		
		1st run	2nd run	1st run	2nd run	1st run	2nd run	average
KHMDS	60 min	–[c]	–[c]	–[c]	–[c]	98	93	96
KHMDS	30 min	–[c]	–[c]	–[c]	2	97	93	95
KHMDS	15 min	–[c]	–[c]	1	2	96	91	94
KHMDS	5 min	–[c]	–[c]	1	2	94	88	91
KHMDS	1 min	3	6	6	10	85	78	82
KO^{t}Bu	60 min	–[c]	–[c]	–[c]	1	92	89	91
KO^{t}Bu	30 min	–[c]	–[c]	2	–[c]	89	92	91
KO^{t}Bu	15 min	–[c]	–[c]	1	2	89	85	87
KO^{t}Bu	5 min	–[c]	–[c]	2	3	82	78	80
KO^{t}Bu	1 min	–[c]	–[c]	8	9	78	78	78
139	60 min	–[c]	–[c]	34	23	65	75	70
139	30 min	–[c]	–[c]	38	49	59	51	55
139	15 min	3	–[c]	41	47	54	50	52
139	5 min	13	–[c]	39	49	53	48	51
139	1 min	15	15	43	51	46	38	42
none	60 min	–[c]	3	77	67	9	13	11
none	30 min	–[c]	5	69	59	13	13	13
none	15 min	–[c]	5	72	59	9	14	12
none	5 min	15	–[c]	84	71	4	6	5
none	1 min	17	6	82	91	4	3	4

[a]Reaction conditions: 2,3-dibromopyridine (**128**; 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, then iodine (2.0 equiv, 6.0 mmol), –78 °C, 1 h. [b]Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard. [c]Not observed.

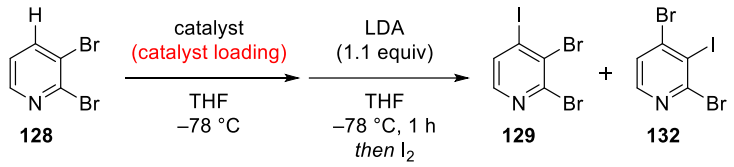
Effects of Catalyst Loading

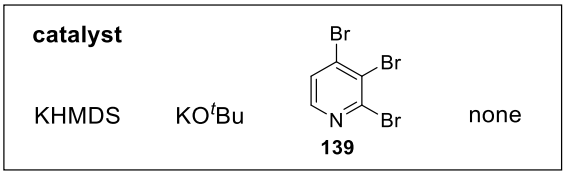
Reaction with 1 mol% of KHMDS (Figure 5–1b)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromopyridine (**128**) (711.9 mg, 3.01 mmol, 1.0 equiv) and anhydrous THF (30 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 60 µL, 0.030 mmol, 1.0 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 1.65 mL, 3.3 mmol, 1.1 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the reaction mixture was treated with

iodine (1.571 g, 6.19 mmol, 2.1 equiv). After stirring at −78 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and saturated aqueous ammonium chloride (25 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-dibromo-4-iodopyridine (**129**) and 2,4-dibromo-3-iodopyridine (**132**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (100.2 mg, 0.597 mmol) as an internal standard by comparing relative values of integration for the peaks observed at 7.91 ppm (1 proton for **129**, whose ^{1}H NMR data were identical with those reported in the literature[20d]) and 8.12 ppm (1 proton for **132**, whose ^{1}H NMR data were identical with those reported in the literature[20d]) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

(b) Yields of 3-iodopyridine vs. catalyst loading[a]



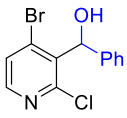


catalyst	loading	**128** (%)[b]		**129** (%)[b]		**132** (%)[b]		
		1st run	2nd run	1st run	2nd run	1st run	2nd run	average
KHMDS	10 mol%	–[c]	–[c]	–[c]	–[c]	98	93	96
KHMDS	5 mol%	–[c]	–[c]	–[c]	5	94	92	93
KHMDS	2.5 mol%	–[c]	–[c]	1	–[c]	94	91	93
KHMDS	1 mol%	–[c]	–[c]	8	11	86	87	87
KHMDS	0.1 mol%	–[c]	2	45	44	44	40	42

KO^{t}Bu	10 mol%	–[c]	–[c]	–[c]	1	92	89	91
KO^{t}Bu	5 mol%	–[c]	–[c]	–[c]	2	91	86	89
KO^{t}Bu	2.5 mol%	–[c]	–[c]	6	4	83	84	84
KO^{t}Bu	1 mol%	–[c]	–[c]	20	25	73	64	69
KO^{t}Bu	0.1 mol%	–[c]	–[c]	61	61	20	17	19
139	10 mol%	–[c]	–[c]	34	23	65	75	70
139	5 mol%	–[c]	–[c]	49	49	49	51	50
139	2.5 mol%	–[c]	–[c]	68	71	29	26	28
139	1 mol%	–[c]	–[c]	72	84	18	11	15
139	0.1 mol%	–[c]	–[c]	71	70	15	14	15

[a]Reaction conditions: 2,3-dibromopyridine (**128**; 1.0 equiv, 3.0 mmol), catalyst, THF (30 mL), then LDA (1.1 equiv, 3.3 mmol), −78 °C, 1 h, then iodine (2.0 equiv, 6.0 mmol), −78 °C, 1 h. [b]Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard. [c]Not observed.

5-8-6 Range of Bromoarenes Synthesized by the KHMDS-Catalyzed Halogen Dance Reaction (Table 5–2)

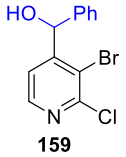


158

(4-Bromo-2-chloropyridin-3-yl)(phenyl)methanol (158) (Table 5–2, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-chloropyridine (**142**) (57.3 mg, 0.298 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 60 µL, 0.030 mmol, 10 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 225 µL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 15 min, the resulting mixture was treated with benzaldehyde (62 µL, 0.61 mmol, 2.0 equiv). After stirring at −78 ºC for 2 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1 to 7:3) to

provide the title compound as a colorless solid (64.3 mg, 0.215 mmol, 72%), whose ^{1}H and ^{13}C NMR data were identical with those reported in the literature.[20e] R_f = 0.34 (hexane/diethyl ether = 7:3); Mp 114–116 ºC; IR (ATR, cm^{-1}): 1553, 1536, 1512, 1454, 1435, 1377, 1183, 1043, 828; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, 1H, *J* = 5.0 Hz), 7.55 (d, 1H, *J* = 5.0 Hz), 7.38–7.26 (m, 5H), 6.63 (d, 1H, *J* = 10.4 Hz), 3.34 (d, 1H, *J* = 10.4 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 151.7, 148.7, 140.3, 136.3, 128.6, 128.4, 127.7, 125.5, 73.6 (one aromatic carbon signal is missing due to overlapping); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3CN): δ 152.5, 149.7, 142.0, 137.6, 136.8, 129.6, 129.0, 127.9, 126.4, 72.9; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_{12}H_{10}{}^{81}Br^{37}ClNO$, 301.9584; found, 301.9588.



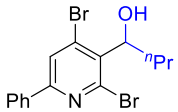
159

(3-Bromo-2-chloropyridin-4-yl)(phenyl)methanol (159) (Table 5–2, entry 1)

The yields of (4-bromo-2-chloropyridin-3-yl)(phenyl)methanol (**158**) and (3-bromo-2-chloropyridin-4-yl)(phenyl)methanol (**159**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 6.63 ppm (1 proton for **158**) and 6.11 ppm (1 proton for **159**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The spectra of (3-bromo-2-chloropyridin-4-yl)(phenyl)methanol (**159**) were obtained according to the following procedure.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 3-bromo-2-chloro-4-iodopyridine (**S6**) (47.6 mg, 0.150 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to −40 ºC. ^{i}PrMgCl·LiCl (1.3 M, 175 µL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −40 ºC for 1 h, the reaction mixture was treated with benzaldehyde (31 µL, 0.30 mmol, 2.0 equiv). After stirring at −40 ºC for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica

gel column chromatography (hexane/ethyl acetate = 10:1 to 4:1) to provide the title compound as a colorless oil (31.1 mg, 0.104 mmol, 70%), whose ^{1}H and ^{13}C NMR data were identical with those reported in the literature.[20e] R_f = 0.38 (hexane/ethyl acetate = 2:1); IR (ATR, cm^{-1}): 1573, 1455, 1436, 1357, 1340, 1184, 1053, 1026, 817; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, 1H, *J* = 5.2 Hz), 7.65 (d, 1H, *J* = 5.2 Hz), 7.38–7.32 (m, 5H), 6.11 (d, 1H, *J* = 3.6 Hz), 2.46–2.41 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 151.7, 147.8, 140.2, 129.0, 128.8, 127.6, 121.5, 120.2, 75.1; HRMS (DART^{+}) *m/z*: $[M+H]^{+}$ calcd. for $C_{12}H_{10}{}^{81}Br^{35}ClNO$, 299.9614; found, 299.9623.

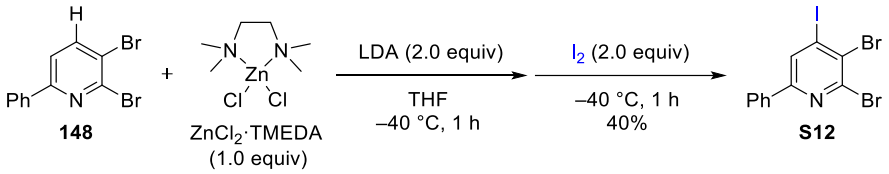


160

1-(2,4-Dibromo-6-phenylpyridin-3-yl)butan-1-ol (160) (Table 5–2, entry 2)

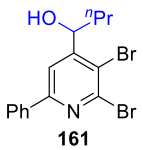
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-phenylpyridine (**148**) (44.9 mg, 0.143 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 30 µL, 0.015 mmol, 10 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 120 µL, 0.24 mmol, 1.7 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the resulting mixture was treated with butyraldehyde (27 µL, 0.30 mmol, 2.1 equiv). After stirring at −78 ºC for 2 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 19:1 to 17:3) to provide the title compound as a colorless oil (33.9 mg, 0.0880 mmol, 61%); R_f = 0.48 (hexane/ethyl acetate = 9:1); IR (ATR, cm^{-1}): 1564, 1547, 1513, 1493, 1453, 1416, 1198, 1069, 838; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.94 (m, 2H), 7.90 (s, 1H), 7.51–7.44 (m, 3H), 5.40 (ddd, 1H, *J* = 9.6, 9.4, 5.7 Hz), 2.80 (d, 1H, *J* = 9.4 Hz), 2.17–2.05 (m, 1H), 1.95–1.84 (m, 1H), 1.71–1.57 (m, 1H), 1.49–1.35 (m, 1H), 1.01 (t, 3H, *J* = 7.6 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.1, 142.4 (br), 136.0, 135.8, 134.9 (br), 130.3, 129.1, 127.1, 125.1 (br), 74.3, 37.4, 19.4, 14.0; $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3CN): δ

157.2, 143.5 (br), 137.4, 136.8, 135.6 (br), 131.1, 129.9, 127.7, 126.3 (br), 73.9, 37.2, 20.0, 14.1; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{16}{}^{79}Br_2NO$, 383.9599; found, 383.9615.



2,3-Dibromo-4-iodo-6-phenylpyridine (S12) (Table 5–2, entry 2)

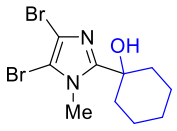
A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-6-phenylpyridine (**148**) (249.5 mg, 0.797 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (206.3 mg, 0.817 mmol, 1.0 Equiv), and anhydrous THF (8.0 mL). The solution was cooled to −40 ºC. LDA (2.0 M, 0.80 mL, 1.6 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at −40 ºC for 1 h, the resulting mixture was treated with iodine (409.4 mg, 1.61 mmol, 2.0 equiv). After stirring at −40 ºC for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (6 mL) and saturated aqueous ammonium chloride (6 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (8 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/diethyl ether = 9:1) to provide the title compound as a colorless solid (139.0 mg, 0.317 mmol, 40%); R_f = 0.23 (hexane); Mp 126–128 ºC; IR (ATR, cm^{-1}): 1544, 1511, 1503, 1487, 1385, 1323, 1257, 1205; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.97–7.91 (m, 2H), 7.49–7.44 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.3, 142.2, 135.5, 130.7, 130.4, 129.15, 129.08, 127.1, 114.4; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_7{}^{79}Br^{81}BrIN$, 439.7970; found, 439.7974.



1-(2,3-Dibromo-6-phenylpyridin-4-yl)butan-1-ol (161) (Table 5–2, entry 2)

The yields of 1-(2,4-dibromo-6-phenylpyridin-3-yl)butan-1-ol (**160**) and 1-(2,3-dibromo-6-phenylpyridin-4-yl)butan-1-ol (**161**) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 5.40 ppm (1 proton for **160**) and 5.12–5.07 ppm (1 proton for **161**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The spectra of 1-(2,3-dibromo-6-phenylpyridin-4-yl)butan-1-ol (**161**) were obtained according to the following procedure.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromo-4-iodo-6-phenylpyridine (**S12**) (65.3 mg, 0.149 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to −40 ºC. ^{i}PrMgCl·LiCl (1.3 M, 175 µL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −40 ºC for 1 h, the reaction mixture was treated with butyraldehyde (27 µL, 0.30 mmol, 2.0 equiv). After stirring at −40 ºC for 3 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to provide the title compound as a colorless solid (44.0 mg, 0.105 mmol, 71%); R_f = 0.32 (hexane/ethyl acetate = 10:1); Mp 105–106 ºC; IR (ATR, cm^{-1}): 1518, 1468, 1454, 1398, 1378, 1358, 1197, 1031; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03–7.98 (m, 2H), 7.91 (s, 1H), 7.50–7.42 (m, 3H), 5.12–5.07 (m, 1H), 2.13–2.10 (m, 1H), 1.84–1.75 (m, 1H), 1.68–1.47 (m, 3H), 1.00 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.1, 156.6, 144.5, 136.9, 130.0, 129.0, 127.0, 120.4, 117.5, 73.3, 39.1, 19.1, 13.8; HRMS (DART^{+}) *m/z*: [M+H]$^{+}$ calcd. for $C_{15}H_{16}{}^{79}Br_2NO$, 383.9599; found, 383.9609.

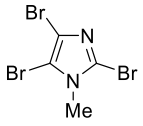


162

1-(4,5-Dibromo-1-methyl-1*H*-imidazol-2-yl)cyclohexan-1-ol (162) (Table 5–2, entry 3)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromo-1-methyl-1*H*-

imidazole (**162**) (36.2 mg, 0.151 mmol, 1.0 equiv) and anhydrous toluene (1.5 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 30 μL, 0.015 mmol, 10 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 120 μL, 0.24 mmol, 1.6 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 15 min, the resulting mixture was treated with cyclohexanone (31 μL, 0.30 mmol, 2.0 equiv). After stirring at −78 ºC for 2 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 2:1) to provide the title compound as a colorless solid (40.9 mg, 0.121 mmol, 80%); R_f = 0.33 (hexane/diethyl ether = 2:1); Mp 164–166 ºC; IR (ATR, cm^{-1}): 1512, 1453, 1378, 1235, 980, 973, 820; ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 2.08–1.98 (m, 2H), 1.94–1.87 (m, 2H), 1.83 (br s, 1H), 1.71–1.63 (m, 5H), 1.38–1.25 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.9, 114.6, 105.9, 72.2, 36.5, 34.8, 25.3, 21.6; HRMS ($DART^+$) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}{}^{81}Br_2N_2O$, 340.9510; found, 340.9523.



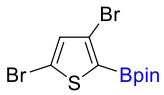
59

2,4,5-Tribromo-1-methyl-1*H*-imidazole (59) (Table 5–2, entry 3)

The yields of 1-(4,5-dibromo-1-methyl-1*H*-imidazol-2-yl)cyclohexan-1-ol (**162**) and 2,4,5-tribromo-1-methyl-1*H*-imidazole (**59**) were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 3.84 ppm (3 protons for **162**) and 3.64 ppm (3 protons for **59**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The spectra of 2,4,5-tribromo-1-methyl-1*H*-imidazole (**59**) were obtained according to the following procedure.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,5-dibromo-1-methyl-1*H*-imidazole (**54**) (72.9 mg, 0.304 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (75.7 mg, 0.30 mmol, 0.99 equiv), and anhydrous THF (3.0 mL). The solution was cooled to −40 ºC. LDA (2.0

M, 0.30 mL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at −40 ºC for 1 h, the resulting mixture was treated with bromine (31 μL, 0.60 mmol, 2.0 equiv) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to provide the title compound as a colorless solid (85.0 mg, 0.267 mmol, 88%), whose ^{1}H NMR data was identical with that reported in the literature.[136] R_f = 0.29 (hexane/ethyl acetate = 10:1); Mp 88–89 ºC; IR (ATR, cm^{-1}): 1511, 1496, 1453, 1404, 1216, 968; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 118.5, 116.4, 105.8, 35.0; HRMS (DART^{+}) *m/z*: [M+H]$^{+}$ calcd. for $C_4H_4{}^{81}Br_3N_2$, 322.7863; found, 322.7853.

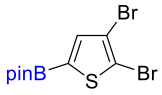


163

2-(3,5-Dibromothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (163) (Table 5–2, entry 4)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromothiophene (**15**) (72.2 mg, 0.298 mmol, 1.0 equiv), anhydrous toluene (3.0 mL), and anhydrous THF (50 μL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 60 μL, 0.030 mmol, 10 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 225 μL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 15 min, the resulting mixture was treated with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (122 μL, 0.60 mmol, 2.0 equiv). After stirring at −78 ºC for 2 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 10:1) to provide the title compound as

a pale yellow solid (62.3 mg, 0.169 mmol, 57%); R_f = 0.55 (hexane/ethyl acetate = 10:1); Mp 45–47 ºC; IR (ATR, cm^{-1}): 1511, 1431, 1343, 1319, 1142, 1027, 853; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 1.34 (s, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 134.8, 119.4, 119.2, 84.7, 24.9 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom); HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{14}{}^{11}B^{79}Br^{81}BrO_2S$, 368.9154; found, 368.9153.



164

2-(4,5-Dibromothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (164) (Table 5–2, entry 4)

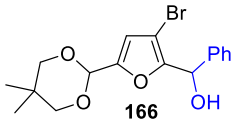
The yields of 2-(3,5-dibromothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**163**) and 2-(4,5-dibromothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**164**) were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 7.04 ppm (1 proton for **163**) and 7.39 ppm (1 proton for **164**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The spectra of 2-(4,5-dibromothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**164**) were obtained according to the following procedure.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2,3-dibromothiophene (**15**) (190.1 mg, 0.786 mmol), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (298.4 mg, 1.60 mmol), and anhydrous hexane (4.0 mL). The solution of 2,3-dibromothiophene (0.20 M, 1.5 mL, 0.30 mmol, 1.0 equiv) was added dropwise for 2 min to the separately prepared hexane solution (1.5 mL) of LDA (2.0 M, 300 µL, 0.60 mmol, 2.0 equiv) at −78 ºC. After stirring at −78 ºC for 2 h, the resulting mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 10:1) to provide the title compound as a pale yellow solid (62.6 mg, 0.170 mmol, 57%); R_f = 0.47 (hexane/ethyl acetate = 10:1); Mp 60–62 ºC; IR (ATR, cm^{-1}): 1528, 1513, 1417, 1340, 1141, 853; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 1H),

1.32 (s, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 139.5, 118.3, 115.6, 84.8, 24.8 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom); HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{14}{}^{11}B^{81}Br_2O_2S$, 370.9133; found, 370.9152.

Preparation of a THF solution of LiTMP

A THF solution of LiTMP was prepared according to the procedure described in Chapter 3, 3-6-3. A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with TMPH (0.13 mL, 0.73 mmol) and THF (0.62 mL). To a THF solution of TMPH was added ^{n}BuLi (1.56 M in hexane, 0.46 mL, 0.72 mmol) dropwise at −78 °C. The resulting solution was stirred at 0 °C for 30 min to provide a THF solution of LiTMP, which was used as a 0.60 M solution in the following experiments.

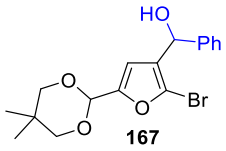


166

(3-Bromo-5-(5,5-dimethyl-1,3-dioxan-2-yl)furan-2-yl)(phenyl)methanol (166) (Table 5–2, entry 5)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 2-(5-bromofuran-2-yl)-5,5-dimethyl-1,3-dioxane (**165**)[49b] (40.2 mg, 0.154 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 60 µL, 0.030 mmol, 19 mol%) was added to the Schlenk tube. After stirring at −78 ºC for 5 min, LiTMP (0.60 M, 375 µL, 0.23 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 1 h, the resulting mixture was treated with benzaldehyde (31 µL, 0.30 mmol, 2.0 equiv). After stirring at −78 ºC for 2 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1) to provide the title compound as a colorless oil (15.0 mg, 0.0408 mmol, 27%), whose ^{1}H and ^{13}C NMR data were identical with those reported in the literature.[26d] ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.45–7.39 (m, 2H), 7.38–7.33 (m, 2H), 7.32–7.26 (m, 1H), 6.52 (s, 1H), 5.95 (d, 1H, J = 5.2 Hz), 5.38 (s, 1H), 3.70 (ddd, 2H, J = 11.3, 2.8, 2.8 Hz), 3.55 (dd, 2H, J = 11.3, 4.6 Hz), 2.42 (d, 1H, J = 5.2 Hz), 1.23 (s, 3H), 0.77 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.5, 151.2, 140.2, 128.6, 128.1, 126.4, 111.5, 98.4, 95.7, 77.4, 68.2, 30.5, 23.0, 21.9.



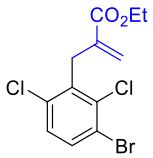
167

(2-Bromo-5-(5,5-dimethyl-1,3-dioxan-2-yl)furan-3-yl)(phenyl)methanol (167) (Table 5–2, entry 5)

The yields of (3-bromo-5-(5,5-dimethyl-1,3-dioxan-2-yl)furan-2-yl)(phenyl)methanol (**166**) and (2-bromo-5-(5,5-dimethyl-1,3-dioxan-2-yl)furan-3-yl)(phenyl)methanol (**167**) were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard by comparing relative values of integration for the peaks observed at 6.52 ppm (1 proton for **166**, whose ^1H NMR data were identical with those reported in the literature[26d]) and 5.74 ppm (1 proton for **167**, whose ^1H NMR data were identical with those reported in the literature[26d]) with that of 1,3,5-trimethoxybenzene observed at 6.09 ppm.

Preparation of a THF solution of CuCN·2LiCl

A THF solution of CuCN·2LiCl was prepared according to the procedure described in Chapter 2, 2-8-10.

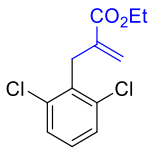


168

Ethyl 2-(3-bromo-2,6-dichlorobenzyl)acrylate (168) (Table 5–2, entry 6)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1-bromo-2,6-dichlorobenzene (**117f**) (67.3 mg, 0.298 mmol, 1.0 equiv) and anhydrous THF (3.0 mL). The solution was cooled to −78 ºC. KHMDS (0.50 M, 60 µL, 0.030 mmol, 10 mol%) was added to the

Schlenk tube. After stirring at −78 ºC for 5 min, LDA (2.0 M, 225 µL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at −78 ºC for 5 h, the resulting mixture was treated with CuCN·2LiCl (1.0 M, 450 µL, 0.45 mmol, 1.5 equiv) and ethyl 2-(bromomethyl)acrylate (85 µL, 0.62 mmol, 2.1 equiv). The reaction mixture was allowed to warm to room temperature with stirring over 2 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1) to provide the title compound as a colorless oil (42.8 mg, 0.127 mmol, 42%); R_f = 0.50 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1721, 1714, 1502, 1434, 1281, 1257, 1161, 1137, 1089, 1024, 806; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 1H, *J* = 8.8 Hz), 7.22 (d, 1H, *J* = 8.8 Hz), 6.19 (t, 1H, *J* = 1.6 Hz), 4.97 (t, 1H, *J* = 1.8 Hz), 4.28 (q, 2H, *J* = 7.2 Hz), 4.02 (dd, 2H, *J* = 1.8, 1.6 Hz), 1.35 (t, 3H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.6, 137.1, 136.5, 136.0, 135.2, 132.6, 128.9, 124.5, 122.0, 61.2, 34.6, 14.3; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{12}{}^{79}Br^{37}Cl_2O_2$, 340.9339; found, 340.9337.



169

Ethyl 2-(2,6-dichlorobenzyl)acrylate (169) (Table 5–2, entry 6)

The yields of ethyl 2-(3-bromo-2,6-dichlorobenzyl)acrylate (**168**) and ethyl 2-(2,6-dichlorobenzyl)acrylate (**169**) were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 4.02 ppm (2 protons for **168**) and 3.95 ppm (2 protons for **169**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The spectra of ethyl 2-(2,6-dichlorobenzyl)acrylate (**169**) were obtained according to the following procedure.

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under nitrogen was charged with 1-bromo-2,6-dichlorobenzene (**117f**) (34.5 mg, 0.153 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The solution was cooled to −40 ºC. ^{i}PrMgCl·LiCl (1.3 M, 175 µL, 0.23 mmol, 1.5 equiv) was added to the

Schlenk tube. After stirring at −40 ºC for 1 h, the reaction mixture was treated with CuCN·2LiCl (1.0 M, 225 μL, 0.23 mmol, 1.5 equiv) and ethyl 2-(bromomethyl)acrylate (42 μL, 0.30 mmol, 2.0 equiv). The reaction mixture was allowed to warm to room temperature with stirring over 2 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (1 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 49:1 to 24:1) to provide the title compound as a colorless oil (28.4 mg, 0.110 mmol, 72%); R_f = 0.50 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1715, 1437, 1278, 1255, 1173, 1135, 1090, 1029, 949; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, 2H, *J* = 8.0 Hz), 7.15 (t, 1H, *J* = 8.0 Hz), 6.19 (td, 1H, *J* = 1.6, 0.9 Hz), 4.97 (td, 1H, *J* = 2.2, 0.9 Hz), 4.28 (q, 2H, *J* = 7.3 Hz), 3.95 (dd, 2H, *J* = 2.2, 1.6 Hz), 1.35 (t, 3H, *J* = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.8, 136.5, 136.3, 135.0, 128.6, 128.3, 124.5, 61.1, 33.0, 14.3; HRMS (DART$^+$) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{13}{}^{35}Cl_2O_2$, 259.0293; found, 259.0296.

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第六章

総括

6-1　総括

本研究では，従来ブロモアレーンの置換様式を簡便に変換できるため有用であったにもかかわらず，適用可能な基質がきわめて限られていたハロゲンダンスがかかえていた課題に対して，一般性が高い新たな反応条件を見出し，幅広いブロモアレーンのハロゲンダンスを実現した。従来のハロゲンダンスは，ハロゲン–金属交換を進行させるために，反応性が高い有機リチウムを用いた反応条件が多く知られていたが，今回，有機リチウムを in situ トランスメタル化によって，反応系中で別の有機金属へ変換する工夫によって，今まで達成されたことのなかったブロモアレーンのハロゲンダンスを達成した (Scheme 6–1)。

第二章では，反応中間体が不安定で，有機リチウムを利用する従来の反応条件では，分解反応が進行するブロモアゾールのハロゲンダンスを進行させた。有機リチウムを in situ トランスメタル化によって，有機亜鉛反応剤へ変換すると，分解反応を抑制でき，チアゾールのハロゲンダンスを実現できた。塩化亜鉛ジアミンを用いた In situ トランスメタル化が最適であり，適切なジアミン配位子を用いると，ハロゲンダンス前後の有機リチウムを完全な選択性で捕捉できた。開発した反応条件は，チアゾールだけでなく，イミダゾール，オキサゾールにも適用可能であり，非ステロイド系抗炎症薬とその構造異性体の短段階合成に成功した。

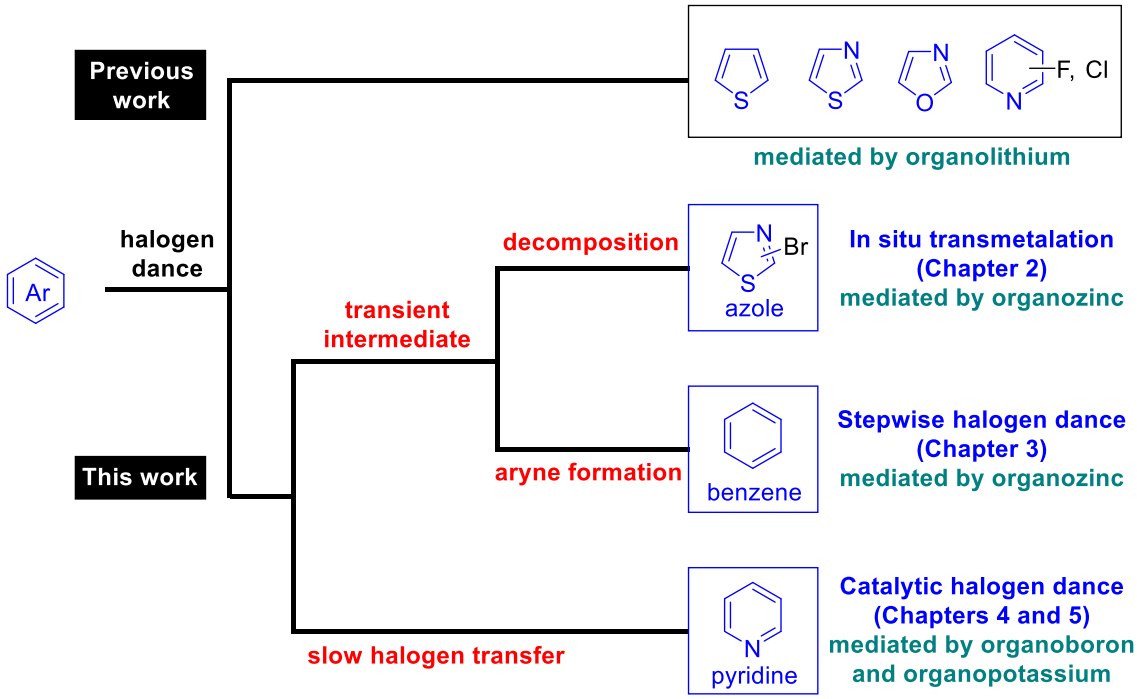

Figure 6–1. Summary of halogen dance of bromoarenes using in situ transmetalation

第三章では，ブロモベンゼンの形式ハロゲンダンスを達成した。ブロモベンゼンのハロゲンダンスは，有機リチウムを用いた従来の反応条件では，ベンザイン形成と分解反応が進行した。そこで，第二章で開発した有機リチウムから亜鉛反応剤への in situ トランスメタル化を用いて，ベンザインの形成を抑制した。発生した有機亜鉛を臭素化し，ハロゲンダンスの中間体として知られている臭素化体を生成させた後，エチルマグネシウムクロリドを用いた選択的な臭素–マグネシウム交換および求電子剤による捕捉によって，二段階でブロモベンゼンの形式的なハロゲンダンスに成功した。形式ハロゲンダンスは，きわめて基質一般性が高く，8 種類のベンゼンに加えて，ピリジン，キノリン，ピリミジン，チアゾールなどの 6 種類のヘテロ芳香環に適用可能であった。開発した二段階の形式ハロゲンダンスは，同一のフラスコ内で実施することもできた。

第四章では，ブロモ基の転位が遅いピリジンのハロゲンダンスを触媒的に促進させた。条件検討の結果，予想外にも触媒量の三フッ化ホウ素がハロゲンダンスを特異的かつ劇的に加速させた。反応機構を詳細に調べた結果，一般的に想定されるピリジン窒素–三フッ化ホウ素錯体ではなく，ピリジン炭素–三フッ化ホウ素錯体，すなわち有機トリフルオロボラートが高い触媒活性を示すことを明らかにした。DFT 計算の結果，有機リチウムとトリフルオロボラート触媒の Li–F 相互作用が，二回の連続的な臭素–リチウム交換の活性化エネルギーを低下させ，ハロゲンダンスを加速させることがわかった。通常，クロスカップリング反応や光レドックス反応に使われる有機トリフルオロボラートが，ブロモ基の受け渡しを加速させる分子触媒として利用できる新たな可能性を見出した。

第五章では，カリウムアミド塩基として一般的に利用される KHMDS が，従来開発されたいずれのハロゲンダンス触媒よりも高活性であることを見出した。反応解析の結果，KHMDS の触媒量を 10 mol%とすると，反応時間を 1 分に短縮できた。開発した KHMDS 触媒は，非常に高い基質一般性を示し，ブロモピリジンだけでなく，ブロモイミダゾール，ブロモチオフェン，ブロモフランのような 5 員環ヘテロ芳香環に加えて，ブロモベンゼンのハロゲンダンスも大幅に加速させた。反応機構として二元触媒反応を想定しており，リチウムとカリウムの部分的な金属交換によって，有機リチウムと KHMDS の会合状態が形成され，ハロゲンダンスが加速されたと考えている。通常，リチウム原子とカリウム原子をあわせもつ Schlosser 型の有機金属は，脱プロトン反応を加速させるが，今回，脱プロトン反応だけでなく，連続的な臭素–金属交換も加速させることに成功した。

本研究の今後期待される波及効果として，医薬品や機能性材料の探索プロセスの簡略化が挙げられる (Figure 6–2)。本研究では，一般性が高いハロゲンダンスの反応条件を確立でき，構造異性体の関係にあるブロモアレーンの網羅的な供給が可能となった。多様な置換様式をもつブロモアレーンは，信頼性の高い合成前駆体であり，置換基の位置によって生物活性や材料物性が変化する医薬品や機能性材料の探索プロセスを大幅に簡略化できると期待している。また，逆合成解析の新たな概念を提示できた。ハロゲンダンスは，導入した臭素原子を別の位置へ移動させる反応であり，芳香族求電子置換反応を用いたブロモ化や，脱プロトン反応を経由したブロモ化によって，水素原子を臭素原子に変換する反応とは異なる。ハロゲンダンスを用いれば，通常の反応では実現できない位置に後の化学変換が容易な臭素原子を導入できるため，幅広い標的化合物が合成可能になることを期待している。また，第四章では，トリフルオロボラートを分子触媒として利用する新たな指針を提示できた。トリフルオロボラートは，通常，化学量論量の反応剤としてクロスカップリング反応や光レドックス反応に利用されるが，本研究では，トリフルオロボリル基が Li–F 相互作用によって，有機リチウムの配向基となることを新たに見出した。一般に，有機リチウムなどの反応性が高い活性種が関与する触媒反応を設計する際，触媒によって反応速度を向上させることが難しく，反応活性種が触媒を失活させる場合も多い。したがって，反応速度が非常に速い有機リチウムのハロゲン–金属交換からなるハロゲンダンスの触媒設計は容易ではなかった。しかし，今回，有機リチウムと共存可能な化学的に安定なトリフルオロボラートを，有機リチウムが関与する触媒反応に利用できる新たな可能性を提示できた。今後，トリフルオロボラートの詳細な構造活性相関に関する研究によって，幅広い触媒反応に展開できる触媒が設計されることを期待している。

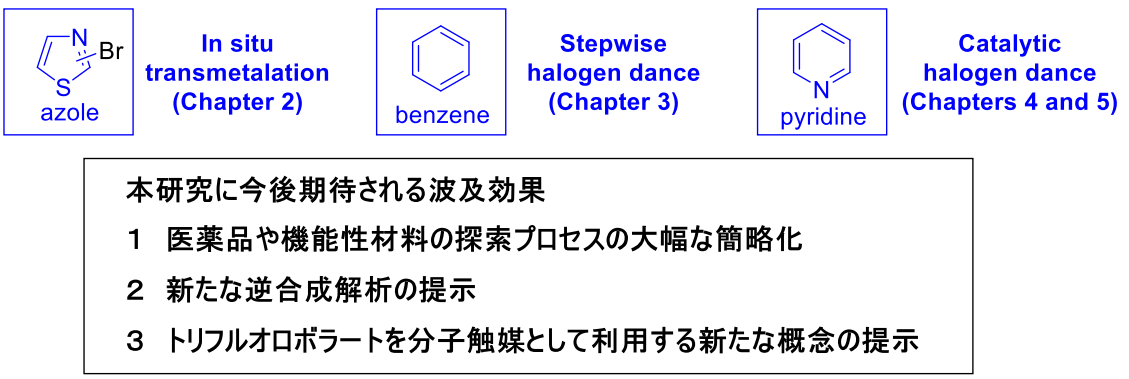

Figure 6–2. Impacts and future perspectives of this work

研究業績リスト

【学術論文】

第二章　ハロゲンダンスにおける短寿命アゾリルリチウムの選択的捕捉
“Snapshot” Trapping of Multiple Transient Azolyllithiums in Batch
Kengo Inoue, Yuxuan Feng, Atsunori Mori, Kentaro Okano, *Chem. Eur. J.* **2021**, *27*, 10267–10273.
編集部が選ぶ重要論文(Hot paper)に選出，Front Cover に採用

第三章　ブロモアレーンの形式ハロゲンダンス
Formal Halogen Transfer of Bromoarenes via Stepwise Reactions
Kengo Inoue, Atsunori Mori, Kentaro Okano, *Org. Lett.* **2023**, *25*, 6693–6698.

第四章　リチウムアリールトリフルオロボラート触媒によるハロゲンダンス
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Kengo Inoue, Keiichi Hirano, Shota Fujioka, Masanobu Uchiyama, Atsunori Mori, Kentaro Okano, *ACS Catal.* **2023**, *13*, 3788–3793.
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第五章　KHMDS 触媒によるハロゲンダンス
Ultra-Fast Halogen Dance Enabled by Catalytic KHMDS
Kengo Inoue, Atsunori Mori, Kentaro Okano, *ChemRxiv* **2023**, in press (DOI: 10.26434/chemrxiv-2023-n89mz).

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〇井上拳悟，平井　俊，岡野健太郎，森　敦紀

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〇井上拳悟，馮　宇軒，平井　俊，岡野健太郎，森　敦紀

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