



in situトランスメタル化を鍵としたハロアレーンの オルト位およびメタ位選択的メタル化の開発

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博士論文

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ハロアレーンのオルト位およびメタ位
選択的メタル化の開発

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神戸大学大学院工学研究科

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Doctoral Dissertation

ortho- and *meta*-Selective Metalation of Haloarenes
using *in situ* Transmetalation

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ハロアレーンのオルト位およびメタ位
選択的メタル化の開発

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研究業績リスト

謝辞

略 語 一 覧

Ar	Aryl
BDE	Bond dissociation energy
Boc	<i>tert</i> -Butoxycarbonyl
<i>n</i> -Bu	Normal butyl
<i>t</i> -Bu	Tertiary butyl
CD ₃ OD	Deuterated methanol
DABAL-Me ₃	Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DIEPA	<i>N,N</i> -Diisopropylethylamine
DMF	<i>N,N</i> -Dimethylformamide
DMG	Direct metalation group
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	<i>N,N'</i> -Dimethylpropyleneurea
D ₂ O	Deuterium oxide
EL	Electroluminescence
equiv	Equivalent
Et	Ethyl
FDA	Food and Drug Administration
FG	Functional group
HMPA	Hexamethylphosphoric triamide
IC ₅₀	Half maximal inhibitory concentration
KHMDS	Potassium hexamethyldisilazide
KIE	Kinetic isotope effect
LDA	Lithium diisopropylamide
LiDMAE	Lithium 2-(dimethylamino)ethanolate
LiHMDS	Lithium hexamethyldisilazide
Me ₃ TACN	1,4,7-Trimethyl-1,4,7-triazacyclononane
mGluR	Metabotropic glutamate receptor
MR	Mineralocorticoid receptor

mTOR	Mammalian target of rapamycin
NBS	<i>N</i> -Bromosuccinimide
neop	Neopentyl glycolato
Ph	Phenyl
pin	Pinacolato
PI3K	Phosphoinositide 3-kinase
p <i>K</i> _a	Acidity constant
PMDTA	<i>N,N,N',N'',N''</i> -Pentamethyldiethylenetriamine
<i>i</i> -Pr	isopropyl
S _N Ar	Nucleophilic aromatic substitution
TMP	2,2,6,6-Tetramethylpiperidine
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TEEDA	<i>N,N,N',N'</i> -Tetraethylethylenediamine
TESCl	Chlorotriethylsilane
TMSCl	Chlorotrimethylsilane
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMPDA	<i>N,N,N',N'</i> -Tetramethyl-1,3-diaminopropane
TPPA	Tripyrrolidinophosphine oxide
Trisyl	2,4,6-Triisopropylbenzenesulfonyl
Ts	<i>p</i> -Toluenesulfonyl

第一章

序論

1-1 ハロアレーンの合成化学的価値

ハロアレーンは、芳香環上の水素原子の 1 つまたは複数個がハロゲン原子で置換された芳香族化合物であり、医薬品、農薬、天然物などに広く存在している (Figure 1-1-1) ¹。ハロゲン元素によって付与された化学的および生理学的性質に加え、これらの化合物は、置換されたハロゲン元素に応じて多様な反応が利用可能である。例えば、ヨードアレーンおよびブロモアレーンは、C-X (X=I, Br) 結合の結合解離エネルギー (BDE) が比較的低い²ため、クロスカップリング反応³、ラジカルが発生⁴、あるいはハロゲン-金属交換を経た有機金属試薬⁵の調製において頻用される。また、クロロアレーンおよびフルオロアレーンは、芳香族求核置換反応 (S_NAr) における優れた反応性を示す⁶。したがって、ハロアレーンは、合成化学上の基幹化合物として重要な役割を果たしている。

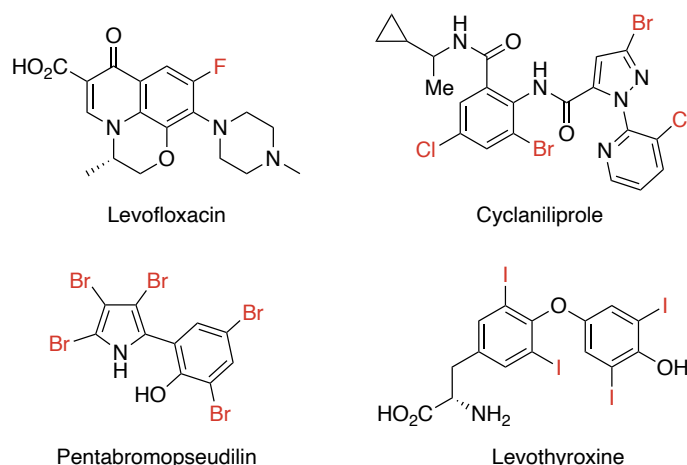
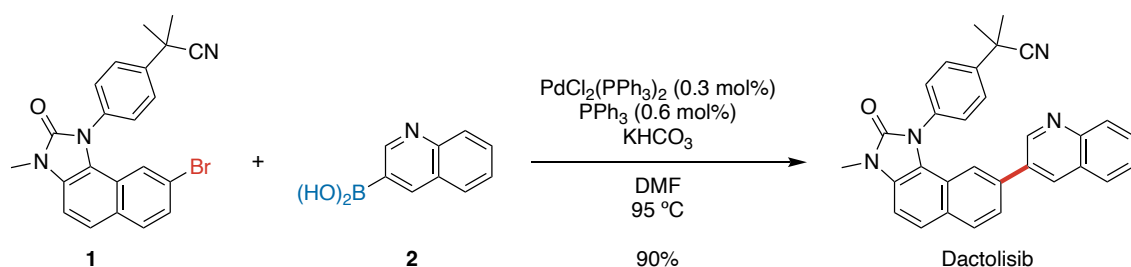


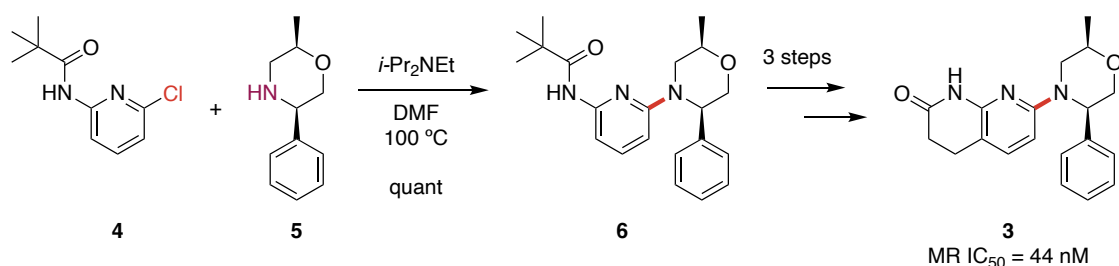
Figure 1-1-1. Drugs, pesticides, and natural products containing haloarenes

高い反応性を有するハロアレーンは、さまざまな医薬品の合成に利用できる。Dactolisib は、ホスファチジルイノシトール 3-キナーゼ (PI3K) および哺乳類ラパマイシン標的タンパク質 (mTOR) の両方を阻害することが知られている⁷。2019 年に Novartis 社の Baenziger らは、ブロモアレーン **1** を合成中間体として用いた Dactolisib の合成を報告している (Scheme 1-1-1) ⁸。すなわち、合成終盤においては、ブロモアレーン **1** と 3-キノリニルボロン酸 (**2**) を用い、パラジウム触媒存在下で鈴木-宮浦カップリング反応によって Dactolisib を効率的に合成している。



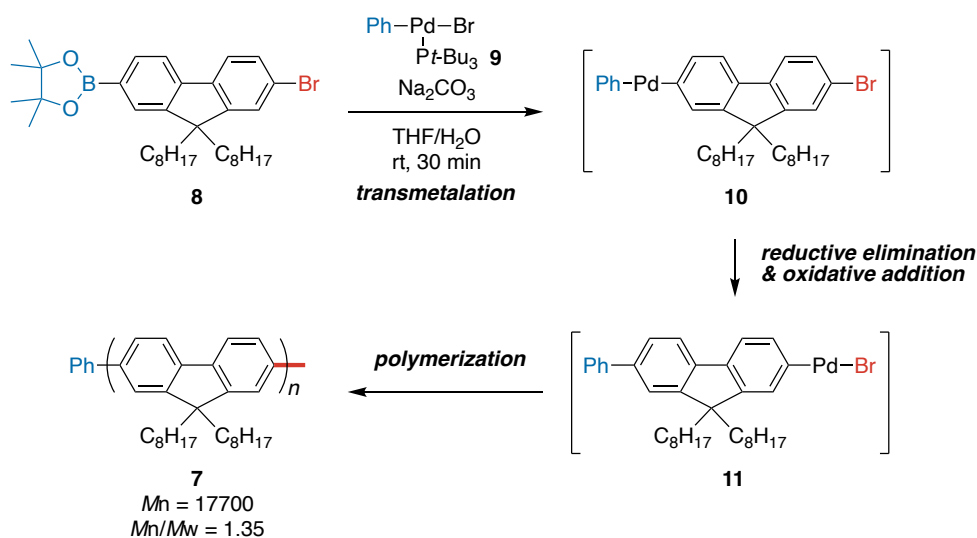
Scheme 1-1-1. Kilogram-scale synthesis of dactolisib

2013 年に Pfizer 社の Piotriwski らは、ミネラルコルチコイド受容体 (MR) 拮抗性を有する化合物 **3** の合成を報告している (Scheme 1-1-2)⁹。クロロピリジン誘導体 **4** とモルホリン **5** を含む DMF 溶液に対して Hünig 塩基 ($i\text{-Pr}_2\text{NEt}$) を作用させ、 $\text{S}_{\text{N}}\text{Ar}$ 反応を通じて中間体 **6** を定量的に得ている。その後、3 工程の反応を経て化合物 **3** を合成している。生理活性評価の結果、化合物 **3** が MR に対して IC_{50} (50%阻害濃度) が 44 nM という高い阻害活性を示している。



Scheme 1-1-2. Synthesis of the mineralocorticoid antagonist using an $\text{S}_{\text{N}}\text{Ar}$ reaction

ハロアレーンは、機能性材料の合成にも利用できる。ポリフルオレンは、発光効率がよく、熱安定性や加工性にも優れているため、青色有機 EL 材料として、電子デバイスへ応用されている¹⁰。2007 年に横澤らは、鈴木-宮浦カップリング反応を用いたポリフルオレン **7** の連鎖成長重合を報告している (Scheme 1-1-3)¹¹。プロモ基を有するフルオレン **8** は、パラジウム触媒 **9** とのトランスメタリ化を経て中間体 **10** へ変換され、さらに還元的脱離および酸化的付加を経て中間体 **11** へと変換されている。その後、鈴木-宮浦カップリング反応により重合を行って、分子量の高い ($M_w = 17700$) かつ分子量分布の狭い ($M_n/M_w = 1.35$) ポリフルオレン **7** を合成している。



Scheme 1-1-3. Synthesis of polyfluorene through Suzuki-Miyaura coupling

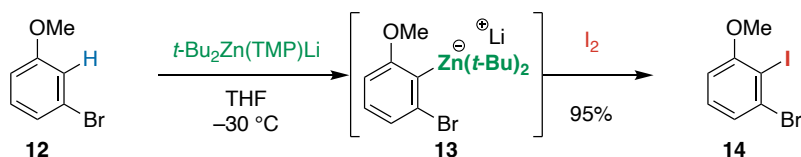
以上の例から、ハロアレーンの合成に関する研究は、医薬品および機能性分子の開発において非常に重要であると考えられる。そこで著者は、ハロアレーンの効率的な合成法の開発に着目している。

1-2 ハロアレーンの合成における課題

ハロアレーンは、芳香族化合物のハロゲン化もしくはハロアレーンの官能基化により得られる。前者の代表的手法である古典的な芳香族求電子置換反応において、オルト位とパラ位に配向性を示す電子供与基を有する芳香族化合物は、穏和な条件下でも高い反応性を示す。しかし、これらの化合物は、過剰反応が起こりやすく、生成物の位置選択性や収率の制御が困難となる。一方、メタ位配向性を示す電子求引基を有する芳香族化合物は、一般に高温や強酸性溶媒などの厳しい反応条件を必要とし、適用可能な官能基の種類も限定される¹²。近年、芳香族化合物に対する位置選択的なハロゲン化に関する研究が進展しているものの、これらの方法は、しばしば高価なハロゲン化試薬や触媒に依存するため、幅広い応用が制限されている¹³。一方、ハロアレーンを起点とした官能基の導入は、入手しやすい出発物質と良好な官能基許容性などの利点があり、実用的な合成戦略である。

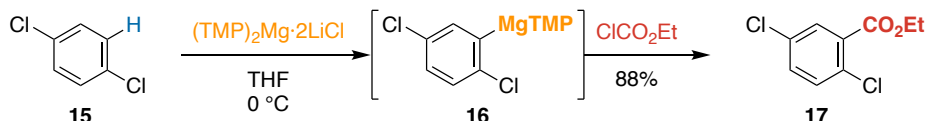
脱プロトンのメタル化は、位置選択性とアトムエコノミーに優れ、芳香族化合物の官能基化手法として広く利用されている¹⁴。この手法は、ハロアレーンにも適用可能である。例えば、2002年に内山らは、アート型塩基 $t\text{-Bu}_2\text{Zn(TMP)Li}$ を用いてハロアレーンの脱プロトンの重鉛化を報告している (Scheme 1-2-1)¹⁵。

アート型塩基とは、ルイス酸性の金属中心にルイス塩基が配位したアニオン性を示す金属錯体である^{14d}。-30 °C で 3-ブロモアニソール (**12**) に対して $t\text{-Bu}_2\text{Zn}(\text{TMP})\text{Li}$ を作用させ、脱プロトン化を経てアリール亜鉛 **13** が生成している。生成した有機亜鉛 **13** をヨウ素化して、対応するヨードアレーン **14** を収率 95%で得ている。本手法は、3-ブロモアニソール (**12**) に限らず、さまざまな官能基を有するブロモアレーンにも適用可能である。一方、ヨードアレーンへの適用例は、これまでに報告されていない。



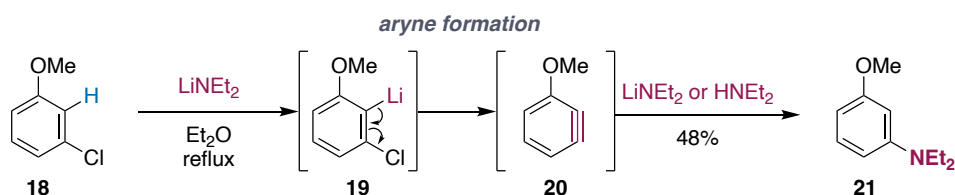
Scheme 1-2-1. Deprotosynthesis of bromoanisole using a TMP-zincate base

2013 年に Knochel らは、マグネシウムビスアミド $\text{TMP}_2\text{Mg} \cdot 2\text{LiCl}$ を用いたクロロアレーン **15** の脱プロトンのマグネシオ化を報告している (Scheme 1-2-2)¹⁶。すなわち、0 °C でクロロベンゼン **15** に対して $\text{TMP}_2\text{Mg} \cdot 2\text{LiCl}$ を作用させると、アリールマグネシウム **16** が生成している。その後、クロロギ酸エチルを加え、エステル基を有するクロロアレーン **17** を収率 88%で合成している。



Scheme 1-2-2. Deprotomagnesiation of chloroarene using a magnesium bisamide

一方、リチウムアミドを用いたハロアレーンの脱プロトンの官能基化は、適用範囲に制限があった。例えば、1952 年に Gilman らは、リチウムアミド LiNEt_2 を用いた 3-クロロアニソール (**18**) の脱プロトン化反応を報告している (Scheme 1-2-3)¹⁷。クロロアレーン **18** に対して LiNEt_2 を作用させるとメトキシ基と塩素原子の間で位置選択的な脱プロトン化が進行している。アリールリチウム **19** の生成に続いて速やかに脱離反応が起こり、高度に歪んだアライン中間体 **20** が生成している¹⁸。その後、ジエチルアミンもしくはリチウムジエチルアミドとの反応により、ジエチルアニリン **21** を収率 48%で合成している。



Scheme 1-2-3. Synthesis of diethylaniline through an aryne intermediate

比較的安定な炭素–亜鉛結合(イオン性が 18%である)および炭素–マグネシウム結合(同 34%)と比較し、炭素–リチウム結合はより高いイオン性(同 43%)を示す¹⁹。この性質により、2-ハロアリールリチウム種は低温下においても迅速に脱離反応が進行し、アライン中間体が生成することが知られている¹⁸。また、亜鉛アミドやマグネシウムアミドを用いると、より安定なアリール金属中間体の生成が可能であるが、金属アミド塩基自体の塩基性に着目すると、亜鉛アミドおよびマグネシウムアミドは、一般にリチウムアミドと比較して塩基性が低いため、脱プロトン化可能な基質が限定されることが課題となる。したがって、著者は、幅広い基質にも適用可能な強塩基性リチウムアミドを用いた脱プロトンのリチオ化により生成した不安定なアリールリチウム種の有効利用に注目している。

1-3 *in situ* トランスメタル化を用いた短寿命アリールリチウムの捕捉

in situ トランスメタル化とは、脱プロトンのリチオ化により生じた不安定なアリールリチウムを直ちにトランスメタル化して安定化させる方法である(Figure 1-3-1)²⁰。まず、反応系に金属塩(MX)と芳香族化合物が共存できると仮定する。脱プロトン化により生じたアリールリチウム(Ar-Li)と金属塩(MX)が十分に速くトランスメタル化できれば、安定なアリール金属種(Ar-M)が効率的に生成すると考えられる。また、汎用なリチウムアミドがかさ高いので、金属塩と反応して安定な金属アミドを形成することが制限される。すなわち、あらかじめ反応系に金属塩(MX)を添加し、脱プロトン化により生じた不安定なアリールリチウムを直ちに別の金属種と金属交換して安定化させる方法により、塩基性条件下で不安定な芳香族化合物を効果的に官能基化することが可能である。

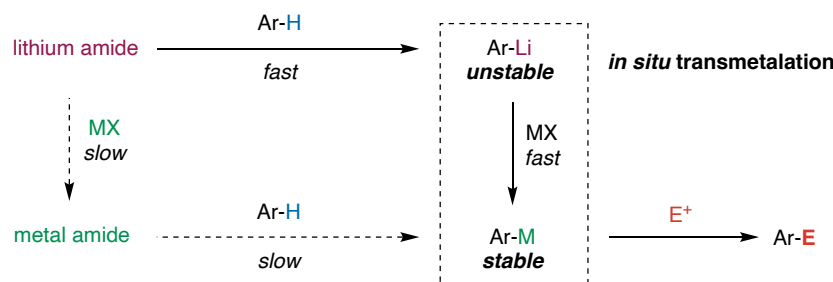
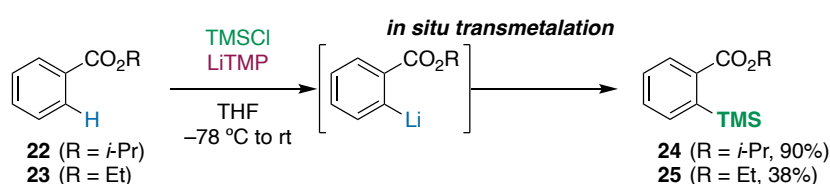


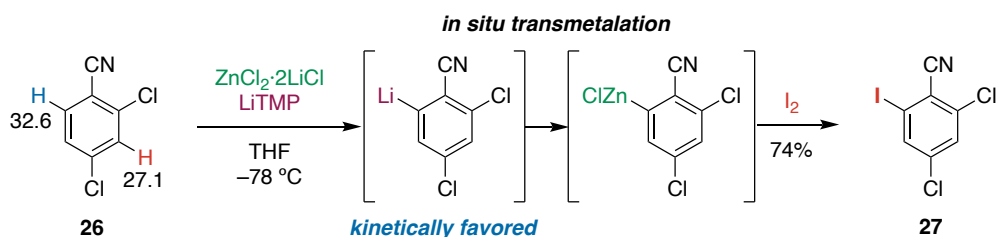
Figure 1-3-1. Theory of *in situ* transmetalation

例えば、安息香酸エステル誘導体から生成したアリールリチウム種は、速やかに自己反応が起こるため、合成化学への幅広い応用が制限されている²¹。1983年に Martin らは、*in situ* トランスメタル化を利用して安息香酸エステル **22** および **23** の脱プロトンの官能基化を初めて報告している (Scheme 1-3-1)²²。-78 °C で安息香酸イソプロピル (**22**) と TMSCl を含む THF 溶液に LiTMP を作用させたところ、エステル基が配向基として働いた結果、脱プロトン化がエステル基のオルト位に進行し、短寿命のアリールリチウムが生成している。その後、あらかじめ添加した TMSCl とのトランスメタル化により、ケイ素置換基が導入された安息香酸イソプロピル **24** を収率 90% で合成している。一方、安息香酸エチル (**23**) を用いた場合は、対応する安息香酸エチル **25** の収率が 38% に低下している。この原因として、アルキル基が小さくなったため、アリールリチウムの自己反応が優先したと理解できる。



Scheme 1-3-1. Functionalization of benzoates using *in situ* transmetalation

2014 年に Knochel らは、*in situ* トランスメタル化を利用してクロロ基を有するベンズニトリル **26** の脱プロトンの官能基化を報告している (Scheme 1-3-2)^{20b}。-78 °C でベンズニトリル **26** と $\text{ZnCl}_2 \cdot 2\text{LiCl}$ の THF 溶液に LiTMP を作用させることで、速度論的により有利なアリールリチウムを生成している。その後、 $\text{ZnCl}_2 \cdot 2\text{LiCl}$ とのトランスメタル化により、安定な有機亜鉛へ変換したのち、ヨウ素化反応により多置換ベンズニトリル **27** を収率 74% で合成している。



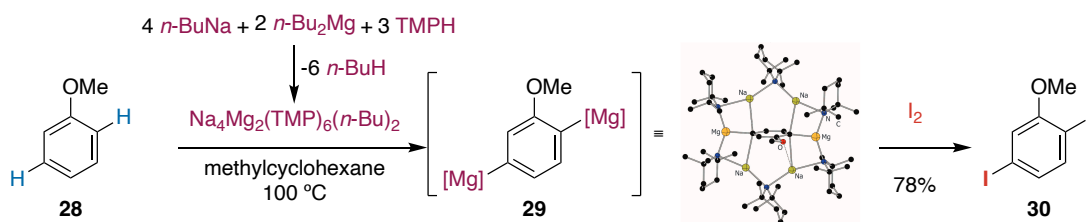
Scheme 1-3-2. Functionalization of benzonitrile via *in situ* transmetalation

上記の例に加え、水銀 (Hg), ホウ素 (B), 銅 (Cu), アルミニウム (Al), ゲルマニウム (Ge), スズ (Sn) などの金属種を用いた *in situ* トランスメタル化に関する研究も数多く報告されている^{20a,c,23}。これらの研究は, *in situ* トランスメタル化によりアリールリチウム種と求電子性置換基との副反応が効果的に抑制されることを示している。一方, *in situ* トランスメタル化を活用したハロアレーンの官能基化に関しては, いまだ十分に検討されておらず, 課題として残されている。そこで著者は, *in situ* トランスメタル化を鍵とするさまざまなハロアレーンの位置選択的な官能基化の実現をめざした (詳細は, 第二章と第四章)。

1-4 ハロアレーンの脱プロトン化における位置選択性の課題

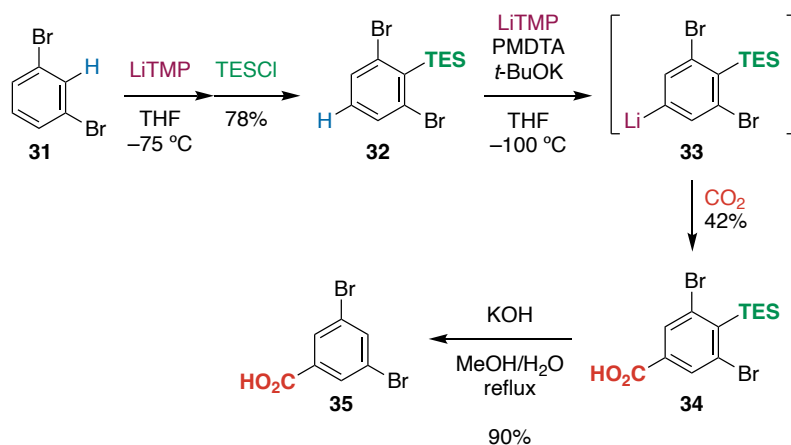
芳香族化合物の脱プロトンのメタル化は, 一般にルイス塩基性官能基の隣接位で進行し, いわゆるオルトメタル化として知られている^{14a-c,g}。すなわち, 芳香環上のルイス塩基性を有する官能基 (配向基: DMG) がルイス酸性を有する金属イオンと相互作用することで, 最も近接するオルト位において選択的に脱プロトン化が進行することが知られている。オルトメタル化は, Gilman^{14a} および Wittig^{14b} によって独立して発見され, その後, Beak^{21b,24}, Snieckus^{14c,g}, Schlosser²⁵, Collum²⁶らにより体系化された。芳香族化合物における求電子置換反応と比較し, オルトメタル化が優れた位置選択性および反応性を示し, 多様な芳香族化合物の位置選択的な官能基化に幅広く応用されている。一方, 脱プロトン化が配向基のオルト位に対して高い位置選択性で進行することから, メタ位など他の位置での選択的な脱プロトン化は, 困難な課題とされている。

2014 年に Mulvey および O'Hara らは, アニソール (28) のオルトおよびメタ位選択的なメタル化を達成している (Scheme 1-4-1)²⁷。アニソール (28) にナトリウム-マグネシウムアミドを作用させたところ, メトキシ基のオルト位とメタ位が脱プロトン化され, アリールマグネシウム 29 を生成している。その後, ヨウ素と反応させ, オルト位とメタ位が位置選択的にヨウ素化されたアニソール 30 が収率 78% で得られている。



Scheme 1-4-1. Directed *ortho*-*meta'*-dimetalations of anisole

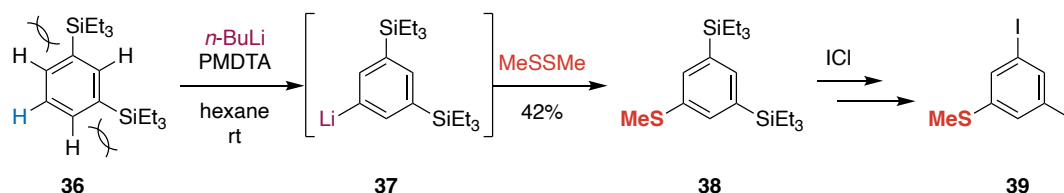
2003 年に Schlosser らは、1,3-ジブロモベンゼン (**31**) に対する形式的なメタ位選択的メタル化を報告している (Scheme 1-4-2) ²⁸。ブロモベンゼン **31** を脱プロトンのケイ素化することにより、対応するブロモアレーン **32** が収率 78% で得られている。ブロモアレーン **32** に LiTMP, PMDTA, および *t*-BuOK の混合を作用させたところ、かさ高いトリエチルシリル基の *buttressing* 効果を通じて、速度論的により有利なアリールリチウム **33** を生成している。その後、二酸化炭素と反応させ、カルボン酸 **34** が収率 42% で得られている。さらに、トリエチルシリル基の除去を経て、メタ位にカルボキシ基を有するブロモアレーン **35** を 3 工程で合成している。



Scheme 1-4-2. Formal *meta*-selective metalation of 1,3-dibromobenzene

Schlosser らによるかさ高いトリエチルシリル基の *buttressing* 効果に関する知見に基づいて、2019 年に Knochel らは、1,3-ジトリエチルシリル基を有するアリール化合物のメタ位選択的メタル化を達成している (Scheme 1-4-3) ²⁹。シリルアリール化合物 **36** に *n*-BuLi と PMDTA を作用させると、トリエチルシリル基のメタ位において脱プロトン化を進行し、アリールリチウム **37** が生成している。この中間体にジメチルジスルフィドを作用させた結果、対応するアリール化合物 **38** が収率 42% で得られている。さらに、一塩化ヨウ素素との反応を行って、ト

リエチルシリル基をヨウ素へ変換し、ヨードアレーン **39** を合成している。すなわち、本手法により、1,3-ジヨードベンゼンの形式的なメタ位選択的なメタル化が実現されている。



Scheme 1-4-3. *meta*-Selective metalation of 1,3-bis-silylated arene

ハロアレーンのメタ位に選択的な脱プロトンのメタル化は、上記の形式的変換に限定された報告しかなく、その研究例がきわめて限られている。したがって、著者は、これまでに報告例がないハロアレーンのメタ位に選択的な脱プロトンのメタル化の開発に着目した（詳細は、第五章）。

1-5 本研究の目的と構成

本研究は、ハロアレーンを起点としたさまざまな多置換芳香族化合物を簡便、迅速、網羅的な供給法の確立を目的とする。そこで、これまでに報告例の少ないハロアレーンの *in situ* トランスメタル化および脱プロトン化における位置選択性の制御に取り組んだ。従来の反応条件ではアラインが発生するハロベンゼン誘導体の適用（第二章）、天然物カルバゾマイシン類の全合成への展開（第二章および第三章）、ヘテロアレーンの C-2 位選択的な官能基化（第四章）、ハロアレーンのメタ位選択的なメタル化（第五章）を通じて、*in situ* トランスメタル化を鍵とした一般性の高いハロアレーンの位置選択的な官能基化に成功した。

第二章：Feng, Y.; Yukioka, T.; Matsuyama, M.; Mori, A.; Okano, K. Deprotonative generation and trapping of haloaryllithium in a batch reactor. *Org. Lett.* **2023**, 25, 3013–3017.

第二章では、*in situ* トランスメタル化を鍵とするさまざまなハロベンゼン誘導体のオルト位選択的な官能基化を達成した。脱プロトン化により生成した 2-ハロフェニルリチウム種は、オルト位に存在するハロゲン原子と迅速に脱離反応が起こし、アライン中間体が生成した。このため、ハロベンゼン誘導体を起点とした多置換ベンゼン化合物への変換が困難であった。また、当研究室はハロゲン

化亜鉛ジアミン錯体を用いた *in situ* トランスメタル化により短寿命のヘテロアリールリチウム種を効果的に利用できることを報告している。そこで、この手法を利用し、これまで利用困難な 2-ハロフェニルリチウムを合成化学へ応用できた。また、ジアミン配位子の構造を調整することで、塩化亜鉛ジアミン錯体とリチウムアミドとの競合反応を制御し、クロロベンゼンに対してもオルト位選択的な官能基化が達成され、基質の適用範囲がさらに拡大した。本手法を活用することで、天然物カルバゾマイシン A の短段階合成を達成した。

第三章 : Feng, Y.; Mori, A.; Okano, K. Gram-scale total synthesis of carbazomycins A-D through late-stage regioselective demethylation of aryl methyl ethers. *J. Org. Chem.* **2024**, *89*, 13472–13484.

第三章では、*in situ* トランスメタル化を鍵とするカルバゾマイシン A–D のグラムスケール合成を達成し、この手法の実用性をさらに拡張した。カルバゾマイシン類は、1980 年に中村らによって放線菌 *Streptovercillium ehimense* から単離された天然物であり、カルバゾール骨格を有する最初の抗生物質として知られている。ユニークな全置換ベンゼン構造を有していることから従来法では出発原料の合成に多段階を要していた。そこで、本研究では、短い合成経路を立案した。対称構造をもつクロロベンゼンを出発原料として、*in situ* トランスメタル化を鍵として 2 工程で新規なアミノビフェニルを合成したのち、アライン中間体を経て、カルバゾール骨格を構築した。その後、メトキシ基の変換を通じて、カルバゾマイシン A–D を全合成した。本合成法は、構造が比較的簡単なハロベンゼン誘導体を出発原料として、効率的に多置換カルバゾール誘導体を構築するとともに、メトキシ基の位置選択的な変換を通じて、天然物カルバゾマイシン A–D の迅速かつ実用的な供給が可能になった。

第四章 : Feng, Y.; Mori, A.; Okano, K. Regioselective deprotonative metalation of heteroarenes with a combination of lithium amide and zinc halide diamine complex. *J. Org. Chem. accepted.* (doi:10.1021/acs.joc.5c01171)

第四章では、第二章で報告した *in situ* トランスメタル化を用い、ヘテロアレーンの C-2 位選択的な官能基化を達成した。報告例がなかった 3-ヨードピリジンの脱プロトンのヨウ素化を行った結果、塩化亜鉛ジアミン錯体を用いた *in situ* トランスメタル化が有用であり、LiTMP を用いると室温で 2,3-ジヨードピリジンが高収率で得られている。一般的には、ハロピリジンの C-4 位選択的に脱プロトン化されるのに対して、この方法を用いると、ハロピリジンの C-2 位が選択

的に脱プロトン化される。3-ヨードピリジンに加え、さまざまなハロピリジン、官能基をもつチオフェン、ブロモフラン、ピロール誘導体などにも適用でき、幅広い多置換ヘテロ芳香族化合物を迅速、網羅的な供給を可能とした。

第五章 : Feng, Y.; Kojima, T.; Mori, A.; Okano, K. Beyond the *ortho*-rule. *meta*-Selective deprotonative metalation of haloarenes. *To be submitted*.

第五章では、報告例のないハロアレーンの直接的なメタ位選択的メタル化を初めて達成した。アザクラウンエーテル Me_3TACN と LiTMP の相互作用により生成した錯体を用い、さまざまなハロアレーンのメタ位選択的な脱プロトン化が可能になった。生成したアリールリチウムは、*in situ* トランスメタル化により安定なアリール亜鉛種あるいはアリールホウ素化合物に変換され、望ましくないハロゲン-リチウム交換が抑制できた。さまざまなハロアレーンを起点として、従来法では数工程を要する官能基の変換が1工程で可能になった。

第六章では、第二章から第五章の内容を総括し、本研究の展望について議論する。

1-6 References

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第二章

in situ トランスメタル化による
短寿命ハロフェニルリチウムの捕捉

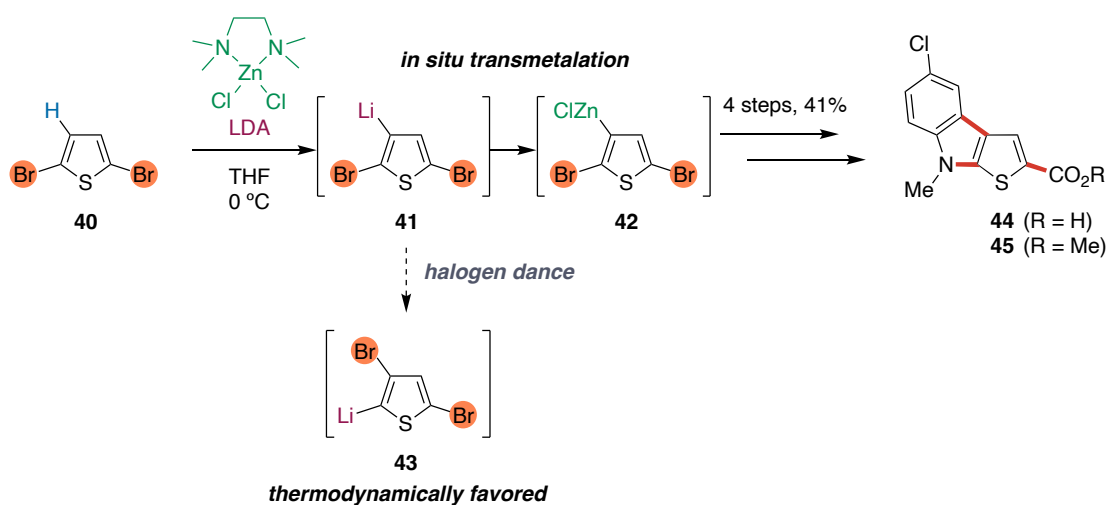
2-1 序論

第一章で述べたように、従来の方法では官能基化できるハロベンゼン誘導体が限られていた。そのため、本研究では、*in situ* トランスメタル化を鍵として短寿命ハロフェニルリチウムを捕捉し、ハロベンゼン誘導体の位置選択的かつ効率的な官能基化法の確立を目的として研究に着手した。

2-2 塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化

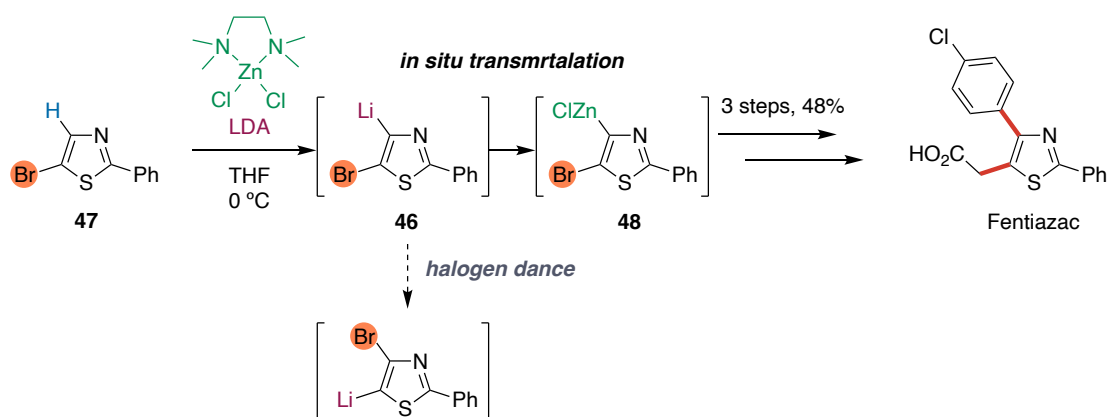
塩化亜鉛 TMEDA 錯体³⁰を用いた *in situ* トランスメタル化は、反応性の高いアリールリチウム種をあらかじめ添加された塩化亜鉛 TMEDA 錯体とトランスメタル化させ、安定なアリール亜鉛種に変換し、根岸カップリング反応^{3e-h}などに利用されている³¹。塩化亜鉛は、安価で入手容易なハロゲン化亜鉛がよく用いられているが^{20c,32}、実験的に利用する上で高い潮解性が問題であったため、潮解性を示さない塩化亜鉛 TMEDA 錯体も用いられている。

塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化を鍵として、さまざまな不安定なアリールリチウムを捕捉して利用できる。例えば、基質がヨードアレーンもしくはブロモアレーンの場合、脱プロトン化により生成したアリールリチウムは、熱力学的により安定なアリールリチウムへハロゲン転位を伴って、速やかに異性化することが知られており、「ハロゲンダンス」として呼ばれている³³。2018年に当研究室の林は、後に誘導しやすい2,5-ジブロモチオフェン(40)から発生する、寿命の短い不安定なアニオンを *in situ* トランスメタル化により利用できることを始めて報告している (Scheme 2-2-1)³⁴。ブロモチオフェン 40 と塩化亜鉛 TMEDA 錯体の共存下で塩基として LDA を加え、脱プロトン化してアリールリチウム 41 を得たのち、*in situ* トランスメタル化により安定なアリール亜鉛 42 に変換している。すなわち、ハロゲンダンスを経由して発生する、熱力学的により安定なアリールリチウム 43 の生成が抑制された。この反応を応用し、代謝型グルタミン酸受容体 (mGluR) に対して拮抗作用を有するチエノインドール誘導体 44 と 45³⁵を 4 工程、総収率 41%で合成している。



Scheme 2-2-1. Regioselective functionalization of bromothiophene

2021 年に当研究室の井上は、ブロモチアゾールのハロゲンダンスに含まれる 2 種類のアニオンのうち、これまで捕捉できなかった寿命の短い不安定なアリールリチウム **46** を *in situ* トランスメタル化により利用できることを報告している (Scheme 2-2-2) ³⁶。ブロモチアゾール **47** と塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して LDA を作用させ、脱プロトン化してアリールリチウム **46** を生成したのち、*in situ* トランスメタル化により安定なアリール亜鉛 **48** を得ている。この反応を応用し、抗炎症薬 fentiazac³⁷ の合成を 3 工程、総収率 48% で達成している。



Scheme 2-2-2. Regioselective functionalization of bromothiazole

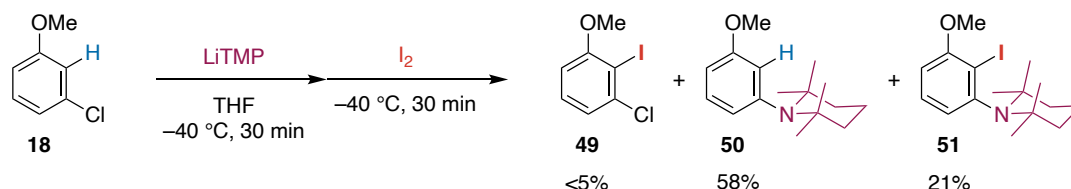
以上の研究背景から、幅広いハロアレーンを脱プロトン化可能なリチウムアミドを用い、生成するハロアリールリチウム種を速やかに *in situ* トランスメタル化することで、ハロゲンダンスを発生せずに、さまざまなハロアレーンを官能

基化できることが明らかになっている。

そこで、本研究は、*in situ* トランスメタル化を活用し、不安定な 2-ハロフェニルリチウム種を合成的に利用することを目的とした。本手法においては、塩基性の高いリチウムアミドの長所を活かしつつ、脱プロトンのリチオ化により生じた 2-ハロフェニルリチウム種を直ちにトランスメタル化することで、アラインの発生を抑制し、さまざまなハロベンゼン誘導体に対する効率的な官能基化が可能となることが期待されている。

2-3 *in situ* トランスメタル化による 2-クロロフェニルリチウムの捕捉

まず、クロロアニソール **18** の脱プロトンのヨウ素化を検討した (Scheme 2-3-1)。クロロアニソール **18** を含む THF 溶液に対して、 $-40\text{ }^{\circ}\text{C}$ で LiTMP を徐々に滴下した。その温度で 30 分間攪拌した後にヨウ素を加え、同じ温度でさらに反応させた結果、目的のヨウ化物 **49** の収率は 5%未満であり、アライン中間体を経て生成したアニリン誘導体 **50** と **51**³⁸ がそれぞれ収率 58%と 21%で得られた。以上の結果から、クロロアニソール **18** から生成する 2-クロロフェニルリチウムは、 $-40\text{ }^{\circ}\text{C}$ でも不安定であり、速やかにアライン中間体に変換されることが明らかになった。



Scheme 2-3-1. Deprotonative functionalization of chloroanisole

そこで、先行研究^{34,36,39}に基づいて、さまざまなハロゲン化亜鉛ジアミン錯体を用いて *in situ* トランスメタル化を検討した (Table 2-3-1)。クロロアニソール **18** とハロゲン化亜鉛ジアミン錯体を含む THF 溶液に対して、 $-40\text{ }^{\circ}\text{C}$ で LiTMP を添加した。 $-40\text{ }^{\circ}\text{C}$ で 30 分間攪拌したのち、ヨウ素を加えて同じ温度でさらに反応させた。塩化亜鉛 TMEDA 錯体を用いた場合、目的のヨウ化物 **49** を単離収率 96%で得た。さらに、グラムスケール合成においても単離収率 92%で目的物を得た (entry 1)。ハロゲン化亜鉛として臭化亜鉛やヨウ化亜鉛を用いたところ、**49** の収率がやや低下した (entries 2 and 3)。また、TMEDA よりもかさ高い TEEDA や TMPDA を用いた場合、**49** の収率が著しく低下したが、アニリン誘導体 **50** の収率が向上した (entries 4 and 5)。この結果から、大きい立体障害を持つジアミ

ン配位子は、2-クロロフェニルリチウムとのトランスメタル化を抑制し、アラインを優先して発生させたと考えられた。ジアミン配位子の必要性を確認するために、塩化亜鉛との反応を行った。その結果、**49** の収率が著しく低下した (entry 6)。この原因は、塩化亜鉛が LiTMP とトランスメタル化し、塩基性の弱い亜鉛アミド TMPZnCl あるいは $(\text{TMP})_2\text{Zn}$ に変換されたと考えられた。そこで、Knochelらの報告⁴⁰を参考にし、反応系で発生した亜鉛アミドを利用して対照実験を実施した。すなわち、塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して $-40\text{ }^{\circ}\text{C}$ で LiTMP を加えて 30 分間反応させた。その後、クロロアニソール **18** を加えて 30 分間攪拌を続けたのち、ヨウ素を処理させた結果、目的のヨウ化物 **49** がわずかに収率 11% でしか生成しておらず、クロロアニソール **18** を収率 47% で回収した (entry 7)。すなわち、LiTMP と塩化亜鉛 TMEDA 錯体との反応により生成された亜鉛アミドは、LiTMP に比べて塩基性が低く、脱プロトン化が困難であるとわかった。以上の結果から、クロロアニソール **18** が LiTMP によって脱プロトン化され、生成した 2-クロロフェニルリチウムが塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化によって安定なフェニル亜鉛種に変換された結果、アライン中間体の発生が抑制されたことが明らかになった。

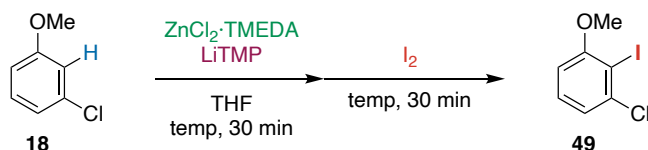
Table 2-3-1. Effect of zinc halide diamine complex on the *in situ* transmetalation of chlorophenyllithium^a

entry	ZnX ₂ ·diamine	49 (%) ^b	50 (%) ^b
1	ZnCl ₂ ·TMEDA	96 ^c (92 ^{c,d})	1
2	ZnBr ₂ ·TMEDA	86	2
3	ZnI ₂ ·TMEDA	81	2
4	ZnCl ₂ ·TEEDA	64	12
5	ZnCl ₂ ·TMPDA	55	8
6	ZnCl ₂	69	5
7 ^e	ZnCl ₂ ·TMEDA	11	— ^f

^aReaction conditions: chloroanisole **18** (0.30 mmol, 1.0 equiv), ZnX₂·diamine (0.30 mmol, 1.0 equiv), LiTMP (0.53 mmol, 1.8 equiv), and I₂ (0.6 mmol, 2 equiv). ^bThe yield was determined from the ¹H NMR spectrum of the crude product, using 1,1,2,2-tetrachloroethane as an internal standard. ^cIsolated yield. ^dChloroanisole **18** (3.0 mmol, 1.0 equiv) was used. ^eLiTMP and ZnCl₂·TMEDA reacted at −40 °C for 30 min prior to the addition of chloroanisole **18**, resulting in 47% recovery of **18**. ^fNot observed.

上述の結果に基づいて、塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化における反応温度の影響を検討した (Table 2-3-2)。クロロアニソール **18** と塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して、表に示した温度で LiTMP を作用させた。続いて、その温度でヨウ素を加え、同じ温度でさらに反応させた。−40 °C で反応させた場合、目的のヨウ化物 **49** が単離収率 96% で得られた (entry 1)。次に、反応温度を −78 °C としたところ、**49** の収率はほぼ同等であった (entry 2)。さらに、反応温度を 0 °C に昇温しても、**49** が収率 90% で得られた (entry 3)。以上の結果から、塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化において、反応温度を 0 °C に上げてアラインの発生を抑制でき、安定なフェニル亜鉛中間体を高収率で発生されたことがわかった。

Table 2-3-2. Effect of reaction temperature on the *in situ* transmetalation of chlorophenyllithium^a



entry	temp (°C)	49 (%) ^b	recovery of 18 (%) ^b
1	−40	98 (96 ^c)	1
2	−78	96	2
3	0	90	<2

^aReaction conditions: chloroanisole **18** (0.30 mmol, 1.0 equiv), ZnCl₂·TMEDA (0.30 mmol, 1.0 equiv), LiTMP (0.53 mmol, 1.8 equiv), and I₂ (0.6 mmol, 2 equiv). ^bThe yield was determined from the ¹H NMR spectrum of the crude product, using 1,1,2,2-tetrachloroethane as an internal standard. ^cIsolated yield.

次に、確立された塩化亜鉛 TMEDA 錯体を用いる *in situ* トランスメタル化が、クロロベンゼン (**52**) に適用可能かどうかを検討した (Table 2-3-3)。クロロベンゼン (**52**) の *in situ* トランスメタル化は、1988 年に Eaton らによって報告されているが、毒性の高い塩化水銀 (HgCl₂) を使用し、さらに収率も 31% と低いため、課題が残されている ^{20a}。まず、最適化された条件で反応を行ったところ、目的のヨウ化物 **53** はわずか収率 3% でしか得られず、**52** が主に回収された (entry 1)。反応時間が 6 時間に延長しても、**53** の収率が改善されなかった (entry 2)。この原因は、クロロベンゼン (**52**) の脱プロトン化がクロロアニソール **19** よりも遅かったと考えられる。その結果、期待された脱プロトン化よりも、LiTMP と塩化亜鉛 TMEDA 錯体の反応が優先的に進行し、塩基性の弱い亜鉛アミドが生成したと考察した。そこで、LiTMP との副反応を抑制するために、よりかさ高いジアミン配位子をもつ塩化亜鉛錯体を利用して検討を続けた。塩化亜鉛 TEEDA 錯体を用いて 0 °C で反応したところ、目的のヨウ化物 **53** の収率が 12% に向上した (entry 3)。さらに、TEEDA によりかさ高い TMPDA に置き換えたところ、**53** の収率はほぼ同等であった (entry 4)。また、反応温度を −40 °C としたところ、**53** の収率が 23% に向上した (entry 5)。反応時間を 2 時間に延長したところ、**53** を単離収率 48% で合成した (entry 6)。

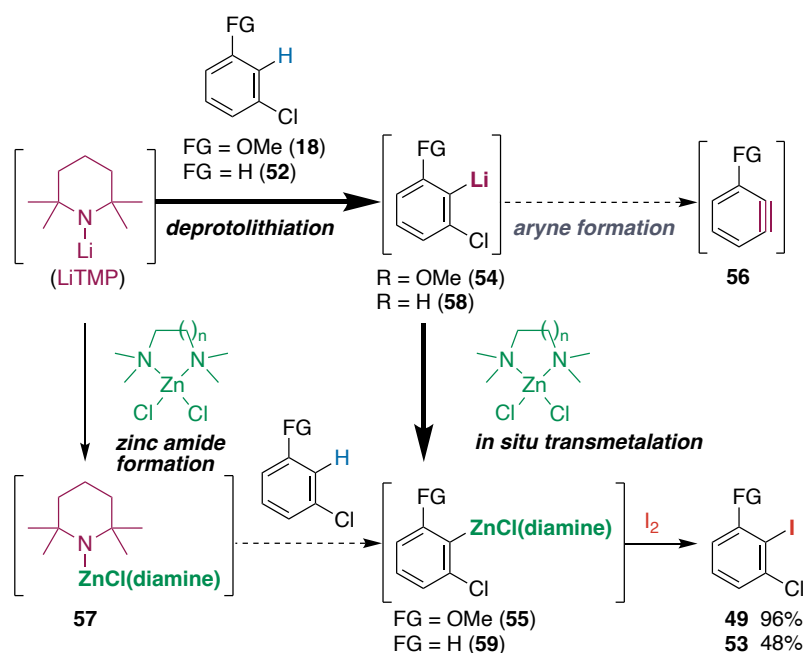
Table 2-3-3. Deprotonative functionalization of chlorobenzene through *in situ* transmetalation^a



entry	ZnCl ₂ ·diamine	temp (°C)	time (h)	53 (%) ^b
1	ZnCl ₂ ·TMEDA	−40	0.5	3
2	ZnCl ₂ ·TMEDA	−40	6	6
3	ZnCl ₂ ·TEEDA	0	0.5	12
4	ZnCl ₂ ·TMPDA	0	0.5	14
5	ZnCl ₂ ·TMPDA	−40	0.5	23
6	ZnCl ₂ ·TMPDA	−40	2	48 ^c

^aReaction conditions: chlorobenzene (**52**) (0.30 mmol, 1.0 equiv), ZnCl₂·diamine (0.30 mmol, 1.0 equiv), LiTMP (0.53 mmol, 1.8 equiv), and I₂ (0.6 mmol, 2 equiv). ^bThe yield was determined from the ¹H NMR spectrum of the crude product, using 1,1,2,2-tetrachloroethane as an internal standard. ^cIsolated yield.

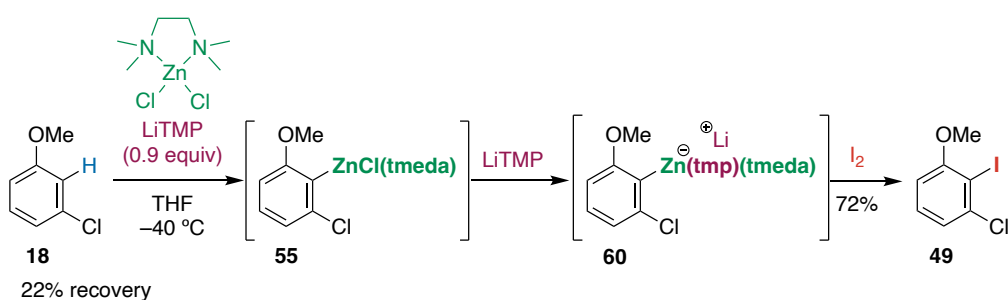
文献調査 ^{20b-d,41} および反応結果に基づいて、反応経路やジアミン配位子の役割は以下のように考察した (Scheme 2-3-2)。クロロアニソール **18** に LiTMP を作用させ、脱プロトン化によって 2-クロロフェニルリチウム **54** が生成している。このフェニルリチウム種は、あらかじめ加えた塩化亜鉛 TMEDA 錯体と速やかにトランスメタル化し、フェニル亜鉛 **55** へと変換されている。すなわち、熱力学的により安定なアライン **56** の発生が抑制された。一方、基質がクロロベンゼン (**52**) である場合、TMEDA よりかさ高い TMPDA 配位子を利用すると、目的のヨウ化物 **53** がより高い収率が得られている。すなわち、塩化亜鉛 TMPDA 錯体の立体障害により、LiTMP との副反応である亜鉛アミド **57** の生成が抑制され、**52** の脱プロトン化が優先的に進行し、2-クロロフェニルリチウム (**58**) を経由してフェニル亜鉛 **59** が生成している。LiTMP を立体障害がより小さくかつ塩基性の弱い LDA に置き換えたところ、**53** の収率は 3% に大きく低下した。この結果から、LDA が脱プロトン化よりも亜鉛アミドの形成を優先すると考えられる。



The yield of **53** decreased to 3%, with recovery of **52** when LDA was used instead of LiTMP.

Scheme 2-3-2. Rationale for the effects of diamine ligands on the *in situ* transmetalation of chlorophenyllithium

さらに、対照実験により、反応には2当量の LiTMP が必要であると確認した (Scheme 2-3-3)。1 当量の LiTMP を用いたところ、**49** の収率が 72% に低下し、**18** が収率 22% で回収された。この原因は、生成したフェニル亜鉛 **55** の一部が LiTMP とさらに反応し、亜鉛アミド **60** を形成していると考えられた。



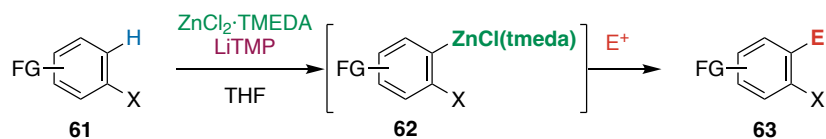
Scheme 2-3-3. Rationale for the formation of aryl(TMP)zinc species

2-4 さまざまなハロベンゼン誘導体のオルト位選択的な官能基化

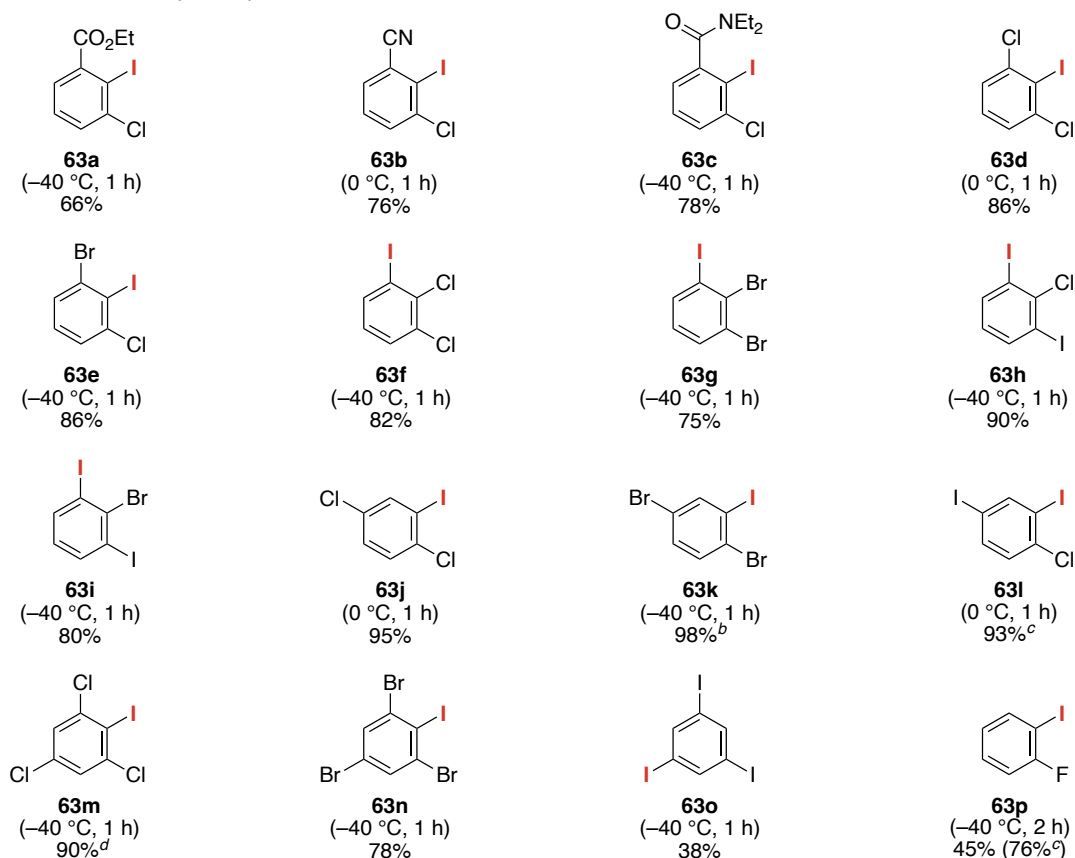
開発した *in situ* トランスメタル化の実用性を明らかにするために、ハロベンゼン誘導体および求電子剤の一般性を検討した (Table 2-4-1)。まず、ヨウ素化反

応によって *in situ* トランスメタル化に適用する基質を調べた (Table 2-4-1a)。ハロベンゼン **61** と塩化亜鉛 TMEDA 錯体の THF 溶液に LiTMP を作用させ、*in situ* トランスメタル化を経てフェニル亜鉛 **62** が生成している。その後、ヨウ素を加えてさらに反応させた。エステル基、シアノ基とアミド基を有するメタ二置換クロロベンゼン **61a-c** からは、対応するヨウ化物 **63a-c** が収率 66%–78% で位置選択的に得られた。ジハロベンゼン **61d-l** やトリハロベンゼン **61m** と **61n** についても同様に、対応するトリハロベンゼン **63d-l** やテトラハロベンゼン **63m** と **63n** が収率 75%–98% で位置選択的に得られた。一方、ジヨードベンゼン **61o** を用いた場合は、収率 38% で 1,3,5-トリヨードベンゼン (**63o**) が得られた。このユニークな位置選択性は、ヨウ素原子の非常に大きい立体障害に起因すると考えられる⁴²。さらに、フルオロベンゼン (**61p**) の *in situ* トランスメタル化を検討した。クロロベンゼン (**52**) を用いた場合、塩化亜鉛 TMPDA 錯体を用いると収率が向上させた結果が得られている。そこで、この条件を利用して 2-フルオロヨードベンゼン (**63p**) を 76% の収率で得た。一方、塩化亜鉛 TMEDA 錯体を用いると収率が 45% に低下した。続いて、求電子剤の一般性を検討した (Table 2-4-1b)。クロロアニソール **18** を基質として、*in situ* トランスメタル化を経て、フェニル亜鉛反応剤を調製したのち、導入可能な官能基を調べた。ヨウ化アリル、フェニルチオフタルイミド⁴³ とは円滑に反応が進行し、**63q** と **63r** がそれぞれ収率 91% と 55% で得られた。塩化ベンゾイルとの根岸カップリング反応⁴⁴を行ったところ、 $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ 錯体と $(4\text{-CF}_3\text{C}_6\text{H}_4)_3\text{P}$ を加え、60 °C で反応させ、**63s** を収率 77% で合成した。 $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ 錯体と $(4\text{-FC}_6\text{H}_4)_3\text{P}$ を用いてパラヨードアニソールと反応した場合、対応する **63t** が収率 73% で得られた。一方、立体障害が高いオルトヨードアニソールと反応すると対応する **63u** の収率が 62% に低下した。

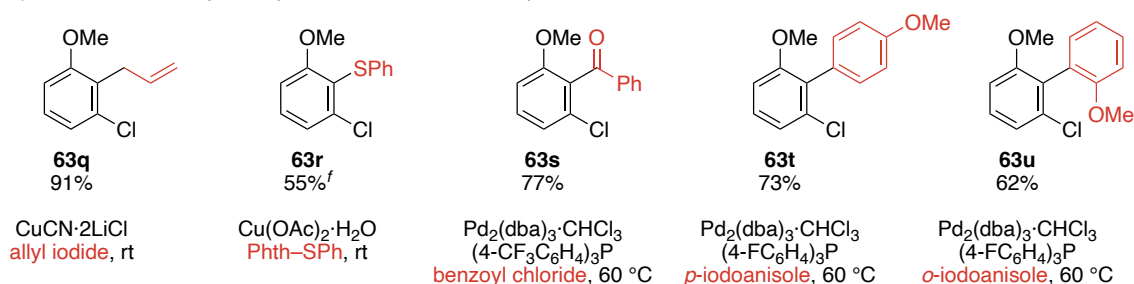
Table 2-4-1. Scope of the *in situ* transmetalation and electrophilic functionalization



a) Reaction of haloarylzinc species with iodine^a



b) Reaction of haloarylzinc species with various electrophiles^e



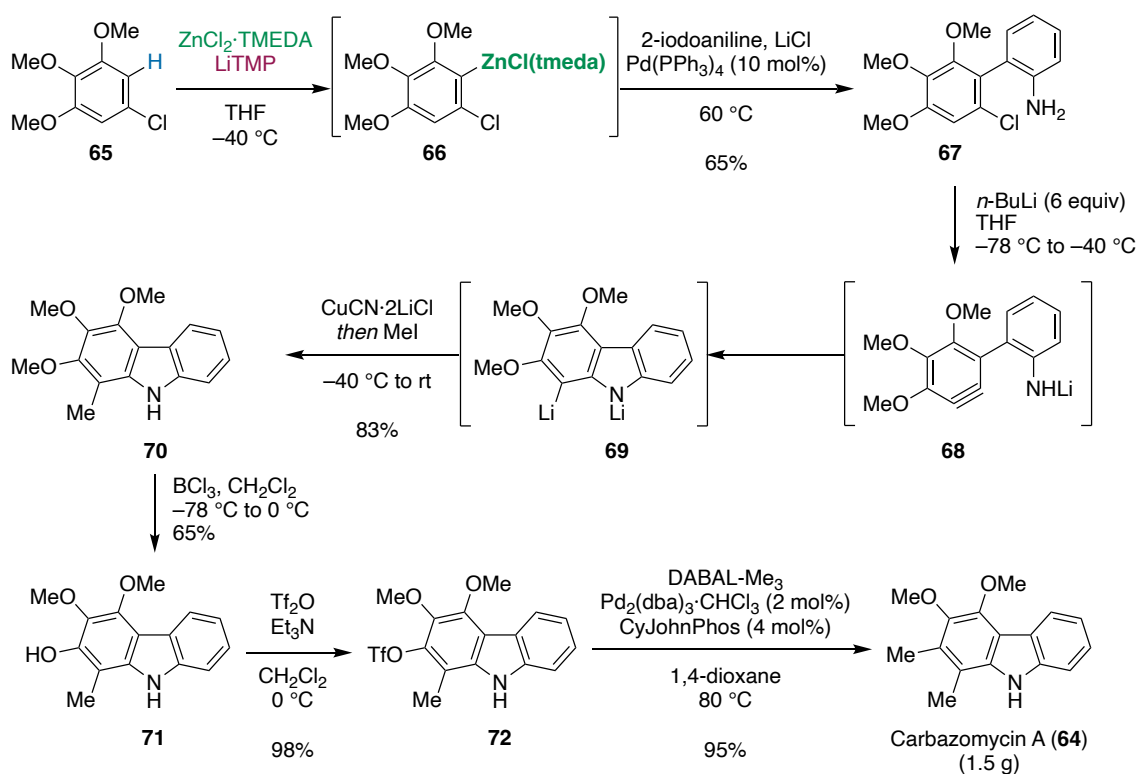
^aReaction conditions: halobenzene **61** (0.30 mmol, 1.0 equiv), ZnCl₂·TMEDA (0.30 mmol, 1.0 equiv), LiTMP (0.53 mmol, 1.8 equiv), THF, -40 °C or 0 °C, 1 h, then I₂ (0.6 mmol, 2 equiv). ^bZnCl₂·TMEDA (1.2 equiv) was used. ^cZnCl₂·TMPDA (0.30 mmol, 1.0 equiv) was used instead of ZnCl₂·TMEDA. ^dLiTMP (1.1 equiv) was used. ^eReaction conditions: chloroanisole **18** (0.30 mmol, 1.0 equiv), ZnCl₂·TMEDA (0.30 mmol, 1.0

equiv), LiTMP (0.53 mmol, 1.8 equiv), THF, $-40\text{ }^{\circ}\text{C}$, 1 h, then electrophile (0.45 mmol, 1.5 equiv).^fElectrophile (1.05 equiv) was used.

2-5 カルバゾマイシン A の短段階合成

カルバゾマイシン A (**64**) は, 1980 年に中村らによって真菌 *Streptoverticillium ehimense* から単離, 構造決定され, カルバゾール骨格を有する最初の抗生物質として報告された⁴⁵。構造上の特徴として, カルバゾマイシン A は高度に非対称なカルバゾール構造を有している。すなわち, カルバゾール骨格の 2 つのベンゼン環のうち, 片方は置換基が存在せず, もう一方は 4 つの置換基で占められ, 全置換ベンゼン構造を形成している。そのため, 従来法⁴⁶では合成に多段階を必要としており, 効率的な合成手段が求められている。

本研究では, *in situ* トランスメタル化を鍵として, 対称構造を有するトリメトキシクロロベンゼン **65** を出発物質としてカルバゾマイシン A の五段階合成を達成した (Scheme 2-5-1)。まず, *in situ* トランスメタル化を用いた **65** の形式的 C-H アリール化を行った。本章の第二節で最適化した反応条件に従い, **65** と塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して, $-40\text{ }^{\circ}\text{C}$ で LiTMP を加え, *in situ* トランスメタル化を経てフェニル亜鉛 **66** を生成した。その後, 2-ヨードアニリンとの根岸カップリング反応により, クロロ基をもつ 2-アミノビフェニル **67** を収率 65% で合成した。次に, **67** に対して 6 当量の *n*-BuLi を作用させ, 脱プロトン化によって生成したフェニルリチウムは, 速やかにアライン **68** に変換され, 分子間の芳香族求核置換反応を経てカルバゾール骨格を構築し⁴⁷, カルバゾールジアニオン **69** が生成した。その後, $\text{CuCN}\cdot 2\text{LiCl}$ ⁴⁸ とヨードメタンを作用させ, メチルカルバゾール **70** を収率 83% で得た。カルバゾマイシン A を効率的に合成するためには, **70** の三つのメトキシ基のうち, 一つを選択的に脱メチル化する必要がある。さまざまな位置選択的脱メチル化の反応条件を検討した結果, **70** に対して三塩化ホウ素⁴⁹を作用させ, 目的のヒドロキシカルバゾール **71** を収率 65% で合成した。**71** に対してトリフルオロメタンスルホン酸無水物を作用させ, 対応するトリフラート **72** を収率 98% で得た。その後, トリメチルアルミニウムの等価体として DABAL- Me_3 を用いる根岸カップリング反応⁵⁰を通じて, カルバゾマイシン A (**64**) を収率 95% で 1.5 グラム合成できた。すなわち, 本研究においてカルバマイシン A の全合成は, 入手しやすいトリメトキシクロロベンゼン **65** から 5 工程, グラムスケール, 総収率 33% で達成している。



Scheme 2-5-1. Total synthesis of carbazomycin A

2-6 結言

本章では、塩化亜鉛ジアミン錯体を用いた *in situ* トランスメタル化において短寿命 2-ハロフェニルリチウムを捕捉する手法を開発した。最適な反応条件によって、報告例の少ないクロロベンゼンを含むさまざまなハロベンゼン誘導体に有用であり、幅広い官能基の導入も可能になった。さらに、この手法を用い、カルバゾマイシン A の短段階合成に成功した。対称性の高いクロロベンゼン誘導体を出発物質として、*in situ* トランスメタル化を鍵としたワンポット根岸カップリング反応により、クロロ基を持つアミノビフェニルを合成した。その後、カルバゾール骨格の構築およびメトキシ基の変換を経て、カルバゾマイシン A を 5 工程、グラムスケール、総収率 33% で全合成した。また、カルバゾマイシン A の合成に関する背景や検討およびカルバゾマイシン A からカルバゾマイシン B-D への誘導は、第三章で詳細に報告する。

2-7 Experimental section

1. General

Analytical thin layer chromatography (TLC) was performed on Wako 70 F₂₅₄ 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 wave numbers (cm⁻¹). ¹H NMR (400 MHz) and ¹³C{¹H} NMR (100 MHz) spectra were measured on JEOL ECZ400 spectrometer. Chemical shifts for ¹H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard (CHCl₃: 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, sept = septet, m = multiplet, br = broad, dd = doublet of doublets, dq = doublet of quartets, ddd = doublet of doublet of doublets, and ddt = doublet of doublet of triplets. Chemical shifts for ¹³C{¹H} NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃: δ 77.16 ppm, CD₃CN: δ 118.26 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, and [electron ionization (EI)] with a JEOL JMS-700 MStation.

2. Materials

Unless otherwise stated, all reactions were conducted in a flame-dried glassware under an inert atmosphere of argon. All work-up 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 Kanto Chemical Co. and further dried by passing through a solvent purification system (Glass Contour) prior to use. *n*-BuLi (1.6 M in *n*-hexane) and TMPH were purchased from Kanto Chemical Co. and used as received. Freshly prepared ZnX₂·diamine complex (ZnCl₂·TMEDA, ZnBr₂·TMEDA, ZnI₂·TMEDA, ZnCl₂·TMPDA, and ZnCl₂·TEEDA),³⁶ Pd(PPh₃)₄,⁵¹ and Pd₂(dba)₃·CHCl₃⁵² were used in the following experiments.

3. Preparation of THF solutions of LiTMP, LiCl, and CuCN·2LiCl

3.1 Preparation of a THF solution of LiTMP⁵³

To a solution of TMPH (0.60 mL, 3.5 mmol) in THF (2.4 mL) was added *n*-BuLi (2.30 mL, 1.52 M in *n*-hexane, 3.5 mmol) dropwise at $-78\text{ }^{\circ}\text{C}$. The resulting solution was stirred at $0\text{ }^{\circ}\text{C}$ for 30 min to provide a THF solution of LiTMP (0.66 M).

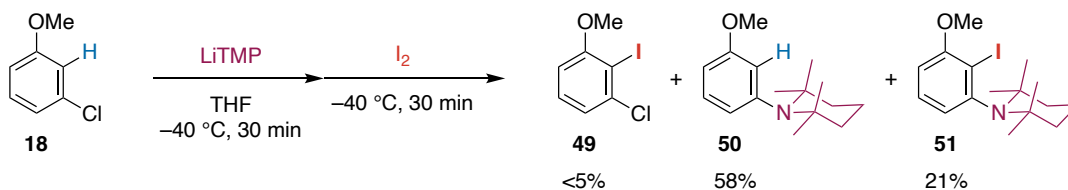
3.2 Preparation of a THF solution of LiCl⁵⁴

Commercially available LiCl (1.27 g, 30 mmol) was heated with a heat gun under vacuum for 15 min in a Schlenk tube. After cooling to room temperature, THF (60 mL) was added to the Schlenk tube and the mixture was stirred at room temperature for 3 h to provide a THF solution of LiCl (0.50 M).

3.3 Preparation of a THF solution of CuCN·2LiCl⁴⁸

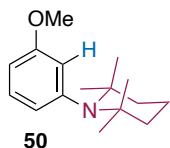
Commercially available LiCl (1.71 g, 40 mmol) was heated with a heat gun under vacuum for 15 min in a Schlenk tube. After cooling to room temperature, anhydrous CuCN (1.79 g, 20 mmol) and THF (20 mL) was added to the Schlenk tube. The mixture was stirred at room temperature for 3 h to provide a THF solution of CuCN·2LiCl (1.0 M).

4. Deprotonative functionalization of chloroarene (Scheme 2-3-1)



A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (42.8 mg, 0.300 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to $-40\text{ }^{\circ}\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^{\circ}\text{C}$ for 30 min, the reaction mixture was treated with iodine (166.4 mg, 0.656 mmol, 2.2 equiv). After stirring at $-40\text{ }^{\circ}\text{C}$ for 30 min, the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 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 brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 1-chloro-2-iodo-3-methoxybenzene (**49**), 1-(3-methoxyphenyl)-2,2,6,6-tetramethylpiperidine (**50**), and 1-(2-iodo-3-methoxyphenyl)-2,2,6,6-tetramethylpiperidine (**51**)³⁸ were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for

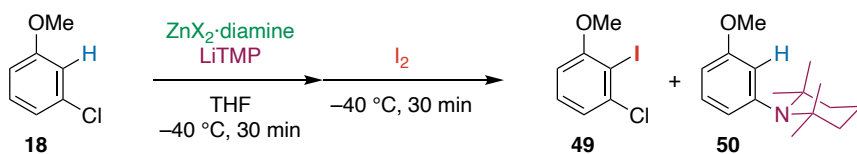
the peaks observed at 3.91 ppm (3 protons for **49**), 1.02 ppm (12 protons for **50**), and 0.91 ppm (6 protons for **51**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.



1-(3-Methoxyphenyl)-2,2,6,6-tetramethylpiperidine (**50**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (42.0 mg, 0.295 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to $-40\text{ }^{\circ}\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^{\circ}\text{C}$ for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 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 brine (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/diethyl ether = 20:1) to provide 1-(3-methoxyphenyl)-2,2,6,6-tetramethylpiperidine (**50**) as a pale yellow oil (46.5 mg, 0.188 mmol, 64%), whose ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁵⁵ R_f = 0.38 (hexane/diethyl ether = 20:1); IR (ATR, cm^{-1}): 2970, 2930, 1592, 1580, 1482, 1285, 1245, 1154, 1133, 1045, 766, 710; ^1H NMR (400 MHz, CDCl_3): δ 7.18–7.13 (m, 1H), 6.84–6.80 (m, 1H), 6.79–6.75 (m, 2H), 3.79 (s, 3H), 1.75–1.69 (m, 2H), 1.57–1.54 (m, 4H), 1.03 (s, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 159.1, 148.3, 127.9, 126.7, 120.3, 110.8, 55.3, 54.2, 42.5, 29.9 (br), 18.5; HRMS (DART⁺) m/z : calcd. for $\text{C}_{16}\text{H}_{26}\text{NO}$, 248.2014 $[\text{M}+\text{H}]^+$; found 248.2010.

5 Effect of reaction temperature on the in situ transmetalation of chlorophenyllithium (Table 2-3-1)



5.1 General procedure for the synthesis of 1-chloro-2-iodo-3-methoxybenzene (**49**) (Table 2-3-1, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (43.0 mg, 0.302

mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.3 mg, 0.302 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution was cooled to $-40\text{ }^\circ\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was treated with iodine (156.7 mg, 0.617 mmol, 2.0 equiv). After stirring at $-40\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 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 brine (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) to provide 1-chloro-2-iodo-3-methoxybenzene (**49**) as a pale yellow solid (77.6 mg, 0.289 mmol, 96%), whose ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁵⁶ R_f = 0.28 (hexane); Mp $50\text{--}51\text{ }^\circ\text{C}$; IR (ATR, cm^{-1}): 1572, 1458, 1428, 1285, 1262, 1046, 1017, 850, 767, 697; ^1H NMR (400 MHz, CDCl_3): δ 7.24 (dd, 1H, J = 8.4, 8.0 Hz), 7.10 (dd, 1H, J = 8.0, 1.2 Hz), 6.69 (dd, 1H, J = 8.4, 1.2 Hz), 3.90 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 160.1, 140.0, 129.9, 122.0, 108.6, 91.4, 56.9; HRMS (DART⁺) m/z : calcd. for $\text{C}_7\text{H}_7^{35}\text{ClIO}$, 268.9230 $[\text{M}+\text{H}]^+$; found 268.9224.

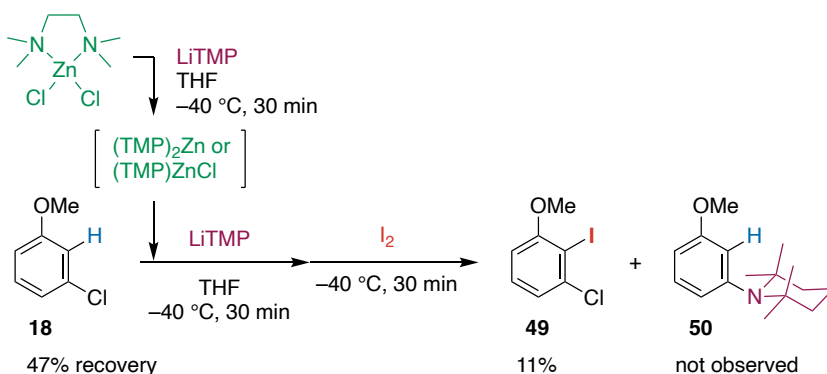
Scale-up synthesis of 1-chloro-2-iodo-3-methoxybenzene (**49**) (Table 2-3-1, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (427.0 mg, 2.99 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (758.7 mg, 3.00 mmol, 1.0 equiv), and THF (20.0 mL). The resulting solution was cooled to $-40\text{ }^\circ\text{C}$. LiTMP (0.66 M, 8.1 mL, 5.3 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was treated with iodine (1.525 g, 6.01 mmol, 2.0 equiv). After stirring at $-40\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was treated with saturated aqueous sodium thiosulfate (30 mL) and saturated aqueous ammonium chloride (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with brine (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) to provide 1-chloro-2-iodo-3-methoxybenzene (**49**) as a pale yellow solid (734.6 mg, 2.74 mmol, 92%).

Other experiments (Table 2-3-1, entries 2–6) were performed using the corresponding zinc halide diamine complex according to the general procedure. The yields of 1-chloro-2-iodo-3-methoxybenzene (**49**) and 1-(3-methoxyphenyl)-2,2,6,6-tetramethylpiperidine

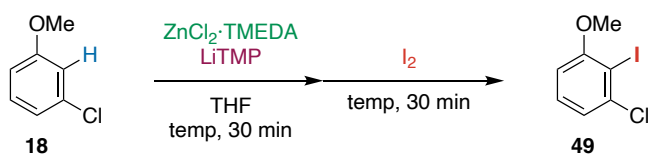
(**50**) were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peaks observed at 3.90 ppm (3 protons for **49**) and 3.79 ppm (3 protons for **50**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

5.2 Control experiment with zinc amides generated from LiTMP and $\text{ZnCl}_2\cdot\text{TMEDA}$ (Table 2-3-1, entry 7)



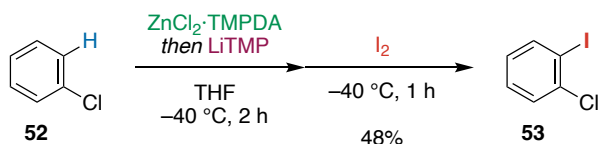
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.3 mg, 0.302 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to $-40\text{ }^\circ\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was treated with 3-chloroanisole (**18**) (43.1 mg, 0.302 mmol, 1.0 equiv). After stirring at $-40\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was treated with iodine (177.7 mg, 0.700 mmol, 2.3 equiv). After stirring at $-40\text{ }^\circ\text{C}$ for 30 min, the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 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 brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 1-chloro-2-iodo-3-methoxybenzene (**49**) and 3-chloroanisole (**18**) were determined to be 11% and 47% by ^1H NMR analysis using 1,1,2,2-tetrachloroethane (20.3 mg, 0.121 mmol) as an internal standard by comparing relative values of integration for the peak observed at 3.90 ppm (3 protons for **49**) and 3.80 ppm (3 protons for **18**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

5.3 Effect of reaction temperature on the in situ transmetalation of chlorophenyllithium (Table 2-3-2)



The experiments (Table 2-3-2, entries 1–3) were performed using $\text{ZnCl}_2\cdot\text{TMEDA}$ according to the general procedure at corresponding reaction temperature. The yields of 1-chloro-2-iodo-3-methoxybenzene (**49**) and 3-chloroanisole (**18**) 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 3.90 ppm (3 protons for **49**) and 3.80 ppm (3 protons for **18**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

6. Deprotonative functionalization of chlorobenzene through *in situ* transmetalation (Table 2-3-2)

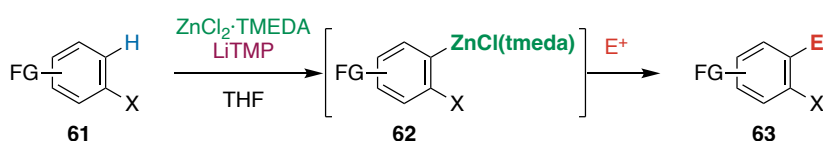


1-Chloro-2-iodobenzene (**53**) (Table 2-3-2, entry 6)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with chlorobenzene (**52**) (113.0 mg, 1.00 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMPDA}$ (267.1 mg, 1.00 mmol, 1.0 equiv), and THF (6.4 mL). The resulting solution was cooled to $-40\text{ }^\circ\text{C}$. LiTMP (0.66 M, 2.7 mL, 1.8 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^\circ\text{C}$ for 2 h, the reaction mixture was treated with iodine (508.6 mg, 2.00 mmol, 2.0 equiv). After stirring at $-40\text{ }^\circ\text{C}$ for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous ammonium chloride (3 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (4 mL) three times. The combined organic extracts were washed with brine (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 (hexane) to provide 1-chloro-2-iodobenzene (**53**) as a yellow oil (114.9 mg, 0.482 mmol, 48%), whose ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁵⁷ $R_f = 0.60$ (hexane); IR (ATR, cm^{-1}): 2924, 1448, 1428, 1013, 747; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (dd, 1H, $J = 8.0, 1.6$ Hz), 7.45 (dd, 1H, $J = 8.0, 1.6$ Hz), 7.29 (ddd, 1H, $J = 8.0, 8.0, 1.6$ Hz), 6.96 (ddd, 1H, $J = 8.0, 8.0, 1.6$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 140.4, 138.6, 129.6, 128.0, 98.3 (one signal is missing due to overlap); HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_4^{35}\text{ClI}$, 237.9046 $[\text{M}]^+$; found 237.9042.

Other experiments (Table 2-3-3, entries 1–5) were performed using the corresponding zinc halide diamine complex and reaction time according to the reaction conditions shown in Table 2-3-3. The yield of 1-chloro-2-iodobenzene (**53**) was determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard by comparing relative values of integration for the peak observed at 7.45 ppm (1 proton for **53**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

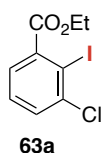
7. Scope of the *in situ* transmetalation and electrophilic functionalization (Table 2-4-1)



7.1 Reaction of haloarylzinc species with iodine (Table 2-4-1a)

General procedure

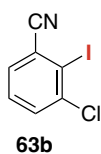
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with haloarene **61** (0.30 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{diamine}$ (0.30 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution was cooled to the reaction temperature ($-40\text{ }^\circ\text{C}$ or $0\text{ }^\circ\text{C}$). LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at the reaction temperature for 1 h, the reaction mixture was treated with iodine (0.6 mmol, 2 equiv). After stirring at the reaction temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 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 brine (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 to provide the corresponding iodinated haloarene **63**.



Ethyl 3-chloro-2-iodobenzoate (**63a**)

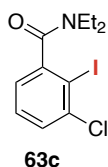
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) to provide the title compound **63a** as a pale yellow oil (61.8 mg, 0.199 mmol, 66%) from ethyl 3-chlorobenzoate (**61a**) (55.5 mg, 0.302 mmol, 1.0 equiv),

ZnCl₂·TMEDA (76.3 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (155.5 mg, 0.613 mmol, 2.0 equiv) according to the general procedure at -40 °C. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.⁵⁸ R_f = 0.40 (hexane/diethyl ether = 5:1); IR (ATR, cm⁻¹): 1730, 1400, 1284, 1249, 1194, 1150, 1020, 759, 732; ¹H NMR (400 MHz, CDCl₃): δ 7.56 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.44 (dd, 1H, *J* = 7.6, 1.6 Hz), 7.33 (dd, 1H, *J* = 8.0, 7.6 Hz), 4.41 (q, 2H, *J* = 7.2 Hz), 1.42 (t, 3H, *J* = 7.2 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 167.4, 140.80, 140.77, 131.3, 129.2, 127.5, 98.1, 62.3, 14.3; HRMS (DART⁺) *m/z*: calcd. for C₉H₉³⁵ClIO₂, 310.9336 [M+H]⁺; found 310.9341.



3-Chloro-2-iodobenzonitrile (63b)

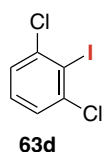
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 5:1) to provide the title compound **63b** as a colorless solid (60.8 mg, 0.231 mmol, 76%) from 3-chlorobenzonitrile (**61b**) (41.8 mg, 0.304 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.2 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (178.2 mg, 0.702 mmol, 2.3 equiv) according to the general procedure at 0 °C. R_f = 0.30 (hexane/diethyl ether = 5:1); Mp 119–120 °C; IR (ATR, cm⁻¹): 2227, 1439, 1399, 1263, 1178, 1147, 1026, 840, 785, 694; ¹H NMR (400 MHz, CDCl₃): δ 7.65 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.50 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.41 (dd, 1H, *J* = 8.0, 8.0 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 141.1, 133.1, 132.4, 129.8, 123.4, 119.3, 103.4; HRMS (DART⁺) *m/z*: calcd. for C₇H₄³⁵ClIN, 263.9077 [M+H]⁺; found 263.9082.



3-Chloro-2-iodo-*N,N*-diethylbenzamide (63c)

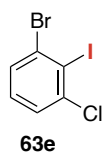
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 1:1) to provide the title compound **63c** as a colorless solid (79.0 mg, 0.234 mmol, 78%) from 3-chloro-*N,N*-diethylbenzamide (**61c**) (63.7 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (77.0 mg, 0.305 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (171.6 mg, 0.676 mmol, 2.2 equiv) according to the general

procedure at $-40\text{ }^{\circ}\text{C}$. $R_f = 0.17$ (hexane/diethyl ether = 1:1); Mp $71\text{--}73\text{ }^{\circ}\text{C}$; IR (ATR, cm^{-1}): 1633, 1427, 1289, 790, 741, 639; ^1H NMR (400 MHz, CDCl_3): δ 7.44 (dd, 1H, $J = 8.0, 1.6\text{ Hz}$), 7.32 (dd, 1H, $J = 8.0, 7.6\text{ Hz}$), 7.06 (dd, 1H, $J = 7.6, 1.6\text{ Hz}$), 3.87 (dq, 1H, $J = 13.6, 7.2\text{ Hz}$), 3.29 (dq, 1H, $J = 14.0, 7.2\text{ Hz}$), 3.21–3.05 (m, 2H), 1.29 (t, 3H, $J = 7.2\text{ Hz}$), 1.08 (t, 3H, $J = 7.2\text{ Hz}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 169.7, 146.0, 139.9, 129.7, 129.1, 124.7, 97.5, 42.9, 39.1, 14.0, 12.4; HRMS (DART $^+$) m/z : calcd. for $\text{C}_{11}\text{H}_{14}^{35}\text{ClINO}$, 337.9809 $[\text{M}+\text{H}]^+$; found 337.9799.



1,3-Dichloro-2-iodobenzene (63d)

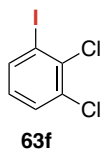
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63d** as a colorless solid (69.9 mg, 0.256 mmol, 86%) from 1,3-dichlorobenzene (**61d**) (44.0 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (164.5 mg, 0.648 mmol, 2.2 equiv) according to the general procedure at $0\text{ }^{\circ}\text{C}$. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁵⁹ $R_f = 0.57$ (hexane); Mp $60\text{--}61\text{ }^{\circ}\text{C}$; IR (ATR, cm^{-1}): 1423, 1186, 1027, 772, 758, 686; ^1H NMR (400 MHz, CDCl_3): δ 7.34 (d, 2H, $J = 8.0\text{ Hz}$), 7.24–7.20 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 140.8, 129.8, 127.4, 103.9; HRMS (EI $^+$) m/z : calcd. for $\text{C}_6\text{H}_3^{35}\text{Cl}_2\text{I}$, 271.8657 $[\text{M}]^+$; found 271.8659.



1-Bromo-3-chloro-2-iodobenzene (63e)

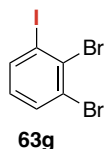
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63e** as a pale yellow solid (82.6 mg, 0.260 mmol, 86%) from 1-bromo-3-chlorobenzene (**61e**) (58.2 mg, 0.304 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.7 mg, 0.304 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (167.3 mg, 0.659 mmol, 2.2 equiv) according to the general procedure at $-40\text{ }^{\circ}\text{C}$. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶⁰ $R_f = 0.63$ (hexane); Mp $68\text{--}70\text{ }^{\circ}\text{C}$; IR (ATR, cm^{-1}): 1552, 1421, 1391, 1184, 772, 756, 683; ^1H NMR (400 MHz, CDCl_3): δ 7.52 (dd, 1H, $J = 8.0, 1.2\text{ Hz}$), 7.38 (dd, 1H, $J = 8.4,$

1.2 Hz), 7.15 (dd, 1H, $J = 8.4, 8.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 140.5, 131.8, 130.8, 130.2, 127.8, 106.8; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{35}\text{Cl}^{79}\text{BrI}$, 315.8151 $[\text{M}]^+$; found 315.8143.



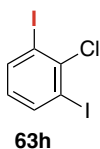
1,2-Dichloro-3-iodobenzene (63f)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63f** as a colorless solid (66.7 mg, 0.244 mmol, 82%) from 1,2-dichlorobenzene (**61f**) (44.0 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.2 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (161.1 mg, 0.635 mmol, 2.1 equiv) according to the general procedure at -40°C . The ^1H NMR spectroscopic data were identical to those reported in the literature.⁶¹ $R_f = 0.65$ (hexane); Mp $31\text{--}32^\circ\text{C}$; IR (ATR, cm^{-1}): 1553, 1426, 1401, 1153, 770, 748, 717, 692; ^1H NMR (400 MHz, CDCl_3): δ 7.77 (dd, 1H, $J = 8.0, 1.6$ Hz), 7.45 (dd, 1H, $J = 8.0, 1.6$ Hz), 6.90 (dd, 1H, $J = 8.0, 8.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 138.7, 136.9, 132.7, 130.5, 128.7, 99.4; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{35}\text{Cl}_2\text{I}$, 271.8657 $[\text{M}]^+$; found 271.8649.



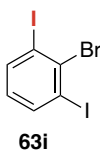
1,2-Dibromo-3-iodobenzene (63g)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63g** as a colorless solid (79.7 mg, 0.220 mmol, 75%) from 1,2-dibromobenzene (**61g**) (74.6 mg, 0.294 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.2 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (155.1 mg, 0.611 mmol, 2.1 equiv) according to the general procedure at -40°C . The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶² $R_f = 0.66$ (hexane); Mp $74\text{--}76^\circ\text{C}$; IR (ATR, cm^{-1}): 1546, 1420, 1386, 1200, 767, 708, 682; ^1H NMR (400 MHz, CDCl_3): δ 7.82 (dd, 1H, $J = 8.0, 1.2$ Hz), 7.61 (dd, 1H, $J = 8.0, 1.2$ Hz), 6.85 (dd, 1H, $J = 8.0, 8.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 139.4, 133.5, 132.0, 129.7, 124.6, 102.3; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{79}\text{Br}_2\text{I}$, 359.7646 $[\text{M}]^+$; found 359.7639.



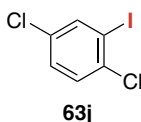
2-Chloro-1,3-diiodobenzene (**63h**)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63h** as a colorless solid (99.1 mg, 0.272 mmol, 90%) from 1-chloro-2-iodobenzene (**61h**) (72.3 mg, 0.303 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.9 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (153.3 mg, 0.604 mmol, 2.0 equiv) according to the general procedure at $-40\text{ }^\circ\text{C}$. $R_f = 0.60$ (hexane); Mp $62\text{--}63\text{ }^\circ\text{C}$; IR (ATR, cm^{-1}): 1543, 1420, 1390, 1262, 1202, 1134, 1097, 1060, 1019, 803, 765, 688; ^1H NMR (400 MHz, CDCl_3): δ 7.85 (d, 2H, $J = 8.0$ Hz), 6.60 (t, 1H, $J = 8.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 141.9, 140.5, 129.3, 97.1; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{35}\text{ClI}_2$, 363.8013 $[\text{M}]^+$; found 363.8016.



2-Bromo-1,3-diiodobenzene (**63i**)

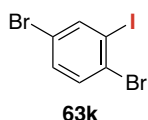
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63i** as a colorless solid (116.9 mg, 0.241 mmol, 80%) from 1-bromo-2-iodobenzene (**61i**) (85.5 mg, 0.302 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.0 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (173.0 mg, 0.682 mmol, 2.3 equiv) according to the general procedure at $-40\text{ }^\circ\text{C}$. $R_f = 0.58$ (hexane); Mp $82\text{--}84\text{ }^\circ\text{C}$; IR (ATR, cm^{-1}): 1541, 1417, 1383, 1199, 1133, 765, 687, 679; ^1H NMR (400 MHz, CDCl_3): δ 7.85 (d, 2H, $J = 8.0$ Hz), 6.63 (t, 1H, $J = 8.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 140.3, 136.2, 129.9, 100.3; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{79}\text{BrI}_2$, 407.7508 $[\text{M}]^+$; found 407.7510.



1,4-Dichloro-2-iodobenzene (**63j**)

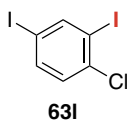
A crude product was purified by silica gel column chromatography (hexane) to provide

the title compound **63j** as a yellow oil (77.3 mg, 0.283 mmol, 95%) from 1,4-dichlorobenzene (**61j**) (43.8 mg, 0.298 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.8 mg, 0.304 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (157.0 mg, 0.619 mmol, 2.1 equiv) according to the general procedure at 0 °C. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶³ $R_f = 0.73$ (hexane); IR (ATR, cm^{-1}): 1563, 1447, 1361, 1107, 1095, 1018, 871, 811, 778, 654; ^1H NMR (400 MHz, CDCl_3): δ 7.84 (d, 1H, $J = 2.4$ Hz), 7.36 (d, 1H, $J = 8.8$ Hz), 7.27 (dd, 1H, $J = 8.8, 2.4$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 139.6, 137.2, 132.9, 129.9, 129.7, 98.5; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{35}\text{Cl}_2\text{I}$, 271.8657 $[\text{M}]^+$; found 271.8652.



1,4-Dibromo-2-iodobenzene (**63k**)

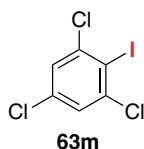
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63k** as a colorless solid (104.6 mg, 0.291 mmol, 98%) from 1,4-dibromobenzene (**61k**) (70.4 mg, 0.298 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (90.9 mg, 0.360 mmol, 1.2 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (162.3 mg, 0.639 mmol, 2.1 equiv) according to the general procedure at -40 °C. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶⁴ $R_f = 0.72$ (hexane); Mp 35–36 °C; IR (ATR, cm^{-1}): 1548, 1437, 1355, 1098, 1080, 1003, 869, 807, 742; ^1H NMR (400 MHz, CDCl_3): δ 7.99 (d, 1H, $J = 2.4$ Hz), 7.47 (d, 1H, $J = 8.4$ Hz), 7.33 (dd, 1H, $J = 8.4, 2.4$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 142.4, 133.7, 132.7, 128.8, 121.3, 102.2; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{79}\text{Br}_2\text{I}$, 359.7646 $[\text{M}]^+$; found 359.7645.



1-Chloro-2,4-diiodobenzene (**63l**)

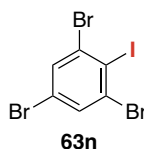
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63l** as a colorless oil (100.8 mg, 0.277 mmol, 93%) from 1-chloro-4-iodobenzene (**61l**) (71.2 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMPDA}$ (80.3 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (154.3 mg, 0.608 mmol, 2.0 equiv) according to the general procedure at 0 °C. The ^1H NMR

spectroscopic data were identical to those reported in the literature.⁶⁵ R_f = 0.62 (hexane); IR (ATR, cm^{-1}): 1548, 1440, 1353, 1114, 1009, 871, 808, 745, 648; ^1H NMR (400 MHz, CDCl_3): δ 8.18 (d, 1H, J = 2.0 Hz), 7.58 (dd, 1H, J = 8.4, 2.0 Hz), 7.17 (d, 1H, J = 8.4 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 147.8, 138.7, 138.5, 130.8, 99.6, 91.7; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3^{35}\text{ClI}_2$, 363.8013 $[\text{M}]^+$; found 363.8018.



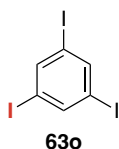
1,3,5-Trichloro-2-iodobenzene (**63m**)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63m** as a colorless solid (83.3 mg, 0.272 mmol, 90%) from 1,3,5-trichlorobenzene (**61m**) (54.5 mg, 0.303 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.50 mL, 0.33 mmol, 1.1 equiv), and iodine (153.7 mg, 0.606 mmol, 2.0 equiv) according to the general procedure at -40°C . The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶⁶ R_f = 0.72 (hexane); Mp $48\text{--}50^\circ\text{C}$; IR (ATR, cm^{-1}): 1552, 1539, 1388, 1365, 1179, 1116, 1098, 865, 852, 821, 800; ^1H NMR (400 MHz, CDCl_3): δ 7.37 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 141.3, 135.3, 127.4, 101.8; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_2^{35}\text{Cl}_3\text{I}$, 305.8267 $[\text{M}]^+$; found 305.8273.



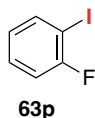
1,3,5-Tribromo-2-iodobenzene (**63n**)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63n** as a brown solid (103.6 mg, 0.235 mmol, 78%) from 1,3,5-tribromobenzene (**61n**) (94.8 mg, 0.301 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.2 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (161.7 mg, 0.637 mmol, 2.1 equiv) according to the general procedure at -40°C . The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶⁷ R_f = 0.70 (hexane); Mp $90\text{--}92^\circ\text{C}$; IR (ATR, cm^{-1}): 1540, 1529, 1396, 1375, 1348, 1112, 858, 760, 734, 671, 612; ^1H NMR (400 MHz, CDCl_3): δ 7.71 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 133.7, 132.0, 123.1, 108.2; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_2^{79}\text{Br}_3\text{I}$, 437.6751 $[\text{M}]^+$; found 437.6744.



1,3,5-Triiodobenzene (63o)

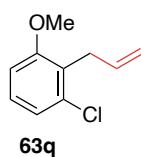
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63o** as a colorless solid (52.0 mg, 0.114 mmol, 38%) from 1,3-diiodobenzene (**61o**) (99.6 mg, 0.302 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (154.5 mg, 0.609 mmol, 2.0 equiv) according to the general procedure at $-40\text{ }^\circ\text{C}$. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶⁸ R_f = 0.58 (hexane); Mp $173\text{--}174\text{ }^\circ\text{C}$; IR (ATR, cm^{-1}): 3078, 3045, 1532, 1395, 1100, 846, 701, 657; ^1H NMR (400 MHz, CDCl_3): δ 8.00 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 144.6, 95.4; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3\text{I}_3$, 455.7369 $[\text{M}]^+$; found 455.7368.



1-Fluoro-2-iodobenzene (63p)

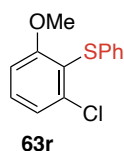
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **63p** as a pale yellow oil (171.0 mg, 0.771 mmol, 76%) from fluorobenzene (**61p**) (97.0 mg, 1.01 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMPDA}$ (266.9 mg, 1.00 mmol, 1.0 equiv), LiTMP (0.66 M, 2.70 mL, 1.8 mmol, 1.8 equiv), and iodine (510.5 mg, 2.01 mmol, 2.0 equiv) according to the general procedure at $-40\text{ }^\circ\text{C}$ for 2 h. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.⁶⁹ R_f = 0.63 (hexane); IR (ATR, cm^{-1}): 1581, 1471, 1442, 1259, 1231, 1040, 1021, 818, 750, 641; ^1H NMR (400 MHz, CDCl_3): δ 7.78–7.73 (m, 1H), 7.35–7.28 (m, 1H), 7.09–7.04 (m, 1H), 6.93–6.88 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 161.8 (d, $^1J_{\text{C-F}}$ = 244 Hz), 139.6, 130.2 (d, $^3J_{\text{C-F}}$ = 6.7 Hz), 125.9 (d, $^3J_{\text{C-F}}$ = 3.9 Hz), 115.9 (d, $^2J_{\text{C-F}}$ = 23.0 Hz), 81.4 (d, $^2J_{\text{C-F}}$ = 24.9 Hz); HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_4\text{FI}$, 221.9342 $[\text{M}]^+$; found 221.9339.

7.2 Reaction of haloarylzinc species with various electrophiles (Table 2-4-1b)



1-Chloro-2-(2-propen-1-yl)-3-methoxybenzene (**63q**)

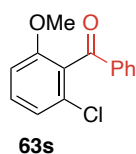
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (42.7 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.2 mg, 0.302 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution 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 30 min, the reaction mixture was treated with $\text{CuCN} \cdot 2\text{LiCl}$ ⁴⁸ (1.0 M in THF, 0.45 mL, 0.45 mmol, 1.5 equiv) and allyl iodide (41 μL , 0.45 mmol, 1.5 equiv). After stirring at room temperature for 2 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 washed with brine (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/diethyl ether = 10:1) to provide the title compound **63q** as a colorless oil (46.0 mg, 0.273 mmol, 91%). R_f = 0.73 (hexane/diethyl ether = 5:1); IR (ATR, cm^{-1}): 2935, 2928, 1591, 1579, 1463, 1436, 1264, 1219, 1047, 771, 731; ^1H NMR (400 MHz, CDCl_3): δ 7.12 (dd, 1H, J = 8.0, 8.0 Hz), 6.99 (dd, 1H, J = 8.0, 0.8 Hz), 6.78 (d, 1H, J = 8.0 Hz), 5.93 (ddt, 1H, J = 16.8, 10.8, 6.4 Hz), 5.04–4.98 (m, 2H), 3.83 (s, 3H), 3.56 (ddd, 2H, J = 6.4, 1.6, 1.6 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 158.5, 135.2, 127.6, 126.8, 121.8, 115.2, 109.1, 56.0, 31.2 (one signal is missing due to overlap); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CD_3CN): δ 159.4, 135.9, 135.3, 129.0, 127.0, 122.2, 115.6, 110.4, 56.6, 31.6; HRMS (DART⁺) m/z : calcd. for $\text{C}_{10}\text{H}_{12}^{35}\text{ClO}$, 183.0577 [$\text{M}+\text{H}$]⁺; found 183.0576.



1-Chloro-2-(phenylthio)-3-methoxybenzene (**63r**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (43.3 mg, 0.304 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.2 mg, 0.302 mmol, 1.0 equiv), and THF (2.0 mL). The resulting 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 30 min, the reaction

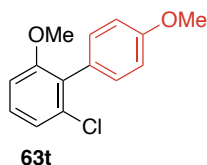
mixture was transferred to a mixture of *N*-phenylthiophthalimide⁴³ (81.6 mg, 0.320 mmol, 1.05 equiv) and copper(II) acetate monohydrate (3.5 mg, 18 μ mol, 6 mol%) in THF (1.0 mL). After stirring at room temperature for 17 h, the reaction mixture was treated with saturated aqueous ammonium chloride (2 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with brine (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/diethyl ether = 10:1) to provide the title compound **63r** as a colorless solid (42.1 mg, 0.168 mmol, 55%). R_f = 0.43 (hexane/diethyl ether = 5:1); Mp 78–80 °C; IR (ATR, cm^{-1}): 1574, 1459, 1429, 1265, 1038, 775, 738, 689; ^1H NMR (400 MHz, CDCl_3): δ 7.32 (dd, 1H, J = 8.4, 8.4 Hz), 7.23–7.14 (m, 3H), 7.13–7.07 (m, 3H), 6.88 (dd, 1H, J = 8.4, 1.2 Hz), 3.81 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 161.8, 141.5, 136.8, 131.1, 128.9, 127.1, 125.5, 122.6, 120.1, 110.0, 56.6; HRMS (DART⁺) m/z : calcd. for $\text{C}_{13}\text{H}_{12}^{35}\text{ClOS}$, 251.0297 $[\text{M}+\text{H}]^+$; found 251.0293.



(2-Chloro-6-methoxyphenyl)-phenylmethanone (**63s**)

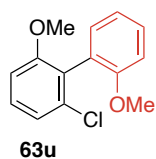
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (43.0 mg, 0.302 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution 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 30 min, the reaction mixture was treated with benzoyl chloride (52.0 μL , 0.447 mmol, 1.5 equiv), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.7 mg, 15.2 μmol , 5 mol%), and tris[4-(trifluoromethyl)phenyl]phosphine (14.2 mg, 30.5 μmol , 10 mol%). After stirring at 60 °C for 18 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 washed with brine (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/diethyl ether = 10:1) to afford the title compound **63s** as a pale yellow solid (57.7 mg, 0.234 mmol, 77%). R_f = 0.18 (hexane/diethyl ether = 5:1); Mp 63–65 °C; IR (ATR, cm^{-1}): 1676, 1590, 1574, 1462, 1432, 1267, 1040, 929, 858, 780, 706; ^1H NMR (400 MHz, CDCl_3): δ

7.86–7.82 (m, 2H), 7.59 (tt, 1H, $J = 7.6, 1.2$ Hz), 7.46 (dd, 2H, $J = 7.6, 7.6$ Hz), 7.35 (dd, 1H, $J = 8.0, 8.0$ Hz), 7.07–7.04 (m, 1H), 6.90 (d, 1H, $J = 8.0$ Hz), 3.73 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 194.1, 157.8, 136.7, 133.9, 131.6, 130.9, 129.6, 128.8, 128.4, 121.9, 109.6, 56.2; HRMS (DART $^+$) m/z : calcd. for $\text{C}_{14}\text{H}_{12}^{35}\text{ClO}_2$, 247.0526 $[\text{M}+\text{H}]^+$; found 247.0524.



2-Chloro-4',6-dimethoxy-1,1'-biphenyl (**63t**)

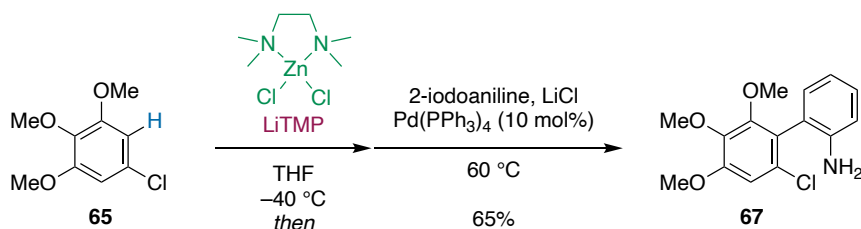
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (43.5 mg, 0.305 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.4 mg, 0.303 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution 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 30 min, the reaction mixture was treated with 4-iodoanisole (105.4 mg, 0.450 mmol, 1.48 equiv), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.8 mg, 15.3 μmol , 5 mol%), and tris(4-fluorophenyl)phosphine (10.1 mg, 31.9 μmol , 11 mol%). After stirring at 60 °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 washed with brine (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/diethyl ether = 10:1) to afford the title compound **63t** as a yellow oil (55.1 mg, 0.222 mmol, 73%). $R_f = 0.43$ (hexane/diethyl ether = 5:1); IR (ATR, cm^{-1}): 1612, 1588, 1517, 1462, 1433, 1291, 1245, 1177, 1040, 828, 779, 741; ^1H NMR (400 MHz, CDCl_3): δ 7.25–7.20 (m, 3H), 7.09 (dd, 1H, $J = 8.0, 1.2$ Hz), 7.00–6.96 (m, 2H), 6.87 (dd, 1H, $J = 8.0, 1.2$ Hz), 3.85 (s, 3H), 3.74 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 158.9, 158.3, 134.7, 131.5, 129.7, 128.7, 127.6, 121.9, 113.5, 109.4, 56.1, 55.2; HRMS (DART $^+$) m/z : calcd. for $\text{C}_{14}\text{H}_{14}^{35}\text{ClO}_2$, 249.0682 $[\text{M}+\text{H}]^+$; found 249.0680.



2-Chloro-2',6-dimethoxy-1,1'-biphenyl (63u)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloroanisole (**18**) (42.9 mg, 0.301 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.1 mg, 0.301 mmol, 1.0 equiv), and THF (2.0 mL). The resulting 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 30 min, the reaction mixture was treated with 2-iodoanisole (59.0 μL , 0.454 mmol, 1.5 equiv), LiCl (0.50 M in THF, 1.8 mL, 0.90 mmol, 3.0 equiv), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.3 mg, 14.8 μmol , 5 mol%), and tris(4-fluorophenyl)phosphine (9.5 mg, 30 μmol , 10 mol%). After stirring at 60°C for 20 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 washed with brine (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/diethyl ether = 10:1) to afford the title compound **63u** as a pale yellow solid (47.2 mg, 0.187 mmol, 62%). R_f = 0.43 (hexane/diethyl ether = 5:1); Mp $46\text{--}47^\circ\text{C}$; IR (ATR, cm^{-1}): 1464, 1458, 1430, 1256, 1235, 1044, 779, 755, 731; ^1H NMR (400 MHz, CDCl_3): δ 7.40–7.35 (m, 1H), 7.25 (dd, 1H, J = 8.4, 8.4 Hz), 7.14 (dd, 1H, J = 7.2, 1.6 Hz), 7.09 (dd, 1H, J = 8.4, 0.8 Hz), 7.06–6.99 (m, 2H), 6.88 (dd, 1H, J = 8.4, 0.8 Hz), 3.77 (s, 3H), 3.73 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 158.5, 157.2, 135.1, 131.6, 129.3, 129.0, 127.0, 124.8, 121.6, 120.5, 111.3, 109.4, 56.2, 55.9; HRMS (DART $^+$) m/z : calcd. for $\text{C}_{14}\text{H}_{14}^{35}\text{ClO}_2$, 249.0682 $[\text{M}+\text{H}]^+$; found 249.0691.

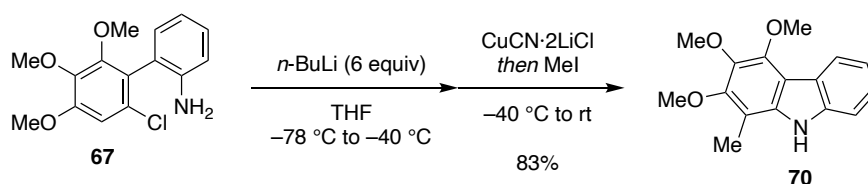
8. Total synthesis of carbazomycin A (Scheme 2-5-1)



6'-Chloro-2',3',4'-trimethoxy-[1,1'-biphenyl]-2-amine (67)

A flame-dried 500-mL two-necked flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock under argon was charged with 3,4,5-trimethoxychlorobenzene (**65**) (2.027 g, 10.0 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (2.526 g, 10.0 mmol, 1.0 equiv), and THF (60.0 mL). The resulting solution was cooled to -40°C . LiTMP (0.50 M, 20.0 mL, 40 mmol, 2.0 equiv) was added to the two-necked flask. After stirring at -40°C for 30 min, the reaction mixture was treated with LiCl (0.50 M in THF,

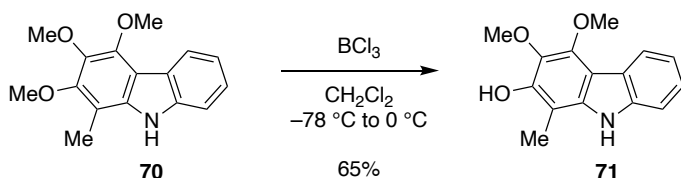
60.0 mL, 30 mmol, 3.0 equiv), 2-iodoaniline (2.193 g, 10.0 mmol, 1.0 equiv), and $\text{Pd(PPh}_3)_4$ (1.158 g, 1.00 mmol, 10 mol%). After stirring at 60 °C for 18 h, the reaction mixture was treated with saturated aqueous ammonium chloride (30 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with brine (50 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/acetone = 3:1) to afford the title compound **67** as a pale yellow solid (1.902 g, 6.47 mmol, 65%). R_f = 0.25 (hexane/acetone = 3:1); Mp 98–99 °C; IR (ATR, cm^{-1}): 3369, 2940, 1616, 1590, 1480, 1457, 1431, 1393, 1312, 1221, 1132, 1095, 1004, 833, 799, 750, 613; ^1H NMR (400 MHz, CDCl_3): δ 7.21 (ddd, 1H, J = 7.6, 7.6, 1.6 Hz), 7.02 (dd, 1H, J = 7.6, 1.6 Hz), 6.849 (s, 1H), 6.848 (ddd, 1H, J = 7.6, 7.6, 1.6 Hz), 6.80 (dd, 1H, J = 7.6, 1.6 Hz), 3.90 (s, 6H), 3.64 (s, 3H), 3.54 (brs, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 153.5, 152.9, 144.5, 141.8, 131.3, 129.2, 129.0, 124.9, 121.6, 118.5, 115.7, 109.2, 61.4, 61.3, 56.4; HRMS (DART $^+$) m/z : calcd. for $\text{C}_{15}\text{H}_{17}^{35}\text{ClNO}_3$, 294.0897 $[\text{M}+\text{H}]^+$; found 294.0893.



2,3,4-Trimethoxy-1-methyl-9H-carbazole (**70**)

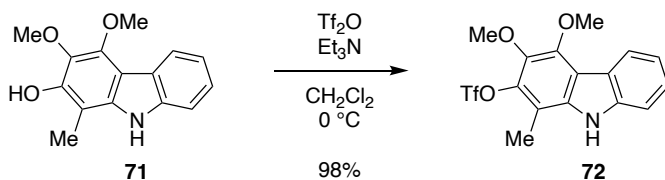
A flame-dried 300-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with biphenyl **67** (1.328 g, 4.52 mmol, 1.0 equiv) and THF (45.0 mL). The resulting solution was cooled to –78 °C. $n\text{-BuLi}$ (1.52 M in THF, 18.0 mL, 27.4 mmol, 6.1 equiv) was added to the Schlenk tube. After stirring at –40 °C for 1 h, the reaction mixture was treated with $\text{CuCN}\cdot 2\text{LiCl}$ (1.0 M in THF, 4.5 mL, 4.5 mmol, 1.0 equiv) and methyl iodide (1.40 mL, 22.5 mmol, 5.0 equiv). After warming to room temperature and stirring for 1 h, the reaction mixture was treated with saturated aqueous ammonium chloride (40 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (10 mL) three times. The combined organic extracts were washed with saturated aqueous ammonium chloride (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/diethyl ether = 4:1) to afford the title compound **70** as a colorless solid (1.022 g, 3.77 mmol, 83%). R_f = 0.27 (hexane/diethyl ether = 2:1); Mp 122–123 °C; IR (ATR, cm^{-1}): 3365, 2935, 1611, 1504, 1455, 1424, 1399, 1355, 1319, 1298, 1232, 1090, 1041, 1015, 982, 748; ^1H NMR

(400 MHz, CDCl₃): δ 8.21 (d, 1H, J = 8.0 Hz), 7.82 (brs, 1H), 7.43–7.39 (m, 1H), 7.36 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 7.21 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 4.13 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 2.41 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 151.0, 146.7, 140.0, 139.6, 135.8, 124.9, 122.9, 122.5, 119.7, 112.4, 110.3, 108.3, 61.7, 61.5, 61.0, 10.3; HRMS (DART⁺) m/z : calcd. for C₁₆H₁₈NO₃, 272.1287 [M+H]⁺; found 272.1285.



3,4-Dimethoxy-1-methyl-9H-carbazol-2-ol (**71**)

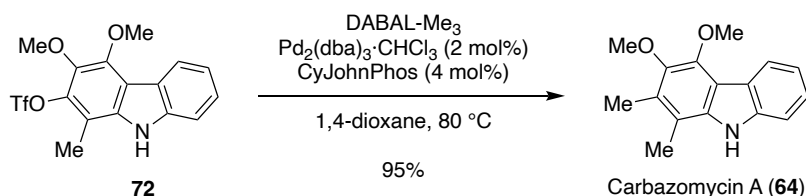
A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 1-methylcarbazole **70** (1.228 g, 4.53 mmol, 1.0 equiv) and CH₂Cl₂ (22.0 mL). The resulting solution was cooled to -78 °C. BCl₃ (1.0 M in CH₂Cl₂, 6.80 mL, 6.8 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 °C for 3 h, the reaction mixture was treated with water (5 mL). After being partitioned, the aqueous layer was extracted with CH₂Cl₂ (5 mL) three times. The combined organic extracts were washed with brine (10 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 = 1:1) to afford the title compound **71** as a colorless solid (760.4 mg, 2.96 mmol, 65%). R_f = 0.32 (hexane/diethyl ether = 1:1); Mp 128–130 °C; IR (ATR, cm⁻¹): 3431, 2937, 1616, 1517, 1456, 1409, 1341, 1320, 1297, 1251, 1167, 1150, 1079, 1036, 974, 881, 746, 640; ¹H NMR (400 MHz, CDCl₃): δ 8.15 (d, 1H, J = 8.0 Hz), 7.81 (brs, 1H), 7.40 (d, 1H, J = 8.0 Hz), 7.32 (ddd, 1H, J = 8.0, 8.0, 1.2 Hz), 7.20 (dd, 1H, J = 8.0, 8.0 Hz), 6.03 (s, 1H), 4.09 (s, 3H), 4.01 (s, 3H), 2.39 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 146.5, 145.4, 139.2, 136.6, 134.0, 124.3, 123.2, 121.9, 119.8, 110.2, 109.0, 100.4, 61.8, 60.7, 9.9; HRMS (DART⁺) m/z : calcd. for C₁₅H₁₆NO₃, 258.1130 [M+H]⁺; found 258.1137.



3,4-Dimethoxy-1-methyl-9H-carbazol-2-yl trifluoromethanesulfonate (**72**)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar

and a rubber septum under argon was charged with 2-hydroxylcarbazole **71** (731.9 mg, 2.84 mmol, 1.0 equiv), triethylamine (1.20 mL, 8.60 mmol, 3.0 equiv), and CH₂Cl₂ (28.0 mL). The resulting solution was cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.72 mL, 4.3 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 °C for 2 h, the reaction mixture was treated with water (5 mL). After being partitioned, the aqueous layer was extracted with dichloromethane (5 mL) three times. The combined organic extracts were washed with brine (10 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 = 3:1) to afford the title compound **72** as a pale brown solid (1.080 g, 2.77 mmol, 98%). *R_f* = 0.18 (hexane/diethyl ether = 3:1); Mp 87–88 °C; IR (ATR, cm⁻¹): 3444, 2944, 1506, 1456, 1415, 1313, 1246, 1211, 1136, 1059, 1038, 972, 887, 839, 751, 613; ¹H NMR (400 MHz, CDCl₃): δ 8.26 (d, 1H, *J* = 8.0 Hz), 7.99 (brs, 1H), 7.48–7.41 (m, 2H), 7.30–7.24 (m, 1H), 4.15 (s, 3H), 3.99 (s, 3H), 2.50 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 146.6, 140.2, 139.9, 138.1, 135.0, 126.3, 123.1, 122.2, 120.4, 118.8 (q, ¹*J*_{C-F} = 318 Hz), 115.8, 110.7, 108.6, 61.9, 60.9, 11.1; HRMS (DART⁺) *m/z*: calcd. for C₁₆H₁₅F₃NO₅S, 390.0623 [M+H]⁺; found 390.0613.



Carbazomycin A (**64**)

A flame-dried 300-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock under argon was charged with triflate **72** (2.415 g, 6.20 mmol, 1.0 equiv), bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct⁵⁰ (DABAL-Me₃) (1.594 g, 6.22 mmol, 1.0 equiv), Pd₂(dba)₃·CHCl₃ (128.6 mg, 0.124 mmol, 2.0 mol%), 2-(dicyclohexylphosphino)biphenyl⁷⁰ (Cy-JohnPhos) (87.7 mg, 0.250 mmol, 4.0 mol%), and anhydrous 1,4-dioxane (124 mL). After stirring at 80 °C for 4 h, the reaction mixture was treated with saturated aqueous ammonium chloride (30 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with brine (50 mL) five times, 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

afford carbazomycin A (**64**) as a pale yellow solid (1.505 g, 5.89 mmol, 95%), whose ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.^{45,71} $R_f = 0.25$ (hexane/diethyl ether = 3:1); Mp 131–132 °C; IR (ATR, cm^{-1}): 3417, 3351, 2935, 1612, 1501, 1455, 1396, 1318, 1293, 1166, 1149, 1089, 1052, 1014, 745; ^1H NMR (400 MHz, CDCl_3): δ 8.23 (d, 1H, $J = 8.0$ Hz), 7.82 (brs, 1H), 7.43–7.35 (m, 2H), 7.24–7.19 (m, 1H), 4.11 (s, 3H), 3.90 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 146.1, 144.6, 139.5, 136.5, 128.9, 125.2, 123.0, 122.6, 119.6, 114.5, 113.7, 110.4, 61.3, 60.7, 13.8, 12.8; HRMS (DART⁺) m/z : calcd. for $\text{C}_{16}\text{H}_{18}\text{NO}_2$, 256.1338 $[\text{M}+\text{H}]^+$; found 256.1348.

9. Tabular comparisons of NMR data of carbazomycin A

Table S1. Chemical shifts of ^1H NMR in CDCl_3 for natural and our synthetic carbazomycin A

Natural (100 MHz) ⁴⁵	Our Synthetic (400 MHz)	Δ
8.25 (dd, 1H, $J = 7.0, 2.0$ Hz)	8.23 (d, 1H, $J = 8.0$ Hz)	−0.02
7.89 (brs, 1H)	7.82 (brs, 1H)	−0.07
7.42–7.13 (m, 3H)	7.43–7.35 (m, 2H), 7.24–7.19 (m, 1H)	–
4.13 (s, 3H)	4.11 (s, 3H)	−0.02
3.92 (s, 3H)	3.90 (s, 3H)	−0.02
2.40 (s, 3H)	2.41 (s, 3H)	0.01
2.40 (s, 3H)	2.39 (s, 3H)	−0.01

Table S2. Chemical shifts of ^1H NMR in CDCl_3 for Knölker's and our synthetic carbazomycin A

Knölker's Synthetic (200 MHz) ⁷¹	Our Synthetic (400 MHz)	Δ
8.23 (dd, 1H, $J = 7.6, 0.5$ Hz)	8.23 (d, 1H, $J = 8.0$ Hz)	0.00
7.82 (brs, 1H)	7.82 (brs, 1H)	0.00
7.45–7.15 (m, 3H)	7.43–7.35 (m, 2H), 7.24–7.19 (m, 1H)	–
4.10 (s, 3H)	4.11 (s, 3H)	0.01
3.89 (s, 3H)	3.90 (s, 3H)	0.01
2.40 (s, 3H)	2.41 (s, 3H)	0.01
2.38 (s, 3H)	2.39 (s, 3H)	0.01

Table S3. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in CDCl_3 for natural and our synthetic carbazomycin A

Natural (25 MHz) ^{45b}	Our Synthetic (100 MHz)	Δ
145.9	146.1	0.2
144.4	144.6	0.2
139.4	139.5	0.1
136.4	136.5	0.1
128.7	128.9	0.2
125.0	125.2	0.2
122.8	123.0	0.2
122.5	122.6	0.1
119.4	119.6	0.2
114.4	114.5	0.1
113.5	113.7	0.2
110.3	110.4	0.1
61.1	61.3	0.2
60.5	60.7	0.2
13.6	13.8	0.2
12.6	12.8	0.2

Table S4. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in CDCl_3 for Knölker's and our synthetic carbazomycin A

Knölker's Synthetic (75 MHz) ⁷¹	Our Synthetic (100 MHz)	Δ
146.1	146.1	0.0
144.6	144.6	0.0
139.5	139.5	0.0
136.5	136.5	0.0
128.9	128.9	0.0
125.1	125.2	0.1
123.0	123.0	0.0
122.6	122.6	0.0
119.5	119.6	0.1
114.6	114.5	−0.1
113.5	113.7	0.2
110.3	110.4	0.1
61.1	61.3	0.2
60.5	60.7	0.2
13.6	13.8	0.2
12.6	12.8	0.2

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第三章

カルバゾマイシン A-D のグラムスケール合成

3-1 序論

第二章では、*in situ* トランスメタル化を用いたさまざまなハロベンゼン誘導体のオルト位選択的な官能基化について述べた。その有用性は天然物カルバゾマイシン A の短段階合成への応用によりさらに実証された。本章では、カルバゾマイシン A の合成に至る背景および合成戦略を概説したのち、鍵反応における反応条件の最適化および反応機構について詳述する。さらに、カルバゾマイシン A を合成中間体として活用し、メトキシ基の位置選択的変換を経て、カルバゾマイシン B-D の効率的な合成も達成した。

3-2 カルバゾマイシン A-D の代表的な合成例

カルバゾマイシン A-D は、1980 年代に中村らによって *Streptoverticillium ehimense* から単離および構造決定され、以下の生物活性を示すことが明らかにされた (Figure 3-2-1)^{45,72}。

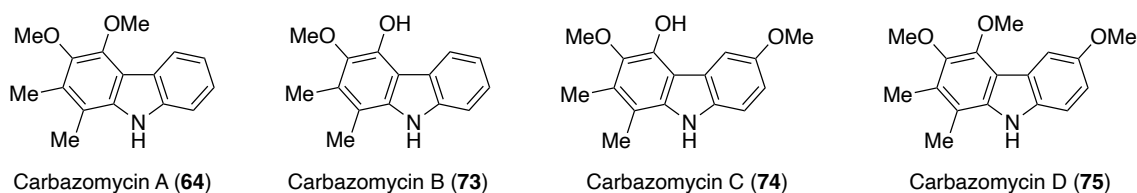
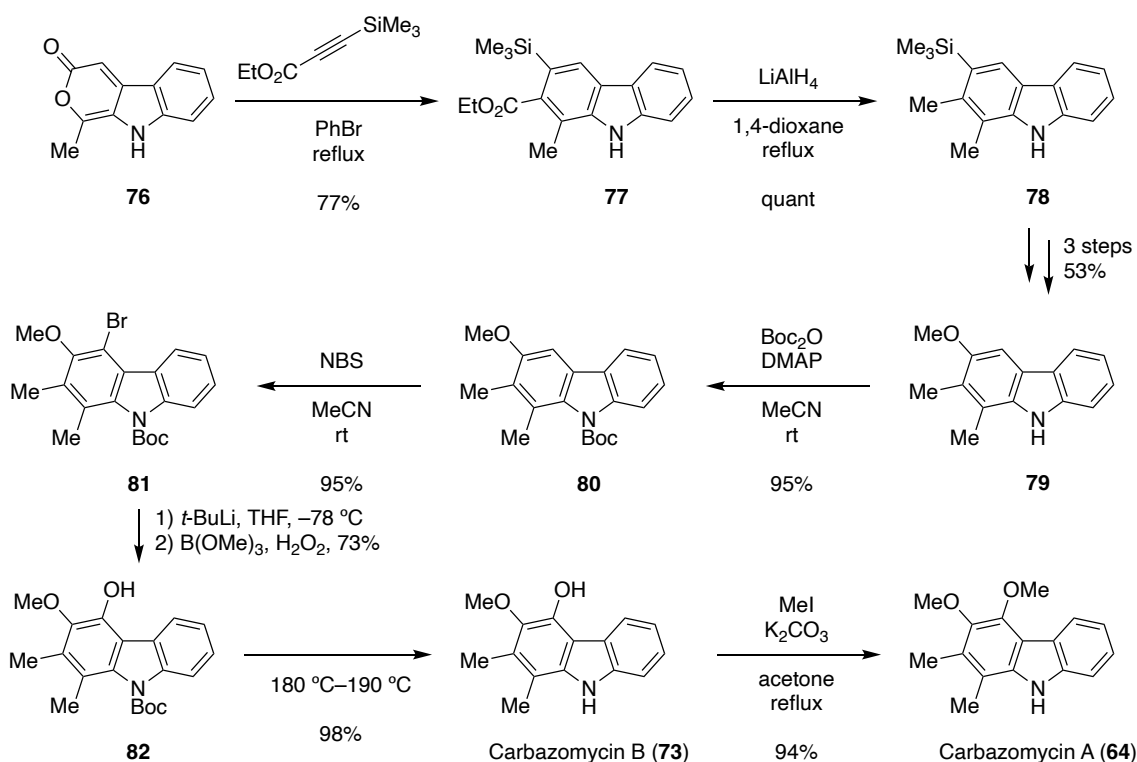


Figure 3-2-1. Structures of carbazomycins A-D

カルバゾマイシン A (64) と B (73) は、イネいもち病菌 *Pyricularia oryzae* の成長を抑制し、抗黄色ブドウ球菌活性および抗酵母活性を示す^{45a}。また、カルバゾマイシン A (64) と比較し、カルバゾマイシン B (73) がより強い抗酸化活性を有することが明らかとなっている⁷³。さらに、カルバマイシン B (73) と C (74) は、5-リポキシゲナーゼ阻害剤としても働くことが知られている⁷⁴。構造上の特徴として、カルバゾマイシン A-D は高度に非対称なカルバゾール構造を有している。すなわち、カルバゾール骨格の 2 つのベンゼン環のうち、片方はほぼ置換基が存在せず、もう一方は 4 つの置換基で占められ、全置換ベンゼン構造を形成している。これらの化合物は、カルバゾール構造を有する最初の抗生物質であり、ユニークな全置換ベンゼン構造を有していることから多くの合成化学者が合成研究に取り組み、現在までに 10 件以上の合成例が報告されている^{46,75,76,77}。

1989年にMoodyらは、カルバゾマイシンA (64) とB (73) の全合成を達成している (Scheme 3-2-1) ^{46b,75a}。ピラノインドール 76 とトリメチルシリルアセチレン誘導体の位置選択的 Diels–Alder 反応を用い、多置換カルバゾール 77 を収率 77%で合成している。反応の位置選択性は、かさ高いトリメチルシリル基によって制御されている。次に、水素化リチウムアルミニウムを作用させ、C-2 位のエステル基をメチル基に還元してカルバゾール 78 を定量的に得ている。その後、C-3 位のシリル基をメトキシ基に変換し、カルバゾール 79 を 3 工程、収率 53%で合成している。続いて、カルバゾール窒素原子を Boc 化して 80 を収率 95%で得たのち、NBS を作用させて位置選択的ブロモ化を行い、4-ブロモカルバゾール 81 を収率 95%で得ている。次に、ハロゲン–リチウム交換反応により生じたアリールリチウムをホウ素化したのち、酸化処理して 4-ヒドロキシカルバゾール 82 を収率 73%で合成している。最後に、Boc 基の熱分解によりカルバゾマイシン B (73) を収率 98%で合成し、さらに、ヒドロキシ基のメチル化によりカルバゾマイシン A (64) を収率 94%で合成している。

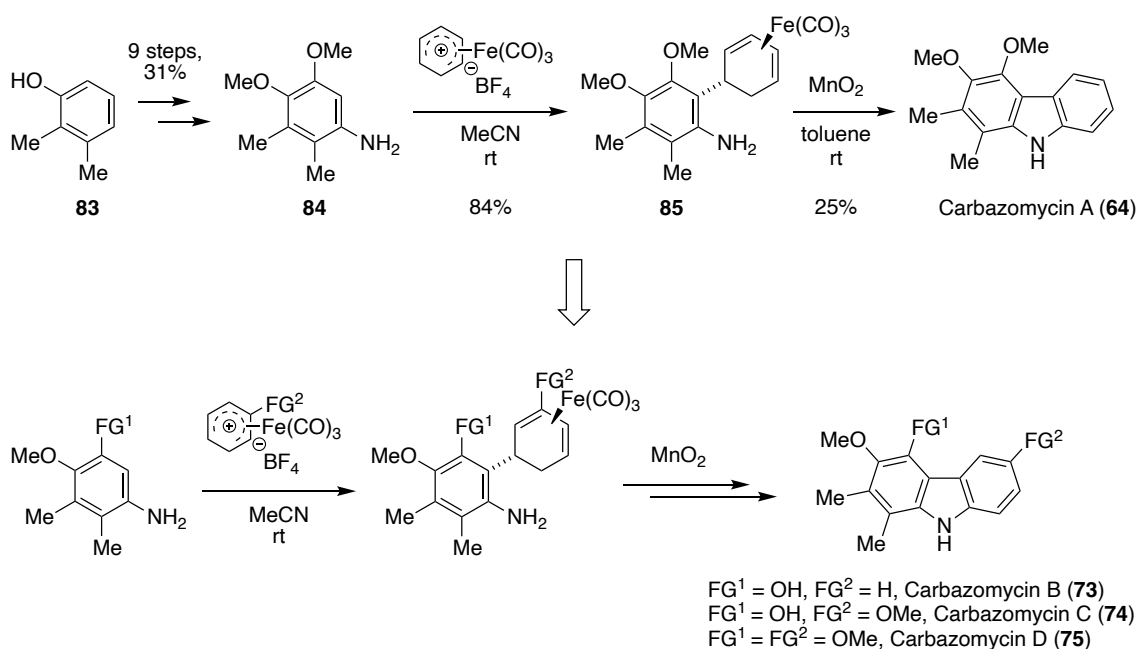


Scheme 3-2-1. Synthesis of carbazomycins A and B through regioselective Diels–Alder reaction

Argade^{46f}, 西田^{46g}, Witulski⁷⁶ⁱ および Parsons^{75b} らはいずれも、類似した合成戦略を採用している。すなわち、全置換ベンゼン骨格を構築したのちカルバゾマイ

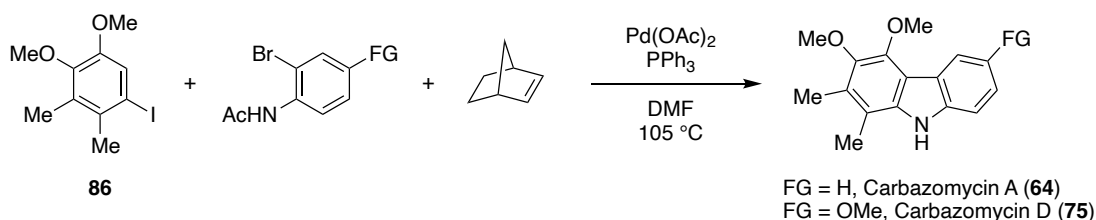
シン B を合成し、さらにメチル化によってカルバゾマイシン A へと誘導している。

1989 年に Knölker らも、トリカルボニル鉄配位シクロヘキサジエニリウムイオンを用いる独自のカルバゾール形成法を利用して、カルバゾマイシン A を全合成している (Scheme 3-2-2)^{46a}。ジメチルフェノール **83** を出発原料として、9 段階、総収率 31% で四置換アニリン **84** を合成している。その後、シクロヘキサジエニリウムイオンとの芳香族求電子置換反応により、トリカルボニル鉄シクロヘキサジエン錯体 **85** を収率 84% で得ている。最後に、二酸化マンガンを用いた酸化的環化反応により、カルバゾマイシン A (**64**) を収率 25% で全合成している。さらに、彼らは本手法を発展させ、**84** と類似の置換様式を有する四置換アニリンを用い、同様の求電子置換反応および酸化的環化反応を経て、カルバゾマイシン B–D^{46c,76} の全合成にも成功している。



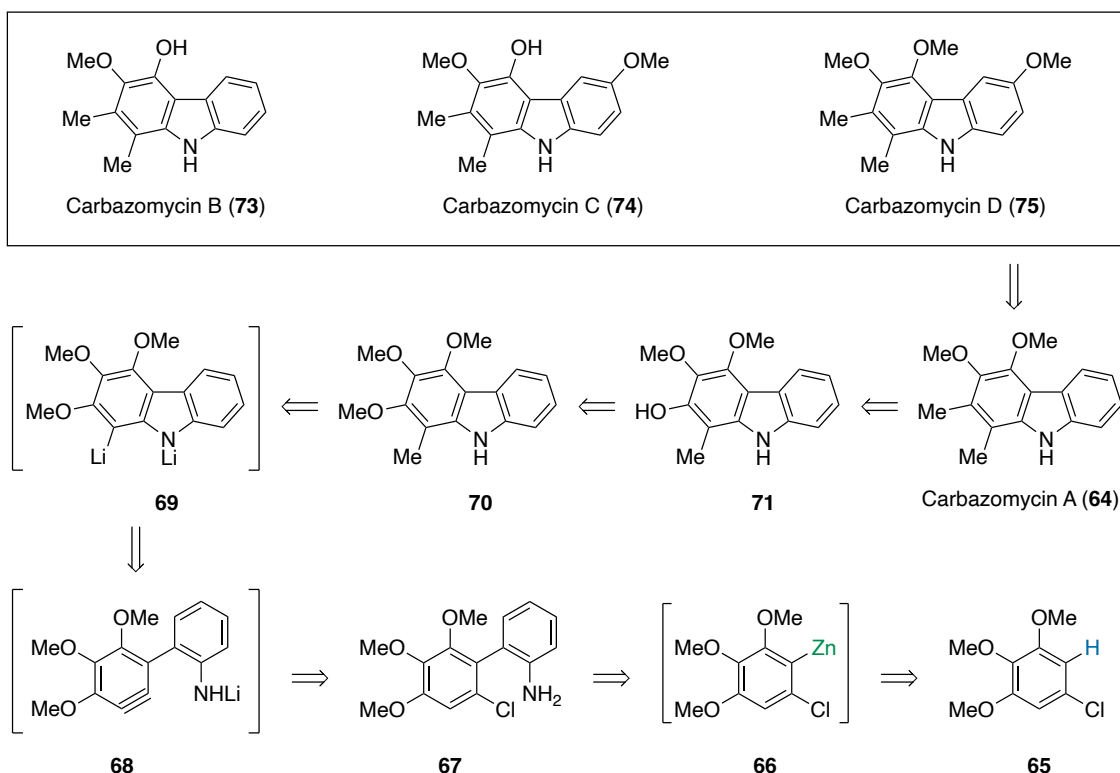
Scheme 3-2-2. Synthesis of carbazomycins A–D through iron-mediated electrophilic aromatic substitution

2008 年と 2010 年に Catellani らは、Catellani 反応と呼ばれるパラジウム触媒を用いる連続反応を鍵としてカルバゾール骨格を構築し、カルバマイシン A と D の高効率合成を達成している (Scheme 3-2-3)^{46c,77}。ヨードベンゼン **86** に対して、酢酸パラジウム、トリフェニルホスフィンおよびノルボルネンを用いて、2-ブロモアニリンとの Catellani 反応により、ワンポットで炭素–炭素結合および炭素–窒素結合を構築し、カルバゾマイシン A と D を合成している。一方、Knölker らの報告と同様に、この手法も、多置換ベンゼン環の修飾に依存している。



Scheme 3-2-3. Synthesis of carbazomycins A and D through palladium-catalyzed one-pot C–C/C–N bond formation

以上の背景から、本研究では、これまで報告されてきた合成例とは異なり、対称性の高い化合物を効率的に非対称化する合成戦略のもと、以下に示すカルバゾマイシン A–D の逆合成解析を考えた (Scheme 3-2-4)。カルバゾマイシン B (**73**) は、カルバゾマイシン A (**64**) のメトキシ基を選択的に脱メチル化することで合成可能であると考えた。カルバゾマイシン C (**74**) は、同様にカルバゾマイシン D (**75**) を脱メチル化することで合成でき、カルバゾマイシン D (**75**) は、カルバゾマイシン A (**64**) にメトキシ基を導入することにより得られると考えた。したがって、カルバゾマイシン A を大量に入手できれば、カルバゾマイシン B–D の効率的な合成が可能になると考えた。カルバゾマイシン A は、2-ヒドロキシカルバゾール **71** のフェノール性ヒドロキシ基をメチル化して合成できると期待した。2-ヒドロキシカルバゾール **71** は、1-メチルカルバゾール **70** の三つのメトキシ基のうち一つを選択的に脱メチル化できれば合成可能である。1-メチルカルバゾール **70** は、カルバゾールジアニオン **69** の選択的メチル化により得られる。このアニオン種は、分子内に窒素求核部位をもつアライン中間体 **68** の環化により発生できると考えた。また、このアライン中間体は、クロロ基を持つ 2-アミノビフェニル **67** を順次脱プロトン化して得られると期待した。2-アミノビフェニル **67** は、フェニル亜鉛 **66** を経由して根岸カップリング反応により合成することを計画した。フェニル亜鉛 **66** の調製は、第二章で紹介された *in situ* トランスメタル化が有用であると考えた。すなわち、対称構造を持つトリメトキシクロロベンゼン **65** に対して、塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化により、フェニル亜鉛 **66** が得られると期待した。

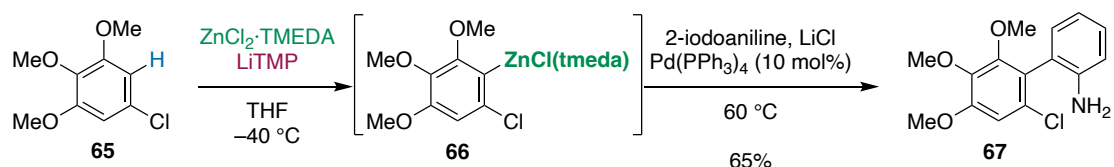


Scheme 3-2-4. Retrosynthetic analysis of carbazomycins A–D

3-3 カルバゾマイシン A–D の全合成

3-3-1 *in situ* トランスメタル化による 2-アミノビフェニルの合成

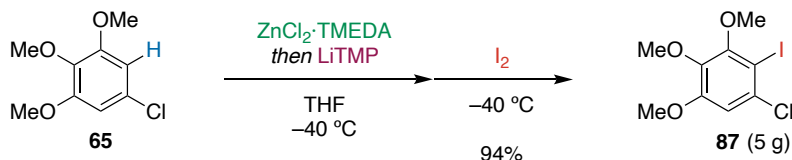
はじめに、*in situ* トランスメタル化を鍵として、2-アミノビフェニル **67** の合成を行った (Scheme 3-3-1)。第二章で最適化した *in situ* トランスメタル化の反応条件に従い、トリメトキシクロロベンゼン **65** と塩化亜鉛 TMEDA を含む THF 溶液に対して、 -40°C で LiTMP を作用させ、対応するフェニル亜鉛反応剤 **66** を得た。この際、対応するアラインの発生は確認できなかった。続いて、10 mol% の $\text{Pd}(\text{PPh}_3)_4$ と塩化リチウムを作用させ、2-ヨードアニリンとのワンポット根岸カップリング反応により、目的の 2-アミノビフェニル **67** を単離収率 65% で合成した。しかし、収率やパラジウム触媒の使用量が課題として残っていた。



Scheme 3-3-1. Synthesis of 2-aminobiphenyl through one-pot Negishi coupling

収率の向上と触媒量の低減を目的として、段階的な変換を検討した。まず、ヨ

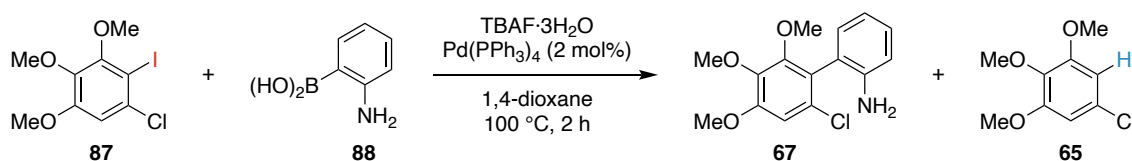
ードアレーン **87** を合成した (Scheme 3-3-2)。上述の *in situ* トランスメタル化を実施してフェニル亜鉛反応剤 **66** を調製したのち、ヨウ素を作用させ、対応するヨードベンゼン **87** を収率 94% で得た。



Scheme 3-3-2. Preparation of the iodobenzene through *in situ* transmetalation

ヨードベンゼン **87** を大量に合成したのち、市販の 2-アミノフェニルボロン酸 (**88**) との鈴木–宮浦カップリング反応 ^{3a–d} による 2-アミノビフェニル **67** の合成を検討した (Table 3-3-1)。ヨードベンゼン **87** と 1.5 当量の 2-アミノフェニルボロン酸 (**88**) を含む 1,4-ジオキサン溶液に対して、2 mol% の $\text{Pd}(\text{PPh}_3)_4$ と 3 当量のテトラブチルアンモニウムフルオリド三水和物 ($\text{TBAF} \cdot 3\text{H}_2\text{O}$) ⁷⁸ を加え、 100°C で 2 時間攪拌した。この結果、2-アミノビフェニル **67** を収率 91% で合成した。さらに、グラムスケールでも **67** を単離収率 91% で得た (entry 1)。反応温度を 125°C に上昇させると、**67** の収率は 84% に低下した (entry 2)。一方、フッ化カリウムとフッ化セシウムを用いたところ、**67** の収率がそれぞれ 11% と 51% に大幅に低下し、ヨードベンゼン **87** がそれぞれ収率 83% と 38% で回収された (entries 3 and 4)。この原因は、1,4-ジオキサン中ではフッ化カリウムとフッ化セシウムが溶解していないためであると考えられる。そこで、フッ化セシウムを溶解するために 1,4-ジオキサンと水の混合溶媒を利用して反応を行った。この結果、アミノビフェニル **67** の収率はほぼ変わらず、トリメトキシクロロベンゼン **65** の収率は 31% に大幅に向上した (entry 5)。文献^{79,80} 参考にして重水 (D_2O) を水に代えて用いたところ、目的のアミノビフェニル **65** の収率が 85% に向上した (entry 6)。この収率の向上は、 D_2O における速度論的同位体効果 (KIE) に起因すると考えられる。すなわち、水と比較して D_2O はボロン酸に対する溶媒和効果が弱く、これにより鈴木–宮浦カップリング反応におけるトランスメタル化が促進される ^{80a}。この弱い溶媒和効果は、2-アミノフェニルボロン酸 (**88**) の安定性を低下させるとともに、トランスメタル化を加速させ、結果として脱ヨウ素化反応を抑制したと理解できる。

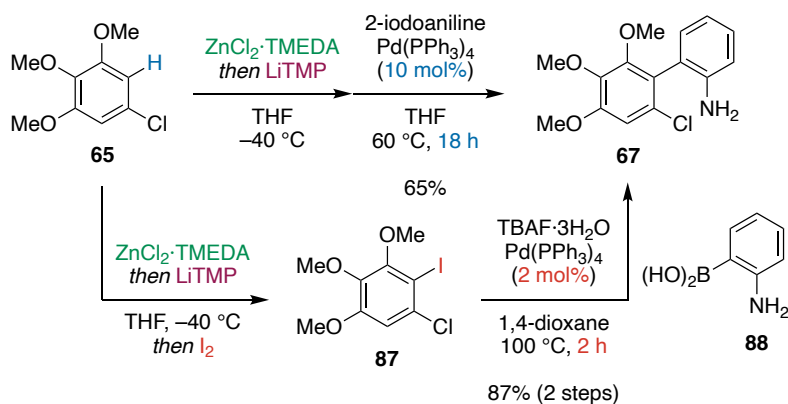
Table 3-3-1. Optimization of Suzuki–Miyaura coupling to synthesize the aminobiphenyl^a



entry	deviations	67 (%) ^b	65 (%) ^b	recovery of 87 (%) ^b
1	none	91 (93 ^{c,d})	5	— ^e
2	125 °C	84	7	— ^e
3 ^f	125 °C, KF instead of TBAF·3H ₂ O	11	4	83
4	125 °C, CsF instead of TBAF·3H ₂ O	51	2	38
5	125 °C, CsF, 1,4-dioxane/H ₂ O = 4:1	50	31	11
6	125 °C, CsF, 1,4-dioxane/D ₂ O = 4:1	85	7	— ^e

^aOptimized reaction conditions: iodobenzene **87** (0.15 mmol, 1.0 equiv), 2-aminophenylboronic acid (**88**) (0.23 mmol, 1.5 equiv), Pd(PPh₃)₄ (0.003 mmol, 2 mol%), TBAF·3H₂O (0.45 mmol, 3 equiv), and 1,4-dioxane (1.5 mL). ^bYield determined from the ¹H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. ^cIsolated yield. ^dIodobenzene **87** (12.9 mmol) was used. ^eNot observed. ^fReaction was performed for 14 h.

この２段階のアミノビフェニル **67** の合成は、ワンポット根岸カップリング反応と比較して収率が 87%に向上し、パラジウム触媒の使用量も 2 mol%に削減された (Scheme 3-3-3)。さらに、カップリング反応に要する反応時間も 2 時間へと短縮できた。

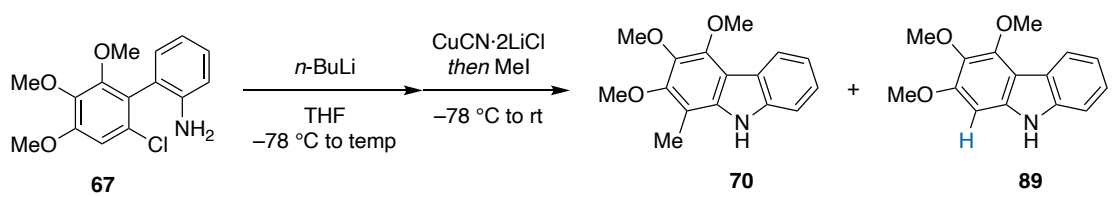


Scheme 3-3-3. Comparison of the modified two-step aminobiphenyl synthesis with the one-pot Negishi coupling approach

3-3-2 アライン中間体を経る 1-メチルカルバゾールの合成

2-アミノビフェニル **67** の効率的な合成法を確立したのち、アミノ基を保護せず、アライン中間体を経てワンポットカルバゾール骨格の構築およびメチル化を検討した。まず、脱プロトン化における反応温度の影響を調べた (Table 3-3-2)。2-アミノビフェニル **67** を含む THF 溶液に対して、 -78°C で 6 当量の *n*-BuLi を加えたのち、 -40°C に昇温して同じ温度で攪拌した。その後、 -78°C に冷やして $\text{CuCN}\cdot 2\text{LiCl}$ 錯体を加え、さらにヨードメタンを加えた。得られた混合物を攪拌しながら室温に昇温すると、1-メチルカルバゾール **70** を収率 83% で得た (entry 1)。脱プロトン化を -78°C で実施したところ、目的の 1-メチルカルバゾール **70** は収率 1% 未満しか得られず、副生成物としてカルバゾール **89** が収率 12% で得られ、2-アミノビフェニル **67** が収率 87% で回収された (entry 2)。この結果から、 -78°C では **67** のアミノ基とベンゼン環両方の脱プロトン化の速度が低下させることが明らかになった。また、少量生成したカルバゾールアニオンは、**67** のアミノ基によって速やかにプロトン化された。脱プロトン化を -60°C で行った場合でも、目的の 1-メチルカルバゾール **70** は収率 22% で得られた (entry 3)。また、**67** は、 -20°C 、 0°C および室温では完全に消失した (entries 4–6)。この原因は、反応温度の上昇により、生成したフェニルリチウム種の分解が促進されたと考えられる。最後に、最適化された反応条件を用い、グラムスケールで 1-メチルカルバゾール **70** を単離収率 83% で合成した (entry 7)。

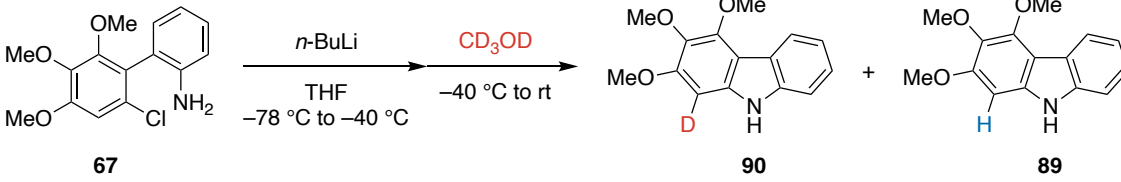
Table 3-3-2. Effects of reaction temperature on the aryne-mediated one-pot carbazole formation and methylation^a

				
entry	temp ($^{\circ}\text{C}$)	70 (%) ^b	89 (%) ^b	recovery of 67 (%) ^b
1	-40	83	4	— ^c
2	-78	<1	12	87
3	-60	22	19	30
4	-20	63	4	— ^c
5	0	71	4	— ^c
6	rt	75	5	— ^c
7 ^{d,e}	-40	83 ^f	— ^g	— ^g

^aReaction conditions: aminobiphenyl **67** (0.30 mmol, 1 equiv), *n*-BuLi (1.8 mmol, 6 equiv), THF (3.0 mL), then CuCN·2LiCl (0.30 mmol, 1 equiv), then iodomethane (1.5 mmol, 5 equiv). ^bYield determined from the ¹H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. ^cNot observed. ^dAminobiphenyl **67** (4.52 mmol) was used. ^eCuCN·2LiCl and iodomethane were added at -40 °C. ^fIsolated yield. ^gNot determined.

次に、最適化された反応温度において *n*-BuLi の量について検討した (Table 3-3)。確立した反応条件でカルバゾール骨格を構築したのち、-40 °Cで重水素化メタノール (CD₃OD) を作用させ、室温に昇温して反応を続けた。*n*-BuLi を 3 当量使用した場合は、重水素化されたカルバゾール **90** と水素化されたカルバゾール **89** の混合物が単離収率 81%、モル比率 68 : 13 で得られた (entry 1)。*n*-BuLi を 6 当量使用したところ、**90** と **89** の混合物の単離収率が 92%に向上し、モル比率が 87 : 5 に改善された (entry 2)。

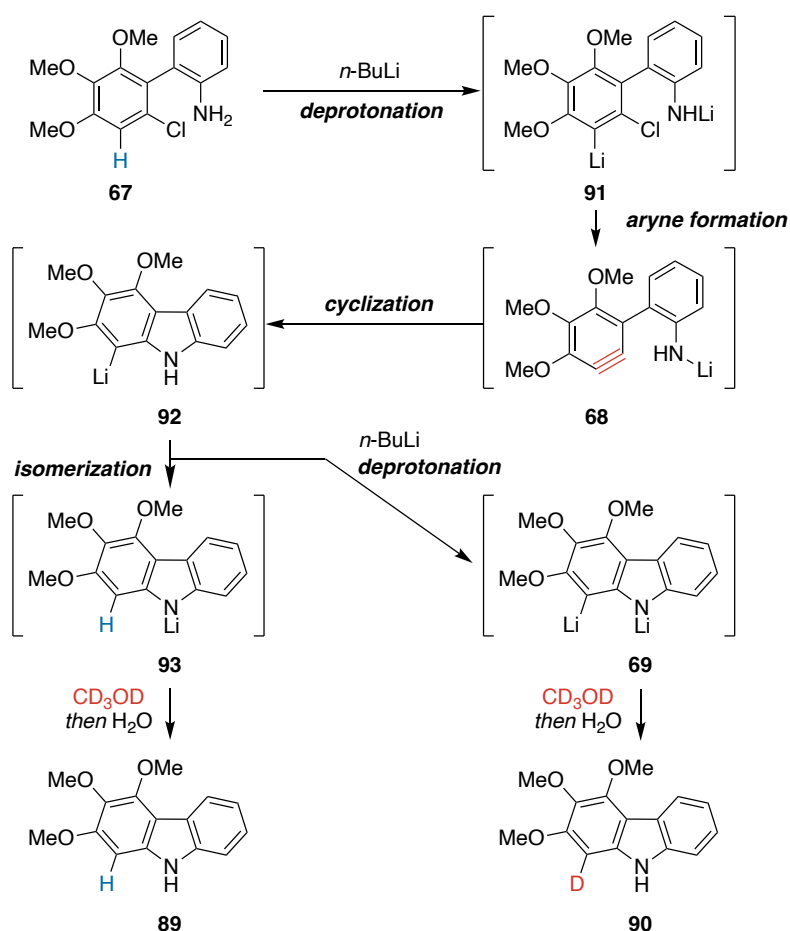
Table 3-3-3. Effects of the amount of *n*-BuLi on the aryne-mediated carbazole formation and deuteration^a

			
entry	<i>n</i> -BuLi (equiv)	yield (%) ^b	D/H ratio ^c
1	3	81	68:13
2	6	92	87: 5

^aReaction conditions: aminobiphenyl **67** (0.30 mmol, 1 equiv), *n*-BuLi, THF (3.0 mL), then CD₃OD (0.5 mL). ^bIsolated yield. ^cRatio determined by ¹H NMR spectroscopy.

n-BuLi の量が反応の結果に与える影響については、以下のように考えている (Scheme 3-3-4)。まず、2 当量の *n*-BuLi により、2-アミノビフェニル **67** のアミノ基およびベンゼン環上の水素が脱プロトン化され、ジアニオン **91** が発生する。これに続いて塩化リチウムの脱離反応を経て、アライン中間体 **68** が生成する。分子内のリチウムアミドがこのアラインに求核付加すると、カルバゾール骨格が構築される。生成したカルバゾールアニオン **92** がそのまま重水素化されれば、目的の **90** が単一生成物として得られる。一方、*n*-BuLi を 3 当量用いた場合、プロトン化された **89** が大量に生成した。この結果は、カルバゾールアニオン **92** の

フェニルリチウム部位が異性化し、より安定なカルバゾールアニオン **93** へと変換されたと理解できる。すなわち、ベンゼン環上の水素の pK_a が 43⁸¹であるのに対し、カルバゾールの N-H プロトンの pK_a が 17⁸²であり、生成したアニオンがより安定化されるように異性化が促進されたと考えられる。*n*-BuLi の量を 6 当量に増やしたところ、この異性化を抑制できた。すなわち、*n*-BuLi の強い塩基性 (*n*-ブタンの pK_a はおよそ 50) により、カルバゾールアニオン **92** の N-H プロトンが速やかに脱プロトン化され、カルバゾールジアニオン **69** が生成したと考えられる。このジアニオンに対して、CuCN·2LiCl 錯体とヨードメタンを順次作用させることでメチル化が進行し、目的の 1-メチルカルバゾール **70** を得た。

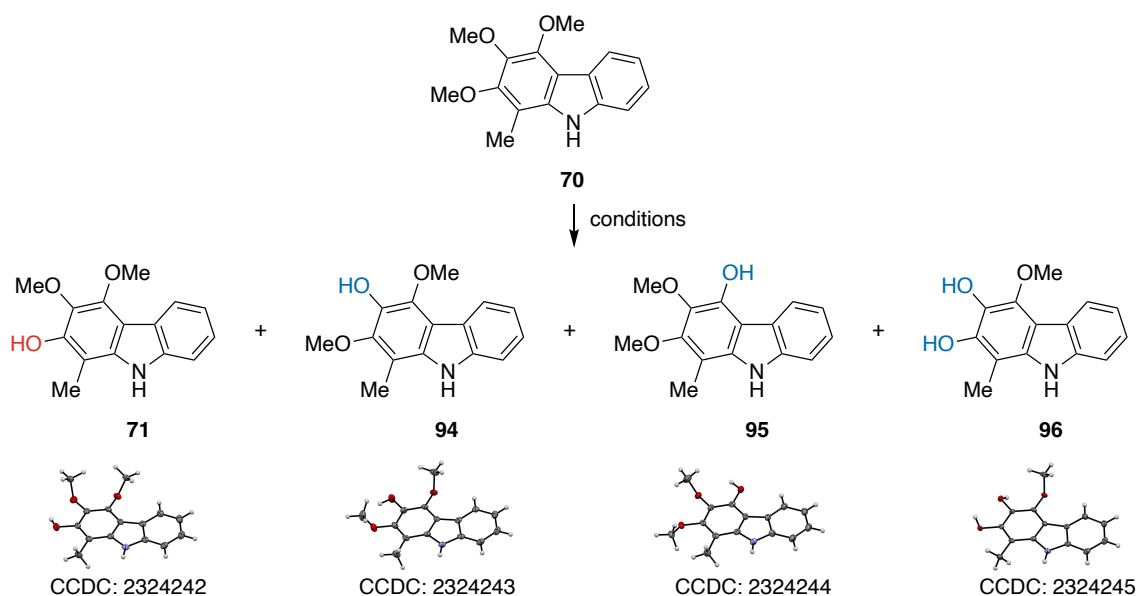


Scheme 3-3-4. Rationale for the effect of excess *n*-BuLi in the double functionalization of aryne

3-3-3 1-メチルカルバゾールの位置選択的な脱メチル化

カルバゾマイシン A の効率的な合成においては、1-メチルカルバゾール **70** の位置選択的な脱メチル化が鍵となる。そこで、さまざまな反応条件を用いて 1-メチルカルバゾール **70** の位置選択的な脱メチル化を検討した (Table 3-3-4)。まず、濃塩酸⁸³を用いたところ、目的の 2-ヒドロキシカルバゾール **71** が収率 8%しか得られず、望まない構造異性体の 3-ヒドロキシカルバゾール **94** と 4-ヒドロキシカルバゾール **95** がそれぞれ収率 3%と 2%得られ、**70** が収率 63%で回収された (entry 1)。クロロトリメチルシラン (TMSCl) とヨウ化ナトリウム⁸⁴を用いた場合、目的の **71** の収率が 23%に向上したが、構造異性体 **94** と **95** をそれぞれ収率 13%と 9%で得た (entry 2)。TMSCl をクロロトリエチルシラン (TESCl) に置き換えても、望ましい結果が得られず、構造異性体 **94** の収率が 23%に向上した (entry 3)。次に、塩基性条件下での求核的な脱メチル化を調べた。1-メチルカルバゾール **70** を含む DMF 溶液に対して、130 °C で 1-ドデカンチオールと水酸化ナトリウム⁸⁵を作用させたところ、**71** が収率 23%で得られ、構造異性体 **95**⁸⁶を単離収率 40%で得た (entry 4)。続いて、ルイス酸を用いる脱メチル化を検討した。西田らの報告⁸⁷を参考し、1.1 当量の塩化ニオブ (NbCl₅) を用いたところ、構造異性体 **94**⁸⁸が主生成物として単離収率 51%で得られた (entry 5)。塩基性条件下での求核的な脱メチル化の結果と比較し、ルイス酸を用いる脱メチル化が異なる位置選択性で進行した。強いルイス酸として三臭化ホウ素⁸⁹を 1.5 当量使用した場合、**71**、**94** と **95** がいずれも得られず、カテコール **96**⁹⁰を単離収率 61%で得た (entry 6)。BBr₃ の量を 1.0 当量に減らし、-60 °C で反応したところ、目的の 2-ヒドロキシカルバゾール **71** は収率 38%で生成したが、カテコール **96** が収率 18%で得られ、**70** が収率 41%で回収された (entry 7)。続いて、BBr₃ と比較してルイス酸性の低い三塩化ホウ素⁴⁹を試したところ、目的の 2-ヒドロキシカルバゾール **71**⁹¹を単離収率 65%で得た (entry 8)。なお、ヒドロキシカルバゾール **71**、**94**、**95** および **96** の構造は、単結晶 X 線構造解析によって決定した。

Table 3-3-4. Product distributions in the regioselective demethylation of the 1-methylcarbazole

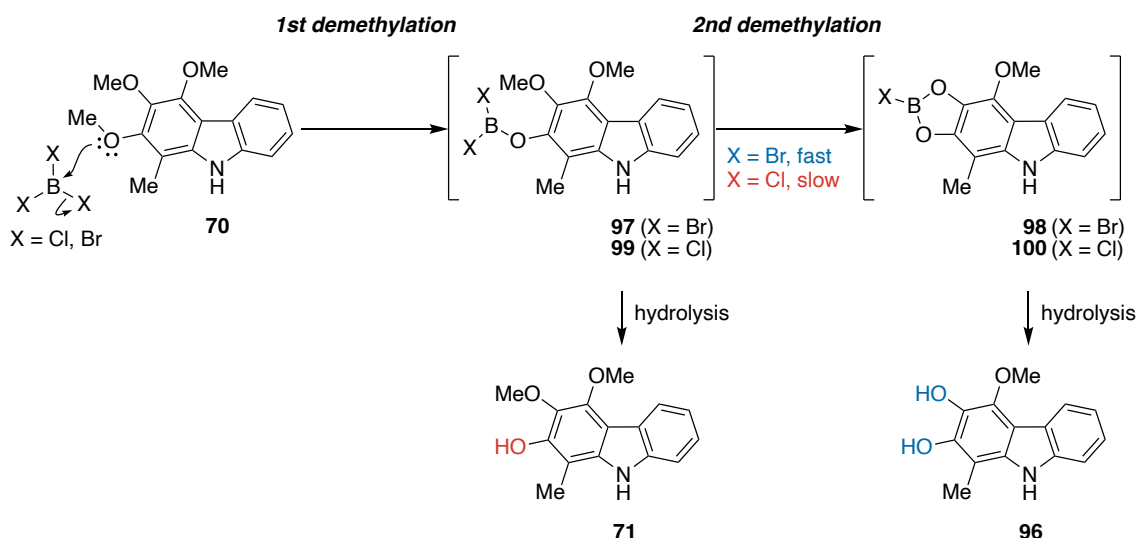


entry	conditions	71 (%) ^a	94 (%) ^a	95 (%) ^a	96 (%) ^a
1 ^b	<i>conc.</i> HCl, 50 °C	8	3	2	— ^c
2	TMSCl, NaI, MeCN, rt	23	13	9	— ^c
3	TESCl, NaI, MeCN, rt	24	23	12	— ^c
4	1-dodecanethiol, NaOH, DMF, 130 °C	23	<1	40 ^d	1
5	NbCl ₅ (1.1 equiv), 1,2-dichloroethane, reflux	28	51 ^d	10	5
6	BBr ₃ (1.5 equiv), CH ₂ Cl ₂ , −78 °C to 0 °C	— ^c	— ^c	— ^c	61 ^d
7 ^e	BBr ₃ (1.0 equiv), CH ₂ Cl ₂ , −78 °C to −60 °C	38	3	— ^c	18
8	BCl ₃ (1.5 equiv), CH ₂ Cl ₂ , −78 °C to 0 °C	65 ^c	20	— ^c	10

^aYield determined from the ¹H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. ^bRecovery of **70** in 63% yield. ^cNot observed. ^dIsolated yield. ^eRecovery of **70** in 41% yield.

位置選択的脱メチル化において、三臭化ホウ素と三塩化ホウ素が異なる結果を与えた理由は、以下のように考えている (Scheme 3-3-5)。Sargent らは、三塩化ホウ素を用いた 1,2,3-トリメトキシベンゼン誘導体の位置選択的脱メチル化に関する研究を報告しており、対応する 2-ヒドロキシ-1,3-ジメトキシベンゼンが得られている⁴⁶。この位置選択性は、ベンゼン環の平面から押し出され、立体

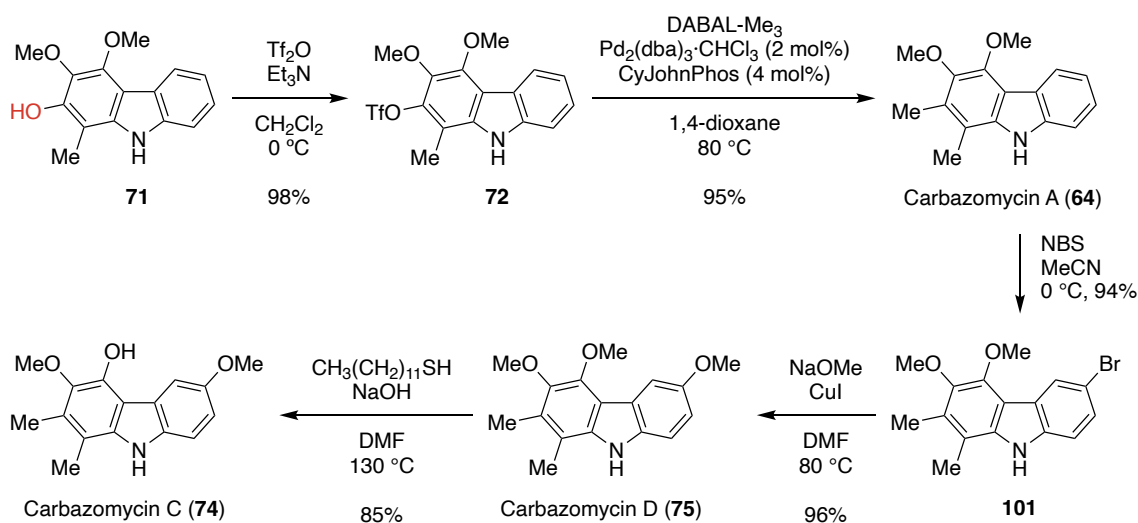
的に混みあった真ん中のメトキシ基の酸素原子の高いルイス塩基性によって説明される。すなわち、真ん中のメトキシ基の酸素原子上の孤立電子対は、ベンゼン環の π 電子系との共役が不十分であるために非局在化されにくく、酸素原子のルイス塩基性が高まり、三塩化ホウ素との配位が優先的に進行したと理解できる。Wilcox らも、酢酸と臭化水素を用いた 1,2,3-トリメトキシベンゼンの脱メチル化における位置選択性は、ビシナルメトキシ基の立体効果によって支配されることを報告している⁹²。これらの 2 つの報告とは異なり、今回三塩化ホウ素を用いると、1-メチルカルバゾール **70** の C-2 位で脱メチル化が進行した。この位置選択性を、以下のように考察した。まず、C-1 位のメチル基と縮環されたインドールの部分は、近接する C-2 位および C-4 位のメトキシ基に対して立体障害になり、この二つのメトキシ基をベンゼン環の平面外に押し出すと考えられる。そこで、C-2 位または C-4 位のメトキシ基のメチル部分による立体障害のため、C-3 位のメトキシ基の酸素原子は三塩化ホウ素との配位が困難であると考えられる。また、C-4 位のメトキシ基に近接するフェニル基の立体障害に加え、弱い電子求引性効果により、C-4 位のメトキシ基のルイス塩基性が低下する可能性がある。3 つのメトキシ基のうち、三臭化ホウ素と三塩化ホウ素 (BX_3) との最初の配位は、立体的に最も空いた C-2 位のメトキシ基の酸素原子で優先的に進行すると考えられる。三臭化ホウ素を用いた場合は、C-2 位に置換するメトキシ基が脱メチル化されて中間体 **97** を生成したのち、ホウ素原子に十分なルイス酸性が残っているため C-3 位のメトキシ基の酸素原子がさらに反応し、カテコールボラン中間体 **98** を生成すると考えられる。一方、実験結果⁹³と理論研究⁹⁴に基づく、三塩化ホウ素は三臭化ホウ素よりもルイス酸性が弱いことを示す。すなわち、三塩化ホウ素を用いて生成した中間体 **99** のホウ素原子は、中間体 **97** のホウ素原子よりもルイス酸性が弱いと理解できる。したがって、二回目の脱メチル化の進行が遅れ、カテコール **96** の収率が 10%に低下した結果、目的の 2-ヒドロキシカルバゾール **71** が主生成物として得られた実験事実を説明できる。



Scheme 3-3-5. A plausible reaction pathway for the regioselective demethylation of the trimethoxycarbazole using boron trihalides

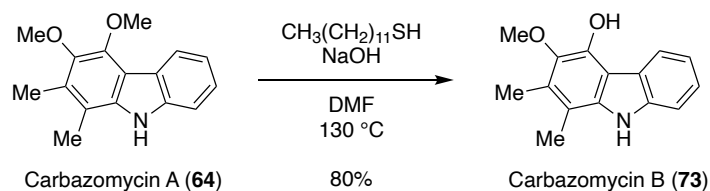
3-3-4 カルバゾマイシン A-D の合成

2-ヒドロキシカルバゾール **71** を効率的に合成できたので、カルバゾマイシン A-D の合成に着手した (Scheme 3-3-6)。2-ヒドロキシカルバゾール **71** に対して、0 °C でトリフルオロメタンスルホン酸無水物 (Tf₂O) とトリエチルアミンを作用させ、対応するトリフラート **72** を単離収率 98% で得た。続いて、トリメチルアルミニウムと DABCO の錯体 (DABAL-Me₃) を用いて根岸カップリング反応を経て、カルバゾマイシン A (**64**) を単離収率 95% で得た。次に、カルバゾマイシン A (**64**) を合成中間体として用い、カルバゾマイシン C と D の合成に取り組んだ。カルバゾマイシン A (**64**) に対し、*N*-ブロモスクシンイミド (NBS) ^{46b} を作用させ、位置選択的なブロモ化によりブロモカルバゾール **101** を単離収率 94% で得た。続いて、ナトリウムメトキシドとヨウ化銅を用いた Ullmann カップリング反応⁹⁵により、カルバゾマイシン D (**75**) をグラムスケール、単離収率 96% で合成した。さらに、前節の検討に基づき、塩基性条件下での求核的な脱メチル化を適用し、カルバゾマイシン D (**75**) の位置選択的な脱メチル化を実施した。すなわち、カルバゾマイシン D (**75**) を含む DMF 溶液に対して、130 °C で1-ドデカンチオールと水酸化ナトリウムを作用させ、カルバゾマイシン C (**74**) をグラムスケール、単離収率 85% で得た。



Scheme 3-3-6. Synthesis of carbazomycins A, C, and D

また、この手法を利用してカルバゾマイシン A (64) を位置選択的に脱メチル化し、カルバゾマイシン B も合成できた (Scheme 3-3-7)。すなわち、カルバゾマイシン A (64) に対して、1-ドデカンチオールと水酸化ナトリウムを作用させ、カルバゾマイシン B (73) をグラムスケール、単離収率 80% で得た。



Scheme 3-3-7. Synthesis of carbazomycin B

3-4 結言

本章では、*in situ* トランスメタル化を鍵とする天然物カルバゾマイシン A-D のグラムスケール合成を達成した。対称構造を持つトリメトキシクロロベンゼンを出発物質として、*in situ* トランスメタル化によって対応するヨードベンゼンを合成したのち、鈴木-宮浦カップリング反応を経て、カルバゾール骨格への変換が容易なアミノビフェニルを効率的に合成した。得られたアミノビフェニルに対し、6 当量の *n*-BuLi を作用させてアライン中間体を生成し、分子内求核付加反応を経てカルバゾール骨格を構築した。さらにワンポットメチル化を行って、1-メチルカルバゾールを合成できた。その後、三塩化ホウ素を用いた位置選択的な脱メチル化を鍵として、カルバゾマイシン A の効率的な全合成を実現し

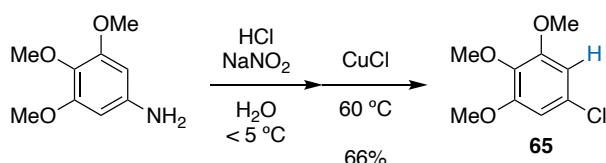
た。カルバゾマイシン A を合成中間体として、カルバゾマイシン B-D の変換も達成した。カルバゾマイシン A に対し、メトキシ基を位置選択的に導入してカルバゾマイシン D を合成した。さらにカルバゾマイシン A と D に対し、チオラートを用いた求核的な脱メチル化により、カルバゾマイシン B と C を合成した。本合成の終盤におけるメチルエーテルの位置選択的脱メチル化は、カルバゾマイシン A-D に加えて他の非天然カルバゾマイシン誘導体への変換にも応用可能であり、カルバゾマイシン類の生理活性解明および構造活性相関 (SAR) 研究への展開が期待される。

3-5 Experimental section

1. General Information

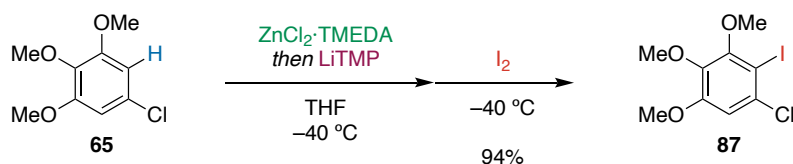
Unless otherwise stated, all reactions were conducted in a flame-dried glassware under an inert atmosphere of argon, and a preheated oil bath was used for the reactions that required heating. All workup and purification procedures were carried out with reagent-grade solvents in the air. Unless otherwise 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 Kanto Chemical Co. and further dried by passing through a solvent purification system (Glass Contour) prior to use. *n*-BuLi (1.6 M in *n*-hexane) was purchased from Kanto Chemical Co. and used as received. Aminophenylboronic acid (**88**) was purchased from BLD Pharmatech Ltd. and used as received. Freshly prepared $\text{ZnCl}_2\cdot\text{TMEDA}$, $\text{Pd}(\text{PPh}_3)_4$, and $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ were used in the following experiments. Analytical thin layer chromatography (TLC) was performed on Wako 70 F₂₅₄ 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 wave numbers (cm^{-1}). ^1H NMR (400 MHz) and $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz) spectra were measured on JEOL ECZ400 spectrometer. Chemical shifts for ^1H 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, $\text{DMSO}-d_5$: δ 2.50 ppm, and $\text{acetone}-d_5$: δ 2.05 ppm), and coupling constants are given in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, m = multiplet, br = broad, dd = doublet of doublets, ddd = doublet of doublet of doublets. Chemical shifts for $^{13}\text{C}\{^1\text{H}\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl_3 : δ 77.16 ppm, $\text{DMSO}-d_6$: δ 39.52 ppm, and $\text{acetone}-d_6$: δ 29.84 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. X-ray crystallographic data were collected on a Rigaku Saturn724 diffractometer with $\text{MoK}\alpha$ radiation. The structures were solved by a direct method (SHELXT)⁹⁶ and refined using a full-matrix least squares technique (SHELXL).⁹⁷

2. Preparation of the iodobenzene through *in situ* transmetalation (Scheme 3-3-2)



3,4,5-Trimethoxychlorobenzene (**65**)

A 300-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with commercially available 3,4,5-trimethoxyaniline (5.497 g, 30.0 mmol, 1.0 equiv), aqueous HCl (35 wt%, 80 mL), and distilled water (25 mL). The resulting suspension was cooled to −4 °C. A solution of sodium nitrite (2.196 g, 31.8 mmol, 1.1 equiv) in distilled water (8.0 mL) was added dropwise to the flask while maintaining the internal temperature below 5 °C. After the addition of an aqueous solution of sodium nitrite, the reaction mixture was treated with a solution of copper(I) chloride (3.865 g, 39.0 mmol, 1.3 equiv) in aqueous HCl (35 wt%, 25 mL) and allowed to warm to room temperature. After stirring at 60 °C for 3 h, the reaction mixture was filtered and washed with diethyl ether (100 mL). The filtrate was extracted with diethyl ether (100 mL) three times. The combined organic extracts were washed with brine (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 = 5:1) to afford the title compound **65** as a colorless solid (4.024 g, 19.9 mmol, 66%), whose ¹H NMR spectroscopic data were identical to those reported in the literature.⁹⁸ *R_f* = 0.26 (hexane/diethyl ether = 5:1); Mp 60–62 °C; IR (ATR, cm^{−1}): 2938, 1591, 1501, 1465, 1453, 1439, 1408, 1311, 1227, 1183, 1128. 996, 873, 814; ¹H NMR (400 MHz, CDCl₃): δ 6.58 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 153.7, 136.8, 129.0, 106.0, 61.0, 56.3; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₉H₁₂³⁵ClO₃ 203.0475; Found 203.0477.



1-Chloro-2-iodo-3,4,5-trimethoxybenzene (**87**)

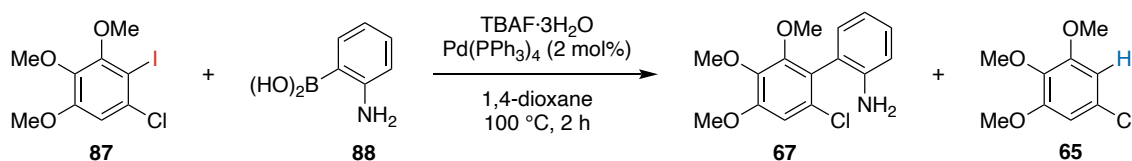
A flame-dried 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under argon was charged with 1,2,3-trimethoxybenzene **65** (3.040 g, 15.0 mmol, 1.0 equiv), ZnCl₂·TMEDA (3.790 g, 15.0 mmol, 1.0 equiv), and THF (96.0 mL). The resulting solution was cooled to −40 °C. Through cannula transfer, LiTMP (0.66 M, 41 mL, 27 mmol, 1.8 equiv) was added to the

round-bottomed flask. After stirring at $-40\text{ }^{\circ}\text{C}$ for 30 min, the reaction mixture was treated with iodine (7.639 g, 30.1 mmol, 2.0 equiv). After stirring at $-40\text{ }^{\circ}\text{C}$ for 30 min, the reaction mixture was treated with saturated aqueous sodium thiosulfate (25 mL) and 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 brine (50 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 = 10:1) to the title compound **87** as a pale yellow solid (4.615 g, 14.0 mmol, 94%). R_f = 0.32 (hexane/diethyl ether = 10:1); Mp $32\text{--}33\text{ }^{\circ}\text{C}$; IR (ATR, cm^{-1}): 2937, 1570, 1473, 1443, 1423, 1374, 1306, 1232, 1193, 1157, 1104, 1007, 929, 883, 824; ^1H NMR (400 MHz, CDCl_3): δ 6.88 (s, 1H), 3.88 (s, 3H), 3.85 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 154.6, 154.2, 141.0, 133.2, 109.1, 86.9, 61.2, 61.0, 56.4; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_9\text{H}_{11}^{35}\text{ClIO}_3$ 328.9441; Found 328.9456.

3. Optimization of Suzuki–Miyaura coupling to synthesize the aminobiphenyl (Table 3-3-1)

General procedure (Table 3-3-1, entries 1–6)

A 15-mL glass screw-thread tube equipped with a Teflon-coated magnetic stirring bar and a screw cup under argon was charged with iodobenzene **87** (49.3 mg, 0.150 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (30.8 mg, 0.225 mmol, 1.5 equiv), $\text{Pd}(\text{PPh}_3)_4$ (3.5 mg, $3.0\text{ }\mu\text{mol}$, 2 mol%), base (0.450 mmol, 3 equiv), and solvent (1.5 mL). After stirring the reaction mixture at the corresponding temperature for 2 h, the solution was treated with saturated aqueous ammonium chloride (1 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with aqueous sodium chloride (10 wt%, 2 mL) three times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 6'-chloro-2',3',4'-trimethoxy-[1,1'-biphenyl]-2-amine (**67**), 5-chloro-1,2,3-trimethoxybenzene (**65**), and 1-chloro-2-iodo-3,4,5-trimethoxybenzene (**87**) 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 7.02 ppm (1 proton for **67**), 6.58 ppm (2 protons for **65**), and 6.88 ppm (1 proton for **87**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.



Reaction performed under the optimal reaction conditions (Table 3-3-1, entry 1)

A crude product was obtained from iodobenzene **87** (49.8 mg, 0.152 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (31.1 mg, 0.227 mmol, 1.5 equiv), Pd(PPh₃)₄ (3.6 mg, 3.1 μmol, 2 mol%), TBAF·3H₂O (142.6 mg, 0.452 mmol, 3 equiv), and 1,4-dioxane (1.5 mL) according to the general procedure at 100 °C. The yields of aminobiphenyl **67** and chlorobenzene **65** were determined to be 91% and 5% by ¹H NMR spectroscopy.

Scale-up synthesis under the optimal reaction conditions (Table 3-3-1, entry 1)

A 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under argon was charged with iodobenzene **87** (4.243 g, 12.9 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (2.655 g, 19.4 mmol, 1.5 equiv), Pd(PPh₃)₄ (299.6 mg, 0.259 mmol, 2 mol%), TBAF·3H₂O (12.38 g, 39.2 mmol, 3 equiv), and 1,4-dioxane (130 mL). After stirring the reaction mixture at 100 °C for 2 h, the solution was treated with saturated aqueous ammonium chloride (40 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (15 mL) three times. The combined organic extracts were washed with aqueous sodium chloride (10 wt%, 60 mL) three times, 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/dichloromethane = 2:1:1) to afford the title compound **67** as a pale yellow solid (3.511 g, 12.0 mmol, 93%). *R_f* = 0.30 (hexane/diethyl ether = 1:1); Mp 96–98 °C; IR (ATR, cm⁻¹): 3381, 2937, 1616, 1590, 1480, 1456, 1431, 1392, 1312, 1256, 1221, 1193, 1131, 1094, 1004, 933, 897, 832; ¹H NMR (400 MHz, CDCl₃): δ 7.21 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.02 (dd, 1H, *J* = 7.6, 1.2 Hz), 6.85 (s, 1H), 6.84 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 6.80 (dd, 1H, *J* = 7.6, 1.2 Hz), 3.90 (s, 6H), 3.64 (s, 3H), 3.54 (br s, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 153.5, 152.9, 144.5, 141.7, 131.2, 129.2, 129.0, 124.8, 121.5, 118.4, 115.7, 109.1, 61.4, 61.3, 56.3; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₁₅H₁₇³⁵ClNO₃ 294.0897; Found 294.0906.

Reaction performed at 125 °C (Table 3-3-1, entry 2)

A crude product was obtained from iodobenzene **87** (49.5 mg, 0.151 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (30.5 mg, 0.223 mmol, 1.5 equiv), Pd(PPh₃)₄ (3.6 mg,

3.1 μmol , 2 mol%), TBAF $\cdot$ 3H₂O (146.9 mg, 0.466 mmol, 3 equiv), and 1,4-dioxane (1.5 mL) according to the general procedure at 125 °C. The yields of aminobiphenyl **67** and chlorobenzene **65** were determined to be 84% and 7% by ¹H NMR spectroscopy.

Reaction performed with KF instead of TBAF $\cdot$ 3H₂O at 125 °C for 14 h (Table 3-3-1, entry 3)

A crude product was obtained from iodobenzene **87** (49.3 mg, 0.150 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (30.2 mg, 0.221 mmol, 1.5 equiv), Pd(PPh₃)₄ (3.6 mg, 3.1 μmol , 2 mol%), potassium fluoride (27.1 mg, 0.466 mmol, 3 equiv), and 1,4-dioxane (1.5 mL) according to the general procedure at 125 °C for 14 h. The yields of aminobiphenyl **67**, chlorobenzene **65**, and the starting iodobenzene **87** were determined to be 11%, 4%, and 83% by ¹H NMR spectroscopy.

Reaction performed with CsF instead of TBAF $\cdot$ 3H₂O at 125 °C (Table 3-3-1, entry 4)

A crude product was obtained from iodobenzene **87** (49.5 mg, 0.151 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (31.0 mg, 0.226 mmol, 1.5 equiv), Pd(PPh₃)₄ (3.4 mg, 2.9 μmol , 2 mol%), cesium fluoride (68.1 mg, 0.448 mmol, 3 equiv), and 1,4-dioxane (1.5 mL) according to the general procedure at 125 °C. The yields of aminobiphenyl **67**, chlorobenzene **65**, and the starting iodobenzene **87** were determined to be 51%, 2%, and 38% by ¹H NMR spectroscopy.

Reaction performed with CsF instead of TBAF $\cdot$ 3H₂O at 125 °C in 1,4-dioxane/H₂O (4:1) as the solvent (Table 3-3-1, entry 5)

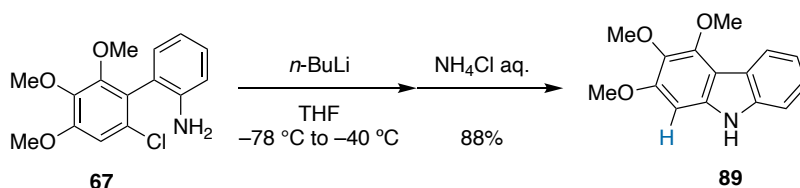
A crude product was obtained from iodobenzene **87** (49.4 mg, 0.150 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (31.1 mg, 0.227 mmol, 1.5 equiv), Pd(PPh₃)₄ (3.5 mg, 3.0 μmol , 2 mol%), cesium fluoride (69.0 mg, 0.454 mmol, 3 equiv), 1,4-dioxane (1.2 mL), and water (0.3 mL) according to the general procedure at 125 °C. The yields of aminobiphenyl **67**, chlorobenzene **65**, and the starting iodobenzene **87** were determined to be 50%, 31%, and 11% by ¹H NMR spectroscopy.

Reaction performed with CsF instead of TBAF $\cdot$ 3H₂O at 125 °C in 1,4-dioxane/D₂O (4:1) as the solvent (Table 3-3-1, entry 6)

A crude product was obtained from iodobenzene **87** (49.4 mg, 0.150 mmol, 1.0 equiv), (2-aminophenyl)boronic acid (**88**) (31.0 mg, 0.226 mmol, 1.5 equiv), Pd(PPh₃)₄ (3.5 mg, 3.0 μmol , 2 mol%), cesium fluoride (69.9 mg, 0.460 mmol, 3 equiv), 1,4-dioxane (1.2

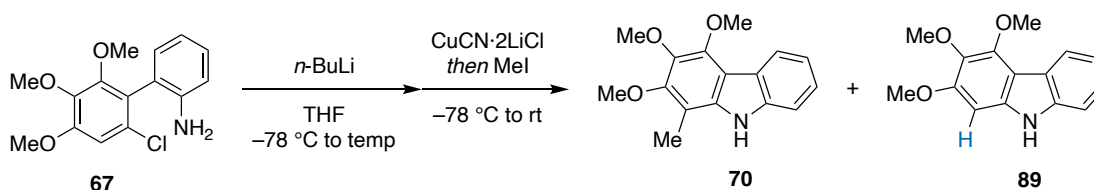
mL), and deuterium oxide (0.3 mL) according to the general procedure at 125 °C. The yields of aminobiphenyl **67** and chlorobenzene **65** were determined to be 85% and 7% by ^1H NMR spectroscopy.

4. Effects of reaction temperature on the aryne-mediated one-pot carbazole formation and methylation (Table 3-3-2)



2,3,4-Trimethoxy-9H-carbazole (**89**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with aminobiphenyl **67** (88.3 mg, 0.301 mmol, 1.0 equiv) and THF (3.0 mL). The resulting solution was cooled to $-78\text{ }^\circ\text{C}$. *n*-BuLi (1.56 M in hexane, 1.2 mL, 1.9 mmol, 6 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^\circ\text{C}$ for 1 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 washed brine (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 = 1:1) to afford the title compound **89** as a colorless solid (68.4 mg, 0.266 mmol, 88%). R_f = 0.22 (hexane/diethyl ether = 1:1); Mp $154\text{--}155\text{ }^\circ\text{C}$; IR (ATR, cm^{-1}): 3404, 2938, 1632, 1611, 1500, 1468, 1456, 1424, 1360, 1312, 1277, 1248, 1197, 1146, 1113, 1101, 1070, 1005, 932, 880, 808; ^1H NMR (400 MHz, CDCl_3): δ 8.18 (d, 1H, J = 7.6 Hz), 7.91 (br s, 1H), 7.37 (d, 1H, J = 7.6 Hz), 7.33 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 7.21 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 6.71 (s, 1H), 4.16 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 153.7, 148.8, 139.2, 136.6, 136.0, 124.4, 122.8, 121.9, 119.7, 110.2, 110.1, 89.7, 61.7, 61.0, 56.3; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_3$ 258.1130; Found 258.1125.



General procedure (Table 3-3-2, entries 1–6)

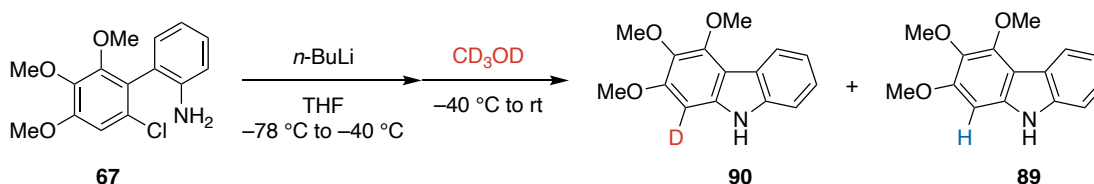
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with aminobiphenyl **67** (88.1 mg, 0.300 mmol, 1.0 equiv) and THF (3.0 mL). The resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (1.51 M in hexane, 1.2 mL, 1.8 mmol, 6 equiv) was added to the Schlenk tube. After stirring at corresponding temperature for 1 h, the reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$. To the resulting solution was added CuCN·2LiCl (1.0 M in THF, 0.30 mL, 0.30 mmol, 1 equiv) and methyl iodide (90 μL , 1.4 mmol, 5 equiv). After warming to room temperature and stirring for 1 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 washed with saturated aqueous ammonium chloride (2 mL) and brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3,4-trimethoxy-1-methyl-9*H*-carbazole (**70**), 2,3,4-trimethoxy-9*H*-carbazole (**89**), and 6'-chloro-2',3',4'-trimethoxy-[1,1'-biphenyl]-2-amine (**67**) 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 2.41 ppm (3 protons for **70**), 6.71 ppm (1 proton for **89**), and 3.64 ppm (3 protons for **67**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The other experiments (entries 2–6) were performed at the corresponding reaction temperature according to the procedure. The yields of carbazole **89**, methylcarbazole **70**, and the starting aminobiphenyl **67** were determined by ^1H NMR spectroscopy.

Scale-up synthesis under the optimal reaction conditions (Table 3-3-2, entry 7)

A flame-dried 300-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with aminobiphenyl **67** (1.328 g, 4.52 mmol, 1.0 equiv) and THF (45.0 mL). The resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (1.52 M in hexane, 18.0 mL, 27.4 mmol, 6 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^{\circ}\text{C}$ for 1 h, the reaction mixture was treated with CuCN·2LiCl (1.0 M in THF, 4.5 mL, 4.5 mmol, 1 equiv) and methyl iodide (1.4 mL, 23 mmol, 5 equiv). After warming to room temperature and stirring for 1 h, the reaction mixture was treated with saturated aqueous ammonium chloride (30 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (10 mL) three times. The combined organic extracts were washed with saturated aqueous ammonium chloride (20 mL) and brine (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/diethyl ether = 4:1) to afford the title compound **70** as a colorless solid (1.022 g,

3.77 mmol, 83%). R_f = 0.27 (hexane/diethyl ether = 2:1); Mp 122–123 °C; IR (ATR, cm^{-1}): 3365, 2935, 1611, 1504, 1455, 1424, 1399, 1355, 1319, 1298, 1232, 1090, 1041, 1015, 982, 748; ^1H NMR (400 MHz, CDCl_3): δ 8.21 (d, 1H, J = 8.0 Hz), 7.82 (br s, 1H), 7.43–7.39 (m, 1H), 7.36 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 7.21 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 4.13 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 2.41 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 151.0, 146.7, 140.0, 139.6, 135.8, 124.9, 122.9, 122.5, 119.7, 112.4, 110.3, 108.3, 61.7, 61.5, 61.0, 10.3; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3$ 272.1287; Found 272.1285.

5. Effects of the amount of *n*-BuLi on the aryne-mediated carbazole formation and deuteration (Table 3-3-3)



Reaction performed with three equivalents of *n*-BuLi (Table 3-3-3, entry 1)

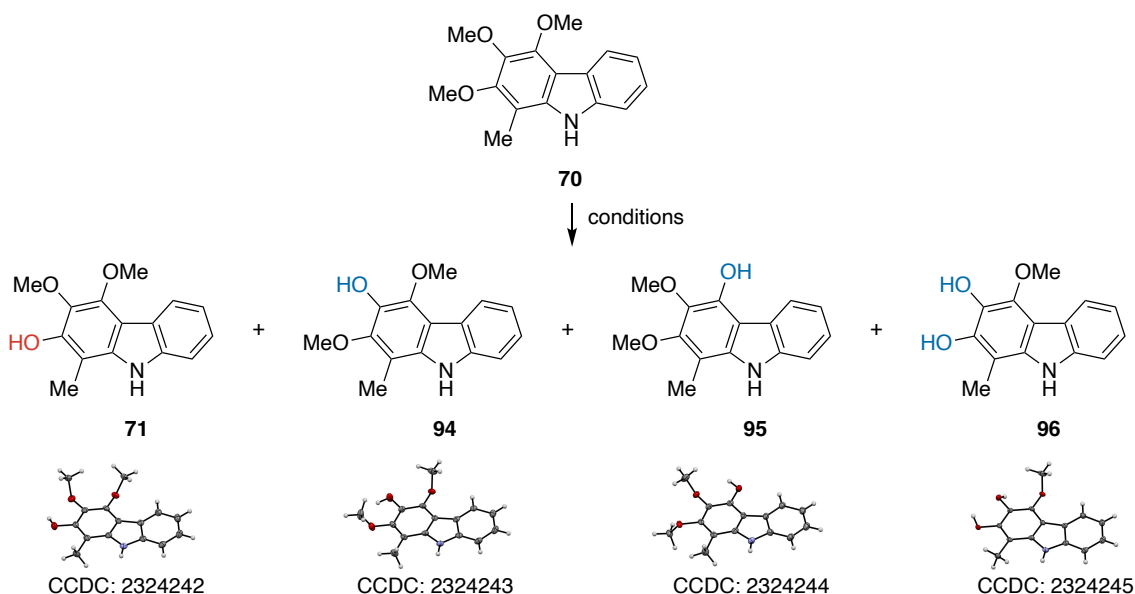
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with aminobiphenyl **67** (88.3 mg, 0.301 mmol, 1 equiv) and THF (3.0 mL). The resulting solution was cooled to -78°C . *n*-BuLi (1.51 M in hexane, 0.6 mL, 0.9 mmol, 3 equiv) was added to the Schlenk tube. After stirring at -40°C for 1 h, the reaction mixture was treated with deuterated methanol (0.5 mL). After warming to room temperature and stirring for 1 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 washed with brine (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 = 3:1) to afford an inseparable mixture (63.4 mg) of 2,3,4-trimethoxy-9*H*-carbazole-1-*d* (**90**) (0.205 mmol, 68%) and 2,3,4-trimethoxy-9*H*-carbazole (**89**) (0.0390 mmol, 13%) as a colorless solid. The ratio was determined by ^1H NMR spectroscopy.

Reaction performed with six equivalents of *n*-BuLi (Table 3-3-3, entry 2)

A crude product was obtained from aminobiphenyl **67** (87.9 mg, 0.299 mmol, 1 equiv), *n*-BuLi (1.51 M in hexane, 1.2 mL, 1.8 mmol, 6 equiv), deuterated methanol (0.5 mL), and THF (1.5 mL) according to the above procedure. Purification was performed by silica gel column chromatography (hexane/diethyl ether = 3:1) to afford an inseparable mixture

(71.2 mg) of 2,3,4-trimethoxy-9*H*-carbazole-1-*d* (**90**) (0.261 mmol, 87%) and 2,3,4-trimethoxy-9*H*-carbazole (**89**) (0.0140 mmol, 4.6%) as a pale brown solid. The ratio was determined by ^1H NMR spectroscopy. Physicochemical properties of 2,3,4-trimethoxy-9*H*-carbazole-1-*d* (**90**): R_f = 0.22 (hexane/diethyl ether = 1:1); Mp 159–160 °C; IR (ATR, cm^{-1}): 3402, 2938, 1627, 1610, 1573, 1499, 1456, 1413, 1359, 1313, 1275, 1197, 1147, 1113, 1098, 1085, 1003, 946, 930; ^1H NMR (400 MHz, CDCl_3): δ 8.18 (d, 1H, J = 7.6 Hz), 7.91 (br s, 1H), 7.37 (d, 1H, J = 7.6 Hz), 7.33 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 7.21 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 4.16 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 153.6, 148.8, 139.2, 136.5, 136.0, 124.4, 122.8, 121.9, 119.7, 110.14, 110.09, 89.4 (t, $J_{\text{C-D}}$ = 24.0 Hz), 61.7, 61.0, 56.3; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{15}^2\text{HNO}_3$ 259.1193; Found 259.1194.

6. Product distributions in the regioselective demethylation of the 1-methylcarbazole (Table 3-3-4)



The yields of 2,3,4-trimethoxy-1-methyl-9*H*-carbazole (**70**), 3,4-dimethoxy-1-methyl-9*H*-carbazol-2-ol (**71**), 2,4-dimethoxy-1-methyl-9*H*-carbazol-3-ol (**94**), 2,3-dimethoxy-1-methyl-9*H*-carbazol-4-ol (**95**), and 4-methoxy-1-methyl-9*H*-carbazole-2,3-diol (**96**) 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 4.01 ppm (3 protons for **71**), 2.45 ppm (3 protons for **94**), 3.96 ppm (3 protons for **95**), 4.06 ppm (3 protons for **96**), and 2.41 ppm (3 protons for **70**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction performed with aqueous HCl (Table 3-3-4, entry 1)

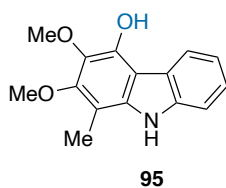
A 10-mL glass screw-thread tube equipped with a Teflon-coated magnetic stirring bar and a screw cup was charged with 2,3,4-trimethoxycarbazole **70** (26.4 mg, 0.0973 mmol, 1.0 equiv) and aqueous HCl (35 wt%, 0.5 mL). After stirring at 50 °C for 18 h, the reaction mixture was treated with water (1 mL). The resulting mixture was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2-hydroxycarbazole **71**, 3-hydroxycarbazole **94**, 4-hydroxycarbazole **95**, and the starting trimethoxycarbazole **70** were determined to be 8%, 3%, 2%, and 63% by ¹H NMR spectroscopy.

Reaction performed with TMSCl and NaI (Table 3-3-4, entry 2)

A flame-dried 5-mL single-necked reaction tube equipped with a Teflon-coated magnetic stirring bar and three-way stopcock under argon was charged with 2,3,4-trimethoxycarbazole **70** (27.2 mg, 0.100 mmol, 1.0 equiv), sodium iodide (75.0 mg, 0.500 mmol, 5.0 equiv), and MeCN (0.3 mL). The resulting solution was cooled to 0 °C. Trimethylsilyl chloride (65 µL, 0.52 mmol, 5.2 equiv) was added dropwise to the reaction tube. After warming to room temperature and stirring for 22 h, the reaction mixture was treated with water (1 mL). The resulting mixture was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2-hydroxycarbazole **71**, 3-hydroxycarbazole **94**, 4-hydroxycarbazole **95**, and the starting trimethoxycarbazole **70** were determined to be 23%, 13%, 9%, and 22% by ¹H NMR spectroscopy.

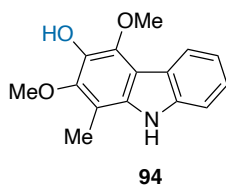
Reaction performed with TESCOI and NaI (Table 3-3-4, entry 3)

A crude product was obtained from 2,3,4-trimethoxycarbazole **70** (26.7 mg, 0.0984 mmol, 1.0 equiv), sodium iodide (75.4 mg, 0.503 mmol, 5.1 equiv), triethylsilyl chloride (85 µL, 0.51 mmol, 5.2 equiv), and MeCN (0.3 mL) for 48 h, according to the above procedure. The yields of 2-hydroxycarbazole **71**, 3-hydroxycarbazole **94**, 4-hydroxycarbazole **95**, and the starting trimethoxycarbazole **70** were determined to be 24%, 23%, 12%, and 29% by ¹H NMR spectroscopy.



Synthesis of 3-dimethoxy-1-methyl-9H-carbazol-4-ol (95) with 1-dodecanethiol and NaOH (Table 3-3-4, entry 4)

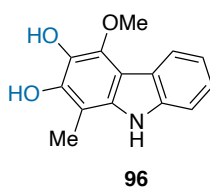
A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar under argon was charged with 2,3,4-trimethoxycarbazole **70** (271.2 mg, 1.00 mmol, 1.0 equiv), sodium hydroxide (380.5 mg, 9.51 mmol, 9.5 equiv), and DMF (10.0 mL). To the mixture was added 1-dodecanethiol (0.36 mL, 1.5 mmol, 1.5 equiv) dropwise at room temperature. After stirring at 130 °C for 12 h, the resulting suspension was treated with aqueous HCl (1 M, 15 mL). The resulting mixture was extracted with ethyl acetate (10 mL) three times. The combined organic extracts were washed with aqueous sodium chloride (10 wt%, 30 mL) three times, 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) and recrystallization (hexane/chloroform = 4:1) to afford the title compound **95** as a pale grey solid (102.4 mg, 0.398 mmol, 40%). R_f = 0.22 (hexane/diethyl ether = 2:1); Mp 154–156 °C; IR (ATR, cm^{-1}): 3426, 2935, 1639, 1614, 1508, 1454, 1415, 1359, 1324, 1305, 1243, 1196, 1147, 1110, 1087, 1025, 1002, 953, 929; ^1H NMR (400 MHz, CDCl_3): δ 8.22 (d, 1H, J = 7.6 Hz), 7.78 (br s, 1H), 7.40 (d, 1H, J = 7.6 Hz), 7.34 (ddd, 1H, J = 7.6, 7.6, 0.8 Hz), 7.22 (ddd, 1H, J = 7.6, 7.6, 0.8 Hz), 6.11 (s, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 2.38 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 149.8, 142.7, 139.5, 136.2, 133.4, 124.6, 123.3, 122.6, 119.8, 110.1, 107.3, 103.9, 61.7, 61.2, 9.9; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_3$ 258.1130; Found 258.1132.



Synthesis of 2,4-dimethoxy-1-methyl-9H-carbazol-3-ol (94) with NbCl_5 (Table 3-3-4, entry 5)

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar under argon was charged with 2,3,4-trimethoxycarbazole **70** (237.0 mg, 0.874 mmol, 1.0 equiv), niobium(V) chloride (247.8 mg, 0.917 mmol, 1.1 equiv), and 1,2-dichloroethane

(9.0 mL). After stirring at 85 °C for 1.5 h, the resulting suspension was treated with water (10 mL). After being partitioned, the aqueous layer was extracted with CH₂Cl₂ (10 mL) three times. The combined organic extracts were washed with brine (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/diethyl ether = 1:1) to afford the title compound **94** as a pale yellow solid (114.5 mg, 0.445 mmol, 51%). *R_f* = 0.23 (hexane/diethyl ether = 1:1); Mp 127–128 °C; IR (ATR, cm⁻¹): 3419, 2930, 1614, 1513, 1456, 1406, 1341, 1319, 1302, 1254, 1225, 1192, 1170, 1149, 1128, 1111, 1080, 1015, 954, 933, 880, 813; ¹H NMR (400 MHz, CDCl₃): δ 8.18 (d, 1H, *J* = 7.6 Hz), 7.78 (br s, 1H), 7.42 (d, 1H, *J* = 7.6 Hz), 7.36 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.21 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 5.39 (s, 1H), 4.10 (s, 3H), 3.92 (s, 3H), 2.45 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 145.5, 139.9, 139.7, 135.9, 133.3, 125.0, 122.5, 122.4, 119.6, 112.3, 110.5, 108.2, 61.6, 60.8, 10.5; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₁₅H₁₆NO₃ 258.1130; Found 258.1131.



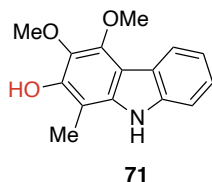
Synthesis of 4-methoxy-1-methyl-9H-carbazole-2,3-diol (96**) with 1.5 equiv of BBr₃ (Table 3-3-4, entry 6)**

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2,3,4-trimethoxycarbazole **70** (271.1 mg, 0.999 mmol, 1.0 equiv) and CH₂Cl₂ (10.0 mL). The resulting solution was cooled to -78 °C. Boron tribromide (1.0 M in CH₂Cl₂, 1.5 mL, 1.5 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0 °C for 1 h, the resulting suspension was treated with water (5 mL). After being partitioned, the aqueous layer was extracted with CH₂Cl₂ (5 mL) three times. The combined organic extracts were washed with brine (10 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 = 2:1) to afford the title compound **96** as a pale brown solid (148.6 mg, 0.611 mmol, 61%). *R_f* = 0.13 (hexane/diethyl ether = 1:1); Mp 168 °C (compound was complete decomposition prior to melting); IR (ATR, cm⁻¹): 3424, 2930, 2915, 1640, 1632, 1619, 1525, 1455, 1429, 1356, 1319, 1284, 1216, 1171, 1150, 1074, 1002, 939, 888; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.72 (s, 1H), 8.41 (s, 1H), 8.35 (s, 1H), 7.93 (d, 1H, *J* = 7.6 Hz), 7.36 (d, 1H, *J* = 7.6 Hz), 7.21 (ddd, 1H, *J* = 7.6, 7.6, 0.8 Hz), 7.04 (ddd,

1H, $J = 7.6, 7.6, 0.8$ Hz), 3.89 (s, 3H), 2.29 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 144.7, 140.5, 139.4, 134.1, 131.4, 123.1, 122.0, 120.7, 118.1, 110.2, 107.4, 101.3, 59.8, 10.5; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3$ 244.0974; Found 244.0976.

Synthesis of 3,4-dimethoxy-1-methyl-9H-carbazol-2-ol (**71**) with 1.0 equiv of BBr_3 at -60°C (entry 7)

A flame-dried 3-mL single-necked reaction tube equipped with a Teflon-coated magnetic stirring bar, a three-way stopcock, and a rubber septum under argon was charged with 2,3,4-trimethoxycarbazole **70** (27.2 mg, 0.100 mmol, 1.0 equiv) and CH_2Cl_2 (1.0 mL). The resulting solution was cooled to -78°C . Boron tribromide (1.0 M in CH_2Cl_2 , 100 μL , 0.1 mmol, 1.0 equiv) was added to the single-necked tube. After stirring at -60°C for 2.5 h, the resulting suspension was treated with water (1 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (1 mL) three times. The combined organic extracts were washed with brine (1 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2-hydroxycarbazole **71**, 3-hydroxycarbazole **94**, catechol **96**, and the starting trimethoxycarbazole **70** were determined to be 38%, 3%, 18%, and 41% by ^1H NMR spectroscopy.

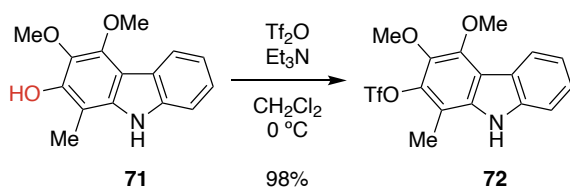


Synthesis of 3,4-dimethoxy-1-methyl-9H-carbazol-2-ol (**71**) with BCl_3 (Table 3-3-4, entry 8)

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2,3,4-trimethoxycarbazole **70** (1.228 g, 4.53 mmol, 1.0 equiv) and CH_2Cl_2 (22.0 mL). The resulting solution was cooled to -78°C . Boron trichloride (1.0 M in CH_2Cl_2 , 6.8 mL, 6.8 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at 0°C for 3 h, the resulting solution was treated with water (5 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (5 mL) three times. The combined organic extracts were washed with brine (10 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 = 1:1) to afford the title compound **71** as a colorless solid (760.4

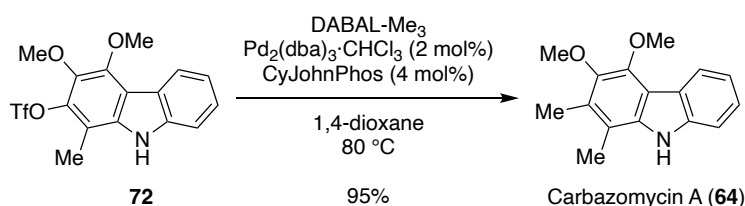
mg, 2.96 mmol, 65%). R_f = 0.32 (hexane/diethyl ether = 1:1); Mp 128–130 °C; IR (ATR, cm^{-1}): 3431, 2937, 1616, 1517, 1456, 1409, 1341, 1320, 1297, 1251, 1167, 1150, 1079, 1036, 974, 881, 746, 640; ^1H NMR (400 MHz, CDCl_3): δ 8.15 (d, 1H, J = 8.0 Hz), 7.81 (br s, 1H), 7.40 (d, 1H, J = 8.0 Hz), 7.32 (ddd, 1H, J = 8.0, 8.0, 1.2 Hz), 7.20 (ddd, 1H, J = 8.0, 8.0, 1.2 Hz), 6.03 (s, 1H), 4.09 (s, 3H), 4.01 (s, 3H), 2.39 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 146.5, 145.4, 139.2, 136.6, 134.0, 124.3, 123.2, 121.9, 119.8, 110.2, 109.0, 100.4, 61.8, 60.7, 9.9; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_3$ 258.1130; Found 258.1137.

7. Synthesis of Carbazomycins A, C, and D (Scheme 3-3-6)



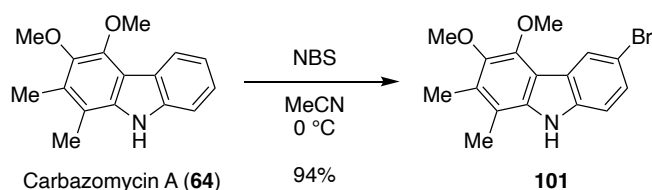
3,4-Dimethoxy-1-methyl-9H-carbazol-2-yl trifluoromethanesulfonate (**72**)

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2-hydroxycarbazole **71** (731.9 mg, 2.84 mmol, 1.0 equiv), triethylamine (1.20 mL, 8.60 mmol, 3.0 equiv), and CH_2Cl_2 (28.0 mL). The resulting solution was cooled to $0\text{ }^\circ\text{C}$. Trifluoromethanesulfonic anhydride (0.72 mL, 4.3 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at $0\text{ }^\circ\text{C}$ for 2 h, the reaction mixture was treated with water (5 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (5 mL) three times. The combined organic extracts were washed with brine (10 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 = 3:1) to afford the title compound **72** as a pale brown solid (1.080 g, 2.77 mmol, 98%). R_f = 0.18 (hexane/diethyl ether = 3:1); Mp 87–88 °C; IR (ATR, cm^{-1}): 3444, 2944, 1506, 1456, 1415, 1313, 1246, 1211, 1136, 1059, 1038, 972, 887, 839, 751, 613; ^1H NMR (400 MHz, CDCl_3): δ 8.26 (d, 1H, J = 8.0 Hz), 7.99 (br s, 1H), 7.48–7.41 (m, 2H), 7.30–7.24 (m, 1H), 4.15 (s, 3H), 3.99 (s, 3H), 2.50 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 146.6, 140.2, 139.9, 138.1, 135.0, 126.3, 123.1, 122.2, 120.4, 118.9 (q, $^1J_{\text{C-F}}$ = 318 Hz), 115.8, 110.7, 108.6, 61.9, 60.9, 11.1; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{NO}_5\text{S}$ 390.0623; Found 390.0613.



Carbazomycin A (**64**)

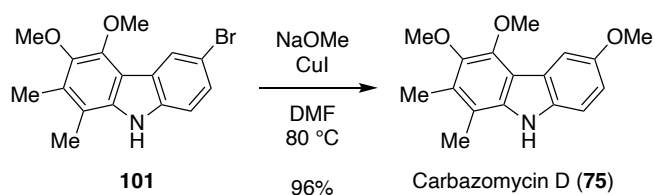
A flame-dried 300-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock under argon was charged with triflate **72** (2.415 g, 6.20 mmol, 1.0 equiv), bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me₃) (1.594 g, 6.22 mmol, 1.0 equiv), Pd₂(dba)₃·CHCl₃ (128.6 mg, 0.124 mmol, 2 mol%), 2-(dicyclohexylphosphino)biphenyl (CyJohnPhos) (87.7 mg, 0.250 mmol, 4 mol%), and anhydrous 1,4-dioxane (124 mL). After stirring at 80 °C for 4 h, the reaction mixture was treated with saturated aqueous ammonium chloride (30 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL) three times. The combined organic extracts were washed with brine (50 mL) five times, 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 afford carbazomycin A (**64**) as a pale yellow solid (1.505 g, 5.89 mmol, 95%), whose ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.^{45,71} *R*_f = 0.38 (hexane/diethyl ether = 2:1); Mp 131–132 °C; IR (ATR, cm⁻¹): 3417, 3351, 2935, 1612, 1501, 1455, 1396, 1318, 1293, 1166, 1149, 1089, 1052, 1014, 745; ¹H NMR (400 MHz, CDCl₃): δ 8.23 (d, 1H, *J* = 8.0 Hz), 7.82 (br s, 1H), 7.43–7.35 (m, 2H), 7.24–7.19 (m, 1H), 4.11 (s, 3H), 3.90 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 146.1, 144.6, 139.5, 136.5, 128.9, 125.2, 122.9, 122.6, 119.6, 114.5, 113.7, 110.4, 61.3, 60.7, 13.8, 12.8; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₁₆H₁₈NO₂ 256.1338; Found 256.1348.



6-Bromo-3,4-dimethoxy-1,2-dimethyl-9*H*-carbazole (**101**)

A 200-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with carbazomycin A (**64**) (1.618 g, 6.34 mmol, 1.0 equiv) and MeCN (32.0 mL). The resulting solution was cooled to 0 °C. *N*-Bromosuccinimide

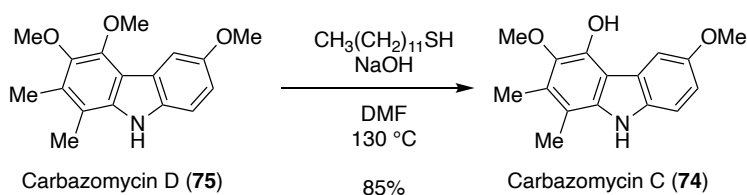
(1.242 g, 6.98 mmol, 1.1 equiv) was added portionwise to the flask. After stirring at 0 °C for 30 min, the reaction mixture was treated with saturated aqueous sodium thiosulfate (10 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (10 mL) three times. The combined organic extracts were washed with aqueous sodium chloride (10 wt%, 10 mL) three times, 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 afford the title compound **101** as a colorless solid (1.989 g, 5.95 mmol, 94%). R_f = 0.27 (hexane/diethyl ether = 2:1); Mp 119–121 °C; IR (ATR, cm^{-1}): 3439, 3355, 2933, 1624, 1608, 1501, 1446, 1388, 1337, 1293, 1251, 1216, 1191, 1159, 1124, 1088, 1059, 1044, 1007, 971, 899, 882; ^1H NMR (400 MHz, CDCl_3): δ 8.33 (d, 1H, J = 2.0 Hz), 7.82 (br s, 1H), 7.45 (dd, 1H, J = 8.6, 2.0 Hz), 7.28 (d, 1H, J = 8.6 Hz), 4.11 (s, 3H), 3.88 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 146.1, 144.7, 138.0, 136.8, 130.0, 127.9, 125.2, 124.8, 113.8, 113.7, 112.2, 111.8, 61.1, 60.7, 13.8, 12.8; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{17}^{79}\text{BrNO}_2$ 334.0443; Found 334.0436.



Carbazomycin D (**75**)

A 500-mL oven-dried three-necked round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, a three-way stopcock, and a condenser under argon was charged with MeOH (45.0 mL). Sodium metal (4.100 g, 0.178 mol) was added portionwise over 1.5 h to the flask. After stirring at room temperature for 1 h, the fresh sodium methoxide (4 M in MeOH, 45 mL) was obtained as a pale yellow solution. To the resulting solution was added bromocarbazole **101** (1.824 g, 5.46 mmol, 1.0 equiv), copper(I) iodide (2.080 g, 10.9 mmol, 2.0 equiv), and DMF (55.0 mL). After stirring at 80 °C for 16 h, the reaction mixture was treated with saturated aqueous ammonium chloride (30 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were washed with aqueous sodium chloride (10 wt%, 50 mL) three times, 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 afford carbazomycin D (**75**) as a colorless solid (1.492 g, 5.23 mmol, 96%), whose ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.^{72a,77}

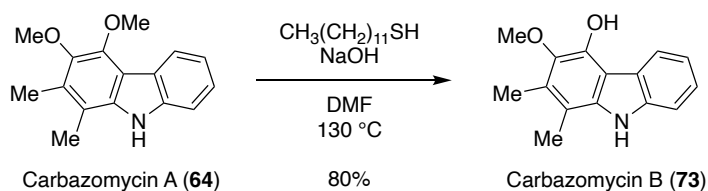
$R_f = 0.28$ (hexane/diethyl ether = 2:1); Mp 114–116 °C; IR (ATR, cm^{-1}): 3356, 2934, 1629, 1583, 1501, 1483, 1461, 1439, 1391, 1339, 1290, 1260, 1215, 1192, 1178, 1143, 1110, 1088, 1051, 1031, 1008, 973, 902, 851, 805; ^1H NMR (400 MHz, acetone- d_6): δ 9.86 (br s, 1H), 7.70 (d, 1H, $J = 2.6$ Hz), 7.34 (d, 1H, $J = 8.8$ Hz), 6.97 (dd, 1H, $J = 8.8$, 2.6 Hz), 4.06 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 2.41 (s, 3H), 2.33 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- d_6): δ 154.4, 146.6, 144.6, 138.6, 135.8, 129.1, 123.8, 115.0, 114.7, 114.6, 112.0, 105.8, 61.0, 60.6, 56.0, 13.7, 12.7; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3$ 286.1443; Found 286.1446.



Carbazomycin C (74)

An oven-dried 200-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock under argon was charged with carbazomycin D (**75**) (1.375 g, 4.82 mmol, 1.0 equiv), sodium hydroxide (2.050 g, 51.3 mmol, 10.6 equiv), and DMF (48.0 mL). To the mixture was added dropwise 1 dodecanethiol (1.7 mL, 7.1 mmol, 1.5 equiv) at room temperature. After stirring at 130 °C for 12 h, the resulting suspension was treated with aqueous HCl (2 M, 30 mL). The resulting mixture was extracted with ethyl acetate (20 mL) three times. The combined organic extracts were washed with aqueous sodium chloride (10 wt%, 50 mL) three times, 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 afford carbazomycin C (**74**) as a yellow solid (1.115 g, 4.11 mmol, 85%), whose ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.^{72a} R_f = 0.18 (hexane/diethyl ether = 2:1); Mp 198–199 °C; IR (ATR, cm⁻¹): 3440, 3334, 2937, 1637, 1590, 1503, 1484, 1161, 1438, 1409, 1323, 1294, 1215, 1190, 1176, 1138, 1108, 1084, 1028, 1002, 886, 850, 805; ¹H NMR (400 MHz, acetone-*d*₆): δ 9.73 (br s, 1H), 8.05 (s, 1H), 7.76 (d, 1H, *J* = 2.8 Hz), 7.31 (d, 1H, *J* = 8.8 Hz), 6.92 (dd, 1H, *J* = 8.8, 2.8 Hz), 3.85 (s, 3H), 3.74 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H); ¹³C{¹H} NMR (100 MHz, acetone-*d*₆): δ 154.3, 143.7, 139.0, 138.9, 135.6, 128.0, 124.7, 113.9, 111.6, 110.8, 109.8, 106.1, 61.4, 56.0, 13.3, 12.8; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₁₆H₁₈NO₃ 272.1287; Found 272.1291.

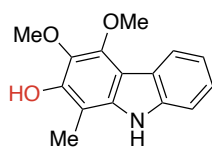
8. Synthesis of carbazomycin B (Scheme 3-3-7)



Carbazomycin B (**73**)

An oven-dried 200-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock under argon was charged with carbazomycin A (**64**) (1.502 g, 5.88 mmol, 1.0 equiv), sodium hydroxide (2.413 g, 60.3 mmol, 10 equiv), and DMF (59.0 mL). To the mixture was added dropwise 1-dodecanethiol (2.1 mL, 8.8 mmol, 1.5 equiv) at room temperature. After stirring at 130 °C for 13 h, the resulting suspension was treated with aqueous HCl (2 M, 35 mL). The resulting mixture was extracted with ethyl acetate (30 mL) three times. The combined organic extracts were washed with aqueous sodium chloride (10 wt%, 100 mL) three times, 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 afford carbazomycin B (**73**) as a pale yellow solid (1.141 g, 4.73 mmol, 80%), whose ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.^{45b,71,72a,75a} R_f = 0.26 (hexane/diethyl ether = 2:1); Mp 148–150 °C; IR (ATR, cm^{-1}): 3433, 3385, 2940, 1640, 1614, 1502, 1454, 1412, 1322, 1301, 1244, 1146, 1085, 1003, 874; ^1H NMR (400 MHz, CDCl_3): δ 8.24 (d, 1H, J = 8.0 Hz), 7.78 (br s, 1H), 7.42–7.32 (m, 2H), 7.28–7.18 (m, 1H), 6.03 (s, 1H), 3.83 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 142.1, 139.3, 138.5, 136.9, 127.1, 124.9, 123.4, 122.8, 119.6, 110.1, 109.4, 61.7, 13.4, 12.9 (one aromatic carbon signal is missing because of overlapping); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- d_6): δ 143.8, 140.8, 139.4, 138.1, 128.0, 124.9, 124.3, 123.1, 119.2, 111.0, 110.6, 109.7, 61.4, 13.4, 12.8; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_2$ 242.1181; Found 242.1183.

9. X-Ray Crystallographic Data



71

CCDC: 2324242

3,4-Dimethoxy-1-methyl-9*H*-carbazol-2-ol (**71**)

The single crystals were obtained by vapor diffusion crystallization from hexane/ethyl acetate. X-ray crystallographic data were collected at $-173\text{ }^{\circ}\text{C}$ on a Rigaku Saturn724 diffractometer with $\text{MoK}\alpha$ radiation. X-ray crystallographic data were collected on a Rigaku Saturn724 diffractometer with $\text{MoK}\alpha$ radiation. The structures were solved by a direct method (SHELXT)¹ and refined using a full-matrix least squares technique (SHELXL).

Space Group: $C 2/c$

Cell: $a\ 16.2213(8)\text{\AA}$ $b\ 16.5859(8)\text{\AA}$ $c\ 18.3221(9)\text{\AA}$, $\alpha\ 90^{\circ}$ $\beta\ 94.863(4)^{\circ}$ $\gamma\ 90^{\circ}$

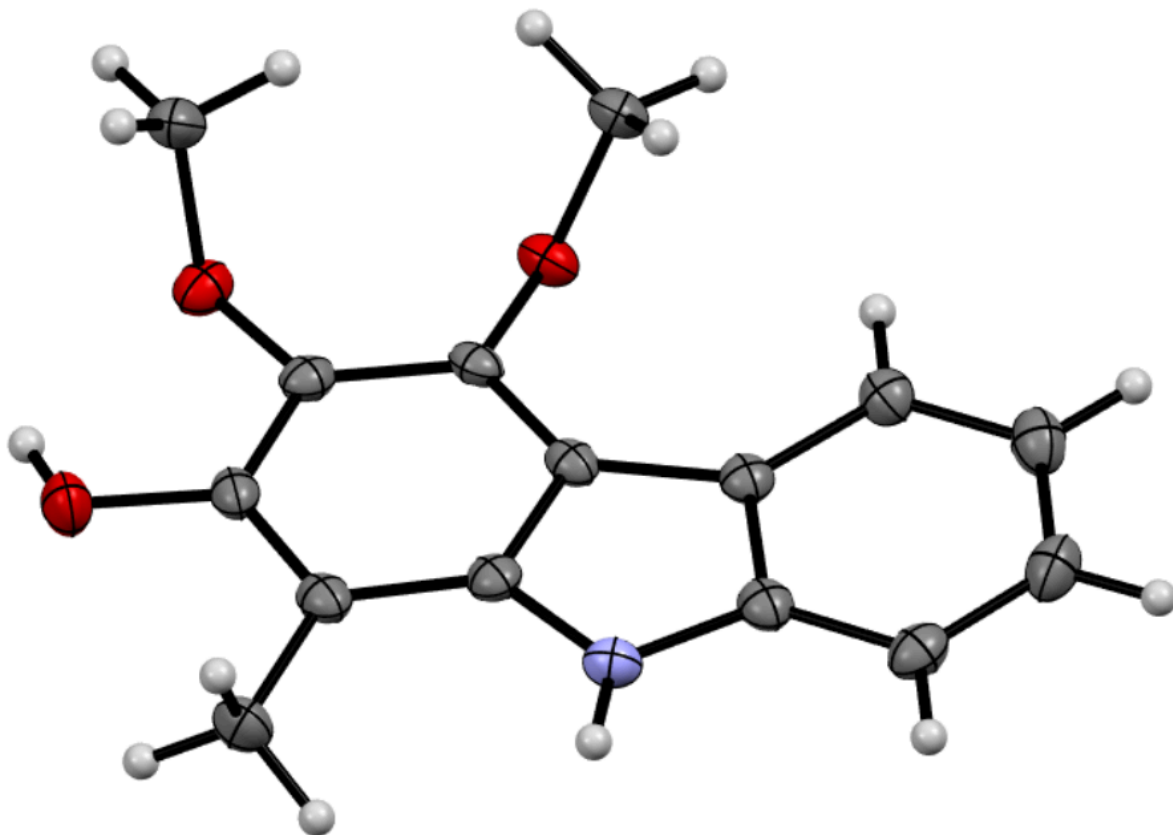
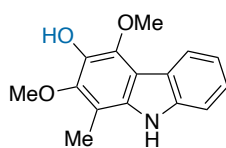


Figure S1. ORTEP drawing of the molecular structure of compound **71** with thermal ellipsoids at 50% probability levels.



94

CCDC: 2324243

2,4-Dimethoxy-1-methyl-9*H*-carbazol-3-ol (**94**)

The single crystals were obtained by vapor diffusion crystallization from hexane/diethyl ether. X-ray crystallographic data were collected at $-173\text{ }^{\circ}\text{C}$ on a Rigaku Saturn724 diffractometer with MoK α radiation. X-ray crystallographic data were collected on a Rigaku Saturn724 diffractometer with MoK α radiation. The structures were solved by a direct method (SHELXT)¹ and refined using a full-matrix least squares technique (SHELXL).²

Space Group: Pna21

Cell: $a\ 13.489\text{\AA}$ $b\ 8.262\text{\AA}$ $c\ 11.593\text{\AA}$, $\alpha\ 90^{\circ}$ $\beta\ 90^{\circ}$ $\gamma\ 90^{\circ}$

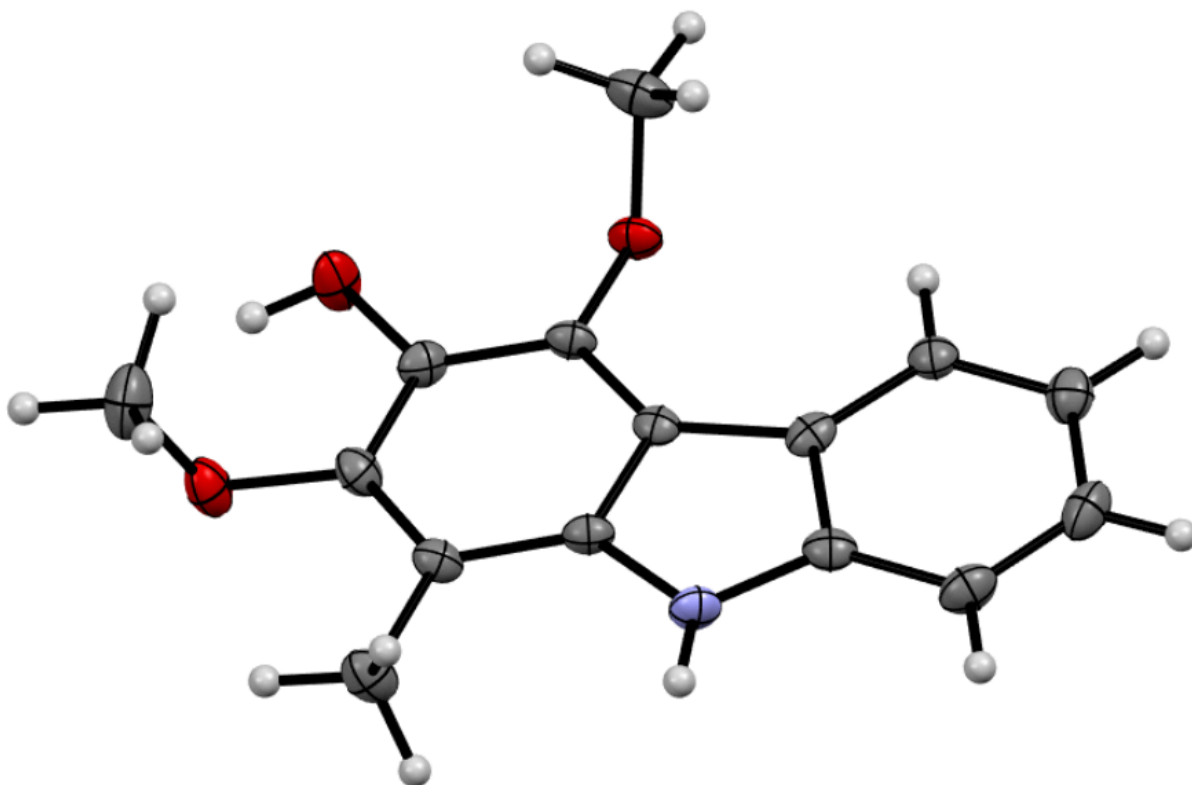
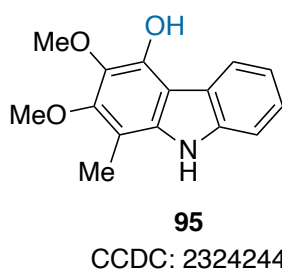


Figure S2. ORTEP drawing of the molecular structure of compound **94** with thermal ellipsoids at 50% probability levels.



3-Dimethoxy-1-methyl-9H-carbazol-4-ol (95)

The single crystals were obtained by vapor diffusion crystallization from hexane/ethyl acetate. X-ray crystallographic data were collected at $-173\text{ }^{\circ}\text{C}$ on a Rigaku Saturn724 diffractometer with $\text{MoK}\alpha$ radiation. X-ray crystallographic data were collected on a Rigaku Saturn724 diffractometer with $\text{MoK}\alpha$ radiation. The structures were solved by a direct method (SHELXT)¹ and refined using a full-matrix least squares technique (SHELXL).

Space Group: P b c a

Cell: a 11.6001(6)Å b 11.1395(7)Å c 19.9966(11)Å, α 90° β 90° γ 90°

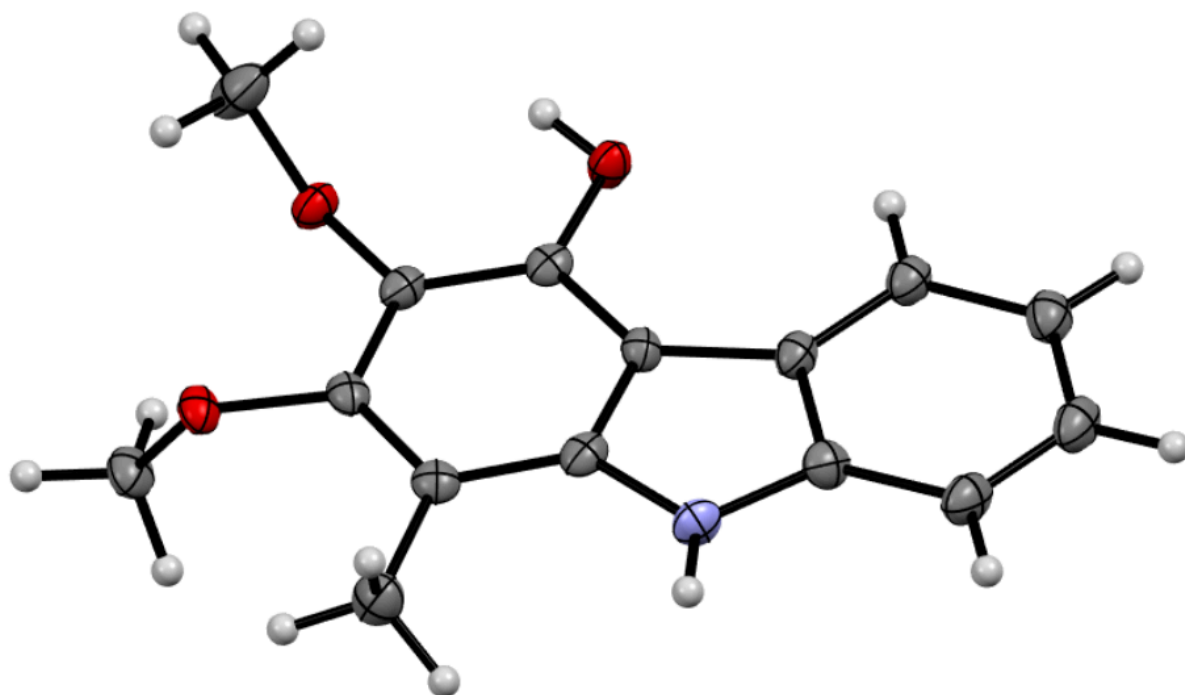
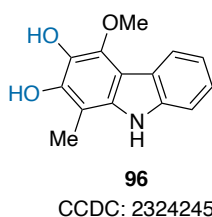


Figure S3. ORTEP drawing of the molecular structure of compound **95** with thermal ellipsoids at 50% probability levels.



4-Methoxy-1-methyl-9*H*-carbazole-2,3-diol (**96**)

The single crystals were obtained by vapor diffusion crystallization from hexane/ethyl acetate. X-ray crystallographic data were collected at $-173\text{ }^{\circ}\text{C}$ on a Rigaku Saturn724 diffractometer with $\text{MoK}\alpha$ radiation. X-ray crystallographic data were collected on a Rigaku Saturn724 diffractometer with $\text{MoK}\alpha$ radiation. The structures were solved by a direct method (SHELXT)¹ and refined using a full-matrix least squares technique (SHELXL).²

Space Group: P 2₁/n

Cell: $a\ 7.5329(4)\text{\AA}$ $b\ 9.6129(4)\text{\AA}$ $c\ 17.1761(8)\text{\AA}$, $\alpha\ 90^{\circ}$ $\beta\ 101.946(5)^{\circ}$ $\gamma\ 90^{\circ}$

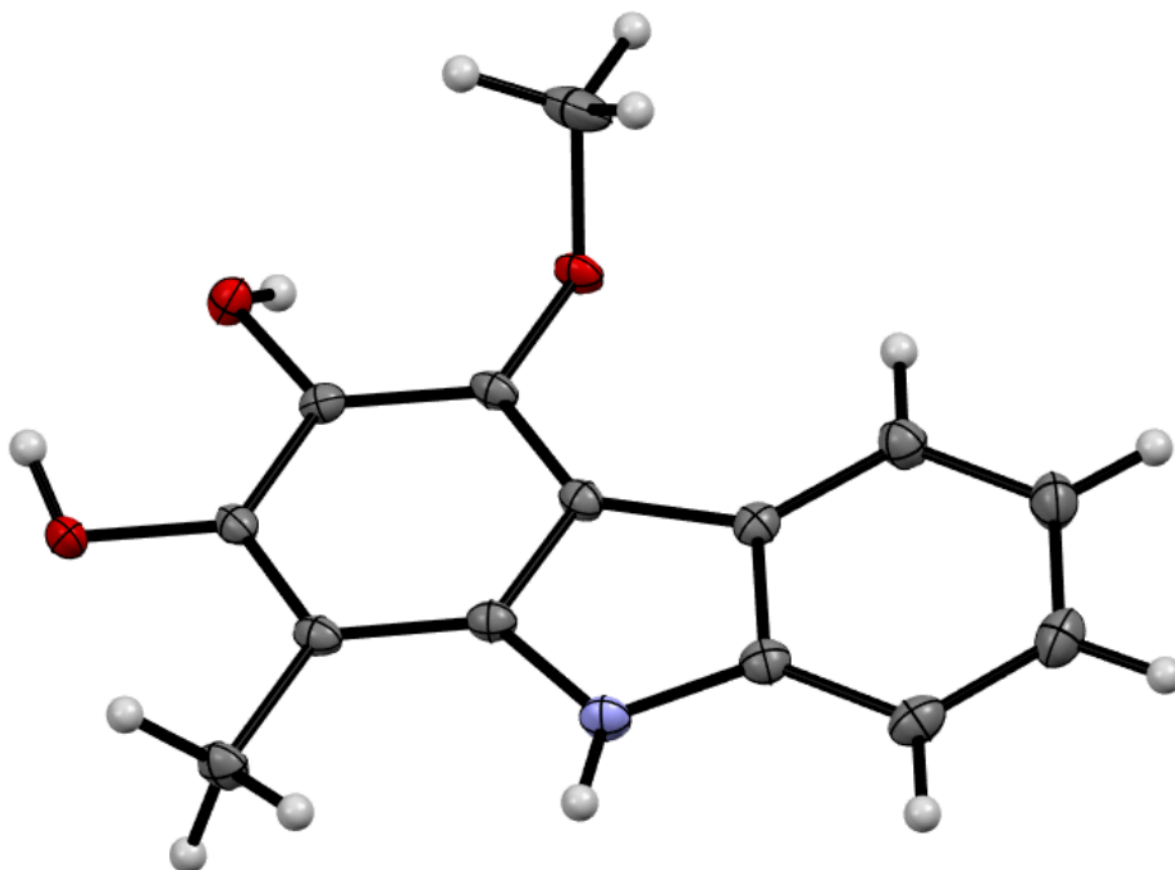


Figure S4. ORTEP drawing of the molecular structure of compound **96** with thermal ellipsoids at 50% probability levels.

10. Tabular comparisons of NMR Data of carbazomycins A–D

10.1 Tabular comparisons of NMR data of carbazomycin A

Table S5. Chemical shifts of ^1H NMR in CDCl_3 for natural and synthetic carbazomycin A

Natural (100 MHz) ^{45b}	Our Synthetic (400 MHz)	Δ
8.25 (dd, 1H, $J = 7.0, 2.0$ Hz)	8.23 (d, 1H, $J = 8.0$ Hz)	−0.02
7.89 (brs, 1H)	7.82 (brs, 1H)	−0.07
7.42–7.13 (m, 3H)	7.43–7.35 (m, 2H), 7.24–7.19 (m, 1H)	–
4.13 (s, 3H)	4.11 (s, 3H)	−0.02
3.92 (s, 3H)	3.90 (s, 3H)	−0.02
2.40 (s, 3H)	2.41 (s, 3H)	0.01
2.40 (s, 3H)	2.39 (s, 3H)	−0.01

Table S5. Chemical shifts of ^1H NMR in CDCl_3 for Knölker's and our synthetic carbazomycin A

Knölker's Synthetic (200 MHz) ⁷¹	Our Synthetic (400 MHz)	Δ
8.23 (dd, 1H, $J = 7.6, 0.5$ Hz)	8.23 (d, 1H, $J = 8.0$ Hz)	0.00
7.82 (brs, 1H)	7.82 (brs, 1H)	0.00
7.45–7.15 (m, 3H)	7.43–7.35 (m, 2H), 7.24–7.19 (m, 1H)	–
4.10 (s, 3H)	4.11 (s, 3H)	0.01
3.89 (s, 3H)	3.90 (s, 3H)	0.01
2.40 (s, 3H)	2.41 (s, 3H)	0.01
2.38 (s, 3H)	2.39 (s, 3H)	0.01

Table S6. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in CDCl_3 for natural and our synthetic carbazomycin A

Natural (25 MHz) ^{45b}	Our Synthetic (100 MHz)	Δ
145.9	146.1	0.2
144.4	144.6	0.2
139.4	139.5	0.1
136.4	136.5	0.1
128.7	128.9	0.2
125.0	125.2	0.2
122.8	122.9	0.1
122.5	122.6	0.1
119.4	119.6	0.2
114.4	114.5	0.1
113.5	113.7	0.2
110.3	110.4	0.1
61.1	61.3	0.2
60.5	60.7	0.2
13.6	13.8	0.2
12.6	12.8	0.2

Table S7. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in CDCl_3 for Knölker's and our synthetic carbazomycin A

Knölker's Synthetic (75 MHz) ⁷¹	Our Synthetic (100 MHz)	Δ
146.1	146.1	0.0
144.6	144.6	0.0
139.5	139.5	0.0
136.5	136.5	0.0
128.9	128.9	0.0
125.1	125.2	0.1
123.0	122.9	−0.1
122.6	122.6	0.0
119.5	119.6	0.1
114.6	114.5	−0.1
113.5	113.7	0.2
110.3	110.4	0.1
61.1	61.3	0.2
60.5	60.7	0.2
13.6	13.8	0.2
12.6	12.8	0.2

10.2 Tabular comparisons of NMR data of carbazomycin B

Table S8. Chemical shifts of ^1H NMR in CDCl_3 for natural and synthetic carbazomycin B

Natural (100 MHz) ^{45b}	Our Synthetic (400 MHz)	Δ
8.31 (dd, 1H, $J = 7.0, 2.0$ Hz)	8.24 (d, 1H, $J = 8.0$ Hz)	−0.07
7.71 (brs, 1H)	7.78 (brs, 1H)	−0.07
7.38–7.14 (m, 3H)	7.42–7.32 (m, 2H), 7.28–7.18 (m, 1H)	–
6.21 (brs, 1H)	6.03 (s, 1H)	−0.18
3.80 (s, 3H)	3.83 (s, 3H)	0.03
2.36 (s, 3H)	2.40 (s, 3H)	0.04
2.28 (s, 3H)	2.38 (s, 3H)	0.10

Table S9. Chemical shifts of ^1H NMR in CDCl_3 for Knölker's and our synthetic carbazomycin B

Knölker's Synthetic (300 MHz) ⁷¹	Our Synthetic (400 MHz)	Δ
8.24 (d, 1H, $J = 7.7$ Hz)	8.24 (d, 1H, $J = 8.0$ Hz)	0.00
7.77 (brs, 1H)	7.78 (brs, 1H)	0.01
7.45–7.15 (m, 3H)	7.42–7.32 (m, 2H), 7.28–7.18 (m, 1H)	–
6.04 (s, 1H)	6.03 (s, 1H)	−0.01
3.82 (s, 3H)	3.83 (s, 3H)	0.01
2.39 (s, 3H)	2.40 (s, 3H)	0.01
2.37 (s, 3H)	2.38 (s, 3H)	0.01

Table S10. Chemical shifts of ^1H NMR in CDCl_3 for Moody's and our synthetic carbazomycin B

Moody's Synthetic (270 MHz) ^{75a}	Our Synthetic (400 MHz)	Δ
8.25 (d, 1H, $J = 7.8$ Hz)	8.24 (d, 1H, $J = 8.0$ Hz)	−0.01
7.77 (brs, 1H)	7.78 (brs, 1H)	0.01
7.42–7.32 (m, 2H)	7.42–7.32 (m, 2H)	–
7.22 (t, 1H, $J = 6.9$ Hz)	7.28–7.18 (m, 1H)	–
6.05 (s, 1H)	6.03 (s, 1H)	−0.02
3.83 (s, 3H)	3.83 (s, 3H)	0.00
2.40 (s, 3H)	2.40 (s, 3H)	0.00
2.37 (s, 3H)	2.38 (s, 3H)	0.01

Table S11. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in CDCl_3 for natural and our synthetic carbazomycin B

Natural (25 MHz) ^{45b}	Our Synthetic (100 MHz)	Δ
142.0	142.1	0.1
139.3	139.3	0.0
138.5	138.5	0.0
136.8	136.9	0.1
127.0	127.1	0.1
124.7	124.9	0.2
123.3	123.4	0.1
122.7	122.8	0.1
119.5	119.6	0.1
110.0	110.1	0.1
110.0	not observed	—
109.3	109.4	0.1
61.4	61.7	0.3
13.1	13.4	0.3
12.7	12.9	0.2

Table S12. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in acetone- d_6 for natural and our Synthetic carbazomycin B

Natural (25 MHz) ^{72a}	Our Synthetic (100 MHz)	Δ
143.6	143.8	0.2
140.7	140.8	0.1
139.3	139.4	0.1
137.9	138.1	0.2
127.8	128.0	0.2
124.8	124.9	0.1
124.3	124.3	0.0
123.1	123.1	0.0
119.2	119.2	0.0
111.0	111.0	0.0
110.6	110.6	0.0
109.7	109.7	0.0
61.3	61.4	0.1
13.3	13.4	0.1
12.8	12.8	0.0

Table S13. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in CDCl_3 for Knölker's and our synthetic carbazomycin B

Knölker's Synthetic (75 MHz) ⁷¹	Our Synthetic (100 MHz)	Δ
142.1	142.1	0.0
139.3	139.3	0.0
138.5	138.5	0.0
136.8	136.9	0.1
127.0	127.1	0.1
124.7	124.9	0.2
123.3	123.4	0.1
122.7	122.8	0.1
119.5	119.6	0.1
110.0	110.1	0.1
109.5	not observed	—
109.4	109.4	0.0
61.5	61.7	0.2
13.1	13.4	0.3
12.7	12.9	0.2

10.3 Tabular comparisons of NMR data of carbazomycin C

Table S14. Chemical shifts of ^1H NMR in acetone- d_6 for natural and synthetic carbazomycin C

Natural (100 MHz) ^{72a}	Our Synthetic (400 MHz)	Δ
9.76 (brs, 1H)	9.73 (brs, 1H)	−0.03
8.06 (s, 1H)	8.05 (s, 1H)	−0.01
7.77 (d, 1H, $J = 2.4$ Hz)	7.76 (d, 1H, $J = 2.8$ Hz)	−0.01
7.31 (d, 1H, $J = 8.8$ Hz)	7.31 (d, 1H, $J = 8.8$ Hz)	0.00
6.91 (dd, 1H, $J = 8.8, 2.4$ Hz)	6.92 (dd, 1H, $J = 8.8, 2.8$ Hz)	0.01
3.84 (s, 3H)	3.85 (s, 3H)	0.01
3.74 (s, 3H)	3.74 (s, 3H)	0.00
2.36 (s, 3H)	2.37 (s, 3H)	0.01
2.33 (s, 3H)	2.34 (s, 3H)	0.01

Table S15. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in acetone- d_6 for natural and our synthetic carbazomycin C

Natural (25 MHz) ^{72a}	Our Synthetic (100 MHz)	Δ
154.0	154.3	0.3
143.6	143.7	0.1
139.0	139.0	0.0
138.9	138.9	0.0
135.6	135.6	0.0
127.9	128.0	0.1
124.7	124.7	0.0
113.9	113.9	0.0
111.5	111.6	0.1
110.8	110.8	0.0
109.8	109.8	0.0
106.2	106.1	−0.1
61.3	61.4	0.1
56.0	56.0	0.0
13.4	13.3	−0.1
12.8	12.8	0.0

10.4 Tabular comparisons of NMR data of carbazomycin D

Table S16. Chemical shifts of ^1H NMR in acetone- d_6 for natural and synthetic carbazomycin D

Natural (100 MHz) ^{72a}	Our Synthetic (400 MHz)	Δ
9.98 (brs, 1H)	9.86 (brs, 1H)	−0.12
7.71 (d, 1H, $J = 2.4$ Hz)	7.70 (d, 1H, $J = 2.6$ Hz)	−0.01
7.36 (d, 1H, $J = 8.8$ Hz)	7.34 (d, 1H, $J = 8.8$ Hz)	−0.02
6.97 (dd, 1H, $J = 8.8, 2.4$ Hz)	6.97 (dd, 1H, $J = 8.8, 2.6$ Hz)	0.00
4.06 (s, 3H)	4.06 (s, 3H)	0.00
3.87 (s, 3H)	3.87 (s, 3H)	0.00
3.83 (s, 3H)	3.83 (s, 3H)	0.00
2.40 (s, 3H)	2.41 (s, 3H)	0.01
2.32 (s, 3H)	2.33 (s, 3H)	0.01

Table S17. Chemical shifts of ^1H NMR in acetone- d_6 for Catellani's and our synthetic carbazomycin D

Catellani's Synthetic (300 MHz) ⁷⁷	Our Synthetic (400 MHz)	Δ
9.88 (brs, 1H)	9.86 (brs, 1H)	−0.02
7.71 (d, 1H, $J = 2.6$ Hz)	7.70 (d, 1H, $J = 2.4$ Hz)	−0.01
7.36 (d, 1H, $J = 8.6$ Hz)	7.34 (d, 1H, $J = 8.8$ Hz)	−0.02
6.98 (dd, 1H, $J = 8.6, 2.6$ Hz)	6.97 (dd, 1H, $J = 8.8, 2.6$ Hz)	−0.01
4.07 (s, 3H)	4.06 (s, 3H)	−0.01
3.88 (s, 3H)	3.87 (s, 3H)	−0.01
3.84 (s, 3H)	3.83 (s, 3H)	−0.01
2.42 (s, 3H)	2.41 (s, 3H)	−0.01
2.34 (s, 3H)	2.33 (s, 3H)	−0.01

Table S18. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in acetone- d_6 for natural and our synthetic carbazomycin D

Natural (25 MHz) ^{72a}	Our Synthetic (100 MHz)	Δ
154.4	154.4	0.0
146.6	146.6	0.0
144.5	144.6	0.1
138.7	138.6	−0.1
135.9	135.8	−0.1
129.0	129.1	0.1
123.8	123.8	0.0
115.0	115.0	0.0
114.5	114.7	0.2
114.5	114.6	0.1
112.0	112.0	0.0
105.9	105.8	−0.1
61.0	61.0	0.0
60.6	60.6	0.0
56.0	56.0	0.0
13.7	13.7	0.0
12.7	12.7	0.0

Table S19. Chemical shifts of $^{13}\text{C}\{^1\text{H}\}$ NMR in acetone- d_6 for Catellani's and our synthetic carbazomycin D

Catellani's Synthetic (75 MHz) ⁷⁷	Our Synthetic (100 MHz)	Δ
154.4	154.4	0.0
146.7	146.6	-0.1
144.6	144.6	0.0
138.7	138.6	-0.1
135.9	135.8	-0.1
129.1	129.1	0.0
123.8	123.8	0.0
115.0	115.0	0.0
114.6	114.7	0.1
114.6	114.6	0.0
112.0	112.0	0.0
105.8	105.8	0.0
61.0	61.0	0.0
60.6	60.6	0.0
56.0	56.0	0.0
13.7	13.7	0.0
12.7	12.7	0.0

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- ⁸⁷ Sudo, Y.; Arai, S.; Nishida, A. Facile and regioselective dealkylation of alkyl aryl ethers using niobium(V) pentachloride. *Eur. J. Org. Chem.* **2006**, 752–758.
- ⁸⁸ CCDC 2324243 contains the supplementary crystallographic data for compound **94**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- ⁸⁹ Mcomie, J. F. W.; Watts, M. L.; West, D. E. Demethylation of aryl methyl ethers by boron tribromide. *Tetrahedron* **1968**, *24*, 2289–2292.
- ⁹⁰ CCDC 2324245 contains the supplementary crystallographic data for compound **96**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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- ⁹² Wilcox, C. F., Jr.; Seager, M. A. Cleavage of hindered aromatic ethers. Kinetics. *J. Org. Chem.* **1969**, *34*, 2319–2323.
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第四章

ヘテロアレーンの C-2 位選択的な官能基化

4-1 序論

第二章では、従来取り扱いが困難であった 2-ハロフェニルリチウムが、塩化亜鉛ジアミン錯体を用いた *in situ* トランスメタル化によって利用可能になることを示した。すなわち、脱プロトン化により生成したハロフェニルリチウムは、*in situ* トランスメタル化され、安定な有機亜鉛種へと変換される。さらにさまざまな求電子剤との反応により、対応するハロベンゼン誘導体が効率的に合成できる。本章では、この手法の基質一般性をハロピリジンとその他のヘテロアレーンへと拡張し、*in situ* トランスメタル化によるさまざまなヘテロアレーンの C-2 位選択的な官能基化について詳述する。

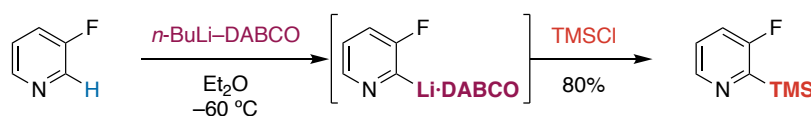
4-2 ハロピリジン誘導体の C-2 位選択的な官能基化

ピリジン誘導体は、医薬品、農薬、天然物などに広く存在している^{1b,99}。米国食品医薬品局 (FDA) による最近の分析によれば、過去 10 年間 (2013–2023 年) に承認された 320 種の低分子医薬品のうち、54 種がピリジン環を含んでおり、ピリジン環が最も頻出する複素環構造とされている¹⁰⁰。さらに構造解析の結果、これらの化合物の約 90% において C-2 位に置換基が導入されていることが明らかとなった。したがって、ピリジン誘導体における C-2 位選択的な官能基化法の開発は、合成化学および医薬品開発において極めて重要な課題である。

脱プロトンのリチオ化は、位置選択性とアトムエコノミーに優れ、芳香族化合物の官能基化手法として広く利用されている^{24–26}。しかし、ピリジンに対する脱プロトンのリチオ化は、窒素原子に隣接する C-2 位ではなく、一般に最も酸性度の高い C-4 位で進行することが知られている¹⁰¹。この原因は、窒素原子の非共有電子対による電子の反発により、2-ピリジルリチウム種の安定性を著しく低下させるためである¹⁰²。

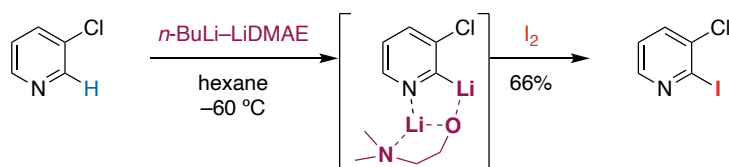
近年、有機リチウム試薬とアミンの錯体を用いた 3-ハロピリジンの C-2 位選択的な官能基化の研究が報告されている^{101c,101d,102b,102e,103}。例えば、1983 年に Quéguiner らは、*n*-BuLi と DABCO の錯体を用いることで、3-フルオロピリジンの C-2 位選択的リチウム化を報告している (Scheme 4-2-1)^{102b}。3-フルオロピリジンを含む Et₂O 溶液に対して、−60 °C で *n*-BuLi と DABCO の錯体を作用させ、溶解性の低いピリジルリチウム中間体が生成されている。さらに、TMSCl と反応し、対応するトリメチルシリル化体を収率 80% で得ている。この位置選択性は、脱プロトン化が速度論的により有利な C-2 位で進行し、生成した中間体の

溶解性の低さにより，熱力学的に安定な C-4 位への異性化が抑制されると理解できる。



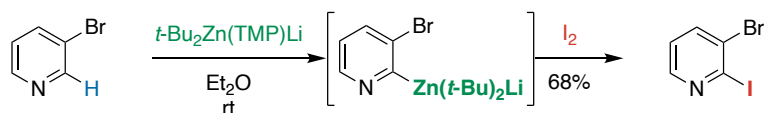
Scheme 4-2-1. Lithiation of 3-fluoropyridine using a *n*-BuLi–DABCO chelate

また，2001 年に Fort は，*n*-BuLi と LiDMAE の錯体を用いて 3-クロロピリジンの C-2 位選択的リチウム化を達成している (Scheme 4-2-2) ^{103d}。3-クロロピリジンを含むヘキサン溶液に対して， -60°C で *n*-BuLi と LiDMAE の錯体を作用させ，さらにヨウ素を加え，対応するヨードアレーンを収率 66% で合成している。



Scheme 4-2-2. Lithiation of 3-chloropyridine using a *n*-BuLi–LiDMAE chelate

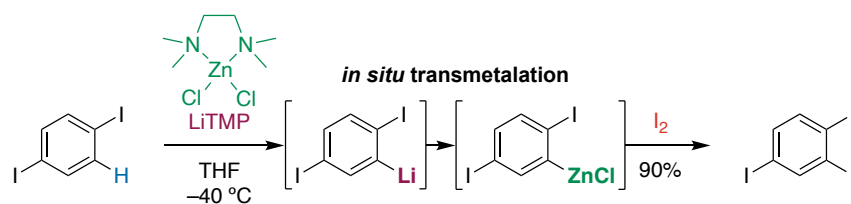
リチウムに比べて電気陰性度の高い金属（亜鉛とマグネシウム）から形成された金属アミド塩基でも有用である。例えば，2001 年に根東らは，*t*-Bu₂Zn(TMP)Li を利用して 3-ブロモピリジンの脱プロトンの亜鉛化を報告している (Scheme 4-2-3) ^{102e}。3-ブロモピリジンを含む Et₂O 溶液に対して，室温で *t*-Bu₂Zn(TMP)Li を作用させ，安定な有機亜鉛中間体を生成している。その後，ヨウ素を加え，対応するヨードアレーンを収率 68% で得ている。



Scheme 4-2-3. Zincation of 3-bromopyridine using a TMP–Zincate base

脱プロトン化反応により，3-フルオロピリジン，3-クロロピリジン，ならびに 3-ブロモピリジンにおいては C-2 位の選択的な官能基化が達成されているものの，同様の手法を 3-ヨードピリジンに適用することは困難である。この原因は，脱プロトン化によって生成されるヨードピリジルリチウムが速やかに脱離反応を起こし，ピリダインへと変換されるためである ^{102c}。一方，第二章で，*in situ* ト

ランスメタル化を用いてヨードフェニルリチウムを捕捉できることが示された (Scheme 4-2-4)。すなわち、1,4-ジヨードベンゼンと塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して、 -40°C で LiTMP を作用させたところ、生成したヨードフェニルリチウムが塩化亜鉛 TMEDA 錯体とランスメタル化され、安定なフェニル亜鉛に変換された。さらに、ヨウ素を作用させ、対応するトリヨードベンゼンを収率 90%で得た。塩化亜鉛 TMEDA 錯体を用いる *in situ* ランスメタル化は、ヨードフェニルリチウムを効果的に捕捉できることが明らかになった。



Scheme 4-2-4. *in situ* Trapping of 2-iodophenyllithium using $\text{ZnCl}_2\cdot\text{TMEDA}$

以上の背景から、本研究は、*in situ* ランスメタル化を活用し、報告例のない 3-ヨードピリジンを含む、さまざまなハロピリジンおよびヘテロアレーンにおける C-2 位選択的な官能基化法の確立を目的とした。

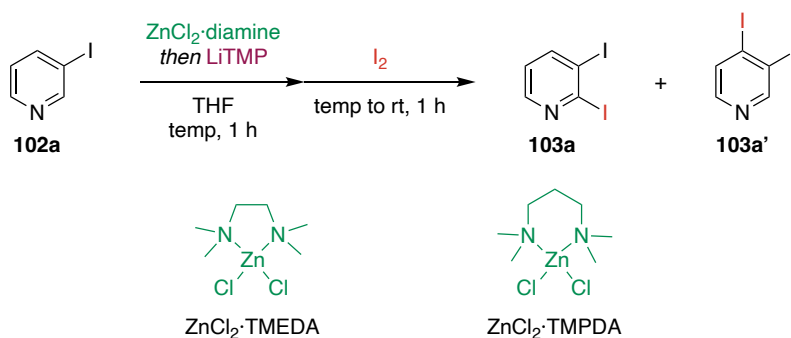
4-3 *in situ* ランスメタル化によるヨードピリジルリチウムの捕捉

4-3-1 LiTMP を用いた *in situ* ランスメタル化

まず、第二章の報告に基づいて LiTMP を塩基として用い、3-ヨードピリジン (**102a**) の *in situ* ランスメタル化条件を検討した (Table 4-3-1)。3-ヨードピリジン (**102a**) と塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して、 -40°C で LiTMP を加えて 1 時間攪拌した。さらにヨウ素を加え、室温に昇温して 1 時間反応させた結果、目的の 2,3-ジヨードピリジン (**103a**) が収率 92%で得られ、構造異性体である 3,4-ジヨードピリジン (**103a'**) はほぼ確認されなかった (entry 1)。一方、塩化亜鉛ジアミン錯体を用いない場合は、LiTMP の添加直後に反応系が黒変し、粘度の高い溶液になった。この条件下では、2,3-ジヨードピリジン (**103a**)、3,4-ジヨードピリジン (**103a'**)、および 3-ヨードピリジン (**102a**) のいずれも確認されなかった (entry 2)。この結果は、生成したヨードピリジルリチウム種が極めて不安定であり、速やかに分解することを示唆している。次に、ジアミン配位子の TMEDA をかさ高い TMPDA に変更したところ、**103a** の収率が 83%に低下した (entry 3)。また、*in situ* ランスメタル化を -78°C 、 0°C 、および室温で実施した場合は、**103a** の収率はほぼ変わらなかった (entries 4–6)。さらに、*in situ*

トランスメタル化を室温で行い, 反応時間を 5 分に短縮したところ, 目的の **103a** を単離収率 79%で得た (entry 7)。

Table 4-3-1. Optimization of *in situ* transmetalation of 3-iodopyridine using a combination of LiTMP and ZnCl₂·diamine complex^a



entry	ZnX ₂ ·diamine	temp (°C)	103a (%) ^b	103a' (%) ^b
1	ZnCl ₂ ·TMEDA	−40	92	2
2 ^c	none	−40	— ^d	— ^d
3	ZnCl ₂ ·TMPDA	−40	83	1
4	ZnCl ₂ ·TMEDA	−78	88	5
5	ZnCl ₂ ·TMEDA	0	88	3
6	ZnCl ₂ ·TMEDA	rt	91	3
7 ^e	ZnCl ₂ ·TMEDA	rt	88 (79 ^f)	3

^aReaction conditions: iodopyridine **102a** (0.30 mmol, 1.0 equiv), ZnCl₂·diamine (0.30 mmol, 1.0 equiv), LiTMP (0.53 mmol, 1.8 equiv), and I₂ (0.6 mmol, 2 equiv). ^bThe yield was determined from the ¹H NMR spectrum of the crude product, using 1,1,2,2-tetrachloroethane as an internal standard. ^cThe iodopyridine **102a** was not observed. ^dNot observed. ^e*in situ* Transmetalation was performed for 5 min. ^fIsolated yield.

4-3-2 市販のリチウムアミドを用いた *in situ* トランスメタル化

LiTMP は反応性が高い一方で, THF 溶液中では長期間の保存が困難であり, 室温下で 12 時間経過すると約 50%が不活性化することが知られている¹⁰⁴。そのため, LiTMP の用事調製が必要である。また, LiTMP 調製するための TMPH は高価であり (東京化成工業製, 250 mL あたり 69,200 円), コスト面からも課題がある。そこで, 市販のリチウムアミドの効果を調べた (Table 4-3-2)。汎用性の

高い LDA を用いたところ、目的の 2,3-ジヨードピリジン (**103a**) と構造異性体である 3,4-ジヨードピリジン (**103a'**) がそれぞれ収率 43% と 16% で得られ、3-ヨードピリジン (**102a**) が収率 29% で回収された (entry 1)。この原因は、LDA と塩化亜鉛 TMEDA 錯体が優先して反応し、塩基性の弱い亜鉛アミドが生成したためであると考えた。この望まない副反応を抑制するために、*in situ* トランスメタル化を -78°C で実施した。この結果、予想に反して **103a** は収率 19% でしか得られず、**103a'** を主生成物として収率 60% で得た (entry 2)。反応時間を 1 時間に延長しても、**103a'** を単離収率 49% で得た (entry 3)。LiTMP を用いた結果と異なる位置選択性については、以下のように考えている。LDA 中のリチウムイオンが 3-ヨードピリジン (**102a**) の窒素原子と相互作用する傾向があるにもかかわらず、LiTMP ($\text{p}K_{\text{a}}$ 37.3)¹⁰⁵ と比較して塩基性が低い ($\text{p}K_{\text{a}}$ 35.7)¹⁰⁵ ため、LDA を用いた脱プロトン化は、より酸性度の高い C-4 位で優先に進行したと理解できる。さらにより塩基性の低いリチウムヘキサメチルジシラジド (LiHMDS) とカリウムヘキサメチルジシラジドを用いた場合、**103a** と **103a'** のいずれも得られず、**102a** をそれぞれ収率 64% と 56% で回収した。

Table 4-3-2. Optimization of *in situ* transmetalation of 3-iodopyridine using a combination of commercially available base and $\text{ZnCl}_2\cdot\text{TMEDA}$ complex^a

Reaction scheme: 3-iodopyridine (**102a**) reacts with $\text{ZnCl}_2\cdot\text{TMEDA}$ (green text) then base (red text) in THF at temperature for 5 min, followed by I_2 (red text) at room temperature for 1 h, to yield 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**).

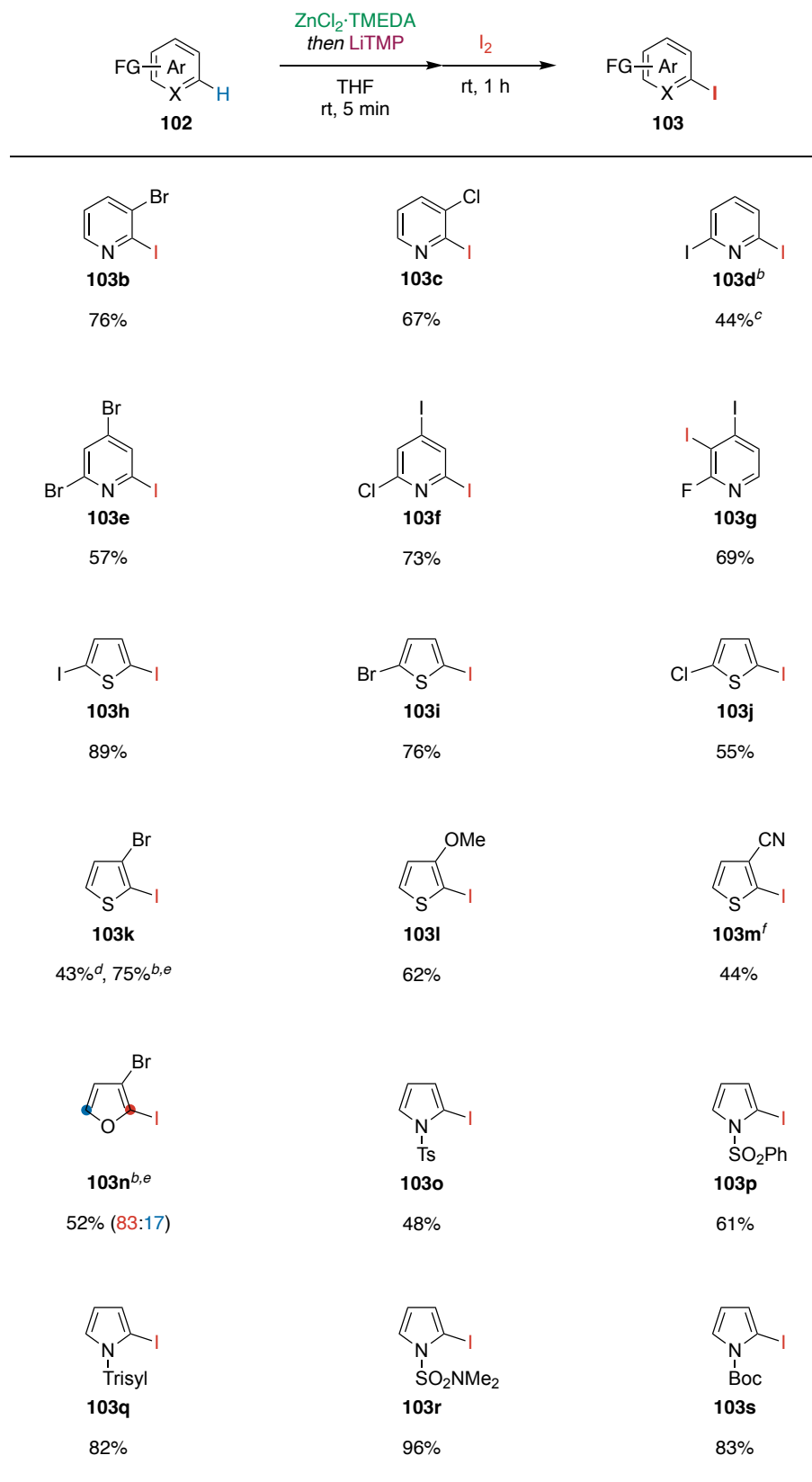
entry	base	temp ($^{\circ}\text{C}$)	103a (%) ^b	103a' (%) ^b	recovery of 102a (%) ^b
1	LDA	rt	43	16	29
2	LDA	-78	19	60	7
3 ^c	LDA	-78	25	55 (49 ^d)	4
4	LiHMDS	rt	— ^d	— ^d	64
5	KHMDS	rt	— ^d	— ^d	56

^aReaction conditions: iodopyridine **102a** (0.30 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (0.30 mmol, 1.0 equiv), base (0.53 mmol, 1.8 equiv), and I_2 (0.6 mmol, 2 equiv). ^bThe yield was determined from the ^1H NMR spectrum of the crude product, using 1,1,2,2-tetrachloroethane as an internal standard. ^cProlonged reaction time to 1 h. ^dIsolated yield. ^eNot observed.

4-4 さまざまなヘテロアレーンの C-2 位選択的な官能基化

in situ トランスメタル化を用いた 3-ヨードピリジン (**102a**) の C-2 位選択的なヨウ素化を実現したのち、ヘテロアレーンや求電子剤の一般性を検討した。まず、ヨウ素化反応によって *in situ* トランスメタル化が適用できるヘテロアレーンを調べた (Table 4-3-3)。ヘテロアレーン **102** と塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して、室温で LiTMP を加えて 5 分間攪拌した。その後、ヨウ素を加えてさらに 1 時間反応させた。C-3 位にブロモ基とクロロ基を有するピリジン **102b** と **102c** からは、対応する C-2 位がヨウ化された生成物 **103b** と **103c** をそれぞれ収率 76%と 67%で位置選択的に得た。2,6-ジヨードピリジン (**103d**) は、2-ヨードピリジン (**102d**) から収率 44%で得られたが、*in situ* トランスメタル化の反応時間を 20 分に延長しても **102d** が収率 36%で回収された。2,4-ジハロピリジン **102e** と **102f** からは、対応する 2,4,6-トリハロピリジン **103e** と **103f** がそれぞれ単離収率 57%と 73%で得られた。一方、2-フルオロ-4-ヨードピリジン (**102g**) を使用した場合、脱プロトン化が C-3 位で起き、2,3,4-トリハロピリジン **103g** を収率 69%で得た。2-クロロ-4-ヨードピリジン (**102f**) を用いた結果と比較すると、フッ素原子の誘導効果によってオルト位のプロトンの酸性度が高まり、より酸性度の高い C-3 位で脱プロトン化が進行したと考えられた¹⁰⁶。次に、基質の一般性をチオフェン誘導体に拡張した。ハロチオフェン **102h-j** と塩化亜鉛 TMEDA 錯体の THF 溶液に LiTMP を作用させ、さらにヨウ素で処理させた結果、対応するヨードチオフェン **103h-j** を収率 55%–89%で合成した。3-ブロモチオフェン (**102k**) を用いた場合、2-ヨードチオフェン **103k** を収率 43%で得たが、構造不明の副生成物も得られた。ブロモチオフェン **102k** の C-3 位でかさ高いブロモ基が存在するため、塩基を LDA に置き換え、反応時間を 20 分に延長することで、**103k** の収率は 75%に向上した。さらに、C-3 位にメトキシ基とシアノ基を有するチオフェン **102l** と **102m** からは、対応するヨードチオフェン **103l** と **103m** をそれぞれ収率 62%と 44%で合成した。また、ブロモフラン **102n** に対しても、*in situ* トランスメタル化を適用した。LDA を用い、*in situ* トランスメタル化を 20 分間実施したところ、3-ブロモ-2-ヨードフラン (**103n**) と 3-ブロモ-5-ヨードフラン (**103n'**) の混合物を収率 52%で得た。最後に、窒素原子が保護基されたピロール誘導体を試した。ベンゼンスルホニル基 (SO₂Ph), *p*-トルエンスルホニル基 (Ts), 2,4,6-トリイソプロピルベンゼンスルホニル基 (Trisyl), *N,N*-ジメチルスルホニル基 (SO₂NMe₂)¹⁰⁷, および *tert*-ブトキシカルボニル基 (Boc) を有する *N*-置換ピロール **102o-s** からは、対応する 2-ヨードピロール **103o-s** を収率 48%–96%で得た。

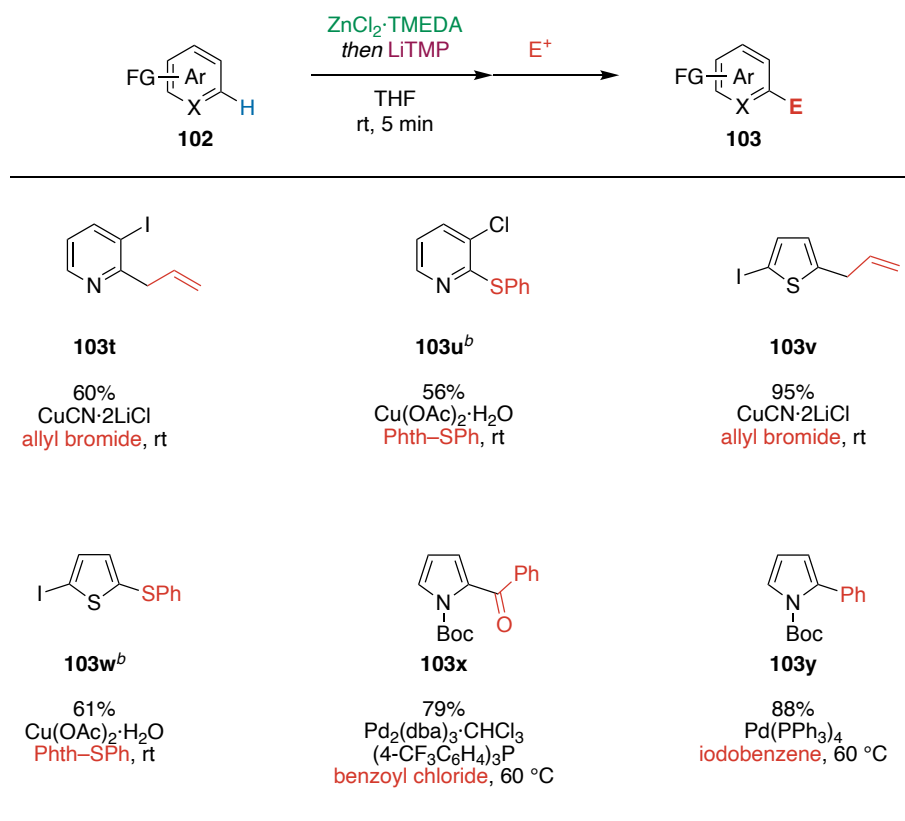
Table 4-3-3. Reaction of generated organozinc species with iodine^a



^aReaction conditions: heteroarene **102** (0.30 mmol, 1.0 equiv), ZnCl₂·TMEDA (0.30 mmol, 1.0 equiv), LiTMP (0.33–0.53 mmol, 1.1–1.8 equiv), and I₂ (0.6 mmol, 2 equiv). ^b*in situ* Transmetalation was performed for 20 min. ^cRecovery of **102d** in 36% yield. ^dThe yield was determined from the ¹H NMR spectrum of the crude product, using 1,1,2,2-tetrachloroethane as an internal standard. ^eUsing LDA instead of LiTMP.

in situ トランスメタル化を用いたさまざまなヘテロアレーンの C-2 位選択的なヨウ素化を達成したのち、生成したアリール亜鉛反応剤を用い、求電子剤の一般性について検討した (Table 4-3-4)。アリル基およびフェニルチオ基は、ハロピリジン **102a** と **102c** の C-2 位選択的に導入され、対応する生成物 **103t** と **103u** を収率 60%と 56%で合成した。本手法は、 π 電子不足芳香族ヘテロ環化合物であるピリジン誘導体の C-2 位選択的な官能基化に対する有効な手段である¹⁰⁸。また、ヨードチオフェン **102h** に対しても本手法を適用したところ、対応する生成物 **103v** と **103w** を収率 95%と 61%で得た。パラジウム触媒を用いた根岸カップリング反応を行ったところ、*N*-Boc-ピロール **103x** および **103y** をそれぞれ収率 79%と 88%で合成した。

Table 4-3-4. Reaction of generated organozinc species with various electrophiles^a



^aReaction conditions: heteroarene **102** (0.30 mmol, 1.0 equiv), ZnCl₂·TMEDA (0.30 mmol, 1.0 equiv), LiTMP (0.36–0.53 mmol, 1.2–1.8 equiv), and electrophile (0.45 mmol, 1.5 equiv). ^bPhth-SPh was employed in 1.05 equiv.

4-5 結言

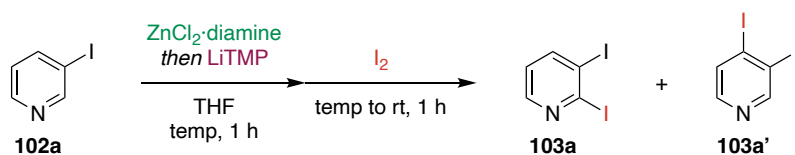
本章では、塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化を鍵として、多様なヘテロアレーンにおける C-2 位選択的な官能基化を開発した。速度論的により有利な C-2 位で脱プロトン化が進行し、生成したヘテロアリアルリチウムは、*in situ* トランスメタル化によって安定なアリアル亜鉛種へと変換される。これにより、熱力学的により有利なプロトンの異性化、ハロゲンダンス、アラインの発生といった競合反応が効果的に抑制された。得られたアリアル亜鉛種はさまざまな求電子剤と反応し、ヘテロアリアル骨格の多様な構造修飾が可能となった。従来のリチウムアミドを用いる手法とは異なり、本手法は低温条件を必要とせず、室温においても良好な反応性を示した。また、3-ヨードピリジンに対する脱プロトンの官能基化は、本研究が初の報告例となる。本手法により得られた多様な C-2 位でヨウ素化されたヘテロアレーンは、クロスカップリング反応を経て C–C および C–N 結合の構築が可能であり、ヘテロ環骨格を有する医薬品および農薬の分子設計に有用であると期待される。

4-6 Experimental section

1. General Information

Unless otherwise stated, all reactions were conducted in a flame-dried glassware under an inert atmosphere of nitrogen, and a preheated oil bath was used for the reactions that required heating. All work-up and purification procedures were carried out with reagent-grade solvents in the 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 Kanto Chemical Co. and further dried by passing through a solvent purification system (Glass Contour) prior to use. *n*-BuLi (1.6 M in *n*-hexane) and TMPH were purchased from Kanto Chemical Co. and used as received. Freshly prepared THF solution of LiTMP (0.66 M), $\text{ZnCl}_2 \cdot \text{TMEDA}$, $\text{Pd}(\text{PPh}_3)_4$, THF solution of $\text{CuCN} \cdot 2\text{LiCl}$ (1.0 M), and $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ were used in the following experiments. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ 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 wave numbers (cm^{-1}). ^1H NMR (400 MHz) and $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz) spectra were measured on JEOL ECZ400 spectrometer. Chemical shifts for ^1H 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, sept = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets. Chemical shifts for $^{13}\text{C}\{^1\text{H}\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl_3 : δ 77.16 ppm and acetone-*d*₆: δ 29.84 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. HPLC with a preparative SEC column (JAI-GEL-1H, JAI-GEL-2H) was performed with JASCO PU-4087.

2. Optimization of *in situ* transmetalation of 3-iodopyridine using a combination of LiTMP and $\text{ZnCl}_2 \cdot \text{diamine}$ complex (Table 4-3-1)



General procedure (Table 4-3-1, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-iodopyridine (**102a**) (61.3 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.6 mg, 0.299 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution was stirred at -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 iodine (154.1 mg, 0.607 mmol, 2.0 equiv). After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were determined to be 92% and 2% 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 8.34 ppm (1 proton for **103a**) and 8.91 ppm (1 proton for **103a'**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction performed in the absence of $\text{ZnCl}_2 \cdot \text{TMEDA}$ (Table 4-3-1, entry 2)

A crude product was obtained from iodopyridine **102a** (61.9 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (150.2 mg, 0.592 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. Neither 2,3-diiodopyridine (**103a**), 3,4-diiodopyridine (**103a'**), nor 3-iodopyridine (**102a**) was observed by ^1H NMR spectroscopy.

Reaction performed using $\text{ZnCl}_2 \cdot \text{TMPDA}$ instead of $\text{ZnCl}_2 \cdot \text{TMEDA}$ (Table 4-3-1, entry 3)

A crude product was obtained from iodopyridine **102a** (60.9 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMPDA}$ (80.5 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (151.6 mg, 0.597 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. The yields of 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were determined to be 83% and 1% by ^1H NMR spectroscopy.

Reaction performed at -78°C (Table 4-3-1, entry 4)

A crude product was obtained from iodopyridine **102a** (61.5 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.7 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (152.0 mg, 0.599 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure at -78 °C. The yields of 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were determined to be 88% and 5% by ¹H NMR spectroscopy.

Reaction performed at 0 °C (Table 4-3-1, entry 5)

A crude product was obtained from iodopyridine **102a** (61.1 mg, 0.298 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.7 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (160.4 mg, 0.632 mmol, 2.1 equiv), and THF (2.0 mL) according to the general procedure at 0 °C. The yields of 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were determined to be 88% and 3% by ¹H NMR spectroscopy.

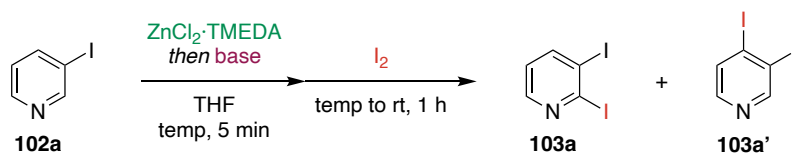
Reaction performed at room temperature (Table 4-3-1, entry 6)

A crude product was obtained from iodopyridine **102a** (61.6 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.2 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (152.8 mg, 0.602 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure at room temperature. The yields of 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were determined to be 91% and 3% by ¹H NMR spectroscopy.

Reaction performed at room temperature for 5 min (Table 4-3-1, entry 7)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the 2,3-diiodopyridine (**103a**) as a pale yellow solid (78.3 mg, 0.237 mmol, 79%) from iodopyridine **102a** (61.6 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.3 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (146.0 mg, 0.575 mmol, 1.9 equiv), and THF (2.0 mL) according to the general procedure at room temperature for 5 min. *R*_f = 0.38 (hexane/diethyl ether = 5:1); Mp 58–60 °C; IR (ATR, cm⁻¹): 1543, 1418, 1373, 1215, 1108, 1046, 994; ¹H NMR (400 MHz, CDCl₃): δ 8.34 (dd, 1H, *J* = 4.8, 2.0 Hz), 8.01 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.02 (dd, 1H, *J* = 8.0, 4.8 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 148.8, 146.6, 130.2, 123.7, 108.1; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₄I₂N 331.8433; Found 331.8443. The yields of 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were determined to be 88% and 3% by ¹H NMR spectroscopy.

3. Optimization of *in situ* transmetalation of 3-iodopyridine using a combination of commercially available base and ZnCl₂·TMEDA complex (Table 4-3-2)



General procedure (Table 4-3-2, entry 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-iodopyridine (**102a**) (61.0 mg, 0.298 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution was stirred at room temperature. LDA (2.0 M in THF/heptane/ethylbenzene, 0.27 mL, 0.54 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated with iodine (154.1 mg, 0.607 mmol, 2.0 equiv). After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 2,3-diiodopyridine (**103a**), 3,4-diiodopyridine (**103a'**), and 3-iodopyridine (**102a**) were determined to be 43%, 16%, and 29% 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 8.34 ppm (1 proton for **103a**), 8.91 ppm (1 proton for **103a'**), and 8.84 ppm (1 proton for **102a**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction performed at $-78\text{ }^\circ\text{C}$ (Table 4-3-2, entry 2)

A crude product was obtained from iodopyridine **102a** (61.7 mg, 0.301 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.3 mg, 0.302 mmol, 1.0 equiv), LDA (2.0 M in THF/heptane/ethylbenzene, 0.27 mL, 0.54 mmol, 1.8 equiv), iodine (160.1 mg, 0.631 mmol, 2.1 equiv), and THF (2.0 mL) according to the general procedure at $-78\text{ }^\circ\text{C}$. The yields of 2,3-diiodopyridine (**103a**), 3,4-diiodopyridine (**103a'**), and 3-iodopyridine (**102a**) were determined to be 19%, 60%, and 7% by ^1H NMR spectroscopy.

Reaction performed at $-78\text{ }^\circ\text{C}$ for 1 h (Table 4-3-2, entry 3)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 97:3) to provide the 3,4-diiodopyridine (**103a'**) as a colorless solid (48.2 mg, 0.146 mmol, 49%) from iodopyridine **102a** (61.8 mg, 0.301 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.8 mg, 0.300 mmol, 1.0 equiv), LDA (2.0 M in THF/heptane/ethylbenzene, 0.27 mL, 0.54 mmol, 1.8 equiv), and iodine (158.9 mg, 0.626 mmol, 2.1 equiv) according to the general procedure at $-78\text{ }^\circ\text{C}$ for 1 h. R_f = 0.32 (hexane/diethyl ether = 5:1); Mp $98\text{--}99\text{ }^\circ\text{C}$;

IR (ATR, cm^{-1}): 1547, 1447, 1389, 1265, 1174, 1104, 1055, 1003, 995, 829; ^1H NMR (400 MHz, CDCl_3): δ 8.91 (s, 1H), 8.16 (d, 1H, $J = 4.8$ Hz), 7.84 (d, 1H, $J = 4.8$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 156.6, 148.3, 134.9, 118.8, 108.3; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_4\text{I}_2\text{N}$ 331.8433; Found 331.8441. The yields of 2,3-diiodopyridine (**103a**), 3,4-diiodopyridine (**103a'**), and 3-iodopyridine (**102a**) were determined to be 25%, 55%, and 4% by ^1H NMR spectroscopy.

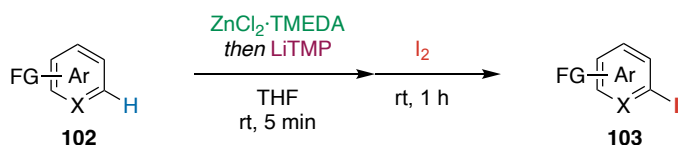
Reaction performed with LiHMDS instead of LDA (Table 4-3-2, entry 4)

A crude product was obtained from iodopyridine **102a** (61.6 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.3 mg, 0.302 mmol, 1.0 equiv), LiHMDS (1.0 M in THF, 0.54 mL, 0.54 mmol, 1.8 equiv), iodine (165.1 mg, 0.650 mmol, 2.2 equiv), and THF (2.0 mL) according to the general procedure. Both 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were not observed, and the yield of 3-iodopyridine (**102a**) was determined to be 64% by ^1H NMR spectroscopy.

Reaction performed with KHMDS instead of LiTMP (Table 4-3-2, entry 5)

A crude product was obtained from iodopyridine **102a** (61.2 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.5 mg, 0.302 mmol, 1.0 equiv), KHMDS (0.5 M in toluene, 1.1 mL, 0.55 mmol, 1.8 equiv), iodine (164.8 mg, 0.649 mmol, 2.2 equiv), and THF (2.0 mL) according to the general procedure. Both 2,3-diiodopyridine (**103a**) and 3,4-diiodopyridine (**103a'**) were not observed, and the yield of 3-iodopyridine (**102a**) was determined to be 56% by ^1H NMR spectroscopy.

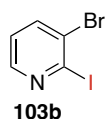
4. Reaction of generated organozinc species with iodine (Table 4-3-3)



General procedure

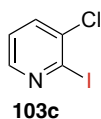
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with heteroarene **102** (0.30 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (0.30 mmol, 1.0 equiv), and THF (2.0 mL). LiTMP (0.66 M, 0.33–0.53 mmol, 1.1–1.8 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated with iodine (0.60 mmol, 2.0 equiv). After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were

washed with brine (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 or preparative SEC–HPLC (chloroform) to provide the corresponding iodinated heteroarene **103**.



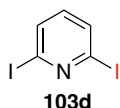
3-Bromo-2-iodopyridine (**103b**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the title compound **103b** as a colorless solid (64.6 mg, 0.228 mmol, 76%) from 3-bromopyridine (**102b**) (47.2 mg, 0.299 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.5 mg, 0.299 mmol, 1.0 equiv), LiTMP (0.66 M, 0.68 mL, 0.45 mmol, 1.5 equiv), and iodine (165.7 mg, 0.653 mmol, 2.2 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹⁰⁹ *R_f* = 0.35 (hexane/diethyl ether = 5:1); Mp 45–47 °C; IR (ATR, cm⁻¹): 1550, 1422, 1380, 1126, 1109, 1048, 1004; ¹H NMR (400 MHz, CDCl₃): δ 8.32 (dd, 1H, *J* = 4.8, 1.6 Hz), 7.82 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.17 (dd, 1H, *J* = 8.0, 4.8 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 148.4, 139.9, 130.1, 124.2, 123.8; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₄⁷⁹BrIN 283.8572; Found 283.8576.



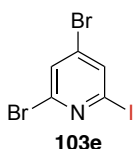
3-Chloro-2-iodopyridine (**103c**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the title compound **103c** as a colorless solid (48.0 mg, 0.200 mmol, 67%) from 3-chloropyridine (**102c**) (33.9 mg, 0.299 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.6 mg, 0.299 mmol, 1.0 equiv), LiTMP (0.66 M, 0.68 mL, 0.45 mmol, 1.5 equiv), and iodine (160.8 mg, 0.634 mmol, 2.1 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹⁰⁹ *R_f* = 0.35 (hexane/diethyl ether = 5:1); Mp 41–42 °C; IR (ATR, cm⁻¹): 1552, 1426, 1385, 1136, 1105, 1050, 1022; ¹H NMR (400 MHz, CDCl₃): δ 8.27 (dd, 1H, *J* = 4.8, 2.0 Hz), 7.67 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.23 (dd, 1H, *J* = 8.0, 4.8 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 148.1, 138.5, 136.4, 123.7, 121.7; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₄³⁵ClIN 239.9077; Found 239.9078.



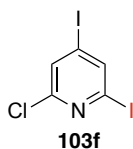
2,6-Diiodopyridine (**103d**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the title compound **103d** as a colorless solid (43.5 mg, 0.131 mmol, 44%) from 2-iodopyridine (**102d**) (61.6 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.9 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.81 mL, 0.53 mmol, 1.8 equiv), and iodine (153.2 mg, 0.604 mmol, 2.0 equiv) according to the general procedure for 20 min. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹¹⁰ *R_f* = 0.25 (hexane/diethyl ether = 10:1); Mp 165–166 °C; IR (ATR, cm⁻¹): 1541, 1526, 1408, 1371, 1168, 1120, 1084, 1068, 974; ¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, 2H, *J* = 8.0 Hz), 6.94 (t, 1H, *J* = 8.0 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 138.5, 134.4, 116.4; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₄I₂N 331.8433; Found 331.8444. The yield of 2-iodopyridine (**102d**) was determined to be 36% 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 8.38 ppm (1 proton for **102d**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.



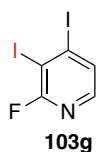
2,4-Dibromo-6-iodopyridine (**103e**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide an inseparable mixture (71.0 mg) of the title compound **103e** (0.171 mmol, 57%) and 2,6-dibromo-4-iodopyridine (**S1**) (0.025 mmol, 8%) as a colorless solid from 2,4-dibromopyridine (**102e**) (71.1 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.8 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.81 mL, 0.53 mmol, 1.8 equiv), and iodine (165.4 mg, 0.652 mmol, 2.2 equiv) according to the general procedure. The ¹H NMR spectroscopic data of 2,6-dibromo-4-iodopyridine (**S1**) was identical to that reported in the literature.¹¹¹ The ratio was determined by ¹H NMR spectroscopy. *R_f* = 0.67 (hexane/diethyl ether = 5:1); Mp 63–64 °C; IR (ATR, cm⁻¹): 1531, 1518, 1506, 1486, 1337, 1271, 1258, 1151, 1089, 850; ¹H NMR (400 MHz, CDCl₃): δ 7.89 (s, 1H), 7.65 (s, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 141.1, 136.6, 134.1, 130.4, 115.7; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₃⁷⁹Br₂IN 361.7677; Found 361.7688.



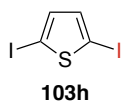
2-Chloro-4,6-diiodopyridine (**103f**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 97:3) and washed with MeOH to provide the title compound **103f** as a pale yellow solid (80.5 mg, 0.220 mmol, 73%) from 2-chloro-4-iodopyridine (**102f**) (71.9 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.6 mg, 0.303 mmol, 1.0 equiv), LiTMP (0.66 M, 0.81 mL, 0.53 mmol, 1.8 equiv), and iodine (155.1 mg, 0.611 mmol, 2.0 equiv) according to the general procedure. R_f = 0.62 (hexane/diethyl ether = 5:1); Mp 122–123 °C; IR (ATR, cm^{-1}): 1529, 1512, 1485, 1342, 1259, 1158, 1093, 851; ^1H NMR (400 MHz, CDCl_3): δ 8.05 (s, 1H), 7.69 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 150.7, 141.6, 132.3, 115.7, 107.1; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_3^{35}\text{ClI}_2\text{N}$ 365.8043; Found 365.8049.



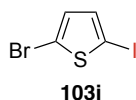
2-Fluoro-3,4-diiodopyridine (**103g**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the title compound **103g** as a colorless solid (71.7 mg, 0.206 mmol, 69%) from 2-fluoro-4-iodopyridine (**102g**) (66.4 mg, 0.298 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.9 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv), and iodine (151.6 mg, 0.597 mmol, 2.0 equiv) according to the general procedure. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.¹¹² R_f = 0.50 (hexane/diethyl ether = 5:1) Mp 101–102 °C; IR (ATR, cm^{-1}): 1554, 1518, 1448, 1427, 1366, 1273, 1216, 1111, 1023, 1012, 872, 825; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (d, 1H, J = 5.2 Hz), 7.66 (d, 1H, J = 5.2 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 162.1 (d, $^1J_{\text{C-F}}$ = 237 Hz), 147.1 (d, $^3J_{\text{C-F}}$ = 15 Hz), 132.3 (d, $^4J_{\text{C-F}}$ = 4.8 Hz), 123.6, 92.3 (d, $^2J_{\text{C-F}}$ = 44 Hz); HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_3\text{FI}_2\text{N}$ 349.8339; Found 349.8355.



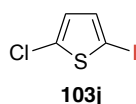
2,5-Diiodothiophene (103h)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **103h** as a pale yellow solid (90.0 mg, 0.268 mmol, 89%) from 2-iodothiophene (**102h**) (63.2 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.7 mg, 0.304 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (149.0 mg, 0.587 mmol, 2.0 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹¹³ *R_f* = 0.60 (hexane); Mp 35–36 °C; IR (ATR, cm⁻¹): 1499, 1388, 1202, 1094, 1053, 950, 922; ¹H NMR (400 MHz, CDCl₃): δ 6.94 (s, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 138.9, 76.3; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₄H₃I₂S 336.8045; Found 336.8059.



2-Bromo-5-iodothiophene (103i)

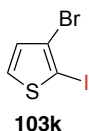
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **103i** as a pale yellow oil (90.0 mg, 0.227 mmol, 76%) from 2-bromothiophene (**102i**) (48.9 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.5 mg, 0.303 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (159.3 mg, 0.628 mmol, 2.1 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹¹⁴ *R_f* = 0.60 (hexane); IR (ATR, cm⁻¹): 1509, 1398, 1203, 970, 930, 906; ¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, 1H, *J* = 4.0 Hz), 6.75 (d, 1H, *J* = 4.0 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 137.6, 131.8, 115.3, 72.4; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₄H₃⁷⁹BrIS 288.8184; Found 288.8183.



2-Chloro-5-iodothiophene (103j)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **103j** as a pale yellow oil (40.9 mg, 0.167 mmol, 55%) from 2-chlorothiophene (**102j**) (36.0 mg, 0.304 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.5 mg, 0.303 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine

(162.4 mg, 0.640 mmol, 2.1 equiv) according to the general procedure. R_f = 0.63 (hexane); IR (ATR, cm^{-1}): 1515, 1408, 1204, 1062, 1002, 934; ^1H NMR (400 MHz, CDCl_3): δ 7.06 (d, 1H, J = 4.4 Hz), 6.62 (d, 1H, J = 4.4 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 136.6, 133.5, 128.0, 70.0; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_4\text{H}_3^{37}\text{ClIS}$ 246.8659; Found 246.8652.

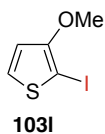


Synthesis of 3-bromo-2-iodothiophene (**103k**) using LiTMP

A crude product was obtained from 3-bromothiophene (**102k**) (49.3 mg, 0.302 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.4 mg, 0.303 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), and iodine (152.8 mg, 0.602 mmol, 2.0 equiv) according to the general procedure. The yield of 3-bromo-5-iodothiophene (**103k**) was determined to be 43% 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 6.90 ppm (1 proton for **103k**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

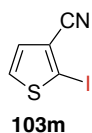
Synthesis of 3-bromo-2-iodothiophene (**103k**) using LDA

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **103k** as a colorless oil (64.5 mg, 0.223 mmol, 75%) from 3-bromothiophene (**102k**) (48.6 mg, 0.298 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.1 mg, 0.301 mmol, 1.0 equiv), LDA (2.0 M in THF/heptane/ethylbenzene, 0.27 mL, 0.54 mmol, 1.8 equiv), and iodine (146.9 mg, 0.579 mmol, 1.9 equiv) according to the general procedure for 20 min. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.¹¹⁵ R_f = 0.50 (hexane); IR (ATR, cm^{-1}): 1489, 1387, 1336, 1144, 958, 856; ^1H NMR (400 MHz, CDCl_3): δ 7.41 (d, 1H, J = 5.6 Hz), 6.90 (d, 1H, J = 5.6 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 132.3, 130.5, 120.7, 77.0; HRMS (APCI/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_4\text{H}_3^{81}\text{BrIS}$ 290.8163; Found 290.8160.



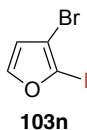
2-Iodo-3-methoxythiophene (**103l**)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **103l** as a green oil (44.5 mg, 0.185 mmol, 62%) from 3-methoxythiophene (**102l**) (34.2 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.0 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.68 mL, 0.45 mmol, 1.5 equiv), and iodine (156.3 mg, 0.616 mmol, 2.1 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹¹⁶ *R_f* = 0.40 (hexane/diethyl ether = 10:1); IR (ATR, cm⁻¹): 1541, 1458, 1376, 1246, 1174, 1104, 1067, 977, 914, 827; ¹H NMR (400 MHz, CDCl₃): δ 7.44 (d, 1H, *J* = 5.6 Hz), 6.70 (d, 1H, *J* = 5.6 Hz), 3.89 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 159.8, 130.1, 115.8, 59.3, 53.5; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₆IOS 240.9184; Found 240.9192.



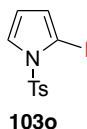
2-Iodo-3-thiophenecarbonitrile (**103m**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the title compound **103m** as a pale yellow solid (31.0 mg, 0.132 mmol, 44%) and 2,5-diiodo-3-thiophenecarbonitrile (**103m'**) as a pale yellow solid (33.9 mg, 0.094 mmol, 31%) from 3-cyanothiophene (**102m**) (33.0 mg, 0.302 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.3 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv), and iodine (156.6 mg, 0.617 mmol, 2.1 equiv) according to the general procedure for 20 min. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹¹⁷ Physicochemical properties of 2-iodo-3-thiophenecarbonitrile (**103m**): *R_f* = 0.20 (hexane/diethyl ether = 10:1); Mp 50–51 °C; IR (ATR, cm⁻¹): 3115, 2953, 2922, 2853, 2226, 1462, 1414, 1213, 984, 930, 885, 821; ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, 1H, *J* = 5.2 Hz), 7.11 (d, 1H, *J* = 5.2 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 133.0, 130.4, 120.6, 115.5, 86.8; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₃INS 235.9031; Found 235.9030. Physicochemical properties of 2,5-diiodo-3-thiophenecarbonitrile (**103m'**): *R_f* = 0.30 (hexane/diethyl ether = 10:1); Mp 118–119 °C; IR (ATR, cm⁻¹): 3103, 2918, 2233, 1391, 1177, 997, 839; ¹H NMR (400 MHz, CDCl₃): δ 7.22 (s, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 139.1, 122.3, 113.9, 89.7, 78.2; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₂I₂NS 361.7997; Found 361.7996.



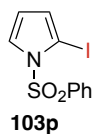
3-Bromo-2-iodofuran (**103n**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide an inseparable mixture (42.7 mg) of the title compound **103n** (0.129 mmol, 43%) and 3-bromo-5-iodofuran (**103n'**) (0.027 mmol, 9%) as a colorless oil from 3-bromofuran (**102n**) (44.2 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.7 mg, 0.300 mmol, 1.0 equiv), LDA (2.0 M in THF/heptane/ethylbenzene, 0.27 mL, 0.54 mmol, 1.8 equiv), and iodine (151.8 mg, 0.598 mmol, 2.0 equiv) according to the general procedure for 20 min. The ¹H NMR spectroscopic data of 3-bromo-2-iodofuran (**103n**) was identical to that reported in the literature.¹¹⁸ The ratio was determined by ¹H NMR spectroscopy. Physicochemical properties of 3-bromo-2-iodofuran (**103n**): R_f = 0.55 (hexane); IR (ATR, cm⁻¹): 2922, 1540, 1465, 1457, 1188, 1142, 1109, 1092, 1036, 960, 944, 922, 901, 879; ¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, 1H, *J* = 2.4 Hz), 6.45 (d, 1H, *J* = 2.4 Hz); ¹³C{¹H} NMR (100 MHz, acetone-*d*₆): δ 150.2, 116.0, 111.3, 95.0; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₄H₃⁸¹BrIO 274.8392; Found 274.8402.



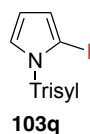
2-Iodo-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole (**103o**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 97:3) and preparative SEC–HPLC (chloroform) to provide the title compound **103o** as a pale yellow solid (64.0 mg, 0.184 mmol, 61%) from 1-tosylpyrrole (**102o**) (66.3 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.4 mg, 0.303 mmol, 1.0 equiv), LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv), and iodine (160.1 mg, 0.631 mmol, 2.1 equiv) according to the general procedure. R_f = 0.20 (hexane/diethyl ether = 10:1); Mp 68–69 °C; IR (ATR, cm⁻¹): 1596, 1419, 1366, 1262, 1207, 1190, 1171, 1141, 1079, 1048, 961, 812; ¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, 2H, *J* = 8.4 Hz), 7.57 (dd, 1H, *J* = 3.2, 1.6 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 6.51 (dd, 1H, *J* = 3.2, 1.6 Hz), 6.25 (dd, 1H, *J* = 3.2, 3.2 Hz), 2.43 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 145.5, 135.3, 130.0, 128.1, 126.71, 126.66, 114.6, 63.6, 21.8; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₁₁H₁₁INO₂S 347.9555; Found 347.9546.



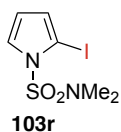
2-Iodo-1-(phenylsulfonyl)-1*H*-pyrrole (**103p**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 97:3) and preparative SEC–HPLC (chloroform) to provide the title compound **103p** as a colorless solid (48.1 mg, 0.144 mmol, 48%) from 1-(phenylsulfonyl)-1*H*-pyrrole (**102p**) (62.4 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (75.7 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv), and iodine (153.6 mg, 0.605 mmol, 2.0 equiv) according to the general procedure. *R*_f = 0.32 (hexane/diethyl ether = 5:1); Mp 85–87 °C; IR (ATR, cm^{−1}): 1448, 1419, 1364, 1260, 1206, 1185, 1168, 1137, 1083, 1050, 816; ¹H NMR (400 MHz, CDCl₃): δ 7.95–7.90 (m, 2H), 7.67–7.61 (m, 1H), 7.59 (dd, 1H, *J* = 3.2, 2.0 Hz), 7.57–7.50 (m, 2H), 6.52 (dd, 1H, *J* = 3.2, 2.0 Hz), 6.27 (dd, 1H, *J* = 3.2, 3.2 Hz); ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 138.3, 134.3, 129.4, 128.0, 126.9, 126.8, 114.8, 63.7; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₁₀H₉INO₂S 333.9399; Found 333.9393.



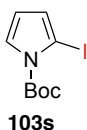
2-Iodo-1-[(2,4,6-triisopropylphenyl)sulfonyl]-1*H*-pyrrole (**103q**)

A crude product was purified by silica gel column chromatography (hexane/dichloromethane = 4:1) and preparative SEC–HPLC (chloroform) to provide an inseparable mixture (125.1 mg) of the title compound **103q** (0.245 mmol, 82%) and 2,5-diiodo-1-[(2,4,6-triisopropylphenyl)sulfonyl]-1*H*-pyrrole (**S2**) (0.021 mmol, 7%) as a pale yellow oil from 1-[(2,4,6-triisopropylphenyl)sulfonyl]-1*H*-pyrrole (**102q**) (100.2 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.6 mg, 0.303 mmol, 1.0 equiv), LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv), and iodine (156.0 mg, 0.615 mmol, 2.1 equiv) according to the general procedure. *R*_f = 0.62 (hexane/diethyl ether = 5:1); IR (ATR, cm^{−1}): 1599, 1506, 1458, 1418, 1373, 1348, 1206, 1172, 1140, 1082, 1048, 909, 883; ¹H NMR (400 MHz, CDCl₃): δ 7.59 (dd, 1H, *J* = 3.6, 1.6 Hz), 7.18 (s, 2H), 6.45 (dd, 1H, *J* = 3.6, 1.6 Hz), 6.24 (dd, 1H, *J* = 3.6, 3.6 Hz), 4.04 (sept, 2H, *J* = 6.8 Hz), 2.92 (sept, 1H, *J* = 6.8 Hz), 1.26 (d, 6H, *J* = 6.8 Hz), 1.12 (d, 12H, *J* = 6.8 Hz); ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 155.2, 151.8, 131.0, 125.5, 125.0, 124.2, 112.9, 63.5, 34.4, 29.9, 24.4, 23.7; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₁₉H₂₇INO₂S 460.0807; Found 460.0815.



2-Iodo-N,N-dimethyl-1*H*-pyrrole-1-sulfonamide (**103r**)

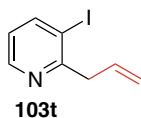
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 4:1) to provide the title compound **103r** as a pale yellow solid (87.9 mg, 0.293 mmol, 96%) from *N,N*-dimethyl-1*H*-pyrrole-1-sulfonamide (**102r**) (53.0 mg, 0.304 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.0 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv), and iodine (167.1 mg, 0.658 mmol, 2.2 equiv) according to the general procedure. *R*_f = 0.30 (hexane/diethyl ether = 5:1); Mp 75–77 °C; IR (ATR, cm⁻¹): 1457, 1419, 1380, 1273, 1261, 1206, 1171, 1132, 1086, 1050, 972, 955, 811; ¹H NMR (400 MHz, CDCl₃): δ 7.35 (dd, 1H, *J* = 3.6, 2.0 Hz), 6.56 (dd, 1H, *J* = 3.2, 2.0 Hz), 6.21 (dd, 1H, *J* = 3.6, 3.2 Hz), 2.92 (s, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 127.6, 125.9, 113.2, 63.2, 38.7; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₆H₁₀IN₂O₂S 300.9508; Found 300.9502.



tert-Butyl 2-iodo-1*H*-pyrrole-1-carboxylate (**103s**)

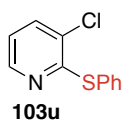
A crude product was purified by silica gel column chromatography (hexane) to provide the title compound **103s** as a yellow oil (73.7 mg, 0.251 mmol, 83%) from *N*-Boc-pyrrole (**102s**) (50.3 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.3 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.50 mL, 0.33 mmol, 1.1 equiv), and iodine (164.0 mg, 0.646 mmol, 2.1 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹¹³ *R*_f = 0.52 (hexane/diethyl ether = 10:1); IR (ATR, cm⁻¹): 1745, 1430, 1371, 1321, 1286, 1153, 1082, 1051, 976, 846; ¹H NMR (400 MHz, CDCl₃): δ 7.40 (dd, 1H, *J* = 3.2, 1.6 Hz), 6.53 (dd, 1H, *J* = 3.2, 1.6 Hz), 6.17 (dd, 1H, *J* = 3.2, 3.2 Hz), 1.62 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 148.4, 125.6, 125.0, 113.7, 85.1, 63.3, 28.2; HRMS (DART/TOF) *m/z*: [M+H]⁺ Calcd for C₉H₁₃INO₂ 293.9991; Found 293.9982.

5. Reaction of generated organozinc species with various electrophiles (Table 4-3-4)



3-Iodo-2-(2-propen-1-yl)pyridine (103t)

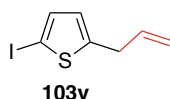
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-iodopyridine (**102a**) (61.5 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.5 mg, 0.303 mmol, 1.0 equiv), and THF (2.0 mL). LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated with $\text{CuCN} \cdot 2\text{LiCl}$ (1.0 M in THF, 0.45 mL, 0.45 mmol, 1.5 equiv) and allyl bromide (38 μL , 0.45 mmol, 1.5 equiv). After stirring at room temperature for 1 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 washed with brine (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 = 5:1) to provide the title compound **103t** as a pale yellow oil (44.0 mg, 0.180 mmol, 60%). R_f = 0.17 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1639, 1566, 1438, 1421, 1129, 1066, 1005, 916; ^1H NMR (400 MHz, CDCl_3): δ 8.51 (dd, 1H, J = 4.8, 1.6 Hz), 8.09 (dd, 1H, J = 8.0, 1.6 Hz), 6.86 (dd, 1H, J = 8.0, 4.8 Hz), 6.06 (ddt, 1H, J = 17.2, 10.4, 6.8 Hz), 5.21–5.12 (m, 2H), 3.78 (ddd, 2H, J = 7.2, 1.2, 1.2 Hz); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 161.0, 148.9, 147.1, 134.5, 122.8, 117.2, 96.4, 45.7; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_8\text{H}_9\text{IN}$ 245.9780; Found 245.9781.



3-Chloro-2-(phenylthio)pyridine (103u)

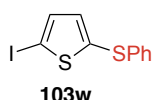
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 3-chloropyridine (**102c**) (34.4 mg, 0.303 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.4 mg, 0.303 mmol, 1.0 equiv), and THF (2.0 mL). LiTMP (0.66 M, 0.68 mL, 0.45 mmol, 1.5 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated with *N*-phenylthiophthalimide (80.1 mg, 0.314 mmol, 1.04 equiv) and copper(II) acetate monohydrate (3.3 mg, 16.5 μmol , 5 mol%). After stirring at room temperature 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 washed with brine (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/diethyl ether = 10:1) to provide the title compound **103u** as a pale yellow solid (37.5 mg, 0.169 mmol, 56%). The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.¹¹⁹ R_f = 0.37 (hexane/diethyl ether = 3:1); Mp 52–53 °C IR (ATR, cm^{-1}): 2883, 1561, 1478, 1438, 1389, 1058, 1023; ^1H NMR (400 MHz, CDCl_3): δ 8.21(dd, 1H, J = 4.8, 1.6 Hz), 7.60–7.54 (m, 3H), 7.46–7.40 (m, 3H), 6.97(dd, 1H, J = 8.0, 4.8 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 157.6, 147.6, 136.4, 135.6, 129.8, 129.3, 129.2, 128.8, 120.8; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_9\text{ClNS}$ 222.0144; Found 222.0141.



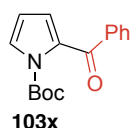
2-Iodo-5-(2-propen-1-yl)thiophene (**103v**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2-iodothiophene (**102h**) (63.0 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.6 mg, 0.303 mmol, 1.0 equiv), and THF (2.0 mL). LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated with $\text{CuCN} \cdot 2\text{LiCl}$ (1.0 M in THF, 0.45 mL, 0.45 mmol, 1.5 equiv) and allyl bromide (38 μL , 0.45 mmol, 1.5 equiv). After stirring at room temperature for 1 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 washed with brine (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) to provide the title compound **103v** as a pale yellow oil (71.1 mg, 0.284 mmol, 95%). R_f = 0.46 (hexane); IR (ATR, cm^{-1}): 1640, 1428, 1042, 990, 943, 919; ^1H NMR (400 MHz, CDCl_3): δ 7.07 (d, 1H, J = 3.6 Hz), 6.50 (dt, 1H, J = 3.6, 0.8 Hz), 5.94 (ddt, 1H, J = 16.8, 10.0, 6.8 Hz), 5.19–5.08 (m, 2H), 3.54 (dd, 2H, J = 6.8, 1.6 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 149.3, 136.9, 135.9, 126.6, 116.9, 70.6, 34.5; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_7\text{H}_8\text{IS}$ 250.9391; Found 250.9398.



2-Iodo-5-(phenylthio)thiophene (**103w**)

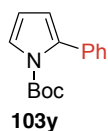
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2-iodothiophene (**102h**) (62.7 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.8 mg, 0.300 mmol, 1.0 equiv), and THF (2.0 mL). LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated with *N*-phenylthiophthalimide (80.9 mg, 0.317 mmol, 1.06 equiv) and copper(II) acetate monohydrate (3.0 mg, 15.0 μmol , 5 mol%). After stirring at room temperature for 11 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 washed with brine (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) to provide the title compound **103w** as a pale yellow oil (57.7 mg, 0.181 mmol, 61%). $R_f = 0.40$ (hexane); IR (ATR, cm^{-1}): 1580, 1477, 1440, 1393, 1201, 1114, 1081, 1068, 1024, 986, 936, 907; ^1H NMR (400 MHz, CDCl_3): δ 7.30–7.16 (m, 6H), 6.96 (d, 1H, $J = 3.6$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 138.0, 137.9, 137.3, 137.1, 129.3, 127.7, 126.7, 78.2; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_8\text{IS}_2$ 318.9112; Found 318.9113.



tert-Butyl 2-benzoyl-1*H*-pyrrole-1-carboxylate (**103x**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with *N*-Boc-pyrrole (**102s**) (50.0 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.2 mg, 0.302 mmol, 1.0 equiv), and THF (2.0 mL). LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated with benzoyl chloride (52 μL , 0.45 mmol, 1.5 equiv), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (15.7 mg, 15.2 μmol , 5 mol%), and tris[4-(trifluoromethyl)phenyl]phosphine (14.2 mg, 30.5 μmol , 10 mol%). After stirring at 60 $^\circ\text{C}$ for 15 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 washed with brine (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/diethyl ether = 95:5) to provide the title compound **103x** as a pale yellow solid (64.1 mg, 0.236 mmol, 79%). The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.¹²⁰ R_f = 0.23 (hexane/diethyl ether = 10:1); Mp 90–92 °C; IR (ATR, cm^{-1}): 1744, 1641, 1452, 1435, 1411, 1372, 1309, 1277, 1261, 1203, 1162, 1122, 1022, 913, 877, 848, 838; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (dd, 2H, J = 7.6, 1.2 Hz), 7.60–7.54 (m, 1H), 7.49–7.42 (m, 3H), 6.66 (dd, 1H, J = 3.2, 0.8 Hz), 6.26 (dd, 1H, J = 3.2, 3.2 Hz), 1.38 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 186.5, 148.7, 138.2, 132.9, 132.8, 129.6, 128.5, 126.3, 121.4, 110.6, 85.2, 27.6; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3$ 272.1287; Found 272.1295.



***tert*-Butyl 2-phenyl-1*H*-pyrrole-1-carboxylate (**103y**)**

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with *N*-Boc-pyrrole (**102s**) (50.1 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (76.5 mg, 0.303 mmol, 1.0 equiv), and THF (2.0 mL). LiTMP (0.66 M, 0.54 mL, 0.36 mmol, 1.2 equiv) was added to the Schlenk tube. After stirring at room temperature for 5 min, the reaction mixture was treated iodobenzene (50 μL , 0.45 mmol, 1.5 equiv), $\text{Pd}(\text{PPh}_3)_4$ (35.1 mg, 30.4 μmol , 10 mol%). After stirring at 60 °C for 15 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 washed with brine (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/diethyl ether = 97:3) to provide the title compound **103y** as a pale yellow oil (63.9 mg, 0.263 mmol, 88%). The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to those reported in the literature.¹²¹ R_f = 0.50 (hexane/diethyl ether = 10:1); IR (ATR, cm^{-1}): 1738, 1470, 1396, 1370, 1337, 1313, 1257, 1146, 1074, 1044, 972, 881, 841, 815; ^1H NMR (400 MHz, CDCl_3): δ 7.37–7.29 (m, 6H), 6.23 (dd, 1H, J = 3.6, 3.2 Hz), 6.20–6.17 (m, 1H), 1.35 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 149.5, 135.2, 134.6, 129.3, 127.7, 127.3, 122.6, 114.5, 110.7, 83.7, 27.7; HRMS (DART/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_2$ 244.1338; Found 244.1341.

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第五章

ハロアレーンの メタ位選択的メタル化

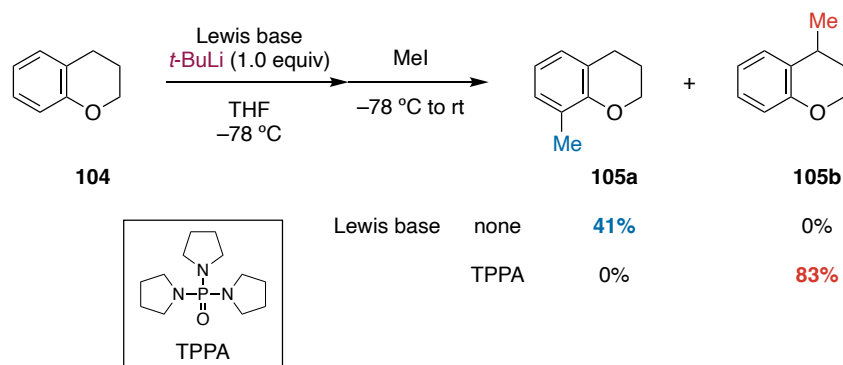
5-1 序論

第二章から第四章では、LiTMP と塩化亜鉛ジアミン錯体を用いた *in situ* トランスメタル化を鍵として、さまざまなハロアレーンの位置選択的な官能基化について述べた。この手法により、従来多段階合成を必要とした多くのハロアレーン誘導体が簡便に合成可能となり、さらに天然物カルバゾマイシン A-D のグラムスケール合成にも応用された。一方、本手法における脱プロトン化反応の位置選択性は、従来通り配向基のオルト位に限定されていた。本章では、Lewis 塩基と LiTMP の錯体を用い、ハロアレーンの脱プロトン化の位置選択性をハロゲン原子のメタ位へ転換できたので報告する。生成した不安定な 3-ハロアリアルリチウムは、*in situ* トランスメタル化によって捕捉され、ハロアレーンの直接的なメタ位選択的官能基化を実現した。

5-2 Lewis 塩基を用いた脱プロトン化の位置選択性の制御

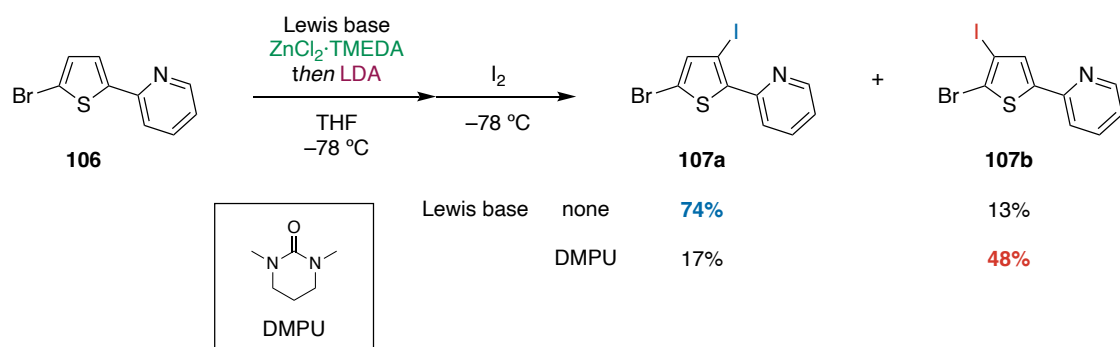
芳香族化合物のオルトメタル化では、一般的に芳香環上のルイス塩基性を有する配向基がルイス酸性を有するリチウムイオンと相互作用し、最も近接するオルト位で脱プロトン化が進行することが知られている¹⁴。この反応は、速度論的に制御されており、配向基とリチウムイオンとの相互作用によって高い位置選択性を示す。一方、リチウムイオンは、他の Lewis 塩基とあらかじめ相互作用することによって配位構造が変化し、脱プロトン化の位置選択性が転換することも報告している¹²²。

例えば、2023 年に Thomas らは、トリストリピロリジノホスフィンオキシド (TPPA)¹²³ の存在下で *t*-BuLi を用い、クロマン (**104**) の脱プロトン化における位置選択性を制御できることを報告している (Scheme 5-2-1)^{122b}。すなわち、クロマン (**104**) を含む THF 溶液に対して、 -78°C で *t*-BuLi を作用させたところ、脱プロトン化は酸素原子に近接するオルト位で進行している。その後、ヨードメタンで処理することで、ベンゼン環がメチル化されたクロマン **105a** を収率 41% で得ている。一方、反応系に TPPA を加えた場合には、脱プロトン化が熱力学的により安定なベンジル位へと変化している。ヨードメタンとの反応により、**105a** は全く得られず、ベンジル位でメチル化されたクロマン **105b** を収率 83% で得ている。この原因は、TPPA がクロマンの酸素原子よりも高いルイス塩基性を有し、*t*-BuLi が優先的に TPPA と配位するため、酸素原子に配向されるオルトメタル化が抑制され、より酸性度の高いベンジル位での脱プロトン化が優先的に進行したと考えられる。



Scheme 5-2-1. Regioselectivity in the metalation of chromane

2024年に当研究室の細谷らは、*N,N'*-ジメチルプロピレン尿素（DMPU）¹²⁴を用い、ブロモ基を有するピリジルチオフェン **106** の脱プロトン化の位置選択性を制御可能であることを報告している（Scheme 5-2-2）^{122c}。ピリジルチオフェン **106** に対し、*in situ* トランスメタル化を経た脱プロトンのヨウ素化を実施したところ、ヨードチオフェン **107a** とその構造異性体 **107b** をそれぞれ収率 74% および 13% で得ている。この位置選択性は、ピリジンの窒素原子が配向基として作用すると考えられる。一方、反応系に DMPU を添加したところ、**107b** を主生成物として収率 48% で得ている。この原因は、DMPU がピリジンの窒素原子よりも高いルイス塩基性を持ち、LDA のリチウムイオンに優先的に配位したためである。さらに、ピリジンよりもブロモ基の誘起効果が強いため、より酸性度の高いブロモ基の隣接位での脱プロトン化が進行すると考察している。



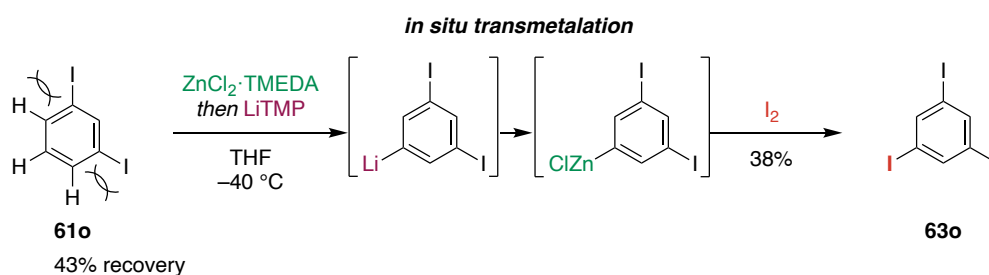
Scheme 5-2-2. Regioselectivity in the metalation of brominated pyridylthiophene

上述の研究背景を踏まえ、本研究では、Lewis 塩基によるリチウムアミドの活性化を鍵とし、*in situ* トランスメタル化を用いたハロアレーンのメタ位選択的な脱プロトンのメタル化の実現を目指した。

5-3 Lewis 塩基を用いたハロアレーンのメタ位選択的メタル化

5-3-1 DMPU を用いたハロアレーンのメタ位選択的メタル化

第二章では、*in situ* トランスメタル化を通じて、さまざまなハロベンゼンに対する位置選択的な官能基化を実現した。幅広いハロベンゼンにおいて、脱プロトン化は主にハロゲンの隣接位で進行することが確認された。一方、1,3-ジヨードベンゼン (**61o**) に対して、*in situ* トランスメタル化を実施したところ、1,3,5-トリヨードベンゼン (**m-63o**) が主生成物として収率 35% で得られ、**61o** が収率 43% で回収された (Scheme 5-3-1)。この結果は、ヨウ素原子の大きな立体障害の影響により、速度論的に支配される脱プロトン化が空間的により有利なメタ位で進行することを示唆している。しかし、このメタ位の酸性度が低いためか、これ以上の収率向上は困難であった。

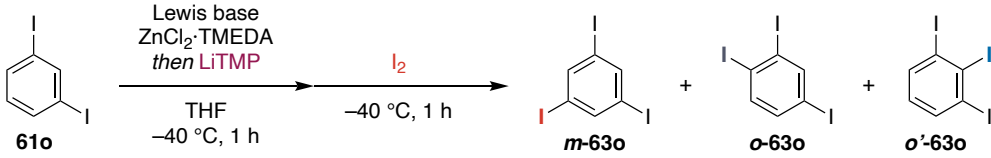
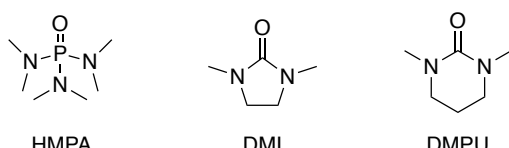


Scheme 5-3-1. meta-selective metalation of 1,3-diiodobenzene through *in situ* transmetalation

以上の知見に基づいて、まず、1,3-ジヨードベンゼンに対して Lewis 塩基が脱プロトン化の位置選択性および反応性に与える影響について検討した (Table 5-3-1)。まず、1,3-ジヨードベンゼン (**61o**) に対して、*in situ* トランスメタル化を実施した。その結果、トリヨードベンゼン **m-63o** と **o-63o** はそれぞれ収率 42% と 14% で得られ、**61o** が収率 43% で回収された (entry 1)。次に、ヘキサメチルリン酸トリアミド (HMPA) を用い、Lewis 塩基の添加効果を確認した。HMPA は、リチウムイオンなどの金属イオンに対して強い配位性を有し、錯体の形成を通じて反応性と位置選択性を制御することが知られている¹²⁴。ジヨードベンゼン **61o**、塩化亜鉛 TMEDA 錯体と 1 当量の HMPA を含む THF 溶液に対して、 -40°C で LiTMP を加えて 1 時間攪拌した。さらにヨウ素を作用させた結果、トリヨードベンゼン **m-63o** が収率 58% で得られ、**61o** が収率 22% で回収された。メタ選択性は 5.3:1.0 を示した。 (entry 2)。すなわち、HMPA を添加することにより、メタ位選択性と反応性のいずれも向上した。一方、HMPA は人間に対する発

がん性があるため、より安全性の高いルイス塩基の検討を行った。毒性の低い1,3-ジメチル-2-イミダゾリジノン (DMI)¹²⁵を用いたところ、結果はほぼ変わらなかった (entry 3)。DMPU を用いたところ、メタ選択性が 7.0:1.0 に向上した (entry 4)。さらに DMPU の量を 5 当量に増やしたところ、***m*-63o** が収率 77%、メタ選択性 77:1.0 で得られたが、**61o** を収率 17%で回収した (entry 5)。**61o** の回収率が高い原因は、ヨウ素化の進行が不完全であったと考えられる。そこで、ヨウ素を添加したのち、室温に昇温して 1 時間攪拌した結果、目的の ***m*-63o** を単離収率 90%で得た (entry 6)。以上の結果から、第二章で確立した *in situ* トランスメタル化に加え、DMPU を添加することにより、1,3-ジヨードベンゼンのメタ位選択的なヨウ素化を高収率かつ高選択性で達成した。

Table 5-3-1. Effect of Lewis base on the regioselectivity of the deprotonation of 1,3-diiodobenzene^a

						
						
entry	Lewis base	<i>m,o,o'</i>-63o (%) ^b			<i>meta</i> -selectivity ^c	recovery of 61o (%) ^b
1	none	42	14	<1	3.0:1.0	43
2	HMPA	58	10	1	5.3:1.0	22
3	DMI	58	11	1	4.8:1.0	27
4	DMPU	63	6	1	7.0:1.0	25
5 ^d	DMPU	77	1	<1	77:1.0	17
6 ^{d,e}	DMPU	90 (90) ^f	1	<1	90:1.0	7

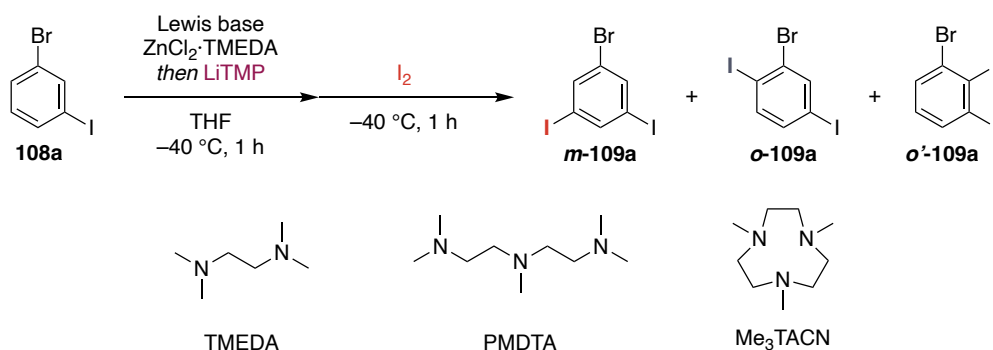
^aReaction conditions: iodobenzene **61o** (0.30 mmol, 1.0 equiv), ZnCl₂·TMEDA (0.30 mmol, 1.0 equiv), ligand (0.30 mmol, 1.0 equiv), LiTMP (0.53 mmol, 1.8 equiv), and I₂ (0.6 mmol, 2 equiv). ^bThe yield was determined from the ¹H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. ^cThe *meta*-selectivity, expressed as ***m*-63o/(*o*-63o+*o'*-63o)**, was determined by ¹H NMR spectroscopy. ^dDMPU (1.5 mmol, 5.0 equiv) was used. ^eIodination was performed at room temperature. ^fIsolated yield.

5-3-2 Me₃TACN を用いたハロアレーンのメタ位選択的メタル化

上述の結果に基づいて、1,3-ジヨードベンゼンより立体障害が少ない 1-ブロモ-3-ヨードベンゼン (**108a**) のメタ位選択的なヨウ素化を検討した (Table 5-3-2)。ブロモベンゼン **108a** と塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して、-40 °C で LiTMP を加えて 1 時間攪拌したのち、ヨウ素を加えてさらに 1 時間反応させた。この結果、ヨウ素化されたブロモベンゼン **m-109a** が収率 14% で得られ、**108a** が収率 21% で回収された。メタ選択性は 1:3.7 を示した (entry 1)。LiTMP を用いたブロモベンゼン **108a** のプロトン化は、主に臭素原子に隣接する位置で進行したことが明らかになった。DMPU を添加したところ、**m-109a** の収率は 61% に向上するとともに、メタ選択性が 2.9:1 に転換した (entry 2)。TMEDA を添加して反応を行った結果、Lewis 塩基を添加しない場合とほぼ同様の結果が得られた (entry 3)。トリアミン *N,N,N',N'',N''*-ペンタメチルジエチレントリアミン (PMDTA) ^{23b} を用いたところ、**m-109a** の収率は 14% に低下したが、メタ選択性は 1.5:1 を示した (entry 4)。PMDTA が興味深い添加効果を示したため、鎖状の PMDTA に代えて、環状のトリアミン 1,4,7-トリメチル-1,4,7-トリアザシクロノナン (Me₃TACN) ¹²⁶ を試した。この結果、目的の **m-109a** の収率が 61% に向上するとともに、メタ選択性も 31:1 に改善したが、**108** が収率 19% で回収された (entry 5)。さらに、Me₃TACN の量を 2 当量に減らしたところ、メタ選択性が少し低下したが、目的の **m-109** を収率 78% で合成した (entry 6)。

以上の結果から、DMPU と比較し、Me₃TACN は LiTMP との相互作用により高い反応性を示した。ヨウ素原子よりも立体障害が小さく、配向性の高い臭素原子に対しても、Me₃TACN を用いた脱プロトン化は臭素原子のメタ位で優先的に進行することが可能となった。また、細谷らの報告 ^{122c} に基づいて、メタ位選択的な官能基化を達成するためには *in situ* トランスメタル化が重要である。脱プロトン化により生成した有機リチウム中間体は非常に不安定であり、安定な有機金属種に変換しなければ、速やかに熱力学的により有利な副反応が進行することが明らかになった。

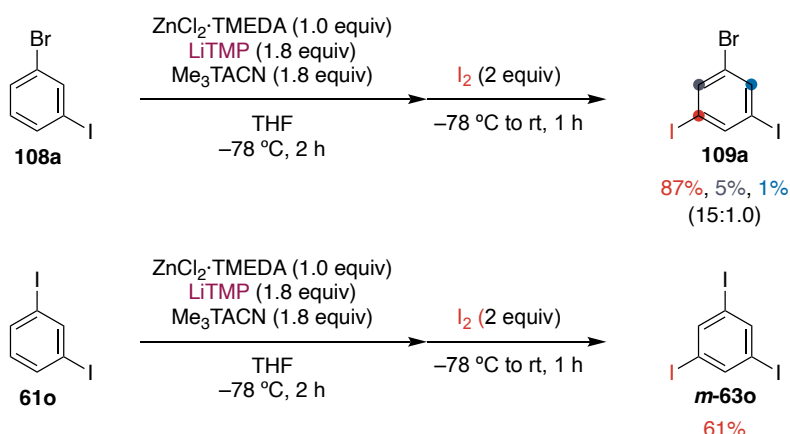
Table 5-3-2. Effect of Lewis base on the regioselectivity of the deprotonation of 1-bromo-3-iodobenzene^a



entry	Lewis base	<i>m,o,o'</i> -109a (%) ^b			<i>meta</i> -selectivity ^c	recovery of 108a (%) ^b
1	none	14	43	9	1.0:3.7	21
2	DMPU	63	21	1	2.9:1.0	7
3	TMEDA	15	40	1	1.0:2.7	29
4	PMDTA	14	4	5	1.5:1.0	14
5	Me_3TACN	61	1	1	31 :1.0	19
6 ^d	Me_3TACN	78	5	2	11 :1.0	11

^aReaction conditions: bromobenzene **108a** (0.30 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (0.30 mmol, 1.0 equiv), ligand (1.5 mmol, 5.0 equiv), LiTMP (0.53 mmol, 1.8 equiv), and I_2 (0.6 mmol, 2 equiv). ^bThe yield was determined from the ^1H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. ^cThe *meta*-selectivity, expressed as *m*-109a/(*o*-109a+*o'*-109a), was determined by ^1H NMR spectroscopy. ^d Me_3TACN (0.61 mmol, 2.1 equiv) was used.

Lewis 塩基の効果を確認したのち、1-ブロモ-3-ヨードベンゼンのメタ位選択的なヨウ素化の反応条件を最適化した (Scheme 5-3-2)。すなわち、調製した LiTMP の THF 溶液に対して $0\text{ }^\circ\text{C}$ で Me_3TACN を加えて 10 分間攪拌し、 LiTMP と Me_3TACN の THF 溶液を調製した。この際に、溶液の色が淡黄色から金色へと変化した。その後、1-ブロモ-3-ヨードベンゼンと塩化亜鉛 TMEDA 錯体を含む THF 溶液に対して $-78\text{ }^\circ\text{C}$ で LiTMP と Me_3TACN を含む THF 溶液を加えて 2 時間反応させた。その後、ヨウ素を処理させた結果、目的の *m*-109 を単離収率 87% で得た。メタ選択性は 15:1.0 を示した。また、1,3-ジヨードベンゼン (**61o**) に対して反応させたところ、*m*-63o のみが収率 61% で得られた。



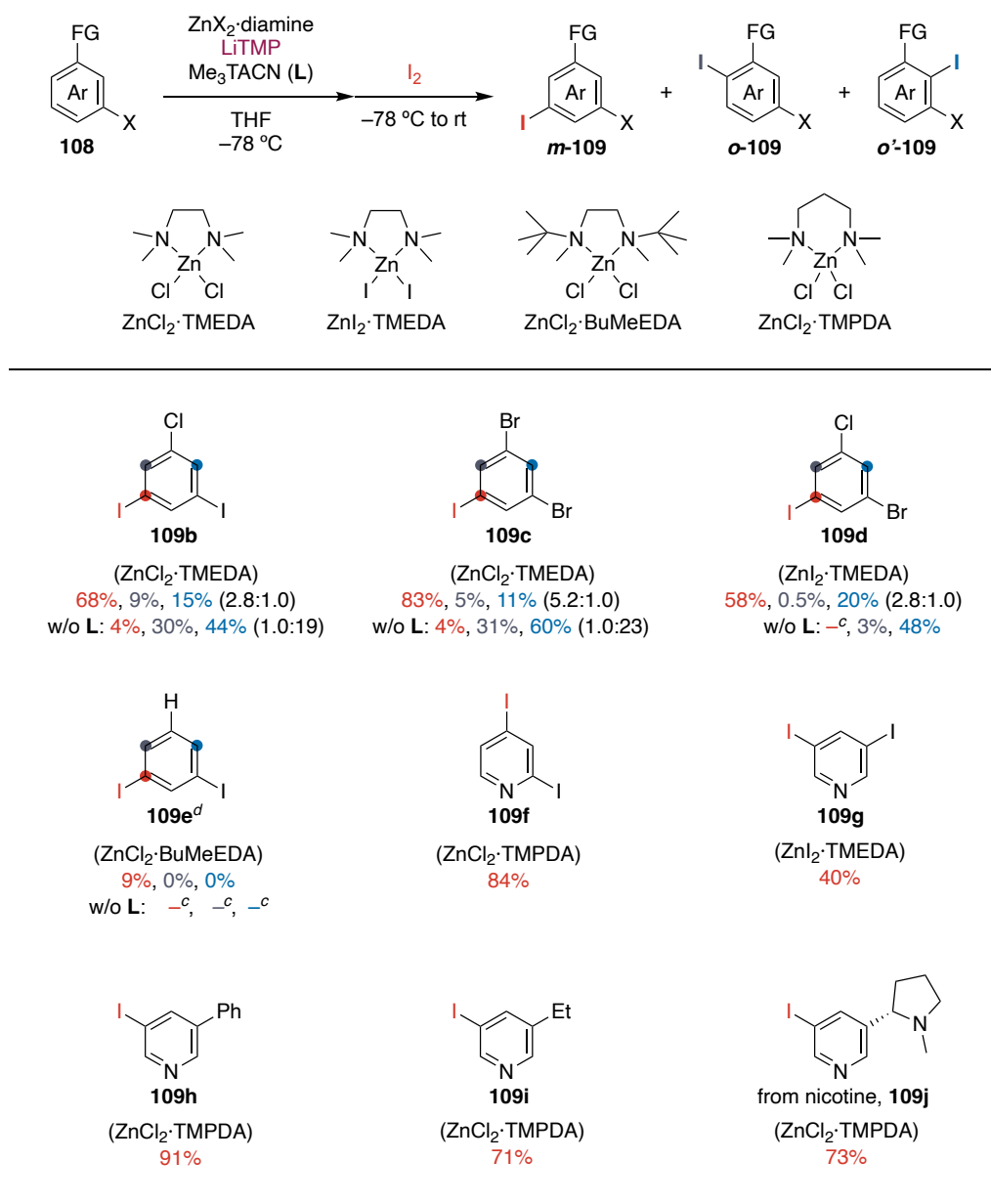
Scheme 5-3-2. Optimization of the deprotonation of iodobenzene derivatives by a combination of LiTMP and Me₃TACN

5-4 さまざまなハロアレーンのメタ位選択的メタル化

開発したハロアレーンのメタ位選択的メタル化の実用性を明らかにするために、ヨウ素化反応によってハロアレーンの一般性を調べた (Table 5-4-1)。ハロアレーン **108** と対応するハロゲン化亜鉛ジアミン錯体を含む THF 溶液に対し、 $-78\text{ }^{\circ}\text{C}$ で LiTMP と Me₃TACN の THF 溶液を加えて 2 時間攪拌した。さらにヨウ素を加え、室温に昇温しながら 1 時間反応させた。クロロ基を有するヨードベンゼン **108b** を反応させたところ、目的の *m*-**109b** が収率 68% で得られ、メタ選択性は 2.8:1.0 を示した。一方、Me₃TACN を用いない場合は、*m*-**109b** は収率 4% しか得られず、*o*-**109b** と *o'*-**109b** がそれぞれ収率 30% と 44% で得られた。1,3-ジブロモベンゼン (**108c**) に対して反応させたところ、*m*-**109c** は収率 83% で得られ、メタ選択性は 5.2:1.0 であった。Me₃TACN を用いない場合のメタ選択性が 1.0:2.3 であったことから、脱プロトン化の位置選択性はオルト位からメタ位へと転換することが明らかになった。より立体障害の少ないクロロ基を有するブロモベンゼン **108d** を用いたところ、*m*-**109d** は収率 58% で得られたが、Me₃TACN を用いない場合には *m*-**109d** を全く得られなかった。さらに、ヨードベンゼン (**108e**) を用いたところ、*m*-**109e** のみが収率 9% で得られた。一方、Me₃TACN を用いない場合は、**109e** が得られず、原料回収した。次に、基質の一般性をピリジン誘導体に拡張した。2-ヨードピリジン (**108f**) を反応させたところ、目的の *m*-**109f** を収率 84% で得た。一方、3-ヨードピリジン (**108g**) を反応させたところ、*m*-**109g** の収率が 40% に低下した。また、ヨードピリジンに加えて、フェニル基とエチル基をもつピリジン **108h** と **108i** にも有用であった。すなわち、Me₃TACN と LiTMP を用いた *in situ* トランスメタル化を実施した結果、*m*-**109h** と *m*-**109i** をそれぞれ収率 91% と 71% で合成した。さらに、天然物であるニコチン (**108j**)

に対して同様の反応を実施した結果、目的のメタヨウ素化体 **m-109j** を収率 73% で合成した。

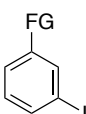
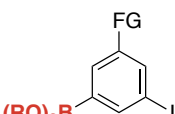
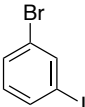
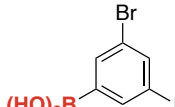
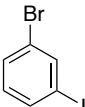
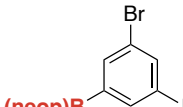
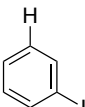
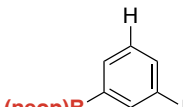
Table 5-4-1. Scope of the *meta*-metalation of haloarenes^a



^aReaction conditions: haloarene **108** (0.30 mmol, 1.0 equiv), ZnX₂·diamine (0.30 mmol, 1.0 equiv), a THF solution of LiTMP and Me₃TACN (0.53 mmol, 1.8 equiv), THF, -78 °C, 2 h, then I₂ (0.6 mmol, 2 equiv), room temperature. ^bThe *meta*-selectivity, expressed as **m-109**/(**o-109**+**o'-109**), was determined by ¹H NMR spectroscopy and is shown in parentheses. ^cNot observed. ^dThe deprotonation was performed at -40 °C.

続いて、塩化亜鉛ジアミン錯体をホウ素化剤 **20d** に置き換え、*in situ* トランスメタル化を検討した (Table 5-4-2)。有機ホウ素化合物は、鈴木–宮浦カップリング反応を通じて炭素–炭素結合の構築において重要な役割を果たしてきた **3a–d**。近年、宮浦¹²⁷、石山¹²⁷、Hartwig¹²⁸、Chirik¹²⁹と Ilies¹³⁰らにより、イリジウム触媒を用いた C–H 活性化による芳香族化合物のメタ位選択的ホウ素化が報告されている。一方、脱プロトン化反応を利用したメタ位選択的なホウ素化は、これまでに報告例がなかった。そこで、本研究は、Me₃TACN を用いた脱プロトン化反応により、*in situ* トランスメタル化に用いた塩化亜鉛ジアミン錯体をホウ素化剤に置き換え、メタ位選択的ホウ素化に取り組んだ。ハロアレーン **108**、Me₃TACN、とホウ酸トリイソプロピル **23b** を含む THF 溶液に対して、–78 °C で LiTMP を加え、さらに室温に昇温して攪拌した。2 M 塩酸で処理したところ、ボロン酸 **m-109k** が収率 50% で得られた。塩酸の代わりに酢酸とネオペンチルグリコール¹³¹ を作用させた場合は、ネオペンチルグリコールエステル基を持つ **m-109l** を収率 41% で得た。さらに、ヨードベンゼン (**108e**) を用いた場合は、目的の **m-109o** を収率 65% で合成した。

Table 5-4-2. *meta*-Metalation of haloarenes using boron reagents

 108	conditions 	 m-109
substrate	conditions	product
 108a	B(O ^{<i>i</i>} Pr) ₃ , Me ₃ TACN LiTMP, THF, –78 °C to rt then HCl (2 M), rt	 m-109k 50%
 108a	B(O ^{<i>i</i>} Pr) ₃ , Me ₃ TACN LiTMP, THF, –78 °C to rt then AcOH, neopentyl glycol, rt	 m-109l 41%
 108e	B(O ^{<i>i</i>} Pr) ₃ , Me ₃ TACN LiTMP, THF, –40 °C then AcOH, neopentyl glycol, rt	 m-109m 65%

5-5 結言

本研究では、Me₃TACN を用いた脱プロトン化反応および *in situ* トランスメタル化により、さまざまなハロアレーンの直接的なメタ位選択的官能基化を初めて実現した。Me₃TACN の存在下で LiTMP を用いた脱プロトン化は、ハロゲン原子のオルト位ではなく、空間的により有利なメタ位で進行することが可能となった。脱プロトン化により生成した 3-ハロアリールリチウムは、ハロゲン化亜鉛ジアミン錯体とのトランスメタル化を経て安定なアリール亜鉛化合物へと変換された。さらに、ヨウ素との反応により、メタ位選択的なヨウ素化を実現した。また、ホウ素化剤を用いた *in situ* トランスメタル化を経て、ハロアレーンのメタ位選択的なホウ素化にも成功した。従来複数段階を要していたヨードアレーン誘導体および有機ホウ素化合物の合成は、本手法により 1 工程で可能になった。一方、本研究では、反応機構や活性中間体の考察には至っておらず、今後

の重要な検討課題として残されている。今後は、基質の一般性と求電子剤の適用範囲をさらに拡張し、本手法の汎用性と実用性を一層高めることを目指す。

5-6 Experimental section

1. General

Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ 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 wave numbers (cm⁻¹). ¹H NMR (400 MHz) and ¹³C{¹H} NMR (100 MHz) spectra were measured on JEOL ECZ400 spectrometer. Chemical shifts for ¹H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard (CHCl₃: δ 7.26 ppm and acetone-*d*₅: δ 2.05 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, br = broad, dd = doublet of doublets, dt = doublet of triplets. Chemical shifts for ¹³C{¹H} NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃: δ 77.16 ppm and acetone-*d*₆: δ 29.84 ppm). High-resolution mass spectroscopy (HRMS) was performed on a Bruker compact ESI-Q-TOF MS spectrometer equipped with a Shimadzu LC (LC 40D XR) [electrospray ionization (ESI)], and [electron ionization (EI)] with a JEOL JMS-700 MStation.

2. Materials

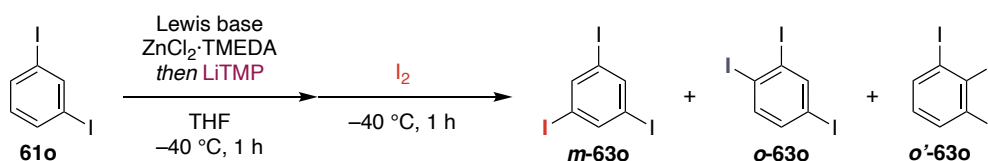
Unless otherwise stated, all reactions were conducted in a flame-dried glassware under an inert atmosphere of argon. All work-up and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel[®] 60N (63–212 μ m, Wako Pure Chemical Industries, Ltd.) or High-efficiency irregular silica (25–40 μ m, Santai Science Inc.). Anhydrous THF (>99.5%, water content: <30 ppm) was purchased from Kanto Chemical Co. and further dried by passing through a solvent purification system (Glass Contour) prior to use. *n*-BuLi (1.6 M in *n*-hexane) and TMPH were purchased from Kanto Chemical Co. and used as received. Me₃TACN was purchased from BLD Pharmatech Ltd. and used as received. Freshly prepared ZnCl₂·TMEDA, ZnCl₂·TMPDA, ZnCl₂·BuMeEDA, and ZnI₂·TMEDA were used in the following experiments.

3 Preparation of a THF solution of LiTMP and Me₃TACN

To a solution of TMPH (0.41 mL, 2.4 mmol) in THF (1.6 mL) was added *n*-BuLi (1.6

mL, 1.51 M in *n*-hexane, 2.4 mmol) dropwise at $-78\text{ }^{\circ}\text{C}$. The resulting solution was stirred at $0\text{ }^{\circ}\text{C}$ for 30 min. To the solution was added Me_3TACN (0.47 mL, 2.4 mmol) dropwise at $0\text{ }^{\circ}\text{C}$. The resulting solution was stirred at $0\text{ }^{\circ}\text{C}$ for 10 min to provide a THF solution of LiTMP and Me_3TACN (0.59 M).

4. Effect of Lewis base on the regioselectivity of the deprotonation of 1,3-diiodobenzene (Table 5-3-1)



General procedure for the synthesis of 1,3,5-trimethoxybenzene (**m-63o**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 1,3-diiodobenzene (**61o**) (99.0 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), Lewis base (0.300 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution was cooled to $-40\text{ }^{\circ}\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^{\circ}\text{C}$ for 1 h, the reaction mixture was treated with iodine (152.3 mg, 0.600 mmol, 2.0 equiv). After stirring at $-40\text{ }^{\circ}\text{C}$ 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 washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yields of 1,3,5-triiodobenzene (**m-63o**), 1,2,4-triiodobenzene (**o-63o**), 1,2,3-triiodobenzene (**o'-63o**), and 1,3-diiodobenzene (**61o**) 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 8.00 ppm (3 protons for **m-63o**), 8.18 ppm (1 proton for **o-63o**), 7.85 ppm (2 protons for **o'-63o**), and 8.07 ppm (1 proton for **61o**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction performed in the absence of a Lewis base (Table 5-3-1, entry 1)

A crude product was obtained from 1,3-diiodobenzene (**61o**) (99.6 mg, 0.302 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (154.5 mg, 0.608 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1,3,5-triiodobenzene (**m-63o**), 1,2,4-triiodobenzene (**o-63o**), 1,2,3-triiodobenzene (**o'-63o**), and 1,3-diiodobenzene (**61o**) were

determined to be 42%, 14%, <1%, and 43% by ^1H NMR spectroscopy.

Reaction performed with HMPA (Table 5-3-1, entry 2)

A crude product was obtained from 1,3-diiodobenzene (**61o**) (99.4 mg, 0.301 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.1 mg, 0.301 mmol, 1.0 equiv), HMPA (52 μL , 0.30 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (168.9 mg, 0.665 mmol, 2.2 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1,3,5-triiodobenzene (**m-63o**), 1,2,4-triiodobenzene (**o-63o**), 1,2,3-triiodobenzene (**o'-63o**), and 1,3-diiodobenzene (**61o**) were determined to be 58%, 10%, 1%, and 22% by ^1H NMR spectroscopy.

Reaction performed with DMI (Table 5-3-1, entry 3)

A crude product was obtained from 1,3-diiodobenzene (**61o**) (99.2 mg, 0.301 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.0 mg, 0.301 mmol, 1.0 equiv), DMI (33 μL , 0.30 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (152.1 mg, 0.599 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1,3,5-triiodobenzene (**m-63o**), 1,2,4-triiodobenzene (**o-63o**), 1,2,3-triiodobenzene (**o'-63o**), and 1,3-diiodobenzene (**61o**) were determined to be 58%, 11%, 1%, and 27% by ^1H NMR spectroscopy.

Reaction performed with DMPU (Table 5-3-1, entry 4)

A crude product was obtained from 1,3-diiodobenzene (**61o**) (99.1 mg, 0.301 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (75.9 mg, 0.301 mmol, 1.0 equiv), DMPU (36 μL , 0.30 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (150.8 mg, 0.594 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1,3,5-triiodobenzene (**m-63o**), 1,2,4-triiodobenzene (**o-63o**), 1,2,3-triiodobenzene (**o'-63o**), and 1,3-diiodobenzene (**61o**) were determined to be 63%, 6%, 1%, and 25% by ^1H NMR spectroscopy.

Reaction performed with 5 equivalents of DMPU (Table 5-3-1, entry 5)

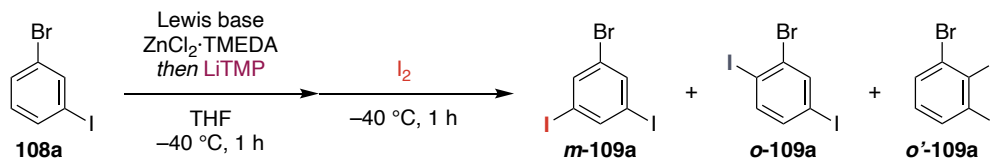
A crude product was obtained from 1,3-diiodobenzene (**61o**) (99.0 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.1 mg, 0.301 mmol, 1.0 equiv), DMPU (0.18 mL, 1.5 mmol, 5.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (162.4 mg, 0.640 mmol, 2.1 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1,3,5-triiodobenzene (**m-63o**), 1,2,4-triiodobenzene (**o-63o**), 1,2,3-triiodobenzene (**o'-63o**), and 1,3-diiodobenzene (**61o**) were determined to be 77%, 1%, <1%, and 17% by

^1H NMR spectroscopy.

Reaction performed with 5 equivalents of DMPU and iodination performed at room temperature (Table 5-3-1, entry 6)

A crude product was purified by silica gel column chromatography (hexane) to provide the 1,3,5-triiodobenzene (***o*-63o**) as a colorless solid (122.2 mg, 0.268 mmol, 90%) from 1,3-diiodobenzene (**61o**) (98.7 mg, 0.299 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (76.3 mg, 0.302 mmol, 1.0 equiv), DMPU (0.18 mL, 1.5 mmol, 5.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (154.0 mg, 0.607 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure and iodination performed at room temperature. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data of ***o*-63o** were identical to those reported in the chapter 2. R_f = 0.58 (hexane); Mp 173–174 °C; IR (ATR, cm^{-1}): 3078, 3045, 1532, 1395, 1100, 846, 701, 657; ^1H NMR (400 MHz, CDCl_3): δ 8.00 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 144.6, 95.4; HRMS (EI^+) m/z : calcd. for $\text{C}_6\text{H}_3\text{I}_3$, 455.7369 $[\text{M}]^+$; found 455.7368. The yields of 1,3,5-triiodobenzene (***m*-63o**), 1,2,4-triiodobenzene (***o*-63o**), 1,2,3-triiodobenzene (***o'*-63o**), and 1,3-diiodobenzene (**61o**) were determined to be 90%, 1%, <1%, and 7% by ^1H NMR spectroscopy.

5. Effect of Lewis base on the regioselectivity of the deprotonation of 1-bromo-3-iodobenzene (Table 5-3-2)



General procedure for the synthesis of 1-bromo-3,5-diiodobenzene (*m*-109a**)**

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 1-bromo-3-iodobenzene (**108a**) (84.9 mg, 0.300 mmol, 1.0 equiv), $\text{ZnCl}_2\cdot\text{TMEDA}$ (75.7 mg, 0.300 mmol, 1.0 equiv), ligand (1.50 mmol, 5.0 equiv), and THF (2.0 mL). The resulting solution was cooled to $-40\text{ }^\circ\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-40\text{ }^\circ\text{C}$ for 1 h, the reaction mixture was treated with iodine (152.3 mg, 0.600 mmol, 2.0 equiv). After stirring at $-40\text{ }^\circ\text{C}$ 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 washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give

a crude product. The yields of 1-bromo-3,5-diiodobenzene (***m*-109a**), 1-bromo-2,5-diiodobenzene (***o*-109a**), 1-bromo-2,3-diiodobenzene (***o'*-109a**), and 1-bromo-3-iodobenzene (**108a**) 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 7.98 ppm (1 proton for ***m*-109a**), 7.55 ppm (1 proton for ***o*-109a**), 6.89 ppm (1 proton for ***o'*-109a**), and 6.97 ppm (1 proton for **108a**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm.

Reaction performed in the absence of a Lewis base (Table 5-3-2, entry 1)

A crude product was obtained from 1-bromo-3-iodobenzene (**108a**) (84.5 mg, 0.299 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.1 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), iodine (171.5 mg, 0.676 mmol, 2.3 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1-bromo-3,5-diiodobenzene (***m*-109a**), 1-bromo-2,5-diiodobenzene (***o*-109a**), 1-bromo-2,3-diiodobenzene (***o'*-109a**), and 1-bromo-3-iodobenzene (**108a**) were determined to be 14%, 43%, 9%, and 21% by ¹H NMR spectroscopy.

Reaction performed with DMPU (Table 5-3-2, entry 2)

A crude product was obtained from 1-bromo-3-iodobenzene (**108a**) (85.5 mg, 0.302 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.3 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), DMPU (0.18 mL, 1.5 mmol, 5.0 equiv), iodine (152.1 mg, 0.599 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1-bromo-3,5-diiodobenzene (***m*-109a**), 1-bromo-2,5-diiodobenzene (***o*-109a**), 1-bromo-2,3-diiodobenzene (***o'*-109a**), and 1-bromo-3-iodobenzene (**108a**) were determined to be 63%, 21%, 1%, and 7% by ¹H NMR spectroscopy.

Reaction performed with TMEDA (Table 5-3-2, entry 3)

A crude product was obtained from 1-bromo-3-iodobenzene (**108a**) (84.2 mg, 0.298 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.1 mg, 0.301 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), TMEDA (0.22 mL, 1.5 mmol, 5.0 equiv), iodine (161.0 mg, 0.634 mmol, 2.1 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1-bromo-3,5-diiodobenzene (***m*-109a**), 1-bromo-2,5-diiodobenzene (***o*-109a**), 1-bromo-2,3-diiodobenzene (***o'*-109a**), and 1-bromo-3-iodobenzene (**108a**) were determined to be 15%, 40%, 1%, and 29% by ¹H NMR spectroscopy.

Reaction performed with PMDTA (Table 5-3-2, entry 4)

A crude product was obtained from 1-bromo-3-iodobenzene (**108a**) (85.2 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.3 mg, 0.302 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), PMDTA (0.31 mL, 1.5 mmol, 5.0 equiv), iodine (150.5 mg, 0.593 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1-bromo-3,5-diiodobenzene (**m-109a**), 1-bromo-2,5-diiodobenzene (**o-109a**), 1-bromo-2,3-diiodobenzene (**o'-109a**), and 1-bromo-3-iodobenzene (**108a**) were determined to be 14%, 4%, 5%, and 14% by ¹H NMR spectroscopy.

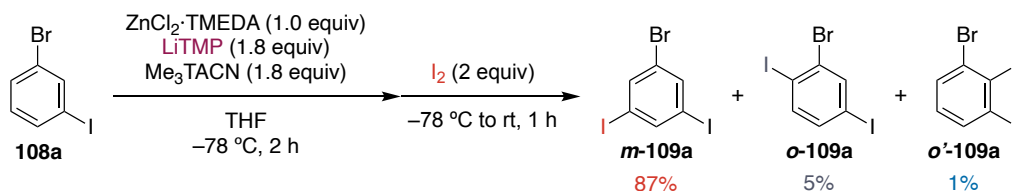
Reaction performed with Me₃TACN (Table 5-3-2, entry 5)

A crude product was obtained from 1-bromo-3-iodobenzene (**108a**) (85.1 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.4 mg, 0.303 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), Me₃TACN (0.29 mL, 1.5 mmol, 5.0 equiv), iodine (155.3 mg, 0.612 mmol, 2.0 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1-bromo-3,5-diiodobenzene (**m-109a**), 1-bromo-2,5-diiodobenzene (**o-109a**), 1-bromo-2,3-diiodobenzene (**o'-109a**), and 1-bromo-3-iodobenzene (**108a**) were determined to be 61%, 1%, 1%, and 19% by ¹H NMR spectroscopy.

Reaction performed with 2 equivalents of Me₃TACN (Table 5-3-2, entry 6)

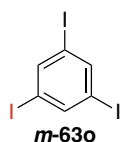
A crude product was obtained from 1-bromo-3-iodobenzene (**108a**) (85.0 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.7 mg, 0.304 mmol, 1.0 equiv), LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv), Me₃TACN (0.12 mL, 0.62 mmol, 2.1 equiv), iodine (161.0 mg, 0.634 mmol, 2.1 equiv), and THF (2.0 mL) according to the general procedure. The yields of 1-bromo-3,5-diiodobenzene (**m-109a**), 1-bromo-2,5-diiodobenzene (**o-109a**), 1-bromo-2,3-diiodobenzene (**o'-109a**), and 1-bromo-3-iodobenzene (**108a**) were determined to be 78%, 5%, 2%, and 11% by ¹H NMR spectroscopy.

6. Optimization of the deprotonation of iodobenzene derivatives promoted by a combination of LiTMP and Me₃TACN (Scheme 5-3-2)



A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 1-bromo-3-iodobenzene (**108a**) (84.5 mg, 0.299 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.3 mg, 0.302 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution was cooled to -78 °C. A THF solution of LiTMP and

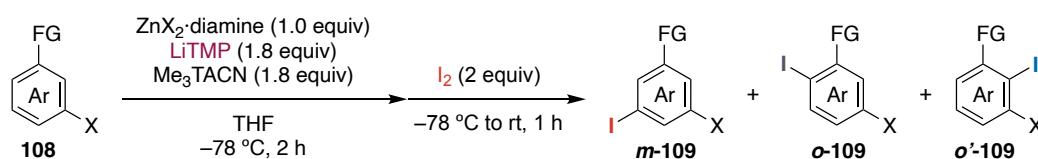
Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at −78 °C for 2 h, the reaction mixture was treated with iodine (161.4 mg, 0.636 mmol, 2.1 equiv). After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (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 washed with brine (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) to provide an inseparable mixture (113.5 mg) of 1-bromo-3,5-diiodobenzene (***m*-109a**) (0.260 mmol, 87%), 1-bromo-2,5-diiodobenzene (***o*-109a**) (0.0150 mmol, 5%), and 1-bromo-3-iodobenzene (***o'*-109a**) (0.0030 mmol, 1%) as a colorless solid. The ¹H and ¹³C{¹H} NMR spectroscopic data of ***m*-109a** were identical to those reported in the literature.¹³² The ratio was determined by ¹H NMR spectroscopy. Physicochemical properties of 1-bromo-3,5-diiodobenzene (***m*-109a**): R_f = 0.60 (hexane); Mp 123–125 °C; IR (ATR, cm^{−1}): 1540, 1439, 1394, 1099, 997, 846; ¹H NMR (400 MHz, CDCl₃): δ 7.98 (t, 1H, *J* = 1.2 Hz), 7.82 (d, 2H, *J* = 1.2 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 144.0, 139.2, 123.5, 95.0.



1,3,5-Triiodobenzene (***m*-63o**)

A crude product was purified by silica gel column chromatography (hexane) to provide the title compound ***m*-63o** (82.8 mg, 0.182 mmol, 61%) as a colorless solid from 1,3-diiodobenzene (**61o**) (98.9 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.1 mg, 0.301 mmol, 1.0 equiv), a THF solution of LiTMP and Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (164.1 mg, 0.647 mmol, 2.1 equiv) according to the above procedure.

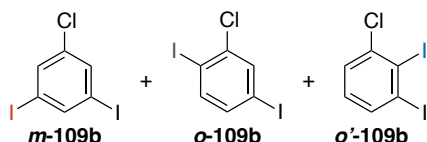
7. Scope of the *meta*-metalation of haloarenes (Table 5-4-1)



General procedure

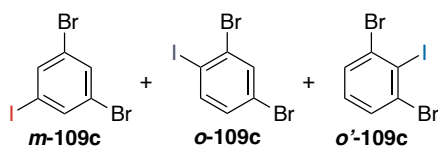
A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar

and a rubber septum under argon was charged with haloarene (**108**) (0.300 mmol, 1.0 equiv), zinc halide diamine complex (0.300 mmol, 1.0 equiv), and THF (2.0 mL). The resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$. A THF solution of LiTMP and Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-78\text{ }^{\circ}\text{C}$ for 2 h, the reaction mixture was treated with iodine (152.3 mg, 0.600 mmol, 2.0 equiv). 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 washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product.



1-Chloro-3,5-diiodobenzene (***m*-109b**)

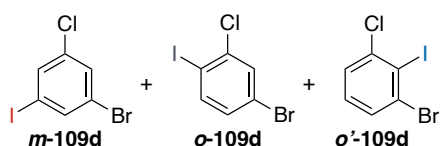
A crude product was purified by silica gel column chromatography (hexane) to provide an inseparable mixture (85.1 mg) of the title compound ***m*-109b** (0.206 mmol, 68%) and 1-chloro-2,5-diiodobenzene (***o*-109b**) (0.0280 mmol, 9%) as a colorless solid, and 1-chloro-2,3-diiodobenzene (***o'*-109b**) (16.9 mg, 0.0464 mmol, 15%) as a colorless solid from 1-chloro-3-iodobenzene (**108b**) (71.7 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.5 mg, 0.303 mmol, 1.0 equiv), A THF solution of LiTMP and Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (164.0 mg, 0.646 mmol, 2.1 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data of ***m*-109b** were identical to that reported in the literature.¹³³ The ratio was determined by ¹H NMR spectroscopy. Physicochemical properties of 1-chloro-3,5-diiodobenzene (***m*-109b**): *R*_f = 0.60 (hexane); Mp 80–82 $^{\circ}\text{C}$; IR (ATR, cm⁻¹): 1545, 1444, 1398, 1385, 1355, 1215, 1104, 1005, 847, 804; ¹H NMR (400 MHz, CDCl₃): δ 7.94 (t, 1H, *J* = 1.2 Hz), 7.67 (d, 2H, *J* = 1.2 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 143.6, 136.7, 135.7, 94.6.



1,3-Dibromo-5-iodobenzene (***m*-109c**)

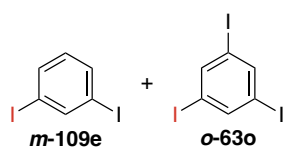
A crude product was purified by silica gel column chromatography (hexane) to provide

an inseparable mixture (106.9 mg) of the title compound ***m*-109c** (0.248 mmol, 83%), 1,3-dibromo-4-iodobenzene (***o*-109c**) (0.0149 mmol, 5%), and 1,3-dibromo-2-iodobenzene (***o'*-109c**) (0.0328 mmol, 11%) as a colorless solid from 1,3-dibromobenzene (**108c**) (70.4 mg, 0.298 mmol, 1.0 equiv), ZnCl₂·TMEDA (76.0 mg, 0.301 mmol, 1.0 equiv), A THF solution of LiTMP and Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (157.1 mg, 0.619 mmol, 2.1 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data of ***m*-109c** were identical to that reported in the literature.¹³⁴ The ratio was determined by ¹H NMR spectroscopy. Physicochemical properties of 1,3-dibromo-5-iodobenzene (***m*-109c**): R_f = 0.67 (hexane); Mp 95–97 °C; IR (ATR, cm⁻¹): 1547, 1399, 1097, 846; ¹H NMR (400 MHz, CDCl₃): δ 7.80 (d, 2H, *J* = 1.6 Hz), 7.64 (t, 1H, *J* = 1.6 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 138.7, 133.8, 123.5, 94.6.



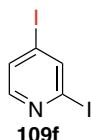
1-Bromo-3-chloro-5-iodobenzene (***m*-109d**)

A crude product was purified by silica gel column chromatography (hexane) to provide an inseparable mixture (56.3 mg) of the title compound ***m*-109d** (0.176 mmol, 58%) and 1-bromo-3-chloro-4-iodobenzene (***o*-109d**) (0.0008 mmol, 0.5%) as a colorless solid, and 1-bromo-3-chloro-2-iodobenzene (***o'*-109d**) (18.9 mg, 0.0596 mmol, 20%) as a colorless solid from 1-bromo-3-chlorobenzene (**108d**) (58.0 mg, 0.303 mmol, 1.0 equiv), ZnI₂·TMEDA (130.6 mg, 0.300 mmol, 1.0 equiv), A THF solution of LiTMP and Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (152.7 mg, 0.602 mmol, 2.0 equiv) according to the general procedure. The ¹H and ¹³C{¹H} NMR spectroscopic data of ***m*-109d** were identical to that reported in the literature.¹³⁵ The ratio was determined by ¹H NMR spectroscopy. Physicochemical properties of 1-bromo-3-chloro-5-iodobenzene (***m*-109d**): R_f = 0.67 (hexane); Mp 69–71 °C; IR (ATR, cm⁻¹): 1553, 1404, 1388, 1215, 1113, 1097, 1007, 848; ¹H NMR (400 MHz, CDCl₃): δ 7.76 (dd, 1H, *J* = 1.6, 1.6 Hz), 7.65 (dd, 1H, *J* = 1.6, 1.6 Hz), 7.49 (dd, 1H, *J* = 1.6, 1.6 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 138.2, 136.0, 135.8, 131.1, 123.2, 94.1.



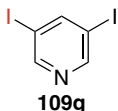
1,3-Diiodobenzene (*m*-109e)

A crude product was purified by silica gel column chromatography (hexane) to provide an inseparable mixture (13.4 mg) of the title compound ***m*-109e** (0.0283 mmol, 9%) and 1,3,5-triiodobenzene (*o*-63o) (0.0089 mmol, 3%) as a pale yellow amorphous solid from iodobenzene (**108e**) (61.4 mg, 0.301 mmol, 1.0 equiv), ZnCl₂·BuMeEDA³⁶ (101.0 mg, 0.300 mmol, 1.0 equiv), A THF solution of LiTMP and Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (164.1 mg, 0.647 mmol, 2.1 equiv) according to the general procedure at -40 °C. The ¹H and ¹³C{¹H} NMR spectroscopic data of ***m*-109e** were identical to that reported in the literature.¹³⁶ The ratio was determined by ¹H NMR spectroscopy. Physicochemical properties of 1,3-diiodobenzene (***m*-109e**): *R*_f = 0.58 (hexane); IR (ATR, cm⁻¹): 1553, 1448, 1099, 1074, 1046, 992; ¹H NMR (400 MHz, CDCl₃): δ 8.07 (dd, 1H, *J* = 2.0, 2.0 Hz), 7.66 (dd, 1H, *J* = 2.0, 2.0 Hz), 6.84 (dd, 1H, *J* = 8.0, 8.0 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 145.3, 136.8, 131.7, 95.1.



2,4-Diiodopyridine (109f)

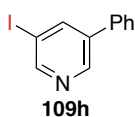
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the title compound **109f** (83.7 mg, 0.253 mmol, 84%) as a colorless solid from 2-iodopyridine (**108f**) (61.4 mg, 0.300 mmol, 1.0 equiv), ZnCl₂·TMPDA (80.6 mg, 0.302 mmol, 1.0 equiv), A THF solution of LiTMP and Me₃TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (158.7 mg, 0.625 mmol, 2.1 equiv) according to the general procedure. *R*_f = 0.47 (hexane/diethyl ether = 3:1); Mp 67–68 °C; IR (ATR, cm⁻¹): 2924, 1540, 1522, 1438, 1341, 1115, 1083, 1069, 816; ¹H NMR (400 MHz, CDCl₃): δ 8.14 (d, 1H, *J* = 1.6 Hz), 8.03 (d, 1H, *J* = 5.2 Hz), 7.63 (dd, 1H, *J* = 5.2, 1.6 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 150.8, 143.0, 132.4, 118.2, 106.1; HRMS (ESI/TOF) *m/z*: [M+H]⁺ Calcd for C₅H₄I₂N 331.8428; Found 331.8426.



3,5-Diiodopyridine (109g)

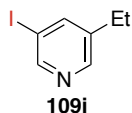
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 95:5) to provide the title compound **109g** (39.4 mg, 0.119 mmol, 40%) as a colorless

solid from 3-iodopyridine (**108g**) (61.7 mg, 0.301 mmol, 1.0 equiv), $\text{ZnI}_2 \cdot \text{TMEDA}$ (130.7 mg, 0.300 mmol, 1.0 equiv), A THF solution of LiTMP and Me_3TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (160.1 mg, 0.631 mmol, 2.1 equiv) according to the general procedure. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to that reported in the literature.¹³⁷ $R_f = 0.67$ (hexane/diethyl ether = 3:1); Mp 160–161 °C; IR (ATR, cm^{-1}): 3069, 3000, 1529, 1411, 1400, 1216, 1108, 1069, 999, 989, 875; ^1H NMR (400 MHz, CDCl_3): δ 8.75 (d, 2H, $J = 2.0$ Hz), 8.36 (t, 1H, $J = 2.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 154.3, 151.6, 94.0.



3-Iodo-5-phenylpyridine (**109h**)

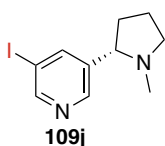
A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 85:15) to provide the title compound **109h** (77.3 mg, 0.275 mmol, 91%) as a colorless solid from 3-phenylpyridine (**108h**) (46.8 mg, 0.302 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMPDA}$ (80.7 mg, 0.303 mmol, 1.0 equiv), A THF solution of LiTMP and Me_3TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (157.7 mg, 0.621 mmol, 2.1 equiv) according to the general procedure. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to that reported in the literature.¹³⁸ $R_f = 0.26$ (hexane/diethyl ether = 5:1); Mp 69–71 °C; IR (ATR, cm^{-1}): 2923, 1572, 1497, 1452, 1421, 1406, 1379, 1171, 1102, 1077, 1044, 1022, 1010, 881; ^1H NMR (400 MHz, CDCl_3): δ 8.80 (d, 1H, $J = 2.0$ Hz), 8.78 (d, 1H, $J = 2.0$ Hz), 8.22 (dd, 1H, $J = 2.0, 2.0$ Hz), 7.57–7.53 (m, 2H), 7.51–7.40 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 154.4, 146.8, 142.7, 138.7, 136.4, 129.3, 128.8, 127.3, 93.8; HRMS (ESI/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_9\text{IN}$ 281.9774; Found 281.9770.



3-Ethyl-5-iodopyridine (**109i**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether = 85:15) to provide the title compound **109i** (48.9 mg, 0.210 mmol, 71%) as a colorless oil from 3-ethylpyridine (**108i**) (31.7 mg, 0.296 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMPDA}$ (79.8 mg, 0.299 mmol, 1.0 equiv), A THF solution of LiTMP and Me_3TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (160.8 mg, 0.634 mmol, 2.1 equiv) according to the general procedure. $R_f = 0.33$ (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 2967, 1573,

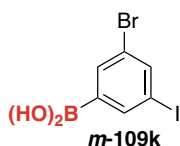
1547, 1461, 1454, 1419, 1308, 1160, 1095, 1054, 1019, 972, 877, 818; ^1H NMR (400 MHz, CDCl_3): δ 8.65 (d, 1H, $J = 1.6$ Hz), 8.40 (d, 1H, $J = 1.6$ Hz), 7.86 (s, 1H), 2.61 (q, 2H, $J = 7.6$ Hz), 1.25 (t, 3H, $J = 7.6$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 153.3, 148.2, 143.8, 141.6, 93.6, 25.9, 15.2; HRMS (ESI/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_7\text{H}_9\text{IN}$ 233.9774; Found 233.9770.



(*S*)-3-Iodo-5-(1-methylpyrrolidin-2-yl)pyridine (**109j**)

A crude product was purified by silica gel column chromatography (hexane/diethyl ether/triethylamine = 100:25:1) to provide the title compound **109j** (63.1 mg, 0.219 mmol, 73%) as a pale yellow oil from (*S*)-3-(1-methylpyrrolidin-2-yl)pyridine (**108j**) (49.0 mg, 0.302 mmol, 1.0 equiv), $\text{ZnCl}_2 \cdot \text{TMPDA}$ (80.4 mg, 0.302 mmol, 1.0 equiv), A THF solution of LiTMP and Me_3TACN (0.59 M, 0.92 mL, 0.54 mmol, 1.8 equiv), and iodine (156.5 mg, 0.617 mmol, 2.0 equiv) according to the general procedure. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data were identical to that reported in the literature.¹³⁸ R_f = 0.22 (hexane/diethyl ether/triethylamine = 100:25:1); IR (ATR, cm^{-1}): 2968, 2943, 2779, 1457, 1432, 1416, 1355, 1293, 1229, 1214, 1160, 1086, 1044, 1018, 902, 879; ^1H NMR (400 MHz, CDCl_3): δ 8.70 (d, 1H, $J = 2.0$ Hz), 8.45 (d, 1H, $J = 2.0$ Hz), 8.05 (dd, 1H, $J = 2.0, 2.0$ Hz), 3.23 (td, 1H, $J = 7.6, 2.0$ Hz), 3.05 (t, 1H, $J = 8.4$ Hz), 2.31 (q, 1H, $J = 8.8$ Hz), 2.26–2.14 (m, 1H), 2.18 (s, 3H), 2.02–1.89 (m, 1H), 1.87–1.77 (m, 1H), 1.74–1.65 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 154.7, 148.1, 143.2, 141.5, 94.0, 68.3, 57.1, 40.6, 35.5, 22.8; HRMS (ESI/TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{14}\text{IN}_2$ 289.0196; Found 289.0195.

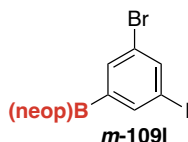
8. *meta*-Metalation of haloarenes using boron reagents (Table 5-4-2)



3-Bromo-5-iodophenylboronic acid (*m*-109k)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 1-bromo-3-iodobenzene (**108a**) (84.2 mg, 0.298 mmol, 1.0 equiv), triisopropyl borate (0.14 mL, 0.61 mmol, 2.0 equiv),

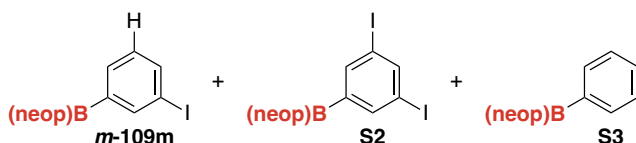
Me₃TACN (0.12 mL, 0.62 mmol, 2.1 equiv), and THF (2.0 mL). The resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-78\text{ }^{\circ}\text{C}$ for 2 h and then warming to room temperature with further stirring for 3 h, the reaction mixture was treated with aqueous HCl (2 M, 2 mL). After stirring at room temperature for 20 min and being partitioned, the aqueous layer was extracted with ethyl acetate (2 mL) three times. The combined organic extracts were washed with brine (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/diethyl ether = 2:1) to provide the title compound **m-109k** as a pale green solid (48.5 mg, 0.148 mmol, 50%), whose ¹H and ¹³C{¹H} NMR spectroscopic data were identical to those reported in the literature.¹³⁹ $R_f = 0.17$ (hexane/diethyl ether = 2:1); Mp $>200\text{ }^{\circ}\text{C}$; IR (ATR, cm^{-1}): 1536, 1461, 1404, 1342, 1282, 1261, 1182, 1101, 864; ¹H NMR (400 MHz, acetone-*d*₆): δ 8.17 (s, 1H), 7.98 (s, 2H), 7.58 (br s, 2H); ¹³C{¹H} NMR (100 MHz, acetone-*d*₆): δ 142.6, 141.6, 136.9, 123.4, 95.3 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom); HRMS (ESI/TOF) m/z : $[\text{M}-\text{H}]^+$ Calcd for C₆H₄B⁷⁹BrIO₂ 324.8538; Found 324.8539.



2-(3-Bromo-5-iodophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**m-109l**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 1-bromo-3-iodobenzene (**108a**) (84.4 mg, 0.298 mmol, 1.0 equiv), triisopropyl borate (0.14 mL, 0.61 mmol, 2.0 equiv), Me₃TACN (0.12 mL, 0.62 mmol, 2.1 equiv), and THF (2.0 mL). The resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$. LiTMP (0.66 M, 0.80 mL, 0.53 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at $-78\text{ }^{\circ}\text{C}$ for 2 h and then warming to room temperature with further stirring for 3 h, the reaction mixture was treated with acetic acid (0.2 mL) and neopentyl glycol (50.3 mg, 0.483 mmol, 1.6 equiv). After stirring at room temperature for 1.5 h, the reaction mixture was diluted with dichloromethane (2 mL) and washed with aqueous potassium dihydrogen phosphate (10 wt%, 2 mL) three times. The combined water phase was extracted with dichloromethane (2 mL). 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 ***m*-109l** as a pale yellow oil (47.8 mg, 0.121 mmol, 41%). R_f = 0.27 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 1537, 1478, 1425, 1376, 1322, 1290, 1255, 1241, 1138, 976, 909, 864, 813; ^1H NMR (400 MHz, CDCl_3): δ 8.03 (dd, 1H, J = 1.6, 0.8 Hz), 7.89 (dd, 1H, J = 1.6, 1.6 Hz), 7.86 (dd, 1H, J = 1.6, 0.8 Hz), 3.75 (s, 4H), 1.01 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 141.6, 141.3, 136.0, 123.0, 94.7, 72.6, 32.1, 21.9 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom).



2-(3-Iodophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (***m*-109m**)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with iodobenzene (**108e**) (61.1 mg, 0.300 mmol, 1.0 equiv), triisopropyl borate (0.14 mL, 0.61 mmol, 2.0 equiv), Me_3TACN (0.12 mL, 0.62 mmol, 2.1 equiv), and THF (2.0 mL). The resulting solution was cooled to -78°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 acetic acid (0.2 mL) and neopentyl glycol (50.6 mg, 0.486 mmol, 1.6 equiv). After stirring at room temperature for 1.5 h, the reaction mixture was diluted with dichloromethane (2 mL) and washed with aqueous potassium dihydrogen phosphate (10 wt%, 2 mL) three times. The combined water phase was extracted with dichloromethane (2 mL). 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 an inseparable mixture (74.7 mg) of the title compound ***m*-109m** (0.196 mmol, 65%), 2-(1,3-diiodophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**S2**) (0.0207 mmol, 7%), and 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**S3**) (0.0193 mmol, 6%) as a colorless solid. R_f = 0.27 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 1478, 1425, 1377, 1335, 1308, 1292, 1270, 1257, 1249, 1216, 1136, 968, 813; ^1H NMR (400 MHz, CDCl_3): δ 8.13 (s, 1H), 7.77–7.72 (m, 2H), 7.09 (dd, 1H, J = 7.6, 7.6 Hz), 3.76 (s, 4H), 1.01 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 142.9, 139.6, 132.9, 129.7, 94.7, 72.5, 32.0, 22.0 (one aromatic carbon signal is missing due to poor sensitivity of the carbon atom attached to the boron atom).

5-7 References

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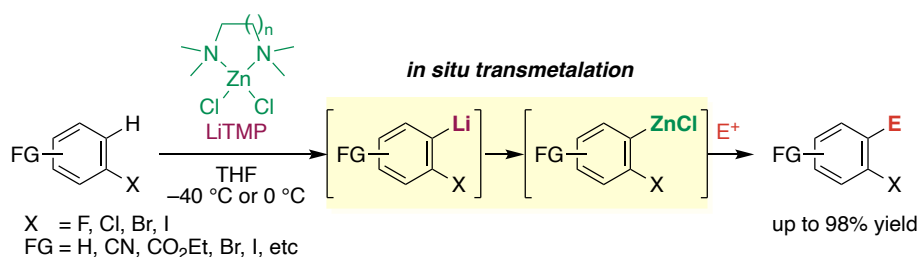
第六章

総括

6-1 総括

有機リチウム反応剤を経由する脱プロトン化反応は、合成化学において極めて信頼性の高い手法として広く用いられている。ハロアレーン誘導体の官能基化に応用する際には、熱力学的に有利な副反応が多く存在するため、有用性が制限されている。本研究では、この課題に対して汎用性の高い *in situ* トランスメタル化を利用し、一般性の高い新たな反応条件を見出し、幅広いハロアレーンの脱プロトンの官能基化を実現した。すなわち、ジアミン配位子を有するハロゲン化亜鉛錯体をトランスメタル化に応用し、配位子の構造を調整することにより、トランスメタル化の速度を精密に制御した。その結果、さまざまな短寿命ハロアリールリチウムの捕捉と反応が可能となった。さらに、Lewis 塩基によって活性化されたりチウムアミドを用い、*in situ* トランスメタル化と組み合わせることで、ハロアレーン誘導体のメタ位選択的なメタル化にも初めて成功した。

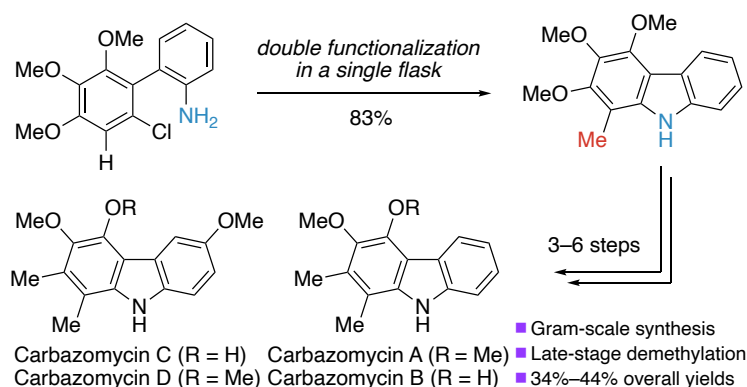
第二章では、塩化亜鉛ジアミン錯体を用いた *in situ* トランスメタル化により、短寿命 2-ハロフェニルリチウムを捕捉する手法を開発した (Scheme 6-1-1)。2-ハロフェニルリチウムは、 -78°C の低温下においても速やかに脱離反応を起こしてアライン中間体へと変化するため、反応への利用が制限されてきた。本研究では、ハロゲン化亜鉛ジアミン錯体を用いた *in situ* トランスメタル化によって、この不安定なフェニルリチウムを熱的に安定なフェニル亜鉛化合物へと変換し、アラインの発生を抑制することができた。この手法を活用し、18 種類のハロベンゼン誘導体に対して、位置選択的な脱プロトン化的官能基化を達成した。また、対照実験を通じて、ジアミン配位子がトランスメタル化の速度および副反応としての亜鉛アミド生成に与える影響についても明らかにした。さらに、本手法を鍵として、天然物カルバゾマイシン A の 5 段階合成にも達成した。



Scheme 6-1-1. Deprotonative generation and trapping of halophenyllithium

第三章では、*in situ* トランスメタル化を鍵反応として、カルバゾマイシン A-D のグラムスケール合成を達成した (Scheme 6-1-2)。カルバゾマイシン類は、

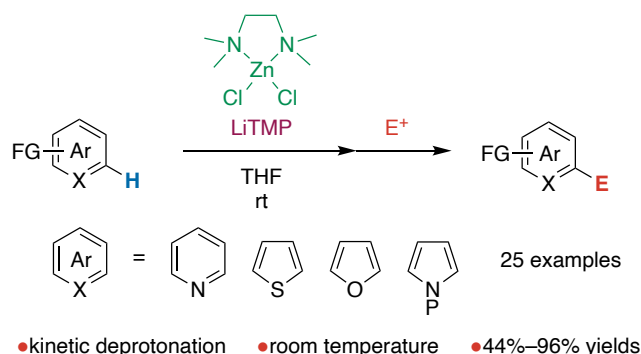
1980 年に中村らによって放線菌 *Streptoverticillium ehimense* から単離された天然物であり、カルバゾール骨格を有する最初の抗生物質として知られている。これら化合物は、全置換ベンゼン構造を有することから、従来の合成法では出発原料の調製に多段階を要するという課題があった。本研究では、より簡便で実用的な合成法の確立を目的とし、短い合成経路を立案した。対称性を有するクロロベンゼンを出発原料とし、*in situ* トランスメタル化を鍵とする 2 段階反応により新規なアミノビフェニルを合成した。続いて、アライン中間体を經由してカルバゾール骨格を構築し、合成の終盤でメトキシ基の位置選択的変換により、カルバゾマイシン A–D の全合成を達成した。また、本合成法により、カルバゾマイシン A–D に加えて他の非天然カルバゾマイシン誘導体への変換にも応用可能であり、カルバゾマイシン類の生理活性解明や構造活性相関 (SAR) 研究への展開が期待される。



Scheme 6-1-2. Gram-scale synthesis of carbazomycins A–D

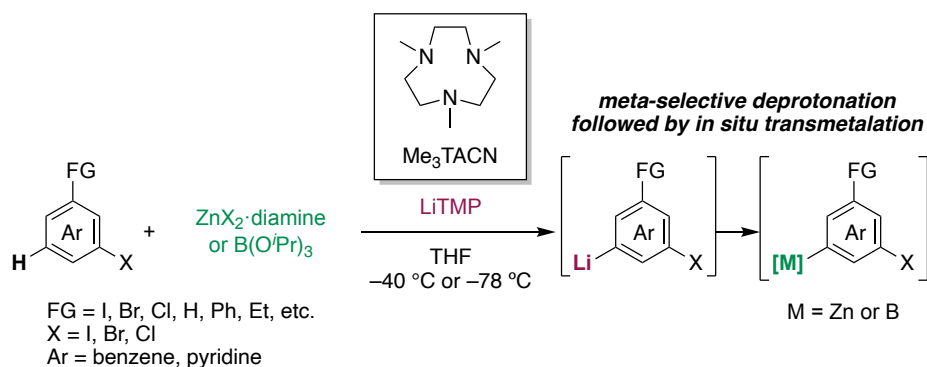
第四章では、塩化亜鉛 TMEDA 錯体を用いた *in situ* トランスメタル化により、ヘテロアリール誘導体に対する C-2 位選択的な官能基化法を開発した (Scheme 6-1-3)。ヘテロアレーン誘導体においては、速度論的により有利な C-2 位で脱プロトン化が進行し、生成したヘテロアリールリチウム種が *in situ* トランスメタル化を経て有機亜鉛化合物へと変換された。この手法により、熱力学的により有利なプロトンの異性化、ハロゲンダンス、アラインの発生といった競合反応が効果的に抑制された。得られた有機亜鉛種は、多様な求電子試剤と反応でき、ヘテロ芳香環骨格の高効率な構造修飾を実現した。従来のリチウムアミドを用いた手法とは異なり、本手法は低温条件を必要とせず、室温でも実施可能であった。本手法により合成された C-2 位でヨウ素化されたヘテロアリール誘導体は、クロスカップリング反応を通じて C–C 結合および C–N 結合の効率的な構築が可能であり、ヘテロ環を骨格とする医薬品や農薬の分子設計において有用な中間

体となることが期待される。



Scheme 6-1-3. Regioselective deprotonative metalation of heteroarenes

第五章では、Lewis 塩基である Me_3TACN によって活性化された LiTMP を用いる *in situ* トランスメタル化により、さまざまなハロアレーンとピリジン誘導体に対する直接的なメタ位選択的官能基化を初めて実現した (Scheme 6-1-4)。 LiTMP は Me_3TACN との相互作用によって、高い塩基性を示した。この塩基を用いた脱プロトン化反応は、従来一般的であった配向基のオルト位ではなく、空間的に有利なメタ位で位置選択的に進行した。脱プロトン化により生成したアリールリチウム種は、塩化亜鉛ジアミン錯体との *in situ* トランスメタル化を経て、安定なアリール亜鉛化合物へと変換された。このアリール亜鉛化合物はヨウ素との反応により、メタ位選択的なヨウ素化を達成した。さらに、ホウ素化剤を用いた *in situ* トランスメタル化により、ハロアレーンのメタ位選択的なホウ素化にも成功した。従来、複数段階を要したヨードアレーン誘導体および有機ホウ素化合物は、本手法により 1 工程で合成可能となり、合成の効率化と実用性の向上が示された。



Scheme 6-1-4. meta-Selective deprotonative lithiation of (halo)arenes

本研究の期待される波及効果として、医薬品や機能性材料の開発における有用な合成中間体の効率的かつ大量な供給が挙げられる。本研究で開発した *in situ* トランスメタル化を鍵とするハロアレーンの位置選択的脱プロトンの官能基化は、市販されている構造が単純なハロアレーンを原料とし、高い位置選択的に官能基を直接導入可能であり、極めて高い実用性を有している。本手法により得られる官能化されたアレーン誘導体は、医薬品や機能性材料開発の初期段階におけるリード化合物の構造多様化およびプロセスの簡略化に展開できる。特に、従来法では複数段階を要する 1,3,5-三置換ハロアレーン誘導体の合成は、本研究で開発したハロアレーンのメタ位選択的脱プロトンの官能基化を利用して 1 段階で高選択的に合成でき、従来法に比べて反応効率およびコストで著しい優位性を有する。一方、第五章で報告したハロアレーンのメタ位選択的な脱プロトンの官能基化の反応機構の詳細や活性中間体の同定に関しては、現時点では十分な検討がなされておらず、今後の重要な研究課題として残されている。今後は、反応経路の解明および中間体の確認を通じて反応メカニズムを明らかにするとともに、基質一般性および適用可能な求電子剤の範囲をさらに拡張し、より高い汎用性を備えた合成手法として確立することを目指す。

研究業績リスト

【学術論文】

第二章 *in situ* トランスメタル化による短寿命ハロフェニルリチウムの捕捉
Deprotonative generation and trapping of haloaryllithium in a batch reactor.

Yuxuan Feng, Taro Yukioka, Mei Matsuyama, Atsunori Mori, Kentaro Okano, *Org. Lett.* **2023**, 25, 3013–3017.

Highlighted in *Org. Process Res. Dev.* **2024**, 28, 805–815.

第三章 カルバゾマイシン A–D のグラムスケール合成

Gram-scale total synthesis of carbazomycins A–D through late-stage regioselective demethylation of aryl methyl ethers.

Yuxuan Feng, Atsunori Mori, Kentaro Okano, *J. Org. Chem.* **2024**, 89, 13472–13484.

第四章 ヘテロアレーンの C-2 位選択的な官能基化

Regioselective deprotonative metalation of heteroarenes with a combination of lithium amide and zinc halide diamine complex.

Yuxuan Feng, Atsunori Mori, Kentaro Okano, *J. Org. Chem.* *accepted*.
(doi:10.1021/acs.joc.5c01171)

第五章 ハロアレーンのメタ位選択的メタル化

Beyond the *ortho*-rule. *meta*-Selective deprotonative metalation of haloarenes.

Yuxuan Feng, Tomoki Kojima, Atsunori Mori, Kentaro Okano, *to be submitted*.

その他

“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

Total synthesis of carbazomycins E and F.

Yunosuke Shima, **Yuxuan Feng**, Atsunori Mori, Kentaro Okano, *J. Org. Chem.* **2024**, 89, 8185–8191.

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カルバゾマイシン A のグラムスケール全合成，K2-4pm-03

○馮 宇軒，行岡太郎，岡野健太郎，森 敦紀

第 121 回有機合成シンポジウム，東京，2022 年 11 月 9 日

短寿命ハロアリアルリチウムの捕捉とカルバゾマイシン A および D の全合成，

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○馮 宇軒，松山芽以，行岡太郎，岡野健太郎，森 敦紀

日本化学会第 104 回春季年会，東京，2024 年 3 月 19 日

（学生講演賞 78 人/266 人）

カルバゾマイシン A-D のグラムスケール合成，H933-2pm-02，英語

○馮 宇軒，岡野健太郎，森 敦紀

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カルバゾマイシン A および D の全合成，PA-27

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短寿命ハロアリアルリチウムの捕捉とカルバゾマイシン A および D の全合成，

O-21

○馮 宇軒，松山芽以，行岡太郎，岡野健太郎，森 敦紀

第 43 回有機合成若手セミナー，京都，2023 年 8 月 8 日

カルバゾマイシン類の網羅的全合成，P-48

○馮 宇軒，島悠之輔，岡野健太郎，森 敦紀

第 57 回天然物化学談話会，名古屋，2024 年 7 月 4 日

カルバゾマイシン A-D のグラムスケール全合成，P-47

○馮 宇軒，森 敦紀，岡野健太郎

第 66 回天然有機化合物討論会，京都，2024 年 9 月 5 日

カルバゾマイシン A-F の全合成，P2-14

○馮 宇軒，島悠之輔，森 敦紀，岡野健太郎

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