博士論文

11 族金属アミドアート型塩基の設計と機能

手塚　則亨

本博士論文を構成する主論文

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"Direct Hydroxylation and Amination of Arenes via Deprotonative Cupration"
J. Am. Chem. Soc. **2016**, *138*, 9166–9171.

(2) **Noriyuki Tezuka**, Keiichi Hirano* and Masanobu Uchiyama*
"A Direct, Chemo-, and Regioselective Cross-Coupling Reaction of Arenes via Sequential Directed *ortho* Cuprations and Oxidation"
Org. Lett. **2019**, *21*, 9536–9540.

(3) **Noriyuki Tezuka**,* Keiichi Hirano,* Andrew J. Peel, Andrew E. H. Wheatley, Kazunori Miyamoto and Masanobu Uchiyama*
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Chem. Sci. **2020**, *11*, 1855–1861.

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(6) Hajime Sato, Kazuya Teramoto, Yui Masumoto, **Noriyuki Tezuka**, Kenta Sakai, Shota Ueda, Yusuke Totsuka, Tetsuro Shinada, Makoto Nishiyama, Chao Wang, Tomohisa Kuzuyama* and Masanobu Uchiyama*
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略語一覧

Ac	Acetyl
AFG	Ancillary Functional Group
Ar	Aryl
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
CAN	Ceric Ammonium Nitrate
cat.	Catalytic Amount
CDC	Cross-Dehydrogenative Coupling
CHP	Cumene Hydroperoxide
CPME	Cyclopentyl Methyl Ether
Cy	Cyclohexyl
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DFT	Density Functional Theory
DMG	Directed Metalation Group
D*o*M	Directed *ortho* Metalation
E	Electrophile
EDG	Electron-Donating Group
eq.	Equivalent
Et	Ethyl
etc.	*et cetera*
EWG	Electron-Withdrawing Group
FG	Functional Group
h	Hour
Hal	Halogene
HMDS	1,1,1,3,3,3-Hexamethyldisilazido
i	*iso*
INT	Intermediate
LDA	Lithium Diisopropylamide
LG	Leaving Group
m	*meta*
M	Metal (Cu, Ag, Pd, *etc*.)
*m*CPBA	*meta*-Chloroperoxybenzoic Acid
min	minute
MOM	Methoxymethyl
Me	Methyl
Mts	Mesitylsulfonyl
n	normal
NBO	Natural Bond Orbital
Nbz	4-Nitrobenzoyl
o	*ortho*
p	*para*
Ph	Phenyl
PD	Product
Pr	Propyl
R	Alkyl or H
RT	Reactant
rt	Room Temperature
sec	*secondary*
t or *tert*	*tertiary*
TBHP	*tert*-Butyl Hydroperoxide
TMP	2,2,6,6-Tetra-methylpiperidido
TMS	Trimethylsilyl
TS	Transition State
Tf	Trifluoromethanesulfonyl

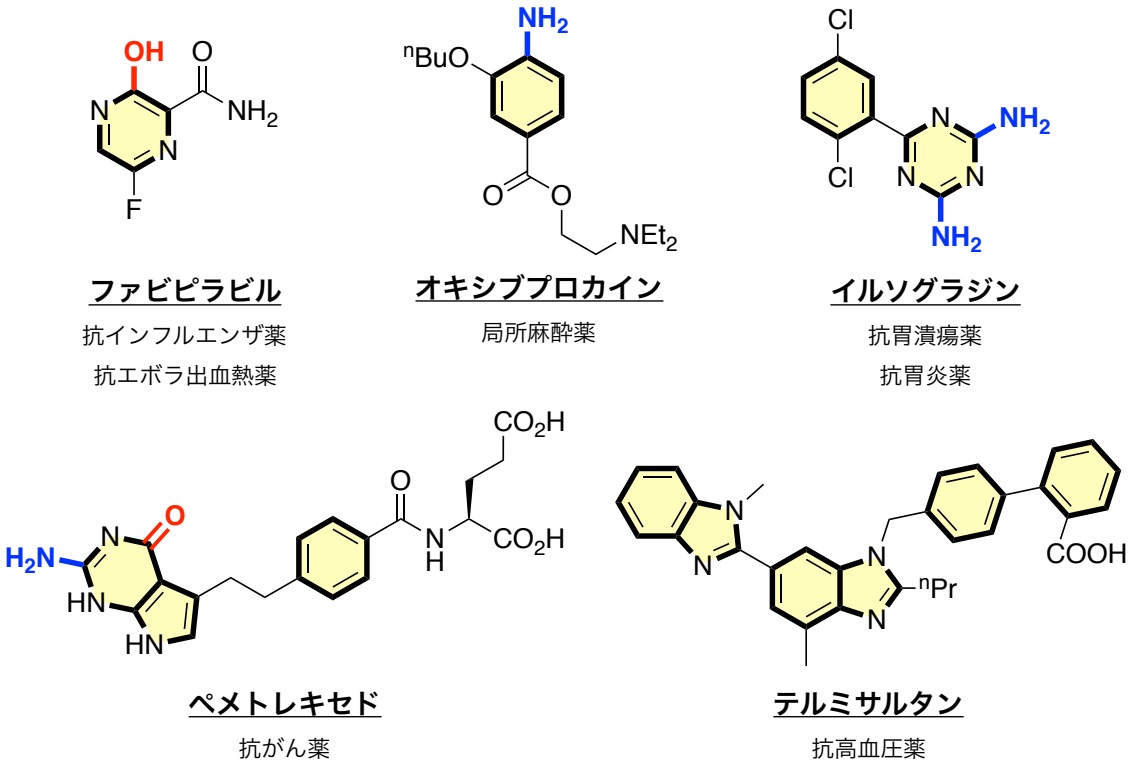
第一章

序論

1-1 芳香族オルトメタル化反応 Directed *ortho* Metalation: DoM

剛直な平面環構造を有する 5、6 員環状芳香族化合物は、その各頂点を官能基化することで分子の立体情報と電子的性質を同時に制御可能することができるため、有機合成における強力なプラットフォームとして医農薬品や機能性材料などの幅広い分野で普遍的な構造である（Figure 1-1）。

Figure 1-1. Selected Pharmaceutical Compounds Containing Aryl Motif



ファビピラビル
抗インフルエンザ薬
抗エボラ出血熱薬

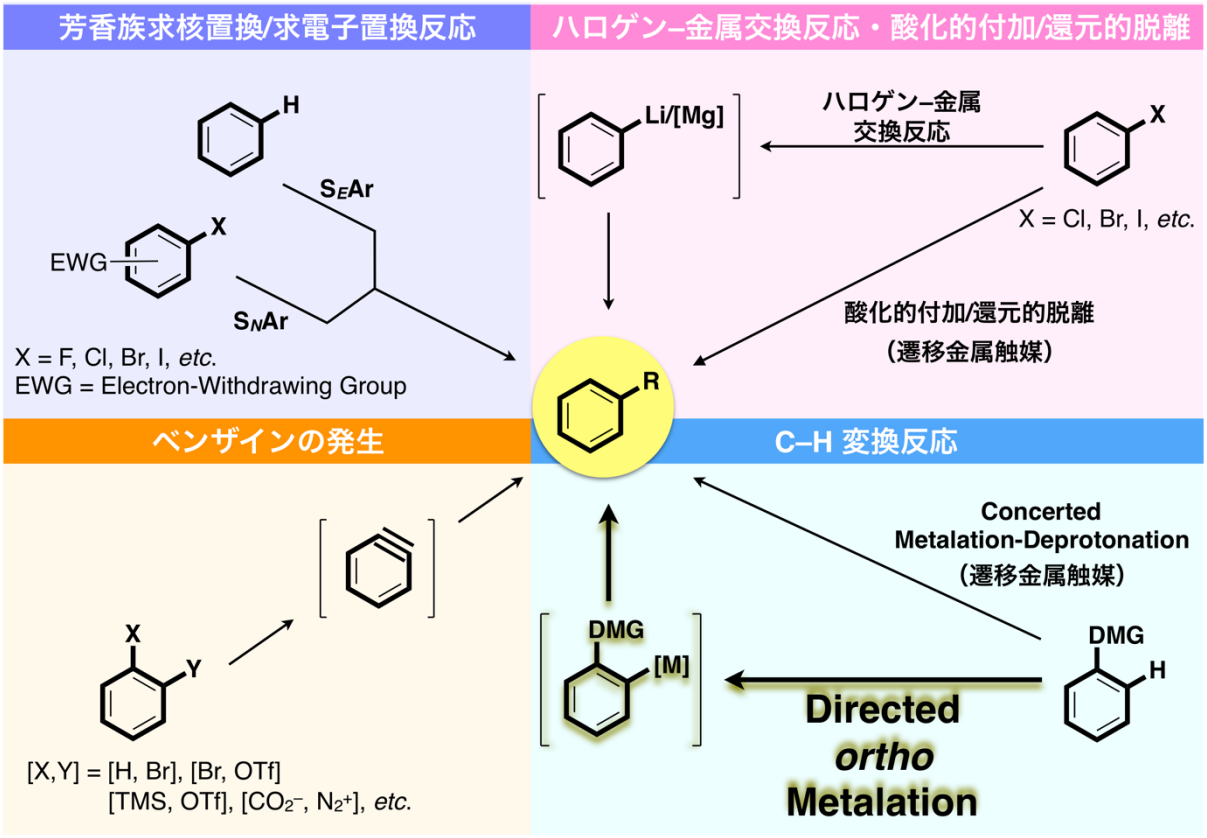
オキシブプロカイン
局所麻酔薬

イルソグラジン
抗胃潰瘍薬
抗胃炎薬

ペメトレキセド
抗がん薬

テルミサルタン
抗高血圧薬

Figure 1-2. General Strategy for Aromatic Functionalizations



そのため、芳香族化合物への置換基導入法は古くから盛んに研究されてきた（Figure 1-2）。

Friedel-Crafts 反応をはじめとする芳香族求電子置換反応や[1-1]、電子不足な芳香環を利用した芳香族求核置換反応は[1-2]、信頼性の高い変換反応として知られる。

ベンザイン中間体を経由する反応も多置換芳香族化合物を一挙に構築できる優れた方法論であり、その前駆体や新しい置換基の導入法が、近年も続々と報告されている[1-3]。

芳香族ハロゲン化物は、置換ベンゼンを合成する際に最も重要な前駆体のひとつである。炭素–ハロゲン結合を反応の起点としたハロゲン–金属交換や、遷移金属を用いた酸化的付加/還元的脱離は、有機合成反応に利用される最も基本的な素反応の一つであり、これを利用することでクロスカップリング反応などの現代有機合成化学に有用かつ不可欠な反応が数多く開発されてきた[1-4]。その一方で、原料が容易に入手できない場合には、あらかじめ、あるいは多段階合成の途中でハロゲン元素を導入しなければならないため、複雑な合成経路を必要とすることがしばしば問題となる。

これに対して、C–H 結合を直接官能基化する手法は、事前の修飾化によって反応点を規定する必要がないため、廃棄物や合成段階数を最小限に抑えることができる理想的な変換反応であり、上記課題を解決する手法としても注目されている[1-5]。しかし、C–H 結合が高い結合解離エネルギー[1-6] を有することや分子内に多数存在することを考慮すると、目的の C–H 結合のみを

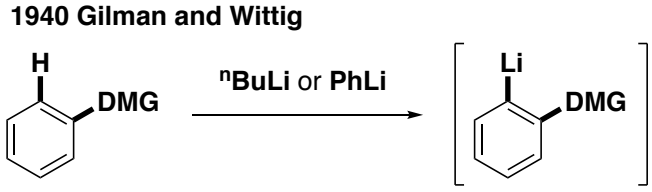
認識し、切断および変換することは依然として挑戦的な課題である。こうした背景の中、1967 年の藤原、守谷による Pd を用いた芳香族 C–H 結合のオレフィン化反応や[1-7]、1993 年に村井、茶谷らにより報告された Ru 触媒を用いた C–H 結合の直接的変換反応[1-8]を契機に、遷移金属触媒を用いた C–H 活性化反応が急速に発展し、活発に研究されるようになってきた。

一方で、金属に対する配向基（Directed Metalation Group: DMG）を用いた芳香族オルトメタル化反応（Directed *ortho* Metalation: D*o*M）は、化学量論量の芳香族メタル種を高い位置選択性にて調製することができ、続く求電子剤との反応によって多様な官能基の導入が可能な信頼性の高い手法である[1-9]。

筆者は、D*o*M を基本戦略として、その中心金属の特性を活用した 3 種の新たな反応を開発したので以降の章にて議論する。本章では、それに先立ち芳香族オルトメタル化反応について概観する。

初めての D*o*M に関する報告は、1940 年にまで遡る。Gilman[1-10]、Wittig[1-11] らは、それぞれ独立に有機リチウムを用いた芳香族オルトリチオ化反応を報告した（Figure 1-3）。

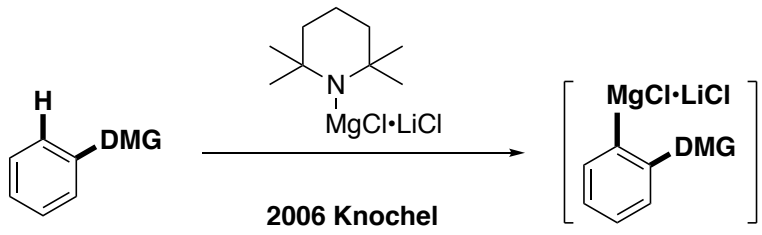
Figure 1-3. D*o*M with Organolithiums



オルトリチオ化反応に頻用される ^{n}BuLi は市販もされており、便利で有用な試薬であるが、その高い求核性のために、例えば電子不足なヘテロ芳香環への付加反応などの副反応を伴いやすい[1-12]。一方で、嵩高いリチウムアミド塩基は、低い求核性と高い塩基性を併せ持つ有用なオルトリチオ化試薬として知られており、代表的なものとして、lithium diisopropylamide（LDA）や lithium 1,1,1,3,3,3-hexamethyldisilazide（LHMDS）、lithium 2,2,6,6-tetra-methylpiperidide（TMPLi）などが挙げられる。しかし、これらのリチウムアミド塩基を用いた D*o*M では、生じるアリールリチウム中間体の高い求核性によって、しばしば基質自身の求電子性官能基の損壊やハロゲン–金属交換反応などの副反応が併発するなど、アリールメタル種の反応性の制御は必ずしも容易ではない。例えば、TMPLi を用いて安息香酸エステルをメタル化すると、生じるアリールリチウム種が基質のエステル基に求核攻撃し、縮合することが知られている[1-13]。このように、リチウムアミド塩基を用いた D*o*M の複雑に置換された芳香環への適用は限定的である。

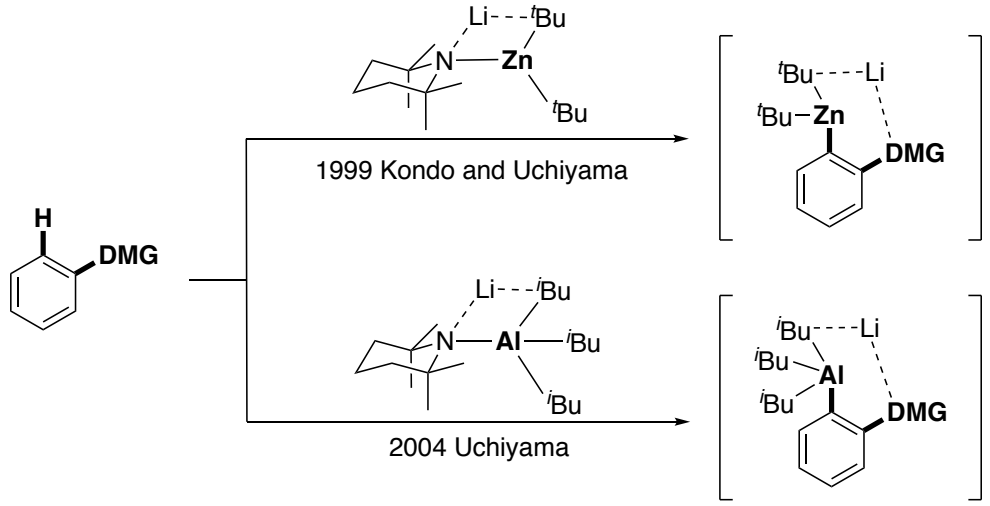
金属アミド塩基を用いた D*o*M はその後、1989 年に Eaton らによってマグネシウムアミド塩基 ($^{i}Pr_2N)_2Mg$ や $(TMP)_2Mg$ へと展開され、よりソフトなマグネシウムを中心金属とすることで、先に問題となったエステルなどの求電子的な官能基も配向基として用いることが可能であることが示された [1-14]。しかし、円滑なメタル化には過剰量（2-12 当量）の塩基を必要とするため、続く変換反応にはさらに多くの求電子剤を用いなければならなかった。これに対して 2006 年、Knochel らはより溶解性が高く、速度論的に塩基性の高いアミドマグネシウム塩基 (TMP)MgCl•LiCl（Knochel-Hauser base）を開発し、これが室温で安定かつ高いメタル化能を有し、官能基許容性の高い実用的なオルトメタル化試薬であることを報告した（Figure 1-4）[1-15]。

Figure 1-4. Knochel-Hauser Base



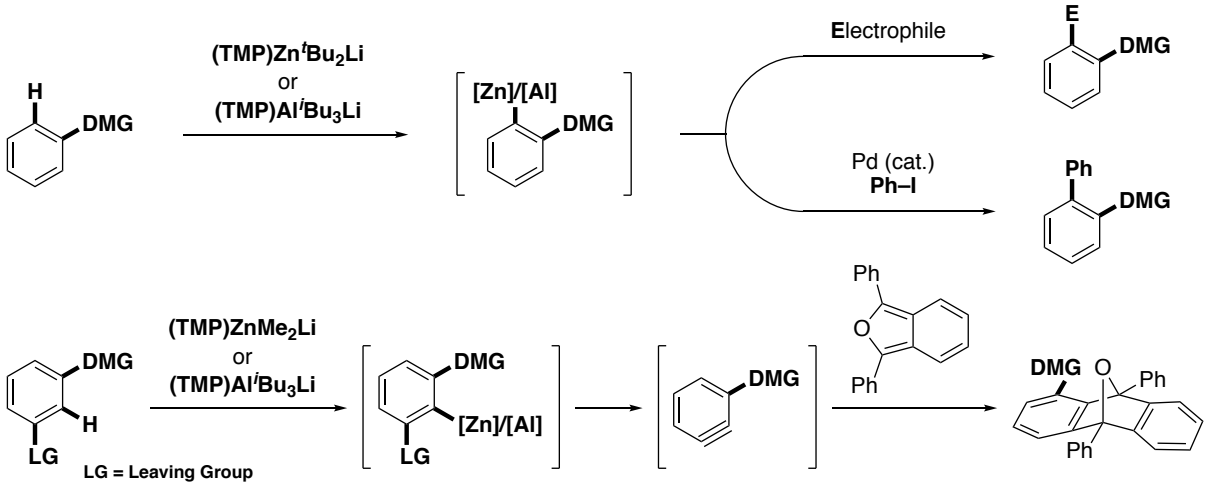
一方、当研究室では 1999 年以降、さらに一般性の高い芳香環の官能基化法の確立を目指し、アミド配位子として TMP、中心金属として亜鉛 [1-16] およびアルミニウム [1-17] を用いたアート型の金属アミド塩基を設計してきた（Figure 1-5）。塩基として $(TMP)Zn^{t}Bu_2Li$ を用いると、求電子性の高いシアノ基やエステル基を配向基として用いても、これらの官能基を損なうことなく高収率でオルトメタル化することが可能である。また、アルミニウムアミドアート塩基 $(TMP)Al^{i}Bu_3Li$ は、ハロゲン–金属交換活性のない有機アルミニウム種の性質によって、ヨウ素を有する芳香環を用いても、これを損なうことなく化学選択的なメタル化が可能である。

Figure 1-5. D*o*M with Zn- and Al-Ate Base



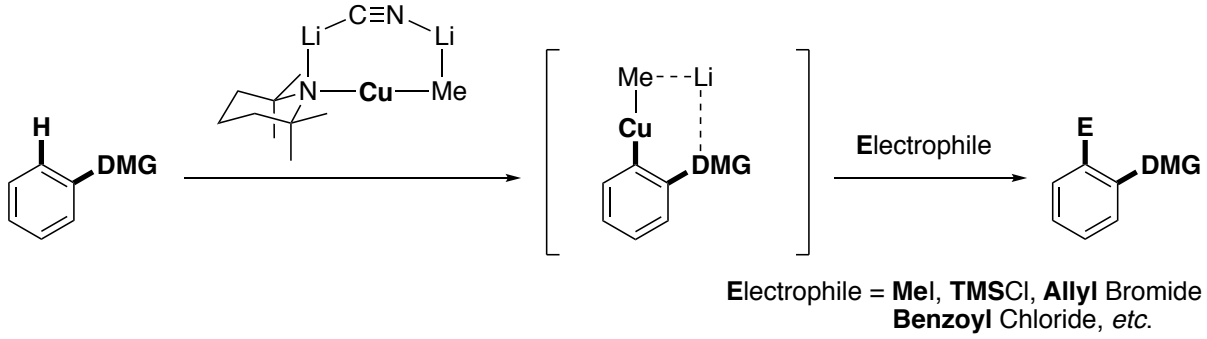
オルトメタル化によって生じるアリール亜鉛アート中間体およびアリールアルミニウムアート中間体は様々な求電子剤と高収率で反応することに加え、クロスカップリング反応やベンザインの発生に有効であることがわかっており、多様な芳香族化合物を様々に修飾可能である（Figure 1-6）。

Figure 1-6. Reactions of Aryl–Zn Ate and Aryl–Al Ate Species



当研究室では、上述の亜鉛やアルミニウムに続いて、銅を用いたアミドアート型塩基の反応性にも着目してきた。2007 年、銅アミドアート型塩基 RCu(TMP)(CN)Li$_2$ を設計することで、従来は不活性なダミー配位子として認識されていたアミド配位子が、塩基としては極めて高い脱プロトン化活性と化学選択性を示すことを見出し、銅アミドアート型塩基を用いた D*o*M を初めて報告した[1-18]。生じたアリール銅種は様々な求電子剤と効率よく反応し、芳香環への多様な官能基導入が可能である（Figure 1-7）。また、X 線結晶構造や計算化学を用いた詳細な解析により、そのメタル化の機構を明らかにしている[1-18c]。

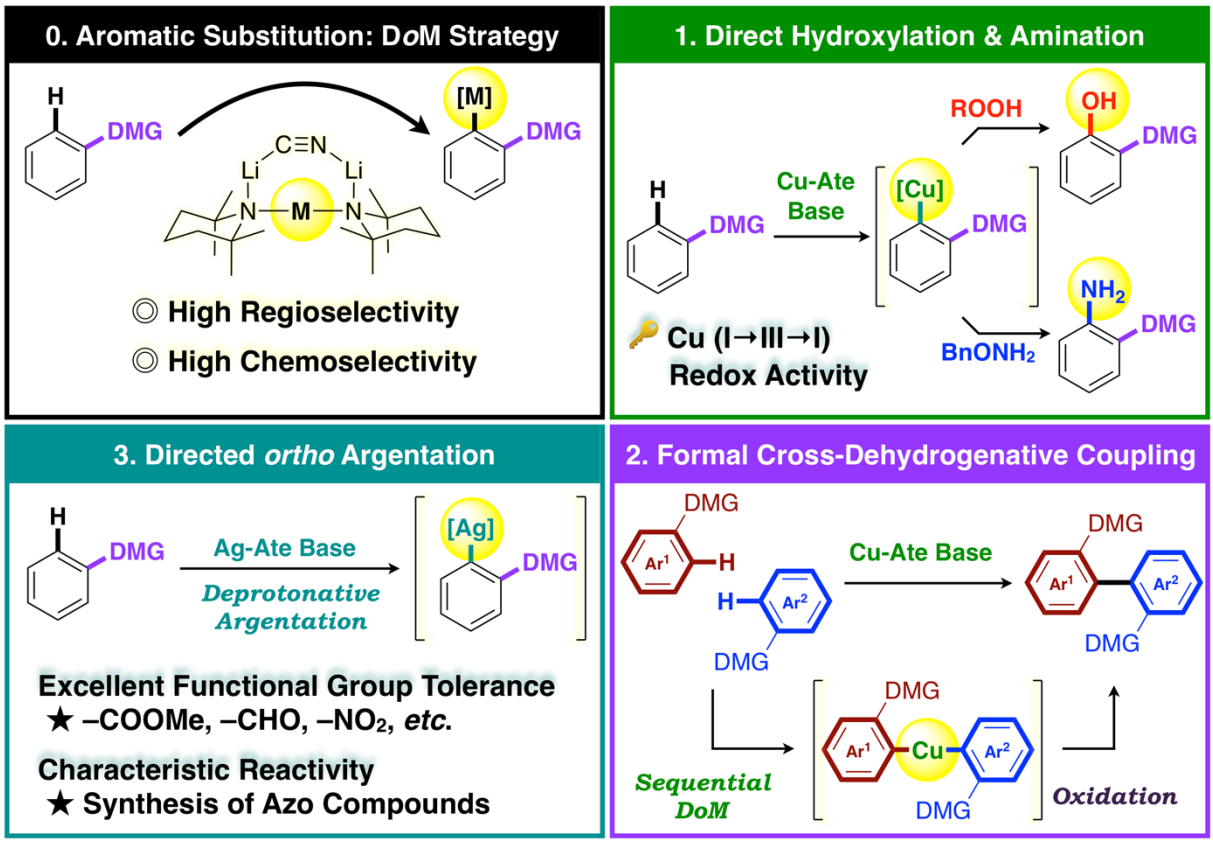
Figure 1-7. D*o*M with Cu-Ate Base



以上のように、80 年あまりの歴史を有する DoM 反応は、近年実用面で飛躍的な発展を遂げているが、これまでの手法では生じるアリールメタル種の変換反応は主に求電子剤に対する求核付加/置換反応に限定的であり、新しい反応形式に基づく新たな展開が求められる。筆者は、銅の酸化還元能に着目し、DoM の化学に酸化反応を取り入れ、精密な反応設計のもと、「銅アミドアート型塩基を用いた芳香環の水酸化・アミノ化反応（第二章）」[1-19] および「銅アミドアート型塩基を用いた形式的芳香族脱水素型クロスカップリング反応（第三章）」[1-20] を開発した（Figure 1-8, 1 and 2）。

また、ここまでで概観したとおり、DoM は配位子と中心金属を様々に組み合わせることで高い反応性と官能基許容性を獲得し、有機合成化学における有用性・実用性を広げてきた。筆者は、新たな選択性や反応性の開拓を目指して、銅と同族の銀に着目した「銀アミドアート型塩基を用いた芳香族オルトメタル化反応（第四章）」[1-21] を開発した（Figure 1-8, 3）。

Figure 1-8. Overview of My Ph.D. Studies



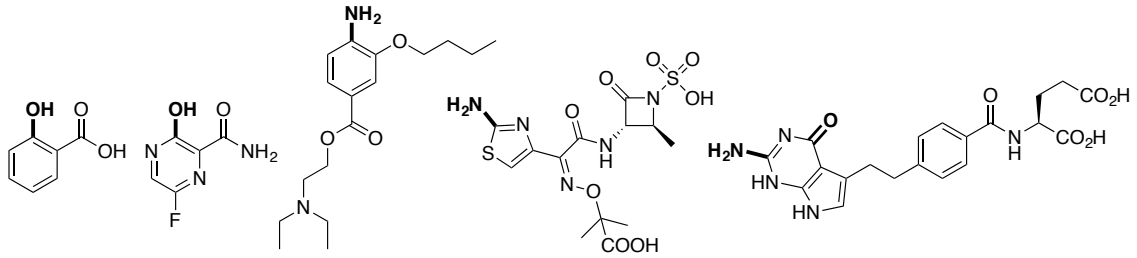
第二章
銅アミドアート型塩基を用いた芳香環の水酸化・アミノ化反応

2-1 序論

第一章で述べたように、これまでに D*o*M は高い官能基許容性を獲得してきたものの、生じるアリールメタル種の変換反応は求電子剤に対する求核付加/置換反応に限定的だった。そこで筆者は、銅の酸化還元能に着目し、D*o*M に後続する反応として酸化反応を新たに取り入れることで、フェノールやアニリンの高位置・化学選択的な合成法を開発したので、本章で述べる。

フェノール構造やアニリン構造は、医農薬を始めとして多くの身近な機能性分子を構成する極めて重要な構造である（Figure 2-1）。古くから解熱鎮痛作用を示すことが知られ、医薬品の開発の歴史とも深い関係があるサリチル酸（salicylic acid）は、代表的なフェノール誘導体である。ファビピラビル（favipiravir）は、新規作用機序を有する抗インフルエンザ薬として開発され、近年ではエボラ出血熱の治療薬としても注目を集めた。眼科治療で麻酔薬として用いられるオキシブプロカイン（oxybuprocaine）、抗菌剤であるアズトレオナム（aztreonam）は芳香環上に第 1 級のアミノ基を有するアニリン誘導体である。また、抗がん剤であるペメトレキセド（pemetrexed）は芳香環上に酸素原子および窒素原子を両方有している。このように、フェノールやアニリン構造を簡便かつ信頼性高く合成する手法の開発は極めて重要な研究課題である。

Figure 2-1. Phenol and Aniline Structures in Drugs

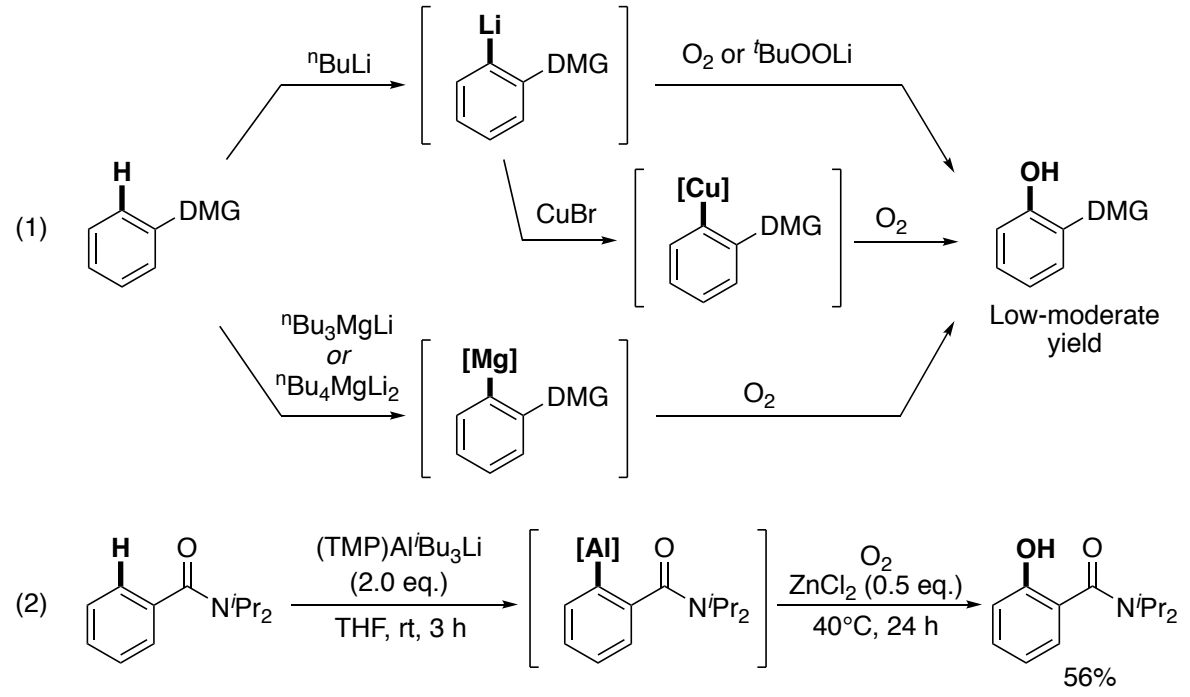


芳香環上での C–O 結合形成は、クメン法[2-1]、芳香族求核置換反応[2-1]、アリール金属種 Ar–M（M = Li[2-2], Mg[2-3], B[2-4], Si[2-5]）の酸化反応による手法が代表的である。また、遷移金属触媒を用いた C–X 結合[2-6]（X = ハロゲン）、さらには C–H 結合[2-7]の変換反応も近年盛んに研究されてきた。ただし、これらの手法は一般に過酷な反応条件を必要とするため、複雑に官能基化された芳香環への適用は限定的であり、多様な骨格に適用可能な信頼性の高い芳香環の水酸化反応が強く求められている。

高位置選択的なフェノールの合成には、D*o*M が有効である。1940 年、Gilman らは D*o*M によって生じたアリールリチウム種に分子状酸素を作用させることで C–O 結合の形成が可能であることを示した[2-8]。その後、酸化剤を ^{t}BuOOLi とする方法や[2-9]、Li から Cu へのトランスメタル化[2-10]、マグネシウム塩基による D*o*M[2-11] を利用した方法など、種々の改良法が考案されてきた。しかし、これらはいずれも収率が中程度に留まることや、有機リチウム/マグネシウム種の高い求核性・塩基性のために限られた官能基しか用いることができない点で課題が残されていた（Scheme 2-1, eq 1)。当研究室でもこれまでに、高い官能基許容性を有するアルミニウムアミドアート型塩基を用いた D*o*M の後、塩化亜鉛存在下、酸素を作用させることでフェノール体の合成が可能であることを報告しているが、収率や再現性に課題があった（Scheme 2-1, eq 2）[1-17a]。

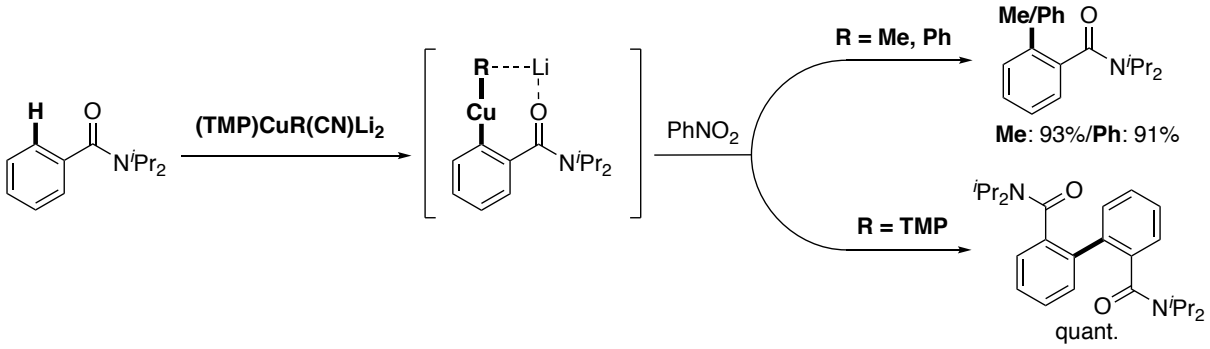
このように、従来の典型金属試薬を用いた D*o*M では芳香環への高収率かつ高化学選択的な酸素原子導入反応、すなわち密に官能基化されたフェノール類の直接的合成は極めて難しかったと言える。

Scheme 2-1. C–O Bond Formations *via* D*o*M



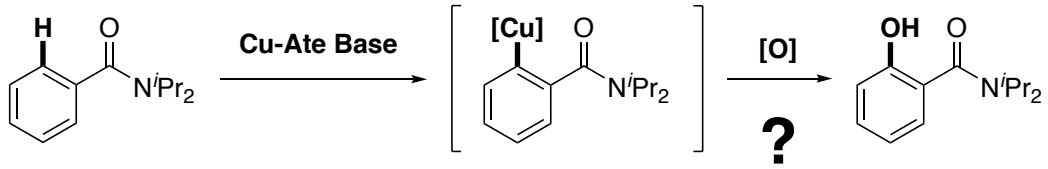
一方で、銅アミドアート型塩基を用いて調製したアリール銅アート中間体は求電子剤に対する求核置換反応のみならず、酸化還元反応を行うこともわかっている（Scheme 2-2）[1-18a]。すなわち、(TMP)CuR(CN)Li_2（R = Me or Ph）を用いた D*o*M の後、酸化剤としてニトロベンゼンを作用させると、基質のオルト位をメチル化またはフェニル化できる。一方で、$(TMP)_2Cu(CN)Li_2$ を用いると、アミノ化反応は進行せず基質の 2 量化が進行する。いずれにおいても銅中心の酸化還元を鍵として C–C 結合形成反応が進行していると考えられる。

Scheme 2-2. Oxidative Functionalizations of Aryl–Cu Ate Species



これらの知見は、アリール銅アート中間体を適切な試薬によって酸化することで、これまでの典型金属を用いた D*o*M ではなし得なかった、新たな芳香環への酸化的官能基導入反応が実現できることを示唆している。そこで筆者は、D*o*M の新たな展開として、銅の酸化還元能を活かした芳香環への直接的水酸基導入反応の開発を目指して研究に着手した（Scheme 2-3）。

Scheme 2-3. Concept of This Study: Direct Hydroxylation of Arenes *via* Oxidation of Aryl-Cu Ate Species



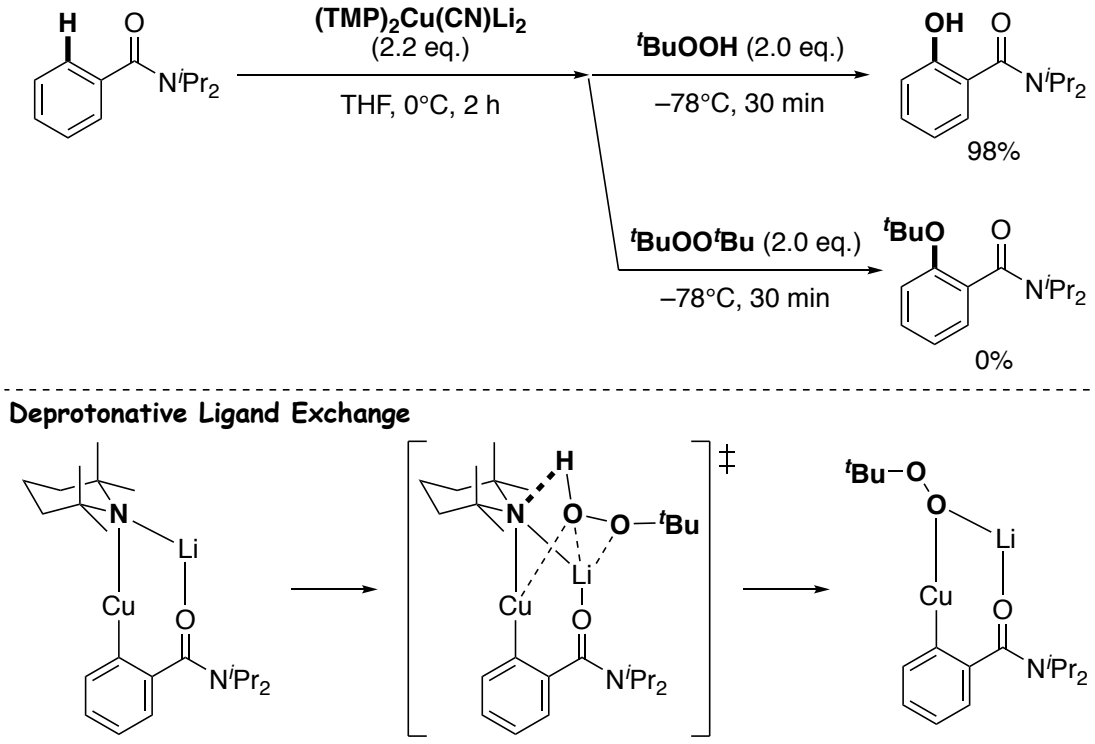
2-2 水酸化反応

2-2-1 条件検討

まず、アリール銅アート中間体に対する酸化剤の検討を行った。当研究室ではこれまでに、アリール銅アート中間体に過マンガン酸カリウムやクロム酸、CAN などの無機酸化剤、DDQ や Oxone®、*m*CPBA などの有機酸化剤を作用させても目的の水酸化体は得られなかったのに対して、再現性や収率に課題が残るものの、分子状酸素や ^{t}BuOOLi を用いることで水酸化体が得られることを見出している。

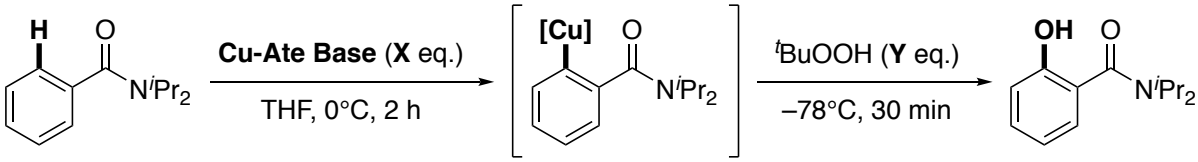
筆者は、^{t}BuOOLi の結果に着目し、その類縁体である ^{t}BuOOH（TBHP）を用いて、$(TMP)_2Cu(CN)Li_2$ と *N*,*N*-diisopropylbenzamide から生じる $ArCu(TMP)(CN)Li_2$ の酸化を試みたところ、水酸化反応が効率よく進行することがわかった（Figure 2-2）。驚くべきことに、強塩基性のアリール配位子のプロトン化による原料の回収はみられなかった。一方、酸性プロトンを持たず、アミド配位子との交換もしないと考えられる ^{t}BuOO^{t}Bu を酸化剤として用いたところ、酸素原子は導入されなかった。これらの結果は、TMP 配位子が選択的にヒドロペルオキシドを脱プロトン化し、それに伴う銅上での円滑な配位子交換が本反応の鍵であることを示唆している（Figure 2-2, 下図）[2-12]。

Figure 2-2. Important Role of Acidic Proton in Oxidation of Arylcuprate



そこで、種々の銅アミドアート型塩基を用いて、*N*,*N*-diisopropylbenzamide をメタル化の後、TBHP を作用させて、水酸化体の収率を比較した（Table 2-1）。

Table 2-1. Optimization of Hydroxylation



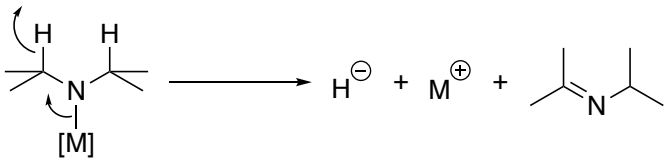
entry	Cu-Ate Base	X	Y	yield (%)
1	$(TMP)_2Cu(CN)Li_2$	2.2	2.0	98
2	$(^iPr_2N)_2Cu(CN)Li_2$	2.2	2.0	79
3	$(TMP)Cu^nBu(CN)Li_2$	2.2	2.0	93
4	$(TMP)Cu^tBu(CN)Li_2$	2.2	2.0	79
5	$(HMDS)_2Cu(CN)Li_2$	2.2	2.0	0
6	$(TMP)_2Cu(CN)Li_2$	1.3	1.2	(92)
7	$(TMP)_2Cu(CN)Li_2$	1.3	1.2[a]	(89)
8	$(TMP)_2Cu(CN)Li_2$	1.3	2.0	(94)

NMR yields based on mesitylene as an internal standard. Isolated yields in parentheses. [a] Oxidized with cumene hydroperoxide. HMDS = 1,1,1,3,3,3-Hexamethyldisilazido.

その結果、$(TMP)_2Cu(CN)Li_2$ を用いた場合に最も良い収率 98% で水酸化体が得られることがわかった（Entry 1 vs. Entries 2-5）。

Lithium diisopropylamide（LDA）をアミド源とした場合には収率の低下が見られた（entry 2）。LDA が有する α プロトンのヒドリド脱離がその原因の一つと考えられる（Scheme 2-4）[2-13]。

Scheme 2-4. Hydride Elimination of Diisopropylamides



アルキル配位子とアミド配位子で構成される非対称銅アート塩基 $(TMP)Cu(R)(CN)Li_2$（R = ^{n}Bu or ^{t}Bu）を用いた場合にも高収率にて目的物が得られた（entries 3 and 4）。これは、生じたアリール銅アート錯体 $ArCuR(CN)Li_2$ の、より塩基性の強いアルキル配位子 R と TBHP との反応が優先するためと考えられる。

より塩基性が低いアミドである 1,1,1,3,3,3-hexamethyldisilazide（HMDS）をアミド配位子とすると、水酸化体は全く得られなかった（entry 5）。この場合には、芳香族の脱プロトン化反応が進行しなかったと考えられる。

塩基を 1.3 当量、酸化剤を 1.2 当量に減じても反応は円滑に進行することがわかった（entry 6）。また、クメンヒドロペルオキシドを酸化剤として用いても反応は円滑に進行した（entry 7）。

酸化剤の当量を 2.0 当量とすることで、94% 単離収率にて水酸化体を得ることができたため、これを最適条件とした（entry 8）。

2-2-2 基質一般性の検討

最適条件下（Table 2-1, entry 8）、基質一般性の検討を行った。なお、メタル化に要する銅アミドアート型塩基と酸化剤の当量は必要に応じて最適化した（Table 2-2）。

はじめに官能基許容性（Ancillary Functional Group: AFG）を検討した。4 位にハロゲンを置換した基質は対応する水酸化体（**2b**–**2d**）を高収率で与えた。強力な電子求引基である CF_3 基や酸化的損壊を受けやすいビニル基を 4 位に有する基質も高収率にて水酸化された（**2e** and **2f**）。特に、リチウム試薬や Grignard 試薬などの高活性な有機金属試薬や遷移金属触媒を用いた反応には適用が困難なヨウ素や二重結合を有する基質が効率よく対応するフェノール体へと変換できたことは本手法の特筆すべき点である（**2d** and **2f**）。

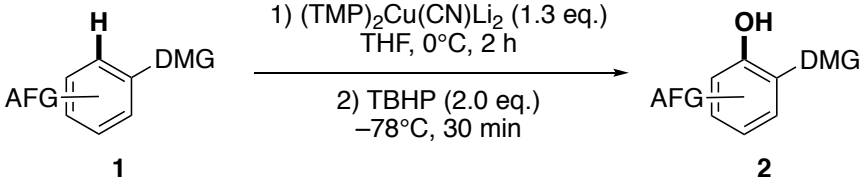
ナフタレン環の 1 位あるいは 2 位に配向基を有する基質の水酸化反応は、極めて高い選択性を示した。1 位に配向基を有する基質では 2 位のみが高収率にて水酸化され、8 位への酸素原子の導入は全く見られなかった（**2g**）。また、2 位に配向基を有する基質を用いると、1 位は全く反応せず、3 位のみが効率よく水酸化された（**2h**）。さらに、2 つの配向基を有する場合には、2 つの配向基に挟まれた 2 位のみが高い収率で水酸化された（**2i**）。

N,*N*-ジイソプロピルアミド基以外の配向基を用いることも出来た。*N*,*N*-ジエチルアミド基（**2j**）やシアノ基（**2k**）、エーテル基（MOM エーテル基：**2l**、メトキシ基：**2m**）、ホスフィンオキシド基（**2n**）は本反応に適した配向基である。さらに、求核攻撃を受けやすいエステル基も、TBHP よりも嵩高い cumene hydroxyperoxide を酸化剤として用いることで官能基を損なうことなくオルト位に水酸基を導入できた（**2o** and **2p**）。また、カルボン酸もあらかじめ Na 塩とすることで円滑に反応が進行し、安息香酸からサリチル酸を容易に合成できた（**2q**）。

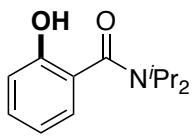
本手法は種々のヘテロ芳香環にも適用可能だった。Isoquinoline や benzothiazole は、芳香環上の窒素原子を配向基として用いることが可能であり、対応する水酸化体を高い位置選択性かつ良好な収率で与えた（**2r** and **2s**）。また、チオフェン環を有する基質を用いても、環を損壊することなく目的物を合成できた（**2t** and **2u**）。

なお、本反応は容易にスケールアップが可能であり、7.0 mmol スケールにおいても **2a** を 91% の単離収率（1.41 g）にて得ることができた。

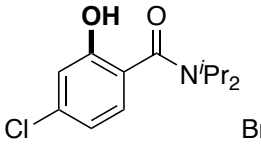
Table 2-2. Substrate Scope of Hydroxylation



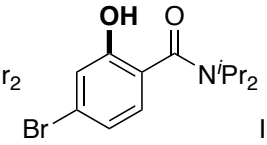
1 2



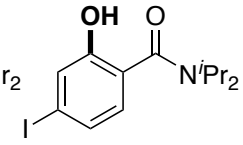
2a: 94%
91% (1.41 g)[a]



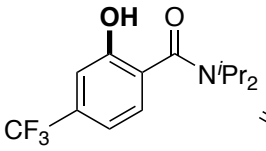
2b: 89%[b]



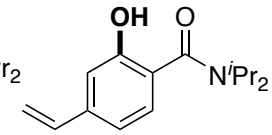
2c: 88%[b]



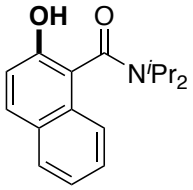
2d: 92%[b]



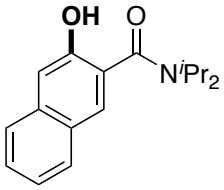
2e: 92%



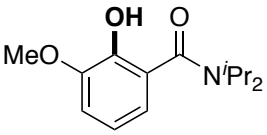
2f: 71%[c]



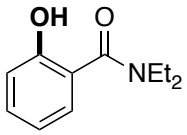
2g: 89%



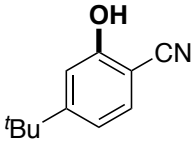
2h: 76%



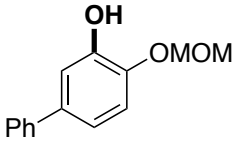
2i: 79%[c]



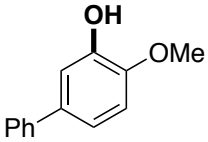
2j: 90%[d]



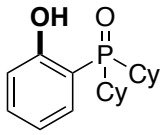
2k: 87%[d,e]



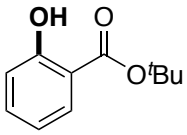
2l: 82%[d,e]



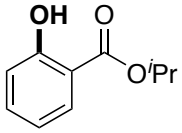
2m: 83%[f]



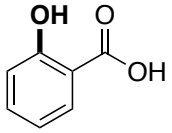
2n: 86%[d]



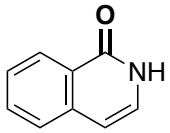
2o: 87%[f,g]



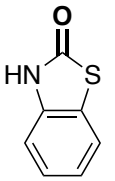
2p: 68%[f,g]



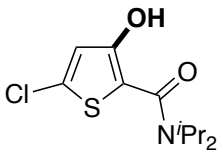
2q: (67%)[f,h]



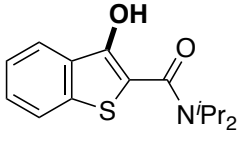
2r: 86%[d,e]



2s: 64%



2t: 81%[b]



2u: 81%[c]

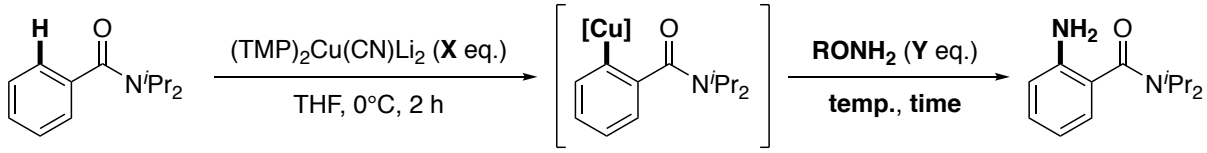
Isolated yields. NMR yield based on mesitylene as an internal standard in parentheses. [a] 7.0 mmol scale. [b] Cupration at –78°C. [c] TBHP (1.2 eq.). [d] Cuprate (1.5 eq.). [e] TBHP (1.4 eq.). [f] Cuprate (2.2 eq.). [g] CHP instead of TBHP. [h] Sodium benzoate as substrate. CHP = Cumene hydroperoxide.

2-3 アミノ化反応

2-3-1 条件検討

水酸化反応と同様の仮説を基に、酸性プロトンを有する酸化剤を用いることで他のヘテロ原子の導入も可能であると考え、窒素原子導入反応の開発に取り組んだ。すなわち、TBHP（^{t}BuOOH）と類似の構造を有するオキシアミン $RONH_2$ を酸化剤として用いれば、対応する第一級のアニリン誘導体が合成できると期待し、*N*,*N*-diisopropylbenzamide と $(TMP)_2Cu(CN)Li_2$ から調製したアリール銅アート中間体と種々のオキシアミンの反応を検討した（Table 2-3）。

Table 2-3. Optimization of Amination



entry	X	$RONH_2$	Y	temp.	time	yield (%)
1	1.5	$MtsONH_2$	1.4	−78°C	30 min	64
2	1.5	$NbzONH_2$	1.4	−78°C	30 min	62
3	1.5	$TMSONH_2$	1.4	−78°C	30 min	54
4	1.5	$MeONH_2$	1.4	rt	30 min	57
5	1.5	$BnONH_2$	1.4	rt	30 min	81 (76)
6	1.3	$BnONH_2$	1.2	rt	30 min	69 (72)
7	1.3	$BnONH_2$	1.2	rt	1 h	72
8	1.3	$BnONH_2$	2.0	rt	1 h	99 (93)

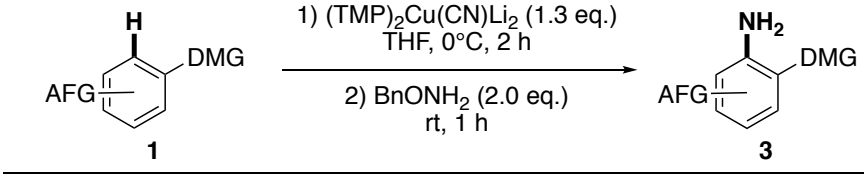
NMR yields based on mesitylene as an internal standard. Isolated yields in parentheses. Mts = Mesitylsulfonyl. NBz = 4-Nitrobenzoyl.

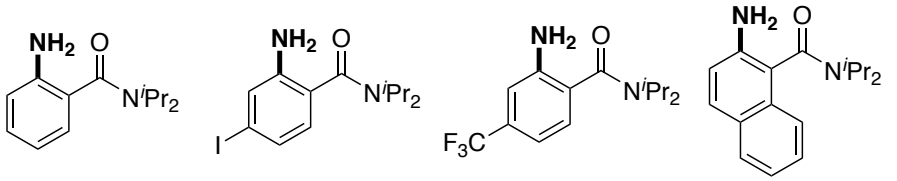
酸化剤として、*O*-(mesitylsulfonyl)hydroxylamine（$MtsONH_2$）、*O*-(4-nitrobenzoyl)hydroxylamine（$NbzONH_2$）、*O*-(trimethylsilyl)hydroxylamine（$TMSONH_2$）、*O*-methylhydroxylamine（$MeONH_2$）を用いたところ、いずれも所望のアニリンの生成は中程度の収率にとどまった（entries 1-4）。一方で、ヒドロキシルアミンの中でも入手が容易で扱いやすい *O*-benzylhydroxylamine（$BnONH_2$）を作用させると高収率にてアミノ化が進行し（entry 5）、銅アート塩基と酸化剤の当量を低減できることもわかった（entry 6）。また、反応系の温度が室温まで上昇する時間（30 min → 1 h）を十分に確保することで、再現性良く目的物が得られることがわかった（entry 7）。さらに、水酸化反応と同様に、小過剰の酸化剤を加えることで、アミノ化体を単離収率 93%（NMR 収率 99%）で得ることができたため、これを最適条件とした（entry 8）。

2-3-2 基質一般性の検討

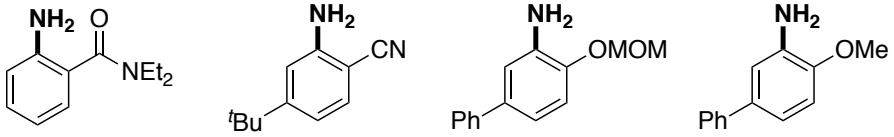
最適条件下、様々な基質に対してアミノ化反応を行った（Table 2-4）。アミノ化反応も水酸化反応と同様にヨウ素やトリフルオロメチル基、ナフタレン環を有する基質を高いオルト位選択性にてアミノ化することができた（**3d**, **3e** and **3g**）。また、様々な配向基を利用できることもわかった（**3j-3o** and **3r**）。チオフェン環（**3t**）やフラン環（**3v**）、インドール環（**3w** and **3x**）といった芳香族複素環化合物も本酸化条件下において環を損なうことなく良好な収率で目的のアニリン誘導体へと導くことができた。また、フェロセンへの直接的窒素原子導入も可能だった（**3y**）。芳香族 C–H 結合の切断を介する直接的な第 1 級のアニリン合成は報告例に乏しく [2-14]、本手法が新たなアニリンの化学を切り拓くきっかけとなることが期待される。

Table 2-4. Substrate Scope of Amination

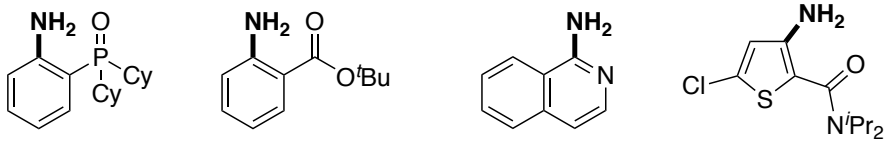




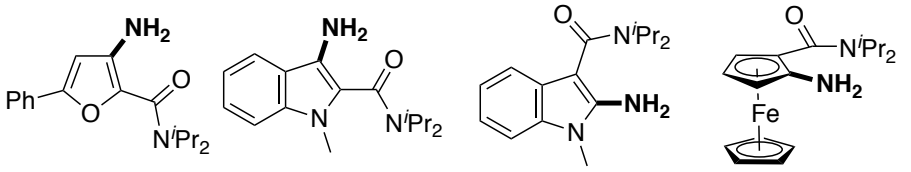
3a: 93% **3d**: 84%[a] **3e**: 70% **3g**: 76%



3j: 92% **3k**: 84% **3l**: 81%[b] **3m**: 86%



3n: 94%[c] **3o**: 79%[d] **3r**: 87% **3t**: 68%[a]



3v: 46%[a] **3w**: 69% **3x**: 69% **3y**: 63%[a]

Isolated yields. [a] Cupration at –78°C. [b] Inseparable contamination of 4-phenylphenol. [c] Cuprate (1.5 eq.). [d] Cuprate (2.2 eq.) and $BnONH_2$ (2.0 eq.).

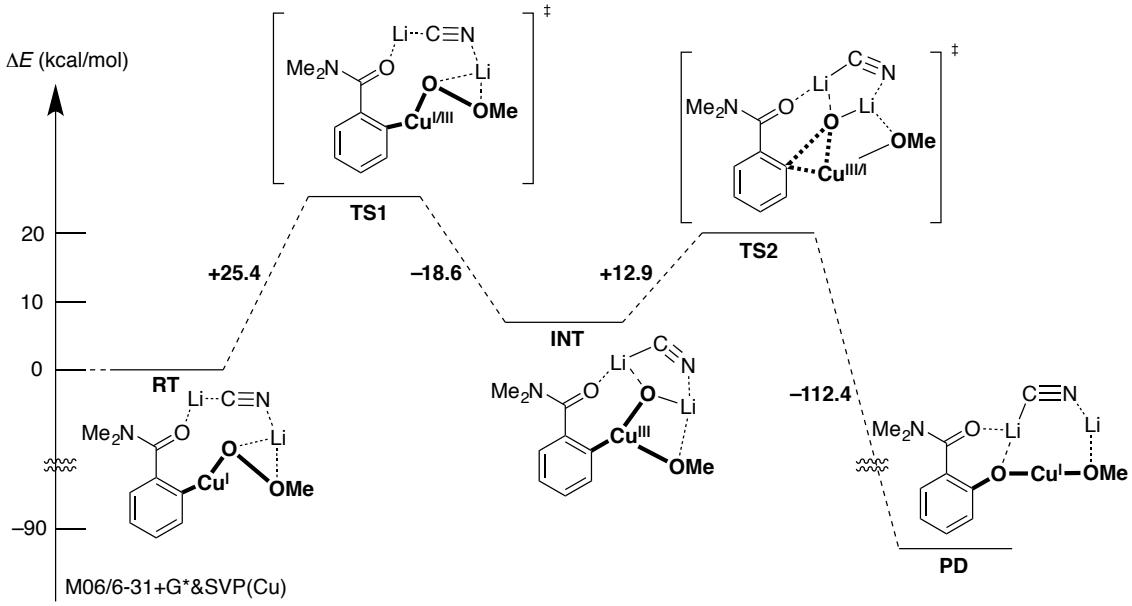
2-4 反応機構

2-4-1 理論化学計算を用いた反応機構解析

本水酸化およびアミノ化反応の反応機構を明らかにするため、DFT 計算を用いて、酸素原子導入反応の詳細を解析した。計算にあたっては、汎関数として非共有結合や長距離間の相互作用も見積もることが可能な半経験的汎関数 M06[2-15] を、基底関数として 6-31+G* を用いた。また、計算コストを軽減する目的で、モデル基質として *N*,*N*-dimethylbenzamide および methyl hydroperoxide（MeOOH）を用いた。

計算の結果（Figure 2-3）、O–O 結合が銅に酸化的付加したと考えられる平面 3 配位構造の中間体（**INT**）を得た。これと反応前駆体（**RT**）および反応成績体（**PD**）を結ぶ反応経路を探索したところ、本酸素原子導入反応を説明するのに十分合理的な反応経路を見出した。すなわち、銅上での配位子交換（**RT**）の後、25.4 kcal/mol の活性化エネルギーを得てペルオキシドの O–O 結合が 1 価の銅中心に酸化的付加（**TS1**）し、3 価銅中間体（**INT**）を与える。続く還元的脱離（**TS2**）には 12.9 kcal/mol の活性化障壁が算出され、**TS2** から見て –112.4 kcal/mol もの大きな安定化エネルギーを獲得しつつ、酸素原子が芳香環上に導入されることが示された（**PD**）。

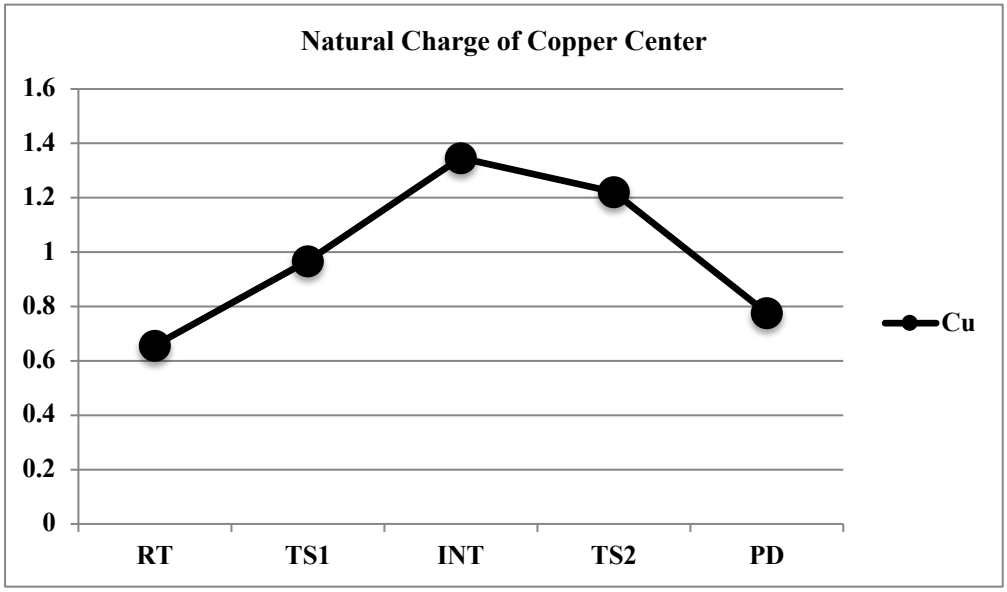
Figure 2-3. DFT Calculations on Reaction Mechanisms of the Introduction of Oxygen



本反応経路における銅中心の酸化数の変化の有無を確かめるために、自然結合軌道解析（NBO解析）を行い、銅中心周辺の電荷（natural charge*）を計算した（Figure 2-4）。その結果、反応前駆体（**RT**）から中間体（**INT**）にかけては natural charge の値の上昇が見られ、中間体（**INT**）から反応成績体（**PD**）に至るまでは減少することがわかった。

以上より、本反応が銅の I 価 → III 価 → I 価の酸化還元を介する反応であることが強く示唆された。

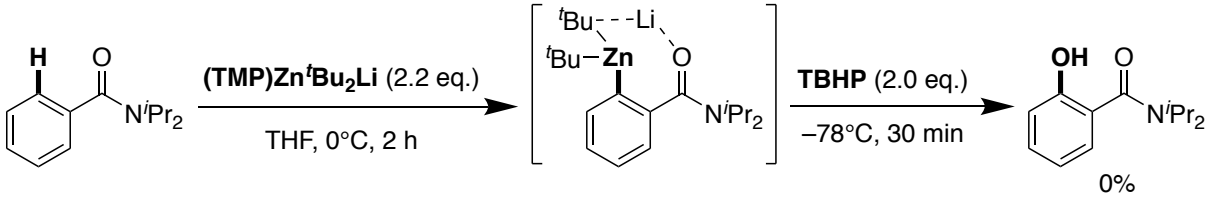
Figure 2-4. Transition of Natural Charge through the Introduction of Oxygen Atom



上記機構を実験化学的にも検証するべく、2 価の亜鉛を中心金属とする亜鉛アミドアート型塩基 (TMP)Zn^{t}Bu$_2$Li から調製した酸化還元活性をもたないアリール亜鉛アート錯体 ArZn^{t}Bu$_2$Li に対して TBHP を作用させたところ、水酸化反応は進行しなかった（Scheme 2-5）。

このように、理論と実験の両面から銅の酸化還元による酸素原子導入機構が明らかになった。

Scheme 2-5. Reaction between Redox-Inactive Arylzincate and TBHP



* Natural charge は、注目している原子周りの電子密度と核電荷の和を表した数値であり、整数値（Cu^{I} に対して 1 や Cu^{II} に対して 2 など）を示さないが、原子の電荷の変化を見積もる指標としてよく用いられる。

2-4-2 銅の触媒化

反応機構解析の結果から、銅は I 価から III 価を経由して反応後には再び I 価に戻るため、理論上は銅の触媒化へ展開できると考え（Figure 2-5）、触媒的水酸化反応を検討した（Table 2-5）。

Figure 2-5. Concept of Cu-Catalyzed Reaction

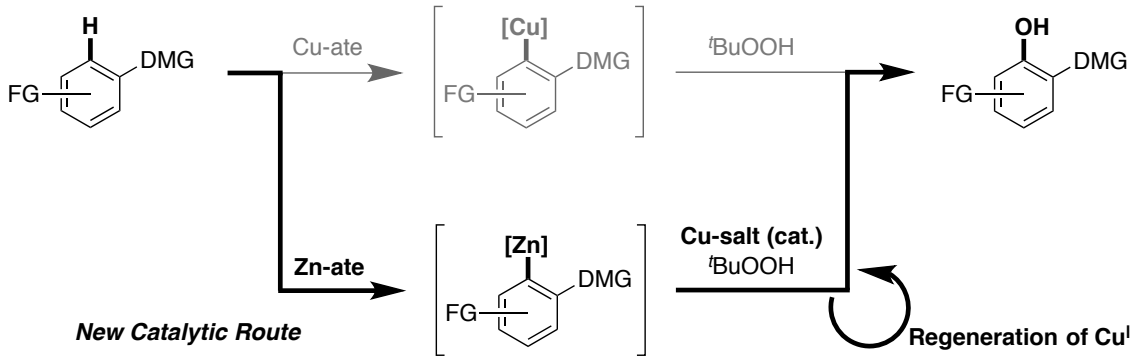
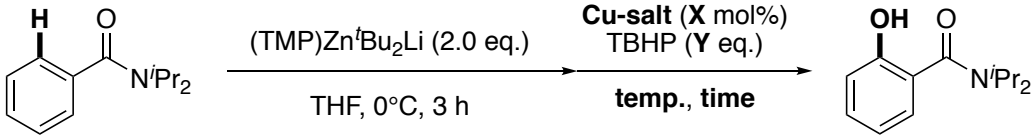


Table 2-5. Optimization of Copper-catalyzed Hydroxylation



entry	Cu-salt	X	Y	temp.	time	yield (%)
1	CuCN	10	2.0	rt	16 h	68[a,b]
2	CuCN	10	2.0	40°C	30 min	67 (66)
3	CuI	10	2.0	40°C	30 min	67
4	CuCN	10	2.5	40°C	1 h	68
5	CuCN	20	2.0	40°C	30 min	65
6	CuCN	10	2.0	40°C	30 min	5[c]
7	CuCN	10	2.0	40°C	30 min	49[d]

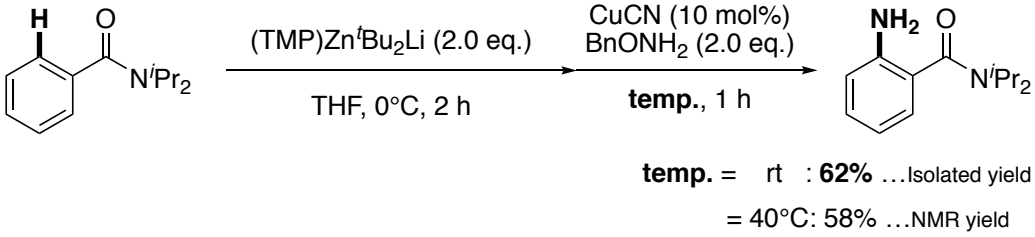
NMR yields based on mesitylene as an internal standard. Isolated yield in parentheses. [a] Zincate (2.2 eq.). [b] Low reproducibility. [c] Dioxane as solvent. [d] CPME as solvent. CPME = Cyclopentyl methyl ether.

まず、これまで用いていた CuCN を 10 mol% 用いて、TBHP 添加後 16 時間室温下で撹拌したところ、NMR 収率 68% で水酸化体を得た（entry 1）。しかし、再現性に問題があったため、この原因を酸化剤添加後の昇温速度が一定でないことだと考え、酸化剤添加後速やかに 40°C に昇温したところ、再現性良く水酸化体を単離収率 66% で得られることを見出した（entry 2）。CuCN と同様に無水かつ扱いが容易な CuI を用いた場合にも同等の結果を与えた（entry 3）。さらに酸化剤の当量や触媒量を増加したが、収率の改善は見られなかった（entries 4

and 5)。Dioxane や cyclopentyl methyl ether（CPME）といったエーテル溶媒も検討したが、収率は向上しなかった（entries 6 and 7)。以上の結果をもとに、entry 2 を最適条件とした。

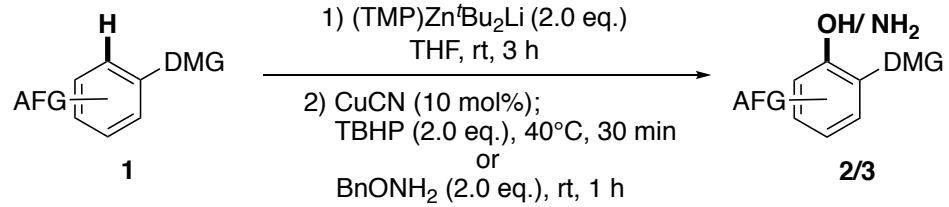
続いてアミノ基導入反応に関しても、反応条件を検討した（Scheme 2-6)。この場合には、アリール銅アート種に酸化剤を添加後、室温で撹拌し続けるほうが、40°C に昇温するよりも良い結果を与えたため、前者を最適条件とした。

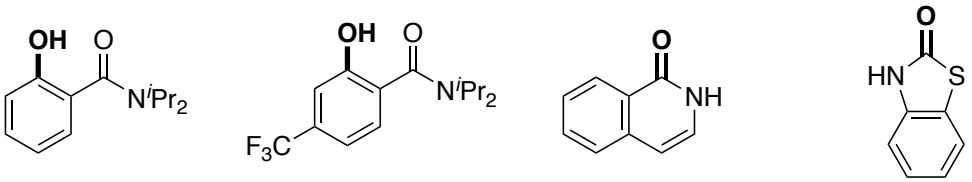
Scheme 2-6. Optimization of Copper-Catalyzed Amination



最適条件下、種々の芳香族化合物の銅触媒を用いた水酸化およびアミノ化反応を行った（Table 2-6)。トリフルオロメチル基を有する基質に加え、isoquinoline や benzothiazole といった複素芳香環にも適用可能だった。

Table 2-6. Substrate Scope of Copper-Catalyzed Hydroxylation and Amination



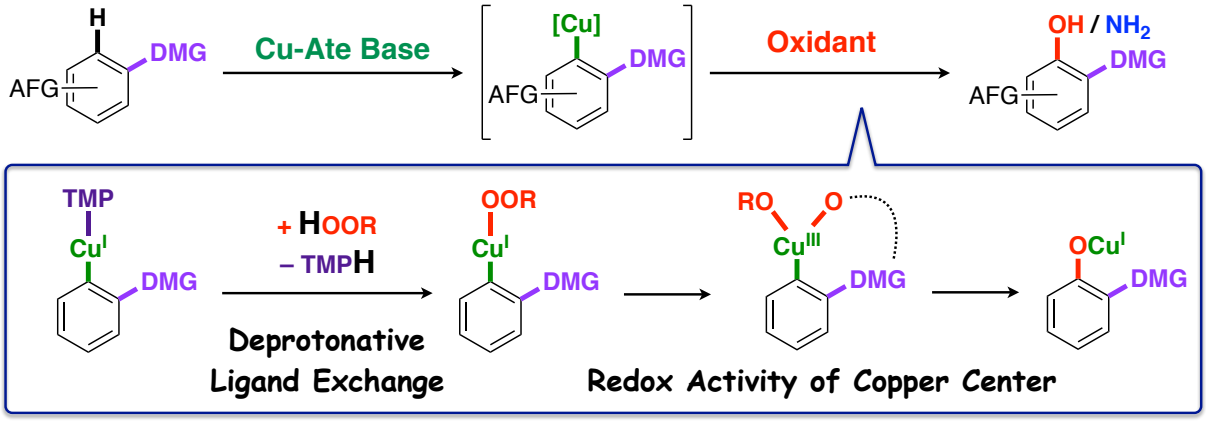


Isolated yields.

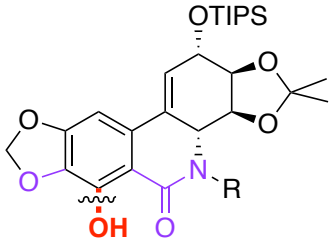
2-5 小括

医薬品や機能性分子には芳香環上に C–O/C–N 結合を有するものが多く存在するが、従来の「DoM + 求核付加/置換反応」という形式では複雑に官能基化された芳香環への酸素・窒素官能基の導入は困難であった。筆者は、銅の酸化還元能に着目し、銅アート塩基による DoM と酸化反応を利用した新たな反応設計によって、フェノールおよびアニリン誘導体の高位置・化学選択的な合成法を開発した。本手法は、様々な（ヘテロ）芳香環に適用可能である。特に、有機金属試薬や遷移金属触媒を苦手とするヨウ素や二重結合を有した基質を用いることが可能な点は本反応の合成的有用性を表す大きな特徴である。さらに、実験と理論の両面から本反応の、酸化剤の脱プロトン化/配位子交換に続く、銅の酸化還元（I → III → I）を活用した反応機構を明らかにした。また、これをもとに触媒量の銅による水酸化・アミノ化反応へも展開した。本研究業績は *Journal of the American Chemical Society* 誌に発表した。

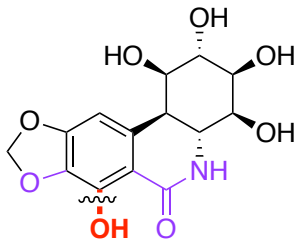
Noriyuki Tezuka, Kohei Shimojo, Keiichi Hirano,* Masanobu Uchiyama* *et al.*
J. Am. Chem. Soc. **2016**, *138*, 9166–9171.



また最近、本反応が天然物全合成の最終段階である水酸化に最適であることが報告され、多様な骨格への利用に耐えうる堅牢な反応であることが改めて示された [2-16]。



(±)-narciclasine



(+)-pancratistatin

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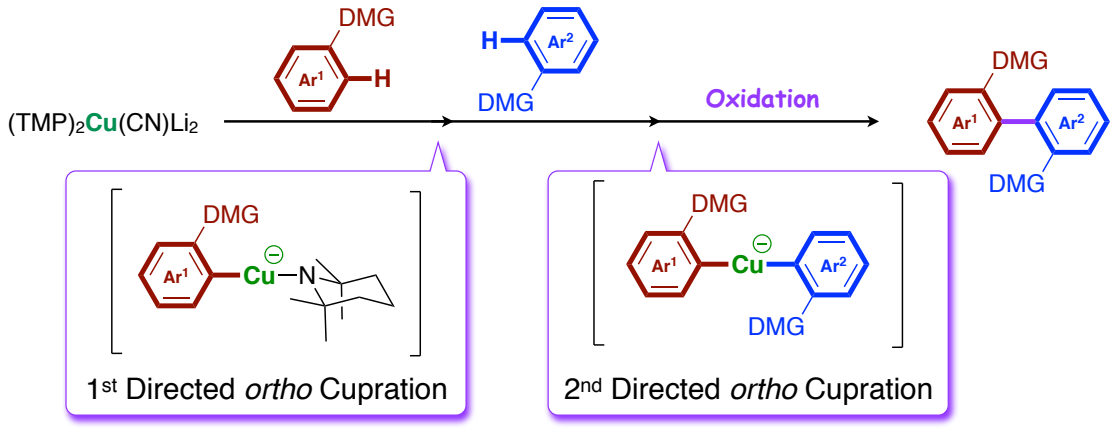
第三章
銅アミドアート型塩基を用いた形式的芳香族脱水素型クロスカップリング反応

3-1 序論

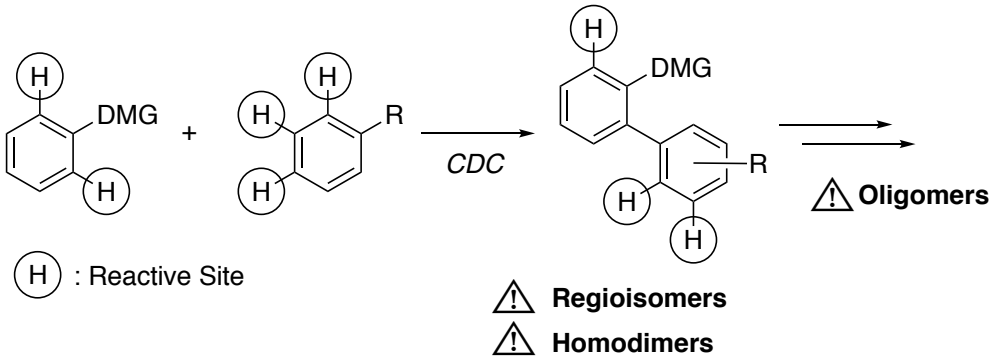
第二章にて、銅アミドアート型塩基による DoM を基盤とした直接的芳香族水酸化反応が、「アリール銅アート中間体による ROOH の脱プロトン化/配位子交換」と「O–O 結合による銅中心の酸化」を鍵とすることを実験と理論の両面から明らかにした。筆者は、銅の高い酸化還元能を活用した新たな展開として、$(TMP)_2Cu(CN)Li_2$ の 2 つのアミド配位子を活用した「異なる 2 種の芳香環の逐次的な DoM」と「生じる非対称ジアリール銅アート中間体の酸化反応」を精密に設計することで、形式的芳香族脱水素型クロスカップリング反応（Cross-Dehydrogenative Coupling: CDC）に展開できるのではないかと考えた（Figure 3-1）。

Figure 3-1. Concept for Formal Cross-Dehydrogenative Coupling *via* Sequential D*o*M and Oxidation



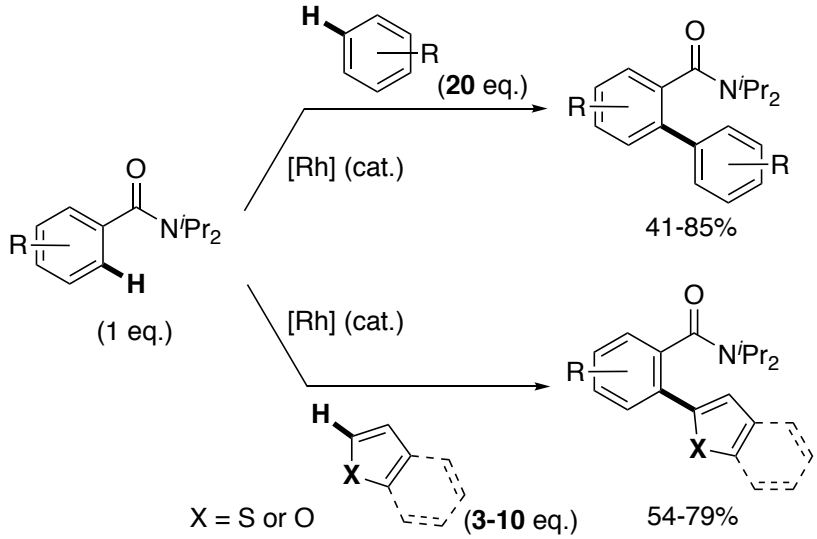
芳香族 CDC 反応は、基質となる芳香環の事前の修飾化・活性化によって反応点を規定することなく C–C 結合を形成できるため、廃棄物や合成段階数の削減の観点で理想的なプロセスとして期待されている[3-1]。Pd 触媒を用いた *N*-アセチルインドールとベンゼンとの CDC 反応が Fagnou らによって初めて報告されて以来[3-2]、今日までに Pd[3-3], Cu[3-4], Rh[3-5], Ru[3-6], Co[3-7] など、様々な遷移金属を用いた CDC 反応が開発されてきた。一方、反応の位置選択性は芳香環上の配向基を利用することで制御できるものの、これまでの手法では一般的に 2 つの基質や生成物を区別することが難しく、望まないホモダイマーやオリゴマーの副生を避けるためには、基質の当量に大きな差を設けるなどの工夫が必要である（Figure 3-2）。

Figure 3-2. General Problems on CDC: Difficulty to Control Reaction Site



また、電子状態が大きく異なる基質を組み合わせることで、適用可能な基質は制限されるものの、より理想的な当量比で反応が進行する。例えば、Glorius らは Rh 触媒を用いたベンズアミドと様々な（ヘテロ）芳香環との CDC 反応を報告している[3-5a]。基質にトルエンなどのアルキルベンゼン類を用いる場合には、20 当量から溶媒量を必要とする一方で、電子過剰なヘテロ芳香環を用いた場合には、より少量（3 から 10 当量）で効率的に反応が進行する（Figure 3-3）。

Figure 3-3. Rh-Catalyzed CDC by Glorius.

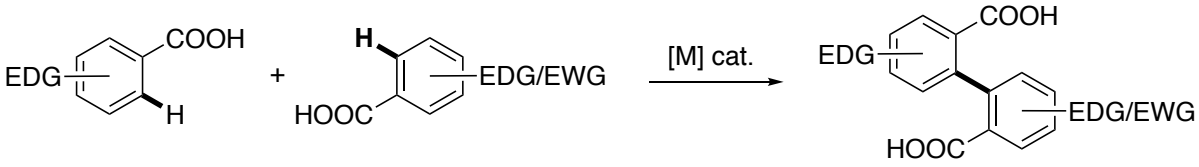


また、電子不足な芳香環同士の CDC 反応は特に報告例が少ない[3-5d,6b,7,8]。Li、Gong らは Rh 触媒存在下、2 種類の異なる安息香酸を中程度から高収率にて非対称ビアリールへと導く手法を報告している（Figure 3-4）[3-5d]。本手法では、一方の基質が電子供与基を有することが重要であり、電子求引性の置換基を有する安息香酸同士のクロスカップリング反応は極めて低い収率となる。

また Baidya らは、Ru 触媒を用いた安息香酸誘導体のホモ 2 量化反応を報告している[3-6b]。この手法はクロスカップリングにも適用可能であるが、先程と同様に、「電子豊富な置換基を有する安息香酸誘導体」と「電子不足な置換基を有する安息香酸誘導体」の組み合わせを用いた場合に反応が良好に進行する（Figure 3-4）。これについて、「反応の選択性には芳香環の電子密度の偏りが極めて重大な影響を与えるため、適切な基質の選択が重要である」と述べられているに留まり、基質一般性はほとんど調べられていない。

Figure 3-4. Rh- or Ru-Catalyzed CDC by Li and Gong, and Baidya

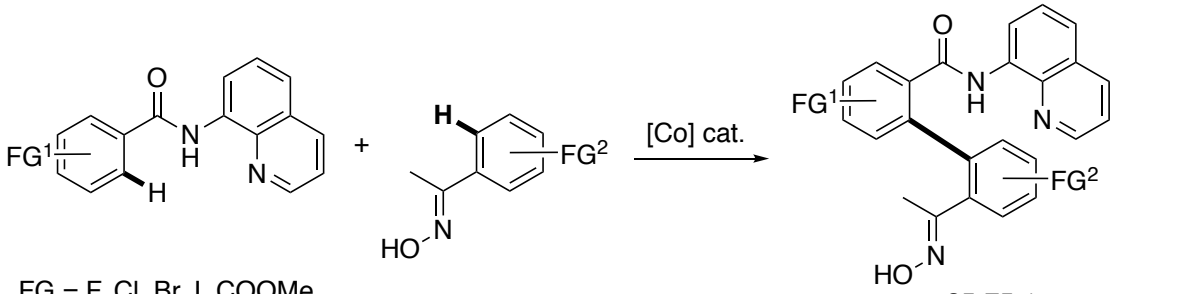
・**Li and Gong**, M = Rh
・**Baidya**, M = Ru



At least one coupling partner should have ***Electron-Donating Group (EDG)***

一方、Zhang らは、Co 触媒を用い、8-アミノキノリン由来の 2 座配位型アミド基とオキシム基を配向基とする電子不足な芳香環同士の CDC を報告している（Figure 3-5）[3-7]。このように、適切な配向基を選択することで一般に困難とされる結合形成に成功している。

Figure 3-5. Co-Catalyzed CDC of Electron-Deficient Aromatics by Zhang



DMG-Controlled Reactivity

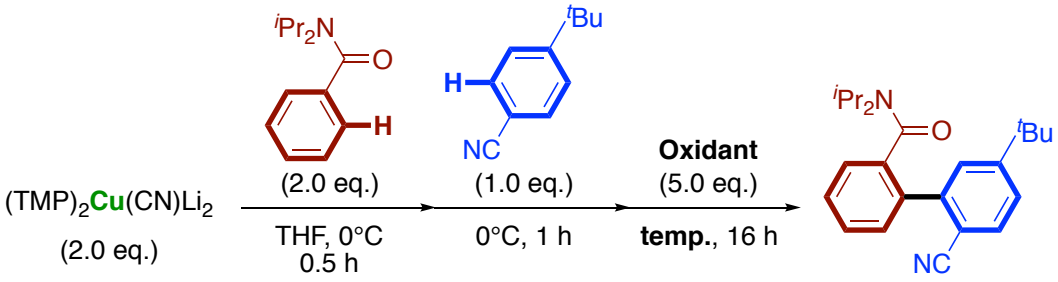
本章の冒頭で提案した「$(TMP)_2Cu(CN)Li_2$ を用いた異なる 2 種の芳香環の逐次的な D*o*M」と「生じる非対称ジアリール銅アート中間体の酸化」を利用した CDC 反応では、TMP 配位子が芳香環の電子状態に大きく依存せず、効率よく脱プロトン化できると考えられるため、金属上のアリール配位子の組み合わせを単純に芳香環を加える順序により制御できると予想される。これにより、芳香環の電子密度の偏りや極端に過剰量の反応剤の使用といった旧来の反応設計に頼ることなく、位置選択性・官能基許容性高く様々な基質を効率よく非対称ビアリールへと導くことが可能な、より一般性の高い方法論を確立できると考えられる。

以上の背景を踏まえて筆者は、D*o*M と銅の酸化還元を活かした形式的芳香族脱水素型クロスカップリング反応の開発に着手した。

3-2 条件検討

3-1 で述べたように、電子不足な芳香環同士の CDC は報告例が少なく、一般に困難な化学変換である。一方で、電子不足な芳香環は DoM には適した基質である。そこでまずは、銅アミドアート型塩基 $(TMP)_2Cu(CN)Li_2$ を用いて *N*,*N*-diisopropylbenzamide および 4-*tert*-butylbenzonitrile を順次メタル化し、非対称ビアリール合成に最適な酸化剤を探索した（Table 3-1）。

Table 3-1. Screening of Oxidants



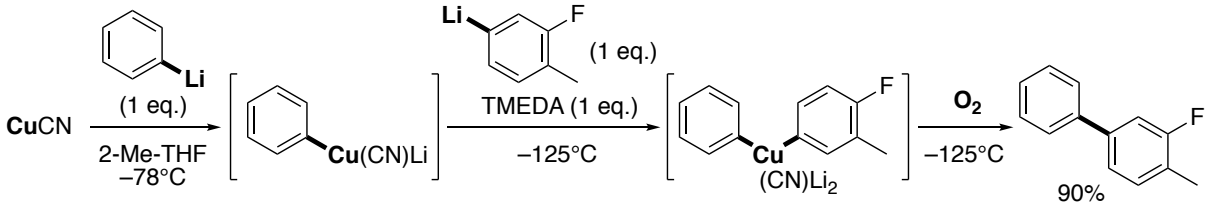
entry	oxidant	temp.	yield (%)
1	$K_2S_2O_8$	–78°C → rt	trace
2	$Pb(OAc)_4$	–78°C → rt	22
3[a]	O_2	0°C → rt	10
4	Nitrobenzene	–78°C → rt	16
5	1,3-Dinitrobenzene	–78°C → rt	35
6	Isopropyl 2,4-dinitrobenzoate	–78°C → rt	44
7	$C_6F_5NO_2$	–78°C → rt	55
8[b]	$C_6F_5NO_2$	0°C → rt	75
9[b]	Chloranil	0°C → rt	75
10[b]	Bromanil	0°C → rt	81
11[c]	Bromanil	0°C → rt	83 (76)
12[d]	Bromanil	0°C → rt	61
13[c]	Bromanil	0°C → rt	0

NMR yields based on mesitylene as an internal standard. Isolated yield in parentheses. [a] Dry O_2 bubbling for 5 min. [b] Oxidant (2.5 eq.). [c] Cuprate (1.55 eq.), *N*,*N*-diisopropylbenzamide (1.5 eq.), bromanil (1.7 eq.) and oxidation for 0.5 h. [d] Cuprate (1.0 eq.), *N*,*N*-diisopropylbenzamide (1.0 eq.) and bromanil (2.5 eq.).

まず無機酸化剤を検討した。$K_2S_2O_8$ を用いた場合には酸化剤が THF に溶解せず、ほとんど反応は進行しなかった（entry 1）。$Pb(OAc)_4$ を用いると、複雑な混合物が得られた（entry 2）。

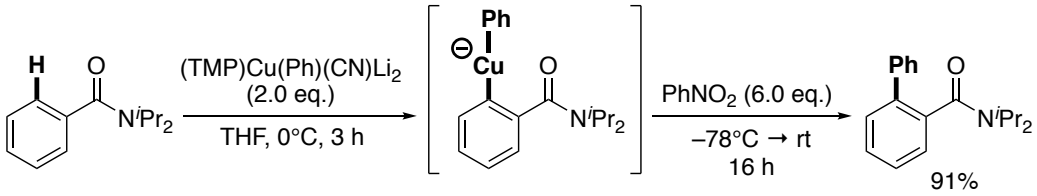
Lipshutz らは、CuCN 存在下、2 種類のアリールリチウムを酸素を用いた酸化反応に付すことで、非対称ビアリールの合成が可能であることを報告しているが（Scheme 3-1）[3-9]、我々の反応系では、クロスカップリング体が 10% 生成したものの、それぞれの基質の水酸化体を含む複雑な混合物が得られた（entry 3）。

Scheme 3-1. CuCN-Mediated Oxidative Heterobiaryl Formation from Aryllithiums by Lipshutz



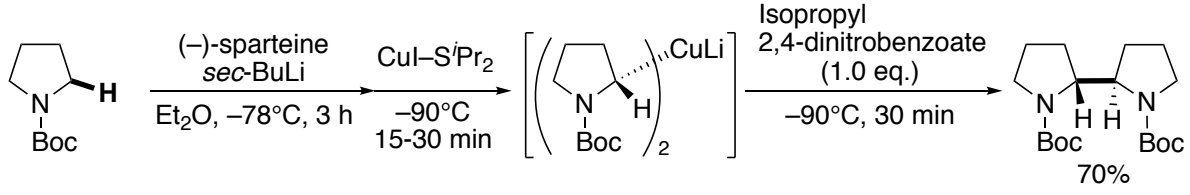
次に、有機酸化剤として nitrobenzene を作用させたところ、目的物は低収率に留まった（entry 4）。当研究室では、(TMP)Cu(Ph)(CN)Li_2 を用いて *N*,*N*-diisopropylbenzamide をメタル化した後、nitrobenzene を作用させることでフェニル化が定量的に進行することを見出しているが、これとは対照的な結果である（Scheme 3-2）[1-18a]。

Scheme 3-2. Ligand Coupling *via* D*o*M and Oxidation by Uchiyama



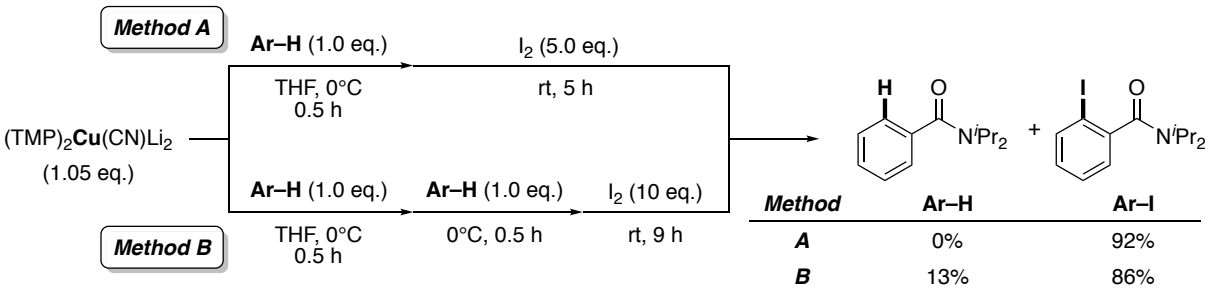
一方、Corey らは酸化力の高いニトロベンゼン類である isopropyl 2,4-dinitrobenzoate を用いたジアルキル銅アート種の二量化反応を報告している（Scheme 3-3）[3-10]。これを参考に種々の電子求引性置換基を有するニトロベンゼン類を検討した（entries 5-8）。併せて添加温度と当量を検討し、pentafluoronitrobenzene を用いることで、75% 収率にて目的物を得た（entry 8）。

Scheme 3-3. Oxidation of Dialkylcuprates with the Highly Electron-Deficient Nitrobenzene by Corey



続いて、ニトロベンゼン類よりもさらに強力な酸化剤として *p*-ベンゾキノン類[†3-11] を検討したところ、bromanil を用いた場合に 81% で目的物を得たため（entry 10）、これを最適な酸化剤とした。$(TMP)_2Cu(CN)Li_2$、*N*,*N*-diisopropylbenzamide、bromanil の当量についてさらに最適化を行い、entry 11 の条件が、最も高収率かつ良好な再現性にてクロスカップリング体を与えることを見出した。一方、塩基とベンズアミドの当量を 1.0 当量にまで減ずると目的物の収率は低下した（entry 12）。これは二回目の D*o*M の効率が比較的低いことが原因である。実際に、*N*,*N*-diisopropylbenzamide（1.0 当量）に $(TMP)_2Cu(CN)Li_2$（1.05 当量）を作用させると、メタル化が定量的に進行したのに対して（Scheme 3-4, Method A）、同様の過程で生じるアリールアミド銅アート中間体に、さらに 1.0 当量の *N*,*N*-diisopropylbenzamide を作用させると、ヨウ素化体に加えて 13% の原料が回収された（Scheme 3-4, Method B）。また、酸化剤を加えなかった場合にはカップリング反応は進行せず、原料が定量的に回収された（entry 13）。以上の結果から、entry 11 を最適条件とした。

Scheme 3-4. Efficacy of Deprotonation: First Metalation (Method A) vs Second Metalation (Method B)



Method	Ar–H	Ar–I
A	0%	92%
B	13%	86%

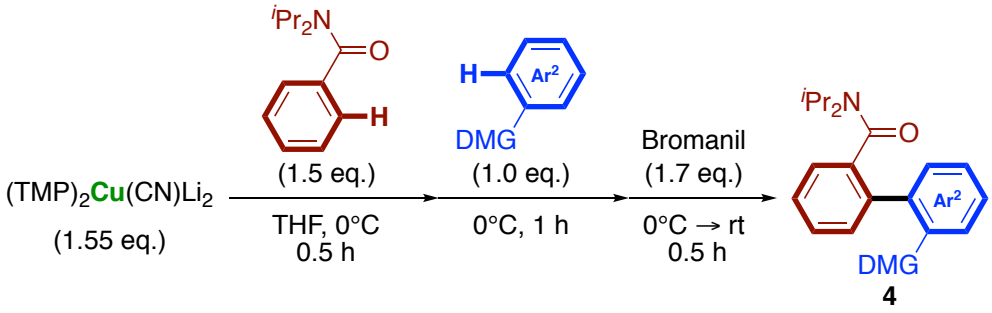
NMR yields based on mesitylene as an internal standard.

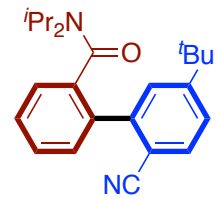
† 還元電位（E^0_{red} vs SCE）は、chloranil 0.02 V、trinitrobenzene –0.42 V であり、*p*-ベンゾキノン系がより強力な酸化剤であることがわかる。Trinitrobenzene は高活性なニトロベンゼンの一例として取り上げた。

3-3 基質一般性の検討

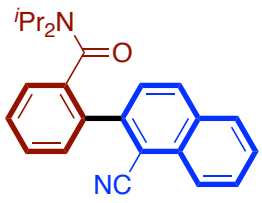
最適条件下（Table 3-1, entry 11）、*N*,*N*-diisopropylbenzamide と様々な芳香環とのクロスカップリング反応を検討した（Table 3-2）。

Table 3-2. Substrate Scope: *N*,*N*-Diisopropylbenzamide with Various Arenes

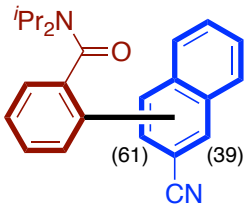




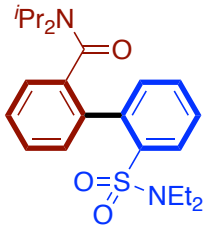
4a: 76% (83%)



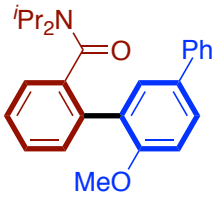
4b: 70%



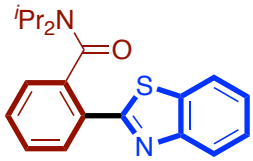
4c: 73%



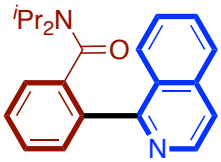
4d: (49%)



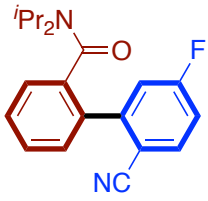
4e: 51% (73%)[a]



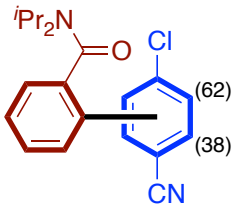
4f: 66%



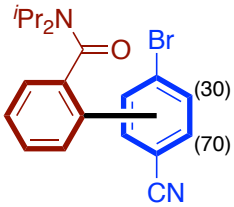
4g: 60%



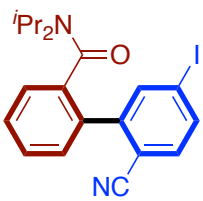
4h: 55%



4i: 66%



4j: 48%



4k: 44%

Isolated yields. NMR yields based on mesitylene as an internal standard in parentheses. [a] Cuprate (2.0 eq.), *N*,*N*-diisopropylbenzamide (2.0 eq.), and $C_6F_5NO_2$ (2.5 eq.) as an oxidant.

ベンゼン環だけでなく、ナフタレン環も本反応に適用可能だった。1-Naphthonitrile を用いると、8 位が置換された異性体は一切得られず、2 位選択的なクロスカップリング反応が高収率にて進行した（**4b**）。一方で、2-naphthonitrile を用いた場合には、1 位あるいは 3 位が反応した異性体が 39 : 61 の比率で得られた（**4c**）。シリンダー構造のシアノ配向基に配位した銅アート塩基は 1 位、3 位のどちらの C–H 結合にも接近可能であり、両方のメタル化が進行したと考えられる。

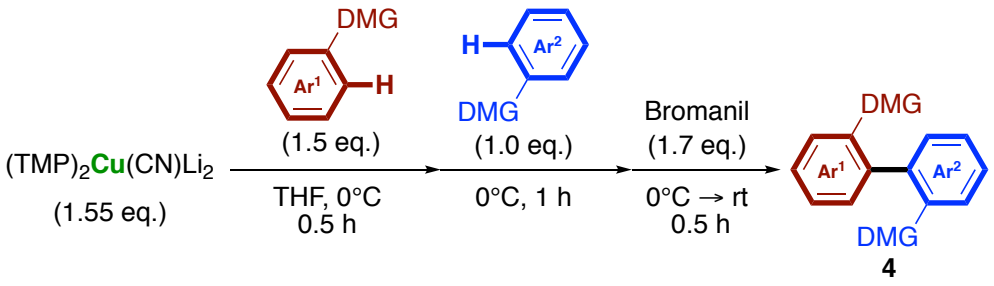
続いて様々な配向基を検討した。まず、電子求引性のスルホンアミドを配向基として用いることが可能であることがわかった（**4d**）。なお、本生成物はシリカゲルクロマトグラフィーやリサイクル分取 HPLC（GPC）による精製を行っても不純物との完全な分離が困難であり、NMR にて収率を決定した。一方、電子供与性のメトキシ基も用いることができた（**4e**）。さらに、ヘテロ芳香環の窒素原子も配向基として利用可能であり（**4f** and **4g**）、本手法が芳香環の電子状態に依らずに様々な組み合わせの非対称ビアリールの合成に適用できることがわかった。

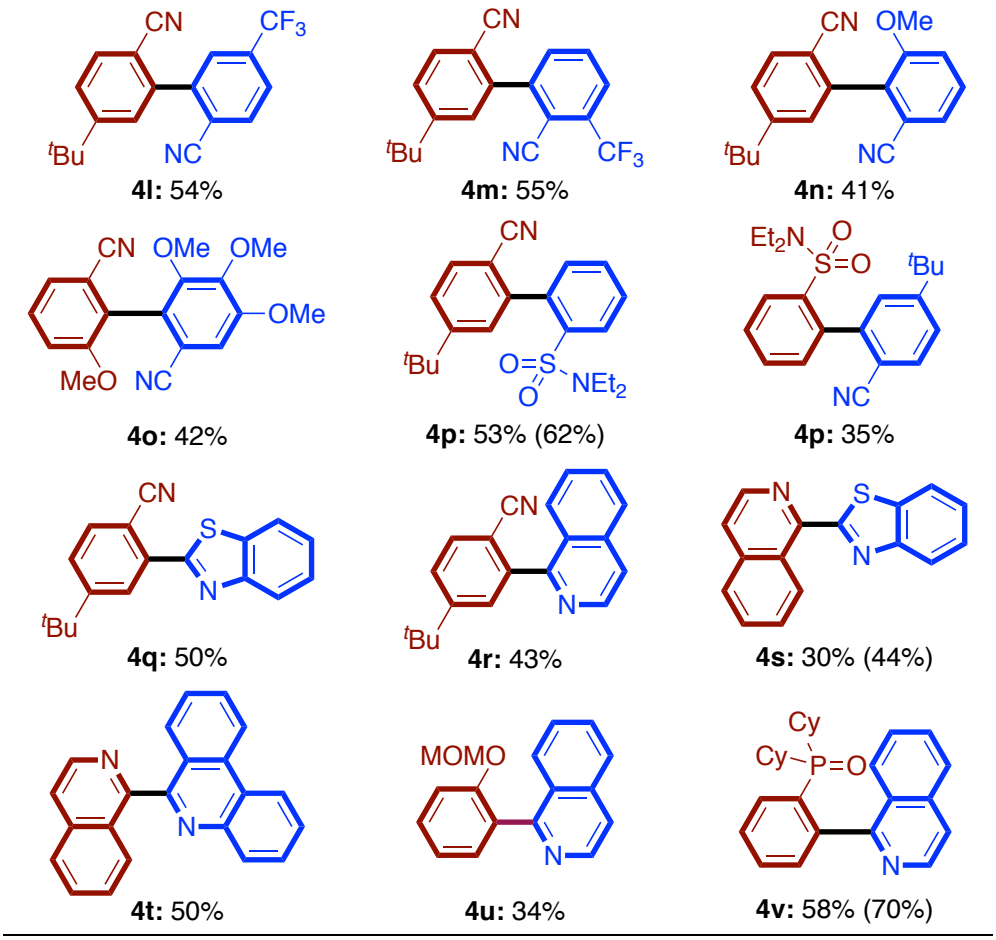
銅アミドアート型塩基の高い官能基許容性は本反応にも極めて有用であった。芳香族ハライドの脱プロトン化では、ベンザインの発生やハロゲンダンスによる異性体の副生が併発しうるが、4 位にフッ素（**4h**）、塩素（**4i**）、臭素（**4j**）、ヨウ素（**4k**）のいずれを有する基質も目的のクロスカップリング反応が高選択的に進行した‡。なお、塩素や臭素置換基を有する基質の場合には、それぞれ位置異性体が生じた。過酷な条件下、遷移金属を用いる従来の CDC 反応ではヨウ素置換基の共存は困難であり、本手法の合成的有用性が示された。

‡ 詳細な副生物の検討を行った結果、4-bromobenzonitrile を用いると *N*,*N*-diisopropylbenzamide の臭素化体が GCMS で検出された。また、4-iodobenzonitrile を用いた場合には、*N*,*N*-diisopropylbenzamide の 2 位ヨウ素化体が 11% の NMR 収率で得られた。これらの結果から、わずかながらハロゲン–金属交換反応が進行していることが示唆される。

第一のメタル化の基質は必ずしも *N*,*N*-diisopropylbenzamide である必要はなく、多様な基質を用いることができた（Table 3-3）[§]。

Table 3-3. Coupling of Arenes with Various DMGs





Isolated yields. NMR yields based on mesitylene as an internal standard in parentheses.

§ 低収率に留まった反応（e.g. **4u**）では、原料やホモカップリング体、シアノ化体を含む複雑な混合物が得られた。

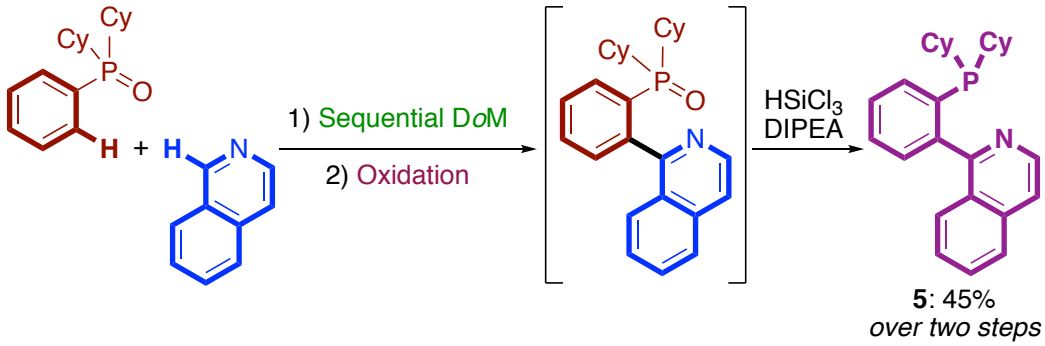
まず、多様な化学変換が可能なシアノ基に着目した。異なる 2 種類のベンゾニトリルを用いて反応を試みたところ、同じ配向基を持つ基質同士でも円滑に反応が進行し、種々の 2,2'-ジシアノビアリール類を合成することができた。シアノ基のパラ位やオルト位に置換基がある場合にも反応は効率良く進行し、医薬化学分野で広く用いられる CF_3 基を有するビアリールを容易に合成することができた（**4l** and **4m**）[3-14]。メタ位にメトキシ基を有するベンゾニトリルを用いると、2 つの配向基に挟まれた位置で選択的に反応が進行し、立体的に嵩高いオルト 3 置換ビアリール **4n** や、さらに嵩高いオルト 4 置換ビアリール **4o** の合成が可能だった。

メタル化の順序を逆転させても所望の生成物を得ることができた（**4p**）。これは、希少な基質を用いる場合には、2 段階目のメタル化の基質として選択できることを示す有用な知見である。

ヘテロ芳香環を用いても反応は効率よく進行し、ベンゾニトリルとベンゾチアゾールのクロスカップリング（**4q**）や、様々なイソキノリン含有ビアリールの合成も可能だった（**4r-4v**）。

さらに、**4v** を含む反応混合物を還元反応に付すことで[**]、わずか 2 工程にて遷移金属触媒の配位子として用いられる P,N-配位子を合成することができた（Scheme 3-5）[3-15]。本手法は phenanthridine など（**4t**）、他のイソキノリン類縁体にも適用できることから、様々な P,N-配位子の迅速合成へも展開できると期待される。

Scheme 3-5. Practical Two-Step Synthesis of P,N-Ligand **5**



[**] クロスカップリング反応にて得られた混合物をシリカゲルパッドで濾過した後、これを濃縮して還元反応を行った。

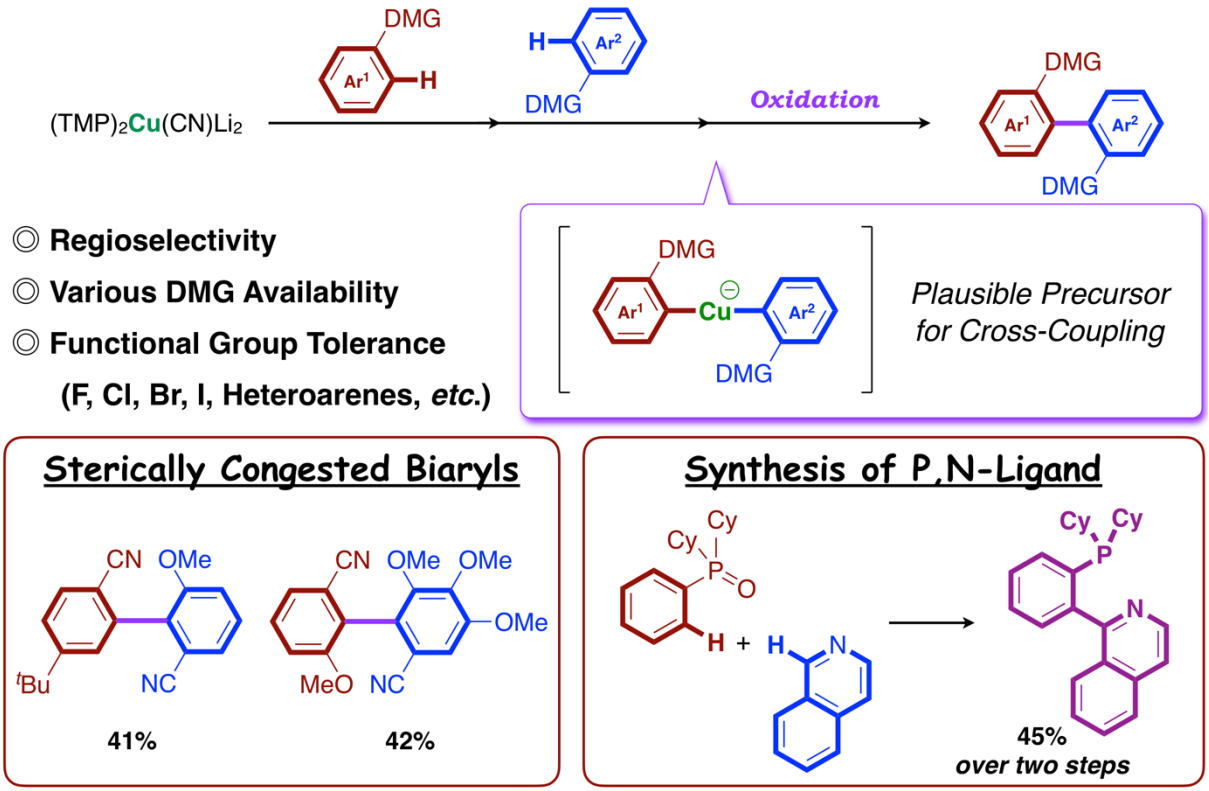
3-4 小括

銅アート中間体の酸化還元活性を活用した新たな展開として、2 つの TMP を有する銅アミドアート型塩基 $(TMP)_2Cu(CN)Li_2$ を用いた「異なる 2 つの芳香環の逐次的な DoM」と「生じる非対称ジアリール銅アート中間体の酸化反応」を精密に設計することで、形式的芳香族脱水素型クロスカップリング反応を開発した。

本手法は、銅アミドアート型塩基の高い位置選択性・官能基許容性を活かして、様々な組み合わせの（ヘテロ）芳香環を用いた多様な非対称ビアリールの合成が可能である。従来の手法とは異なり、基質を区別するために当量関係や芳香環の電子状態に大きな偏りを設ける必要がないことが特徴である。また、これまでの手法では困難で報告例に乏しい「電子不足な芳香環同士」の脱水素型クロスカップリングを実現する強力な合成法である。また、電子豊富な芳香環の組み合わせによっても様々な非対称ビアリールの合成が可能である。さらに、一般的なクロスカップリング反応では高温を要する「立体的に混み合った多置換ビアリール」の室温合成や、遷移金属の P,N-配位子の単工程合成にも展開可能であるなど、高度に官能基化されたビアリール合成に新たな道を拓いた。本研究業績は *Organic Letters* 誌に発表した。

Noriyuki Tezuka, Keiichi Hirano* and Masanobu Uchiyama*

Org. Lett. **2019**, *21*, 9536–9540.



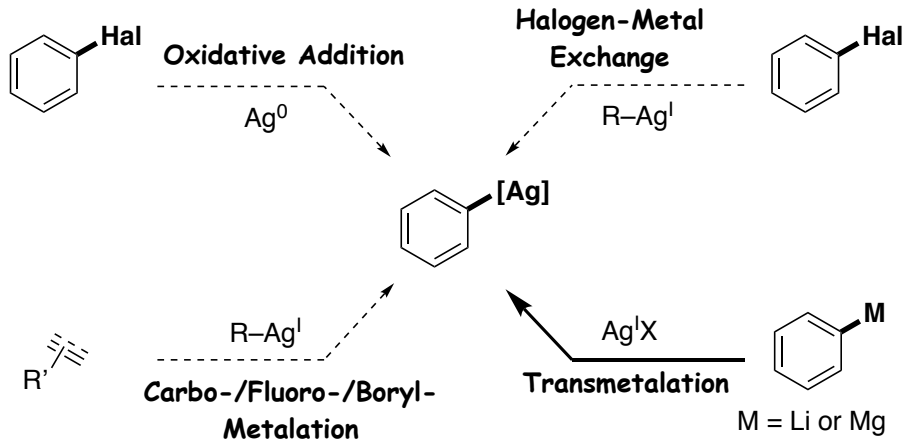
第四章
銀アミドアート型塩基を用いた芳香族オルトメタル化反応

4-1 序論

銅は、共役付加反応[4-1]、Ullmann 反応[4-2]、Glaser カップリング[4-3]などをはじめとする様々な変換反応に用いられ、有機合成化学の発展の一翼を担ってきた[4-4]。銅アート種の物性や反応性に関しても多くの報告例が存在し、SciFinder® での検索によると、銅アート種「cuprate」の文献は 97,268 件見つかった。一方で、銀アート種「argentate」の報告例はわずか 3,760 件であり（いずれも 2020 年 1 月 1 日現在)、銅のおよそ 25 分の 1 に過ぎない報告数である。中でも、筆者がこれまで着目してきた芳香族アート種、すなわちアリール銀アート錯体に関する報告はさらに限られ、その物性や反応性はほとんど知られていない。

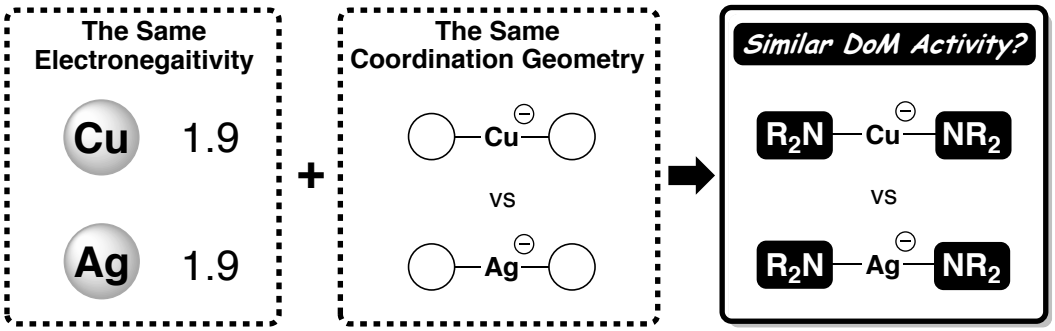
その原因のひとつとして、有機銀化合物の調製法が未発達であることが考えられる[4-5]。例えば、有機銅化合物は有機ハロゲン化物による銅への酸化的付加によって調製できるが[4-6]、銀を用いた同反応は報告されていない（Figure 4-1, 左上)。これは、銀の高い酸化還元電位が原因であると考えられる[4-7]。また、銀を用いたハロゲン–金属交換反応も知られていない(Figure 4-1, 右上)。有機銀種を用いたカルボメタル化反応[4-8]やフルオロメタル化[4-9]、ボリルメタル化[4-10]では芳香族銀の調製は不可能である（Figure 4-1, 左下)。アリール銀種はアリールリチウム種やマグネシウム種から銀へのトランスメタル化によって調製されるが、高反応性金属種を前駆体に用いるため、多様な官能基を有する芳香族化合物への適用は困難であるなど、芳香族銀種の調製法は全くの未開拓である（Figure 4-1, 右下)。

Figure 4-1. Preparation of Arylsilvers



一方、第二章、第三章で述べたとおり、筆者は DoM による芳香族銅アート種の調製とその反応による芳香環の修飾化反応を開発してきた。銀と銅は、同じ電気陰性度を有し[4-11]、1 価の金属錯体がともに直線 2 配位構造を取ることから、銀と銅は DoM 反応において同様に振る舞うことが期待できるため、銀を用いたオルトメタル化反応の開発は十分に可能であると考えられる（Figure 4-2）。また、銀は貴金属でありながら、例えば AgCN や $AgNO_3$ は比較的安価で入手が容易な試薬であるため[††]、有機合成において十分に実用的であると言える。

Figure 4-2. Directed *ortho* Argentation



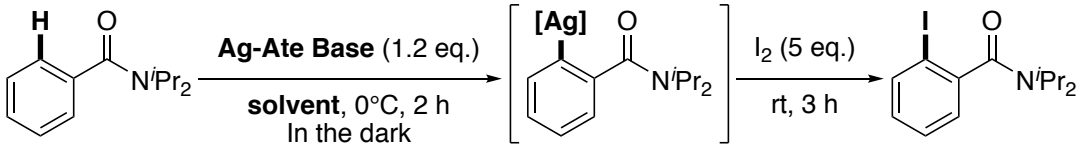
以上の背景を踏まえて筆者は、銀の特性を活かした新たな DoM の開発を目指し、銀アミド塩基の設計、および生じる芳香族銀種の反応性の開拓に着手した。

[††] 富士フイルム和光純薬株式会社：AgCN（7,000 円 / 25 g）vs CuCN（2,500 円 / 25 g）@ 2020 年 1 月 1 日現在

4-2 条件検討

銀アミド塩基の D*o*M 活性を評価するために種々の銀塩とアミド配位子を検討した（Table 4-1）。モデル基質として、*N*,*N*-diisopropylbenzamide を選択し、メタル化の効率はヨウ素による捕捉で評価した。また、銀の感光性が反応に影響しうることから、反応系を暗幕によって遮光した。

Table 4-1. Optimization of Conditions



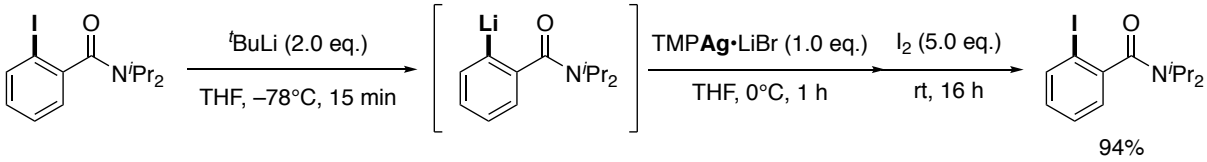
entry	Ag-Ate Base	solvent	yield (%)
1	(TMP)Ag(NO_3)Li	THF	ND
2	(TMP)Ag(CN)Li	THF	ND
3	(TMP)$_2$Ag(NO_3)Li$_2$	THF	ND
4	(TMP)$_2$Ag(1/2•CO_3)Li$_2$	THF	ND
5	(TMP)$_2$Ag(OTf)Li$_2$	THF	ND
6	(TMP)$_2$Ag(CN)Li$_2$	THF	99(92)
7[a]	(TMP)$_2$Ag(CN)Li$_2$	THF	93
8	(HMDS)$_2$Ag(CN)Li$_2$	THF	ND
9	(^{i}Pr$_2$N)$_2$Ag(CN)Li$_2$	THF	11
10	(Cy$_2$N)$_2$Ag(CN)Li$_2$	THF	99
11	Me(TMP)Ag(CN)Li$_2$	THF	ND
12	(TMP)$_2$Ag(CN)Li$_2$	Et$_2$O	31
13[b]	(TMP)$_2$Ag(CN)Li$_2$	Dioxane	ND
14	(TMP)$_2$Ag(CN)Li$_2$	Benzene	49
15	(TMP)$_2$Ag(CN)Li$_2$	Hexane	46
16[c]	(TMP)$_2$Ag(CN)Li$_2$	THF	99

NMR yields based on mesitylene as an internal standard. Isolated yield in parentheses. ND: Not detected. [a] Ag-ate base (0.5 eq.). [b] Deprotonation at rt. [c] Exposed to light. TMP: 2,2,6,6-Tetramethylpiperidido. TfO: Trifluoromethanesulfonato. Cy: Cyclohexyl. HMDS: 1,1,1,3,3,3-Hexamethyldisiladido.

始めに、等量の銀源と TMPLi から調製した非アート型のモノアミド銀塩基を検討したところ、$AgNO_3$、AgCN のいずれを用いた場合にも反応は全く進行しなかった（entries 1 and 2）。そこで、銀塩に対して 2 当量の TMPLi を用いて調製したアート型のビスアミド銀塩基を検討したところ、$AgNO_3$ や Ag_2CO_3、AgOTf を銀源とした場合にはメタル化は全く進行しなかったのに対して、AgCN から調製した $(TMP)_2Ag(CN)Li_2$ は非常に高活性であり、目的のヨウ素化体が定量的に得られた（entry 6 vs entries 3-5）。また、$(TMP)_2Ag(CN)Li_2$ は、2 当量の基質をメタル化することもできた（entry 7）。

ここで、本 D*o*M–ヨウ素化プロセスにおけるシアニドの特異性を調査した。アリールリチウムと銀アミド (TMP)Ag•LiBr から調製したシアニド非含有アリール銀アート種 [4-5g] に対してヨウ素を作用させたところ、高収率にてヨウ素化体が得られた（Scheme 4-1）。この結果は、シアニドはヨウ素化過程ではなくメタル化の段階に必要であることを強く示唆している。

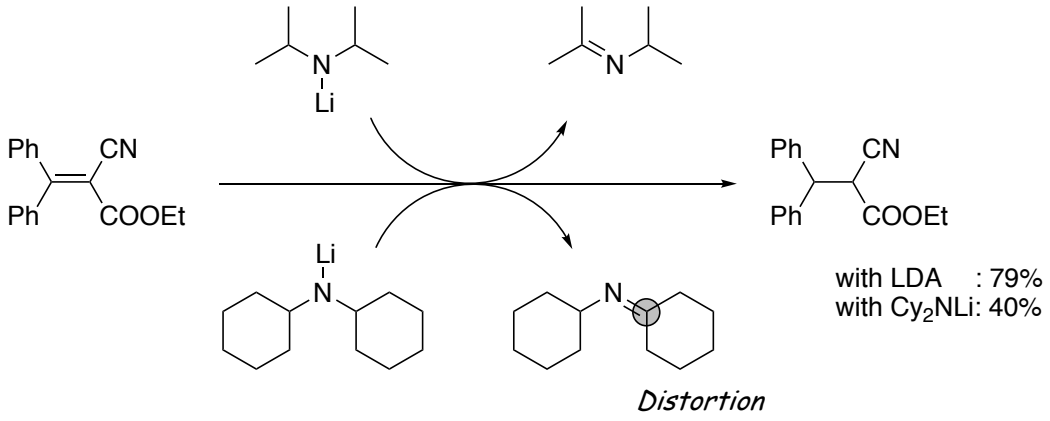
Scheme 4-1. Control Experiment: Iodination of Cyanide-Free Arylargentate



次に、銀源を AgCN に固定して、アミド配位子を検討した。まず、より塩基性の低い LHMDS から調製したアート型銀塩基を用いた場合には反応は進行しなかった（entry 8）。LDA を用いた場合には、メタル化は低収率に留まった（entry 9）。その理由の一つとして、イソプロピル基の α 水素のヒドリド脱離が考えられる [2-13]。一方で、dicyclohexylamine[‡‡] から調製した $(Cy_2N)_2Ag(CN)Li_2$ は定量的に目的物を与えた。ジイソプロピルアミドと比較してジシクロヘキシルアミドでは、ヒドリド脱離で生じるイミンのより大きな分子歪みのために副反応が進行しづらく、結果として目的の D*o*M が優先し、円滑に進行したと考えられる（Figure 4-3）[2-13b]。

‡‡ Dicyclohexylamine（Cy_2NH）は TMPH よりも安価であるため合成上有用な知見である：Cy_2NH（1,600 円 / 25 mL）vs TMPH（12,000 円 / 25 mL）@ 富士フイルム和光純薬株式会社 2020 年 1 月 1 日現在

Figure 4-3. Hydride Transfer from Lithium Amides by Feit



アルキル配位子とアミド配位子を有する非対称なアート型塩基 $Me(TMP)Ag(CN)Li_2$ を検討したが、目的物は全く得られなかった（entry 11）。

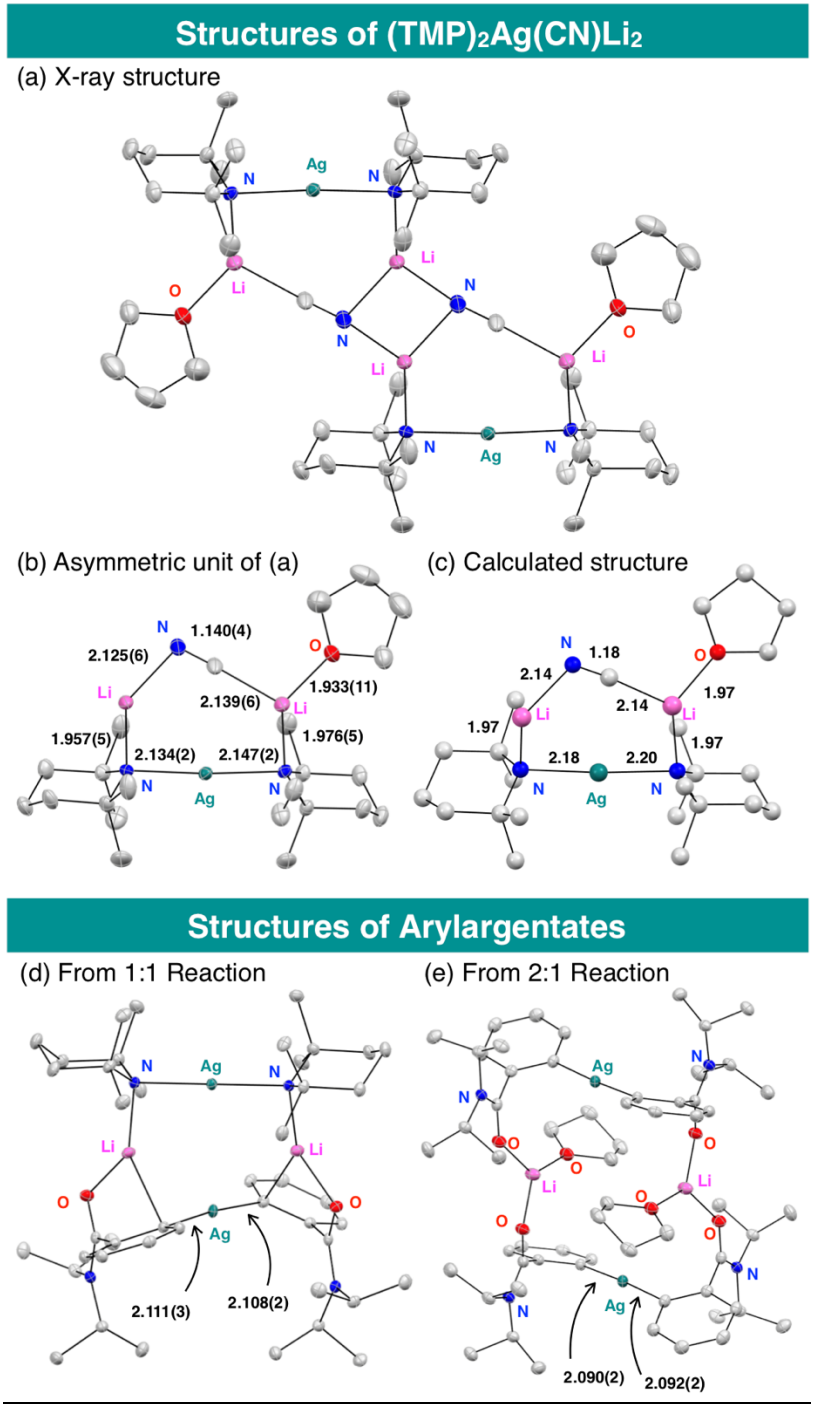
溶媒検討の結果、THF が最も良い収率を与え（entry 6 vs entries 12-15）、THF 中、自然光や蛍光灯に暴露しても反応は遜色なく進行することがわかった（entry 16）。

以上のことから、entry 16 を D*o*M の最適条件とした。

今回新たに設計した銀アミドアート型塩基 $(TMP)_2Ag(CN)Li_2$ の単結晶 X 線結晶構造解析を行ったところ、2 つの TMP が銀中心に対してほぼ直線型（176°）に配位し、Li がシアニドによって架橋された Lipshutz 型の構造をとることがわかった（Figure 4-4）。また、結晶構造の結合長や結合角は DFT 計算により得た構造とも良い一致を示した。

さらに、反応後の混合物からアリール銀アート種の単結晶を得ることもできたため、これらについても X 線結晶構造解析を行った。*N*,*N*-Diisopropylbenzamide と当量の $(TMP)_2Ag(CN)Li_2$ より得られた結晶は予想外にもジアリール銀アート錯体（Ar_2AgLi）とビス TMP 銀アート錯体（$(TMP)_2AgLi$）の 1：1 複合体であることがわかった。これは、メタル化の後に不均化が進行したためであると考えられる。*N*,*N*-Diisopropylbenzamide と $(TMP)_2Ag(CN)Li_2$ を 2：1 の比率で反応させると Gilman 型のジアリール銀アート種が得られた。得られた錯体の炭素–銀結合の長さは、van Koten らが報告したジアリール銀アート化合物とも良い一致を示した（2.117(3) and 2.127(3)Å）[4-5g]。

Figure 4-4. X-ray and Calculated Structures of Argentates



(a) Crystal structure of $[(TMP)_2Ag(CN)Li_2(THF)]_2$; (b) the asymmetric unit (monomer) from (a); (c) the asymmetric unit extracted from the structure of $[(TMP)_2Ag(CN)Li_2(THF)]_2$ calculated at the M06/6-31+G*&LanL2DZ(Ag) level; (d) crystal structure of a diarylargentate adduct obtained by 1 : 1 reaction of *N*,*N*-diisopropylbenzamide and $(TMP)_2Ag(CN)Li_2$ and (e) of a diarylargentate dimer from the 2 : 1 reaction of *N*,*N*-diisopropylbenzamide and $(TMP)_2Ag(CN)Li_2$. All atomic displacement parameters in crystal structures shown at 30% probability, with H atoms (and THF disorder in (a and b)) omitted. Selected bond lengths in Å.

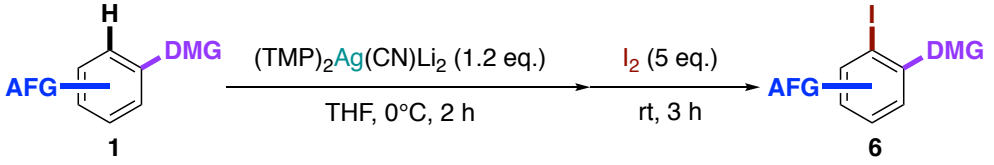
4-3 基質一般性の検討

最適条件下（Table 4-1, entry 16）、銀アミドアート型塩基を用いた D*o*M によって種々の芳香環のメタル化を試みた（Table 4-2）。

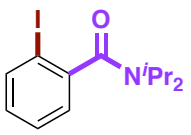
まず、配向基の検討を行った。*N*,*N*-ジイソプロピルアミド基以外にも、より嵩低いジエチルアミドやモルホリンアミドを配向基として用いることができた（**6b** and **6c**）。シアノ基も求核攻撃を受けることなく、オルトメタル化が高収率にて進行した（**6d**）。種々のエステルも配向基として用いることが可能だった（**6e**-**6i**）。特に、リチオ化反応では縮合反応が進行する安息香酸メチルを基質として用いてもヨウ素化体を高収率で得られたことは本反応の高い官能基許容性を如実に示す結果である（**6h**）[1-13]。また同様に、求核攻撃を受けやすいラクトンも開環することなくメタル化が定量的に進行した（**6i**）。アリールケトンのオルトヨウ素化も可能であった（**6j**）。さらに、フッ素系官能基も配向基として用いることが可能であり、α,α,α-トリフルオロトルエンを中程度のオルト選択性（*ortho* : meta : *para* = 78 : 15 : 7）で得ることができた（**6k**）[4-12]。SF_5 基を有する芳香環は完全なオルト選択性でメタル化が進行した（**6l**）[§§]。最適化の余地はあるものの、本結果は SF_5 ベンゼン類の初めての D*o*M であり、「スーパー CF_3 基」とも呼ばれ、医薬品などの機能性分子として大きな注目を集める SF_5 含有芳香族化合物の誘導体化における強力な方法論となることが期待される[4-13]。

[§§] $PhCF_3$ および $PhSF_5$ のメタル化により生じるアリール銀アート種の NBO 解析から、$PhCF_3$ では中程度の Li–F 相互作用（6.1 kcal/mol）、$PhSF_5$ では強力な Li–F 相互作用（10.2 kcal/mol）がみられた。

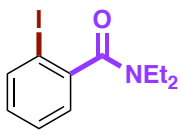
Table 4-2. Directed *ortho* Argentation



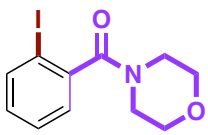
• **Directed Metalation Group**



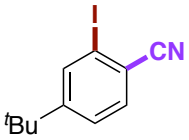
6a: 92%



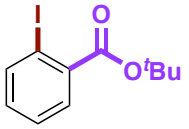
6b: 98%



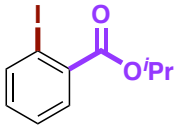
6c: 48%[a]



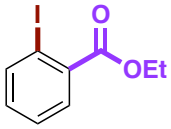
6d: 95%



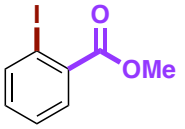
6e: 92%



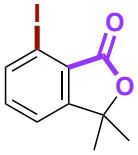
6f: 90%



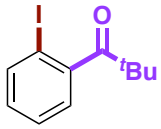
6g: 93%[a]



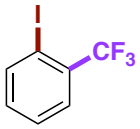
6h: 86%[a]



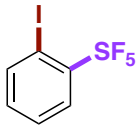
6i: 99%[a]



6j: 85% (96%)

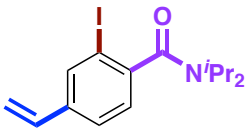


6k: (56%)[b]

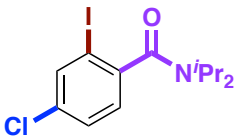


6l: (14%)

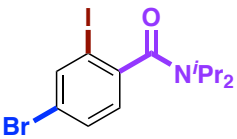
• **Ancillary Functional Group**



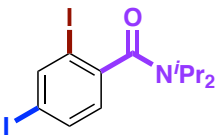
6m: 86%[a]



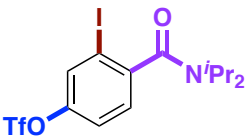
6n: 95%[a,c]



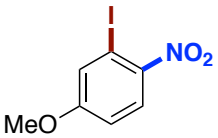
6o: 98%[a,c]



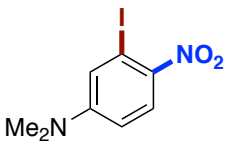
6p: 97%[a]



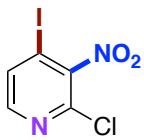
6q: 43%[a,d]



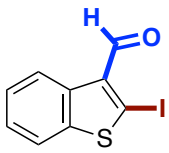
6r: 80%[a]



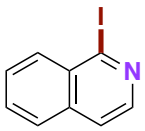
6s: 81%[a]



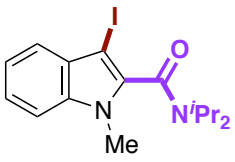
6t: 90%[a]



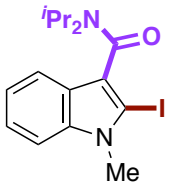
6u: 87%[a]



6v: 81%

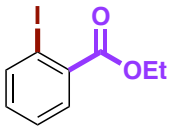


6w: 79%

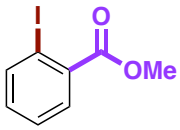


6x: 99%

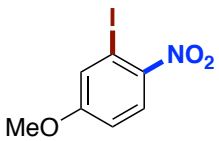
cf. Cupration using (TMP)$_2$Cu(CN)Li$_2$



6g: (37%)[a]



6h: (29%)[a]



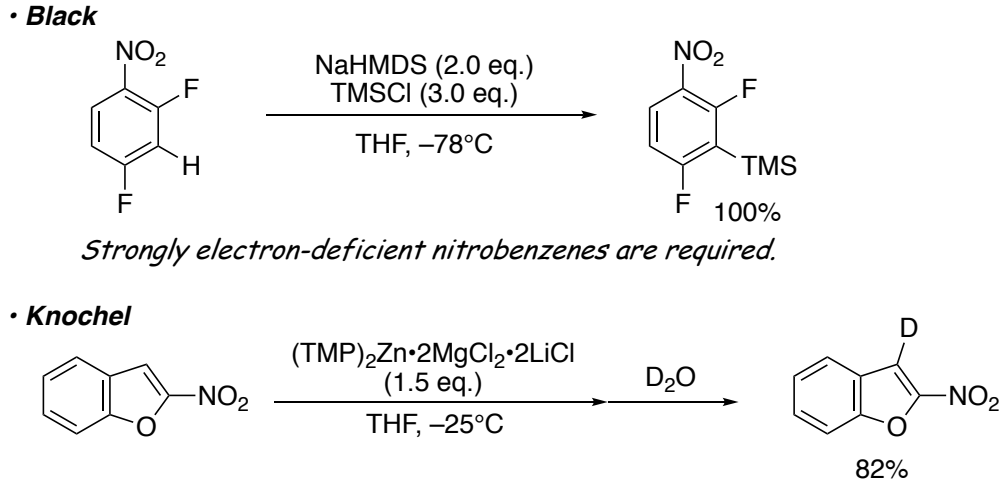
6r: (6%)[a]

Isolated yields. NMR yields in parentheses, based on mesitylene as an internal standard. [a] Argentation at –40°C. [b] *ortho* : *meta* : *para* = 78 : 15 : 7. [c] *ortho* : *meta* = >29 : 1. [d] *ortho* : *meta* = 16 : 1.

次に、官能基許容性についても検討した。スチレン構造を有する基質を用いても、ポリマーなどの副生成物を生じることなく高収率にて目的物が得られた（**6m**）。また、(擬)ハロゲン（Cl、Br、I、TfO）を有する基質についても円滑に反応が進行した（**6n-6q**）。特に、TfO 基を有する基質の D*o*M 反応は筆者の知る限り初めての例である（**6q**）。

さらに、本手法の極めて高い官能基許容性はニトロベンゼン類のメタル化を可能にした（**6r-6t**）。ニトロ基は有機金属種によって容易に求核的あるいは還元的に分解されるため[4-14]、ニトロベンゼン類のメタル化による官能基化反応は極めて限定的である（Scheme 4-2）[4-15]。

Scheme 4-2. Limited Scope of Metalation of Nitrobenzenes



さらに、アルデヒドのメタル化も可能であり（**6u**）[4-15b,c,16]、イソキノリンやインドールといったヘテロ芳香環も高収率でメタル化することができた（**6v-6x**）。

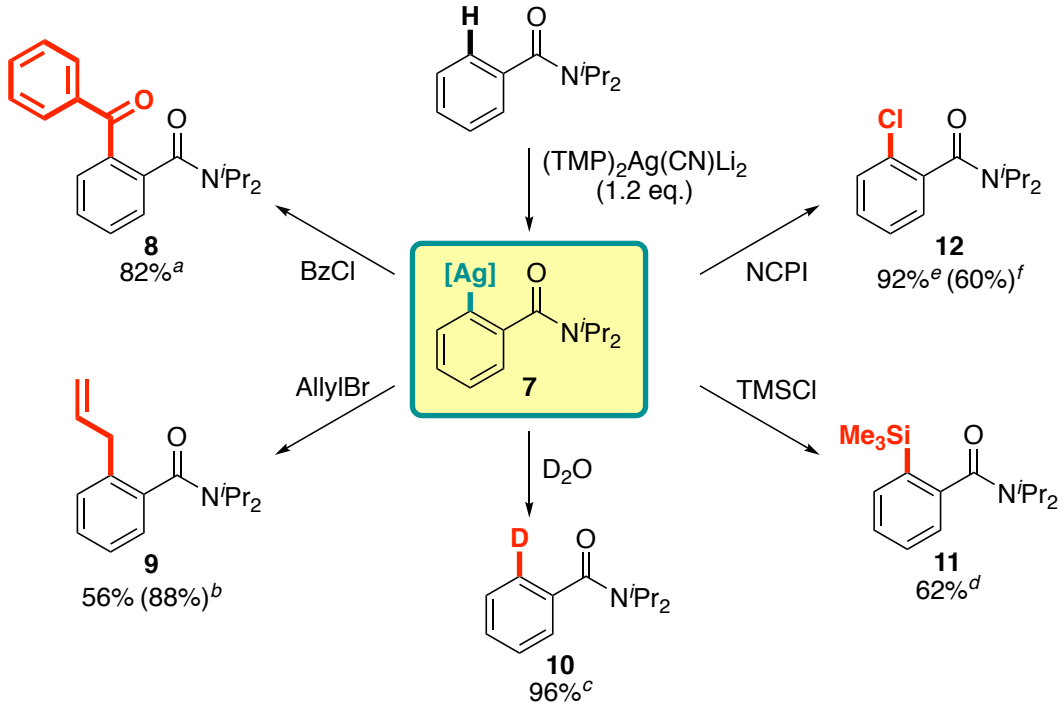
同族の銅アミドアート塩基 $(TMP)_2Cu(CN)Li_2$ による立体的に嵩低いエチルエステルやメチルエステルを有する基質のメタル化は低収率に留まった（**6g** and **6h**）。また、ニトロベンゼンの D*o*M では、痕跡料のヨウ素化体とともに、ニトロ基による銅の酸化に起因するビアリール生成がみられるなど、複雑な混合物が得られた（**6r**）。

以上のように、銀アミドアート型塩基 $(TMP)_2Ag(CN)Li_2$ は極めて高い官能基許容性にて D*o*M を進行させることがわかった。

続いて、生じるアリール銀アート種 **7** の反応性を精査した。

Benzoyl chloride（**8**）や allyl bromide（**9**）、D_2O（**10**）、trimethylsilyl chloride（TMSCl: **11**）[4-17]、*N*-chlorophthalimide（NCPI: **12**）との反応は高収率にて進行した（Scheme 4-3）。一方、アリール銅アート種を用いて NCPI との反応を行ったところ、クロロ化体 **12** が 60%、酸化によるビアリール体が 35% の NMR 収率で得られ、ここでもアリール銀アート種 **7** の高い化学選択性・酸化耐性がみられた。

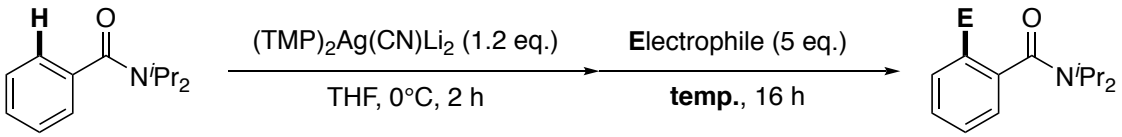
Scheme 4-3. Reaction Scope of Arylargentate **7**



Isolated yields. D*o*M was conducted with $(TMP)_2Ag(CN)Li_2$ (1.2 eq.), 0°C, 2 h. [a] BzCl (3.5 eq.), 80°C, 16 h. [b] AllylBr (5.0 eq.), 80°C, 16 h.; NMR yield in parentheses. [c] D_2O (55 eq.), rt, 16 h.; D/H = 97/3. [d] TMSCl (5.0 eq.), 80°C, 16 h. [e] D*o*M for 0.5 h.; NCPI (3.0 eq.), rt, 1 h. [f] NMR yield when using $(TMP)_2Cu(CN)Li_2$ instead of Ag-base. Bz: Benzoyl. TMS: Trimethylsilyl. NCPI: *N*-Chlorophthalimide.

一方で、benzyl bromide や iodomethane、benzaldehyde、cyclohexenone との反応はほとんど、あるいは全く進行しなかった（Table 4-3）。また、**7** を求核剤として用いた Pd および Ni 触媒によるクロスカップリング反応は現在のところ実現しておらず、今後の課題である[4-5l-n]。

Table 4-3. Electrophiles Unreactive to Arylargentate



entry	Electrophile	temp.	yield (%)
1	Benzyl bromide	80°C	(14)
2	Iodomethane	80°C	trace
3	Benzaldehyde	rt	ND
4	2-Cyclohexen-1-one	80°C	ND

NMR yields based on mesitylene as an internal standard. Isolated yield in parentheses. ND: Not detected.

4-5 ジスルフィドとの反応

アリール銀アート種 **7** は、ジスルフィドと温和な条件下、効率よく反応することを見出した。ジアリールスルフィドは、医薬品や天然物化学において重要な構造である[4-18]。これらはアリールリチウム試薬[4-19]やマグネシウム試薬[4-20]とジスルフィドとの反応によっても合成することができるが、それらの高い塩基性・求核性のために分子デザインは限定的である[4-21]。これに対して、極めて官能基許容性の高い本 D*o*M を用いることで、より多彩なジアリールスルフィドの合成が可能になると考え、基質一般性の検討を行った（Table 4-4）。なお、D*o*M が 30 分で完結することがわかったため、以降ではこの条件を用いた。

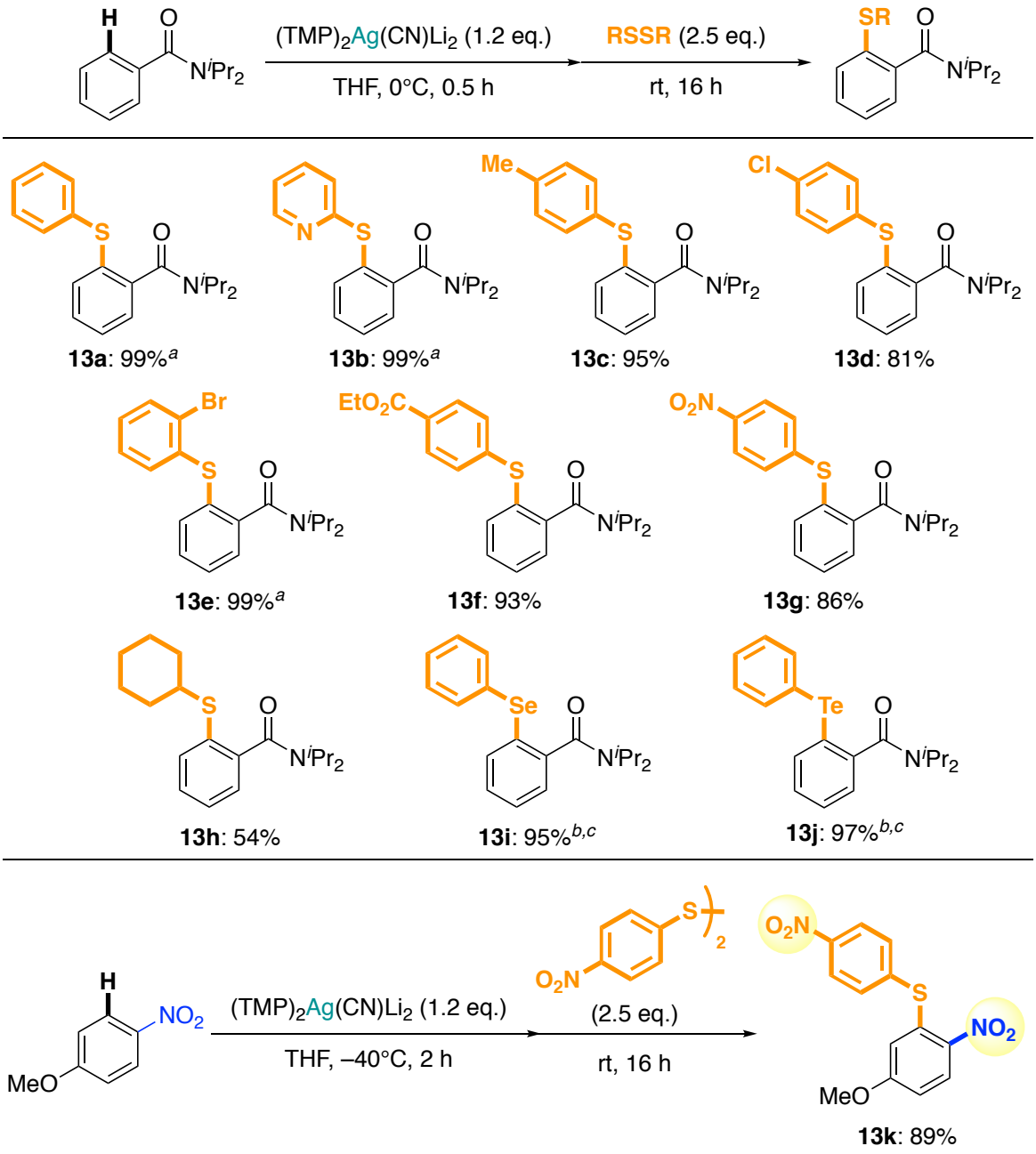
Diphenyl disulfide や 2,2'-dipyridyl disulfide を用いることで定量的に非対称ジアリールスルフィドが得られた（**13a** and **13b**）。これらの反応は室温でも円滑に進行するが、痕跡量の *N*,*N*-diisopropylbenzamide をシリカゲルカラムクロマトグラフィーで分離することが困難であったため、完全に原料が消費されるように反応温度を 40°C まで昇温した。

ベンジル位水素や塩素だけでなく、より高反応性の臭素やエステル、ニトロ基を有するジスルフィドを用いても、これらを損壊することなく目的物が高収率で得られた（**13c**-**13g**）。

さらに、本手法のニトロ基との互換性を活かして 4-methoxynitrobenzene と bis(4-nitrophenyl) disulfide を基質とすることで、両方の芳香環にニトロ基を有するジアリールスルフィドを高収率で合成することも可能であった（**13k**）。

また、ジスルフィドの置換基はアリールに限らず、アルキル置換体も反応活性であった（**13h**）。同族のセレンやテルルの導入も可能であり（**13i** and **13j**）[4-22]、本 D*o*M がその高い官能基許容性により、多様なジアリールカルコゲン化合物の合成に有効であることを示した。

Table 4-4. Chalcogen Introduction



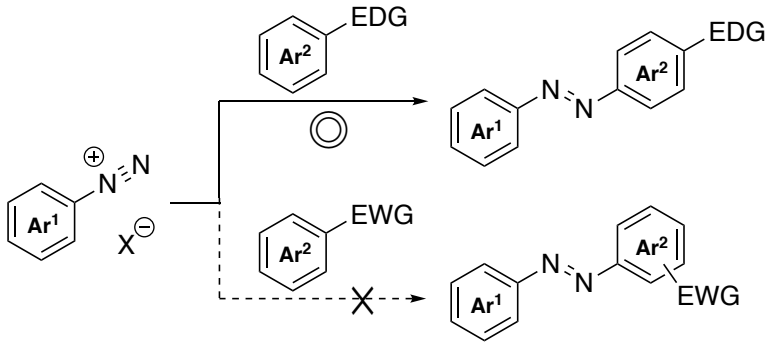
Isolated yields. [a] 40°C. [b] 80°C. [c] Chalcogen source (5.0 eq.).

4-6 ジアゾニウム塩との反応

続いて、ジアゾニウム塩との反応による多官能基化された非対称アゾ化合物の合成へと展開した。

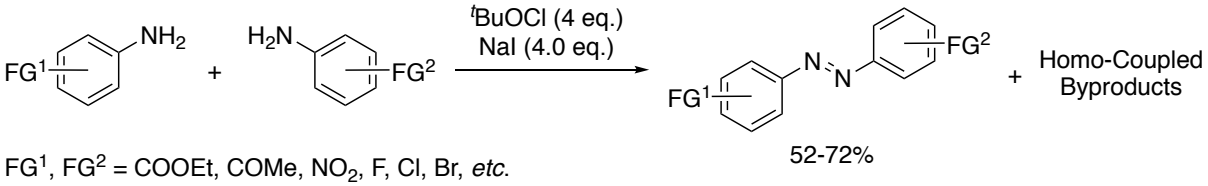
通常のアゾカップリングでは、ジアゾニウム塩による電子豊富な芳香環の芳香族求電子置換反応によってアゾ化合物が合成されるが[4-23]、電子不足な芳香環を用いた場合には反応は進行しない（Scheme 4-4）。

Scheme 4-4. Azo Coupling *via* S_EAr



近年南方らは、^{t}BuOCl と NaI の組み合わせによるアニリンの酸化的クロスカップリング反応が、両端に電子不足な芳香環を有する非対称アゾ化合物の合成にも適用できることを報告しているが、本手法では対称アゾ化合物の副生が伴う（Scheme 4-5）[4-24]。

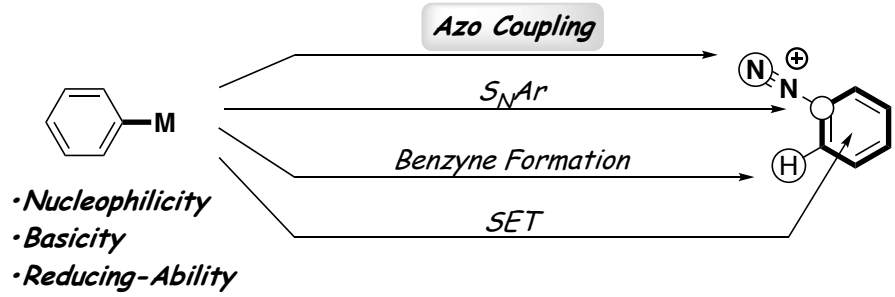
Scheme 4-5. Synthesis of Azo Compounds *via* Oxidative Cross-Coupling of Anilines by Minakata



FG^1, FG^2 = COOEt, COMe, NO_2, F, Cl, Br, *etc.*

対称アゾ化合物の副生のない、より一般性の高いアゾ化合物の合成には、有機金属求核剤とジアゾニウム塩との反応が理想的である。しかしながら、一般に高活性な有機金属試薬は求核性・塩基性・還元性を示すため、ジアゾニウム塩との反応では、アゾカップリングのみならず芳香族求核置換反応、ベンザインの生成、一電子移動によるラジカル反応といった複数の副反応が同時に進行しうることから、化学選択的なアゾ化合物の合成は困難である（Figure 4-5）。

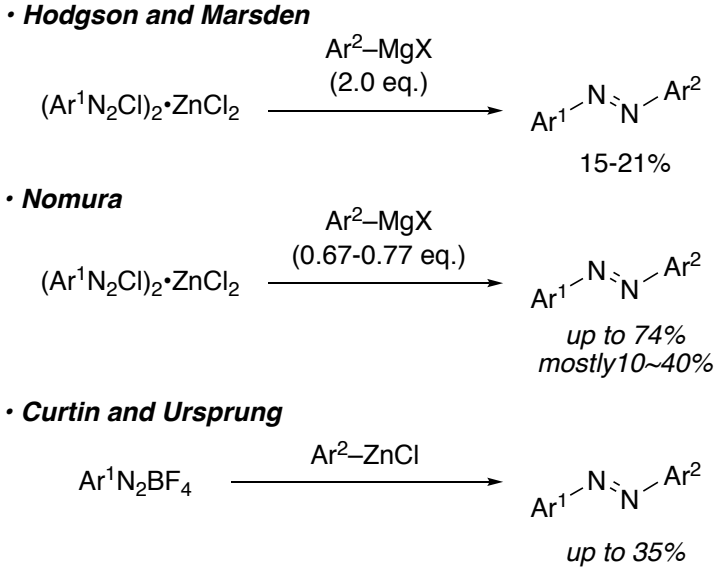
Figure 4-5. Reactivity of Diazonium with Organometallic Species



Hodgson と Marsden は、ジアゾニウム塩の塩化亜鉛付加物[***]に対して 2 当量の Grignard 試薬を作用させると 15-21% のアゾ化合物が得られることを報告している [4-25]。その後、野村らは、Grignard 試薬の当量を制御することで生成したアゾ化合物の還元を防ぎ、収率の改善に成功したが、依然として一般に低収率であった [4-26]。

Curtin と Ursprung は、Hodgson らの結果を受けて、C–N 結合形成における亜鉛の重要性を指摘した [4-27]。すなわち、Grignard 試薬の代わりにアリール亜鉛試薬を用い、ジアゾニウムテトラフルオロボラート塩との反応により収率の改善に成功した（Figure 4-6）。一方、ジアゾニウムテトラフルオロボラート塩と Grignard 試薬あるいはリチウム試薬との反応は複雑化し、アゾ化合物は得られない。

Figure 4-6. Low Yields of Azo Compounds by Reaction of Diazonium Salts and Arylmetals



[***] Hodgson と Marsden によると、ジアゾニウム塩の塩化亜鉛付加物は乾燥しても長時間安定であり、このような禁水条件に適している。

こうした背景のもと、筆者のアリール銀アート種とジアゾニウム塩との反応を検討したところ、目的のアゾカップリングが選択的に進行し、非対称ジアリールアゾ化合物が効率よく得られた（Table 4-5）。なお、本アゾカップリング反応は、室温下 5 分で完結することを確認しているが、シス体とトランス体の混合物として得られるため、80°C にて全てトランス型に異性化させた後に精製操作を行った。

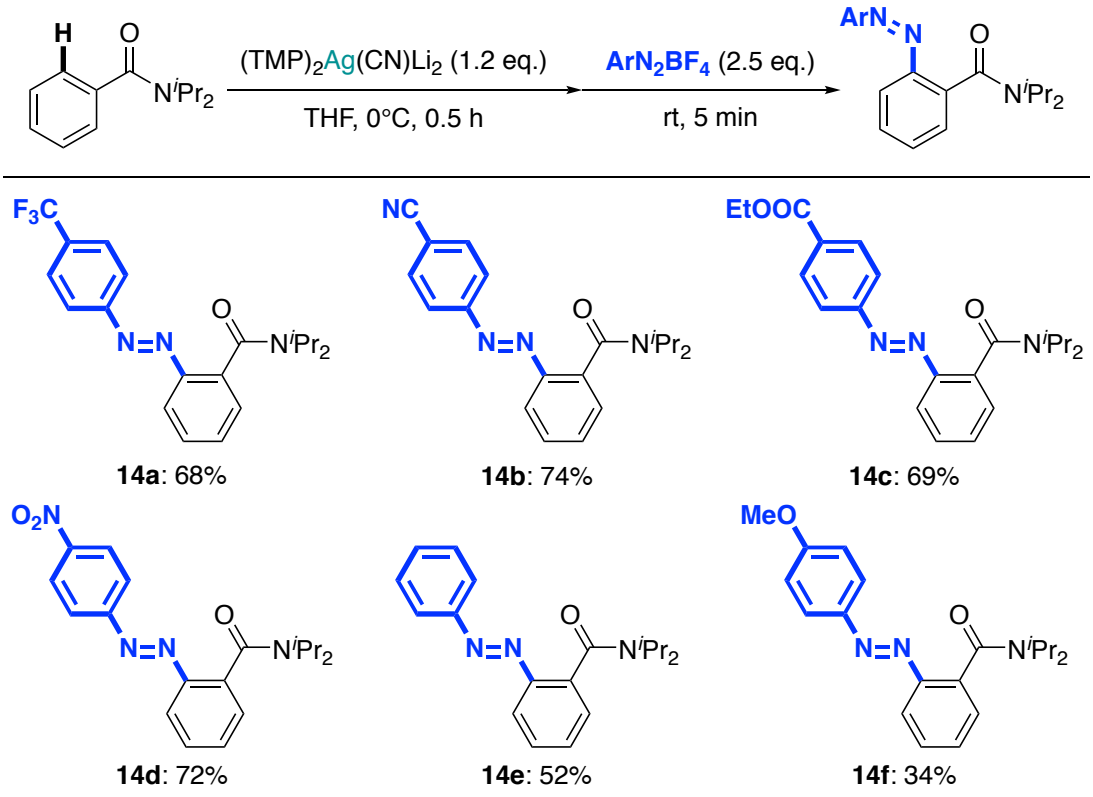
銀を基盤とした本 D*o*M を用いることで、トリフルオロメチル基のみならず、シアノ基やエステル基、さらにはニトロ基といった、いずれも強力な電子求引性基であり有機金属種との共存が困難な官能基を有する非対称ジアリールアゾ化合物を合成できた（**14a-14d**）。先に述べたように、このような電子不足な芳香環を両端に有するアゾ化合物は、芳香族求電子置換反応による一般的なアゾカップリングでは合成が困難である。

電子求引性基を持たないアリールジアゾニウム塩を用いても、中程度ながら目的の非対称アゾ化合物を得ることができた（**14e** and **14f**）。特に、4-methoxybenzenediazonium tetrafluoroborate を用いた際、反応後の GCMS 解析にてわずかながら anisole が検出されたことから、一電子移動反応によるジアゾニウム塩の脱窒素化反応の併発が示唆された。電子豊富なアリールジアゾニウム塩を用いた場合には、アゾカップリングの反応速度が一電子移動に対して相対的に遅くなったことが原因であると考えられる。

また、$(TMP)_2Cu(CN)Li_2$ から調製したアリール銅アート種を用いて同様の反応を行ったところ、アゾ化合物に加えて、銅中心の酸化反応によるビアリール体が 50% 前後の収率で得られることがわかり（Scheme 4-6）、銀の特異な反応性が改めて示された。

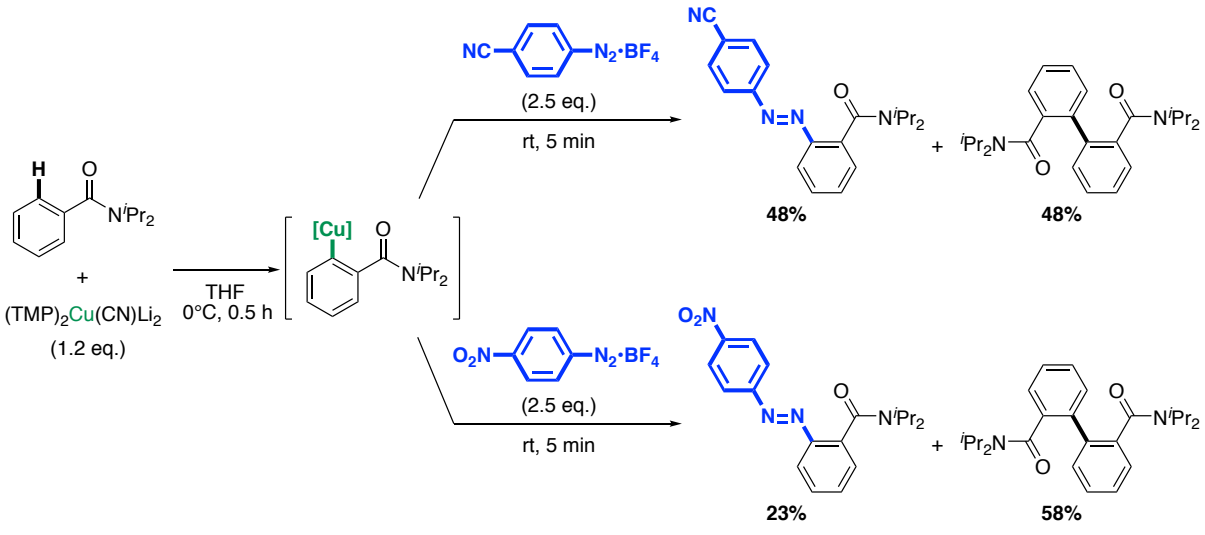
以上のように、銀の特性を活かすことでこれまで合成が困難であったアゾ化合物群を簡便かつ高収率にて合成する手法を開発した。

Table 4-5. Synthesis of Azo Compounds



Isolated yields. Azo compounds were isomerized to their *trans* form at 80°C for 16 h.

Scheme 4-6. Reaction of Arylcuprate and Diazonium Tetrafluoroborates



NMR yields based on mesitylene as an internal standard. Azo compounds were isomerized to their *trans* form at 80°C for 16 h.

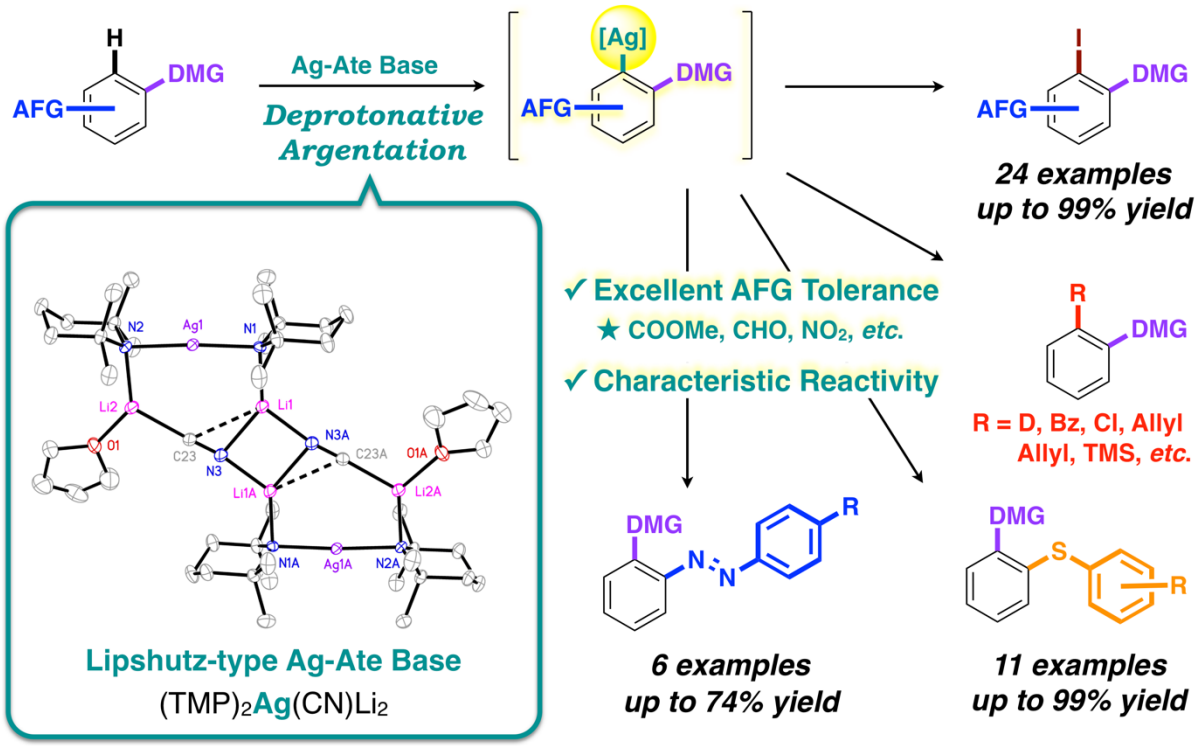
4-7 小括

これまでの DoM にはない反応性や選択性の開拓を目指して、新たに銀アミドアート型塩基 $(TMP)_2Ag(CN)Li_2$ を設計した。本塩基を用いることで、様々な（ヘテロ）芳香環を極めて高い官能基許容性にて効率よくオルトメタル化することができた。特に、メチルエステルやアルデヒドなどの極めて求核攻撃を受けやすい官能基や、通常は有機金属種に対して強力な酸化剤・求電子剤として振る舞うニトロ基を有する基質を用いても、これらを損なうことなく効率よく反応が進行することは本 DoM の大きな特徴である。また、$(TMP)_2Ag(CN)Li_2$ が Lipshutz 型の構造をとることを X 線結晶構造解析によって明らかにした。

さらに、生じる芳香族銀アート中間体と求電子剤との反応を精査し、その特異な反応性と選択性を見出した。中でも、求電子剤としても酸化剤としても振る舞うジアゾニウム塩との反応が円滑に進行し、他の方法では合成することが難しいアゾ化合物を高い化学選択性にて合成することができたことは、銀の特性を顕著に表している。今後の検討によって銀の特性を活かした新たな変換反応へとさらに展開したい。

以上のように、銀アミドアート型塩基による DoM を開発したことによって、これまで全くの未開であった芳香族銀アート種の化学に新たな道筋を示した。本研究業績は、*Chemical Science* 誌に発表した。

Noriyuki Tezuka,* Keiichi Hirano,* Andrew J. Peel, Andrew E. H. Wheatley, Kazunori Miyamoto and Masanobu Uchiyama* *Chem. Sci.* **2020**, *11*, 1855–1861.



第五章
総括

筆者は、11 族金属の銅と銀を中心金属とするアミドアート型塩基を設計し、これらを用いた Directed *ortho* Metalation（D*o*M）および生じるアリールメタル種の反応性を精査することで、新たな芳香環の官能基化反応を開発した。

第二章では、銅の酸化還元能に着目し、銅アミドアート型塩基 $(TMP)_2Cu(CN)Li_2$ を用いた「D*o*M + 酸化反応」という新たな反応設計によって、高位置・化学選択的な芳香環の直接的水酸化およびアミノ化反応によるフェノールやアニリン誘導体の新規合成法を開発した。これらの化合物は、従来の「D*o*M + 求核付加/置換反応」では合成困難であった。理論と実験を両輪として、本反応が銅の酸化還元（I → III → I）を鍵とすることを明らかにし、これをもとに触媒量の銅を用いた水酸化・アミノ化反応へと展開した。

Noriyuki Tezuka *et al*. *J*. *Am*. *Chem*. *Soc*. **2016**, *138*, 9166–9171.

第三章では、銅アート中間体の酸化還元を活かした新たな展開として、$(TMP)_2Cu(CN)Li_2$ を用いた「異なる 2 種の芳香環の逐次的な D*o*M」と「生じる非対称ジアリール銅アート中間体の酸化反応」を精密に設計することで、芳香族 C–H 結合同士の形式的脱水素型クロスカップリング反応を開発した。従来の手法とは異なり、基質の当量関係や電子状態に大きな偏りを設ける必要がないことが特徴である。本手法は、一般に困難で報告例に乏しい「電子不足な芳香環同士」のクロスカップリング反応をも可能とする強力な方法論である。また、電子豊富な芳香環の組み合わせによる様々な非対称ビアリールの合成にも適用可能である。

Noriyuki Tezuka *et al*. *Org*. *Lett*. **2019**, *21*, 9536–9540.

第四章では、未開の銀の化学に着目した。新たに銀アミドアート型塩基 $(TMP)_2Ag(CN)Li_2$ を設計し、本塩基を用いた D*o*M が極めて高い官能基許容性を示すことを見出した。また、X 線結晶構造解析から、本塩基が Lipshutz 型の構造を取ることを明らかにした。メタル化によって生じる芳香族銀アート中間体の反応性を精査し、その特異な反応性・選択性を見出した。特に、多様な反応性を有するジアゾニウム塩との反応ではアゾカップリングが選択的に進行し、他の方法では合成することが難しいアゾ化合物を高化学選択的かつ高収率にて与えることは、銀の特異な反応性を顕著に表している。

Noriyuki Tezuka *et al*. *Chem*. *Sci*. **2020**, *11*, 1855–1861.

以上のように筆者は、元素の特性を巧みに活用することで D*o*M を新たな展開に導いた。本研究にて設計・開発した活性種の反応性や、新たに合成を可能にした化合物群が、今後の有機合成化学・医農薬化学・材料化学など幅広い分野の発展に資することを願う。

第六章
実験項

6-1 General

Instrumentation.

NMR spectra were obtained on a Bruker AVANCE III HD 500 spectrometer and a Bruker Ascend 400 spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). ^{1}H and ^{13}C NMR spectra were referenced to tetramethylsilane, $CDCl_3$, $(CD_3)_2SO$ or C_6D_6. For ^{7}Li, an external reference was used (1 M LiCl in D_2O). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet, brs = broad singlet, brd = broad doublet, brq = broad quartet and br = broad peak. Automated medium pressure liquid chromatography (MPLC) system (YAMAZEN Parallel Frac FR-260 with PUMP 580D and UV-10VW, or YAMAZEN EPCLC-Wprep2XY-10VHM) and recycling gel permeation chromatography (GPC) system (JAI LC-9201 HPLC with JAIGEL 1H, JAI LC-5060 HPLC with JAIGEL 2HR or JAI LC-9210 II HPLC with JAIGEL 2HR, mobile phase: $CHCl_3$) were used for purification of products. IR spectra were obtained on a METLER TOLEDO ReactIR 4000 and a JASCO FT/IR-4700 spectrophotometer or (for air-sensitive argentates) as a nujol mull using NaCl plates on a Bruker Alpha spectrophotometer. Melting points were determined with an SRS MPA 100 OptiMelt automated melting point system, a Yanaco micro melting point apparatus or a Griffin melting point apparatus and were uncorrected. Compositions were established for C, H and N with a Perkin Elmer 240 elemental analyser. EI-MS spectra were obtained by GC-MS using either an Agilent 7890A/5975C or 7890B/5977A spectrometers. HRMS spectra were measured by ESI-MS using a Bruker micrOTOF-II spectrometer.

X-ray data of biaryls $\mathbf{4i_{major}}$, $\mathbf{4i_{minor}}$ and $\mathbf{4j_{major}}$ were collected on a Rigaku XtaLAB Synergy-S (Cu-K_α, λ = 1.54184 Å). For X-ray data of argentates, the minimum contact with the air was needed. The sample of cyanoargentate $(TMP)_2Ag(CN)Li_2(THF)$ was transported to a microscope in a bath of anti-freeze, which was pre-chilled to –27°C, and samples of two kinds of arylargentates were manipulated in a glove box at room temperature. Crystals were transferred quickly using a spatula to a drop of perfluoropolyether oil on a microscope slide. A stream of cold nitrogen (~ 0°C) was passed over the slide whilst a suitable crystal of cyanoargentate $(TMP)_2Ag(CN)Li_2(THF)$ was selected. The crystal was transferred to a pin fitted with a MicroLoop™ and attached quickly to the goniometer head. Data for cyanoargentate $(TMP)_2Ag(CN)Li_2(THF)$ was collected on a Bruker D8 Quest diffractometer (Cu-K_α, λ = 1.54184 Å) and data for two kinds of arylargentates were collected on a Rigaku XtaLAB Synergy-S (Cu-K_α, λ = 1.54184 Å). Structures were solved with the program SHELXT[6-1] with refinement, based on F^2, by full-matrix least squares refinement[6-2]. Non-hydrogen atoms were refined anisotropically (for disorder, standard restraints and constraints were applied, as appropriate) and a riding model, with idealized geometry was employed for H-atoms. X-ray data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 1959872, 1959875, 1959876, 1919739, 1957572 and 1960037. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Materials.

Unless otherwise noted, materials were purchased from Wako Pure Chemical Industries, Ltd., Tokyo Chemical Industry Co., Ltd., Sigma-Aldrich Co., LLC., Kishida Chemical Co., Ltd. and other commercial suppliers. ^{n}BuLi in ^{n}hexane and ^{t}BuLi in ^{n}pentane, MeLi in Et_2O were obtained from Kanto Chemical Co., Inc. Anhydrous THF was purchased from Kanto Chemical Co., Inc. Chemicals were of reagent grade and used as received, except for TMP-argentate syntheses for X-ray analysis where solvents were freshly distilled from Na/K amalgam (toluene) or Na (THF, hexane). Air- and moisture-sensitive manipulations were performed with standard Schlenk techniques under argon atmosphere. Normal-phase column chromatography was performed with silica gel 60 (230–400 mesh) from Merck and thin-layer chromatography was carried out on 0.25 mm Merck silica gel plates (60 F_{254}). Preparative thin-layer chromatography (PTLC) was performed with 0.5 mm Merck silica gel plates (60 F_{254}).

Preparation of Cuprates

Preparation of LiTMP in THF (1.0 mmol scale)

To a solution of 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in 1 mL of anhydrous THF was added ^{n}BuLi (2.53 M ^{n}hexane solution, 0.40 mL, 1.0 mmol) at –78°C under Ar. The mixture was stirred for 30 min at 0°C to give the solution of LiTMP (lithium 2,2,6,6-tetramethylpiperidide) in THF.

Preparation of $(TMP)_2Cu(CN)Li_2$ in THF (1.0 mmol scale)

To a suspension of copper cyanide (89.6 mg, 1.0 mmol) in 2 mL of anhydrous THF was added the prepared solution of LiTMP in THF (2.0 mmol) at –78°C under Ar. The mixture was stirred at 0°C for 30 min to give the solution of $(TMP)_2CuCNLi_2$ in THF.

Preparation of $(^{i}Pr_2N)_2Cu(CN)Li_2$ in THF (1.0 mmol scale)

To a solution of diisopropylamine (0.28 mL, 2.0 mmol) in 2 mL of anhydrous THF was added ^{n}BuLi (2.53 M ^{n}hexane solution, 0.79 mL, 2.0 mmol) at –78°C under Ar. The mixture was stirred for 30 min at 0°C to give the solution of LDA in THF. To a suspension of copper cyanide (89.6 mg, 1.0 mmol) in 2 mL of anhydrous THF was added the solution of LDA in THF (2.0 mmol) at –78°C under Ar, and the reaction mixture was stirred at 0°C for 30 min to give the solution of $(^{i}Pr_2N)_2Cu(CN)Li_2$ in THF.

Preparation of ^{n}BuCu(TMP)(CN)Li$_2$ in THF (1.0 mmol scale)

To a suspension of copper cyanide (89.6 mg, 1.0 mmol) in 2 mL of anhydrous THF was added ^{n}BuLi (2.53 M ^{n}hexane solution, 0.40 mL, 1.0 mmol) at –78°C under Ar. The mixture was stirred at 0°C for 30 min to give a solution of ^{n}BuCu(CN)Li in THF. To the prepared ^{n}BuCu(CN)Li solution was added the LiTMP solution (1.0 mmol) at –78°C under Ar, and the reaction mixture was stirred at 0°C for 30 min to give the solution of ^{n}BuCu(TMP)(CN)Li$_2$ in THF.

Preparation of ^{t}BuCu(TMP)(CN)Li$_2$ in THF Solution (1.0 mmol scale)

To a suspension of copper cyanide (89.6 mg, 1.0 mmol) in 2 mL of anhydrous THF was added ^{t}BuLi (1.50 M ^{n}pentane solution, 0.67 mL, 1.0 mmol) at –78°C under Ar. The mixture was stirred at 0°C for 30 min to give the solution of ^{t}BuCu(CN)Li in THF. To the prepared ^{t}BuCu(CN)Li solution was added the LiTMP solution (1.0 mmol) at –78°C under Ar, and the reaction mixture was stirred at 0°C for 30 min to give the solution of ^{t}BuCu(TMP)(CN)Li$_2$ in THF.

Preparation of $(HMDS)_2Cu(CN)Li_2$ in THF (1.0 mmol scale)

To a suspension of copper cyanide (89.6 mg, 1.0 mmol) in 2 mL of anhydrous THF was added LiHMDS (1.00 M, 1.00 mL, 1.0 mmol) at –78°C under Ar. The mixture was stirred at 0°C for 30 min to give the solution of $(HMDS)_2Cu(CN)Li_2$ in THF.

Preparation of $^{t}Bu_2Zn(TMP)Li$ in THF (1.0 mmol scale)

To zinc chloride (0.5 M THF solution, 2.00 mL, 1.0 mmol) was added ^{t}BuLi (1.50 M ^{n}pentane solution, 1.33 mL, 2.0 mmol) at –78°C under Ar. The mixture was stirred at 0°C for 30 min to give the solution of di-^{t}butylzinc in THF. To the prepared di-^{t}butylzinc solution was added the LiTMP solution (1.0 mmol) at –78°C under Ar, and the reaction mixture was stirred at 0°C for 30 min to give the solution of $^{t}Bu_2Zn(TMP)Li$ in THF.

Preparation of $(TMP)_3ZnLi$ in THF (2.0 mmol scale)

To zinc chloride (0.5 M THF solution, 2.00 mL, 1.0 mmol) was added the LiTMP solution (3.0 mmol) at –78°C under Ar, and the reaction mixture was stirred at 0°C for 30 min to give the solution of $(TMP)_3ZnLi$ in THF.

Preparation of Substrates

N,N-Diisopropylbenzamide substrates were prepared from the corresponding acyl chlorides or acids using General Procedure A or B.

General Procedure A

To a solution of the amine (1.7 mL, 12 mmol) and Et_3N (1.8 mL, 12.5 mmol) in 20 mL of CH_2Cl_2 was added acyl chloride (10 mmol) in one portion at room temperature leading the mixture to self-reflux. The reaction mixture was stirred for 20 min at room temperature and then diluted with CH_2Cl_2. The solution was transferred to a separation funnel and was washed with 1M HCl aq (20 mL × 3). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the diisopropylarylamide substrates. The substrates were used without further purification.

General Procedure B

Thionyl chloride (4.02 mg, 33.8 mmol) was added to a solution of carboxylic acid (6.8 mmol) and DMF (8 mL, 3.3 mmol) in 34 mL of CH_2Cl_2 at room temperature. The mixture was heated under reflux for 5 h, and then the excess thionyl chloride and CH_2Cl_2 were removed *in vacuo*. The resultant acyl chloride was dissolved in dry CH_2Cl_2 and cooled to 0°C, then diisopropylamine (1.1 mL, 8.1 mmol) was added. After 5 min, Et_3N (1.2 mL, 8.5 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The mixture was diluted with CH_2Cl_2 and washed with 3 M HCl aq. (20mL × 2), water (20 mL × 1), and brine (20 mL × 1). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel afforded the *N,N*-diisopropylbenzamide substrates.

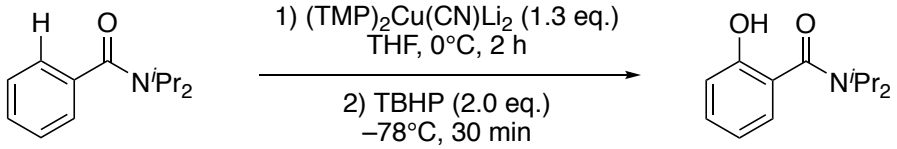
4-Methoxymethoxybiphenyl (**1l**) was prepared using the following procedure; To a stirred suspension of NaH (0.80 mg, 20 mmol) in 20 mL of THF at 0°C was added dropwise a solution of 4-hydroxybiphenyl (3.40 g, 20 mmol) in 30 mL of THF. The reaction mixture was stirred for 15 min at room temperature, the $ClCH_2OCH_3$ (3 mL, 40 mmol) was added at 0°C, and stirring was continued for 1 h at room temperature. The mixture was quenched with aqueous NH_4Cl (30 mL), followed by extraction with Et_2O (30 mL × 3). The combined Et_2O layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel afforded the title compound.

***ortho* Hydroxylation of Aromatics (Table 2-2)**

General Procedure:

Unless otherwise noted, the reaction was performed on 0.3 mmol scale.

2-Hydroxy-*N,N*-diisopropylbenzamide (2a)

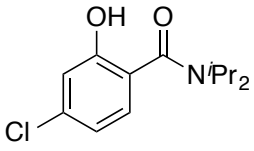


N,N-Diisopropylbenzamide (61.5 mg, 0.3 mmol) and dry THF (0.3 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Cu(CN)Li_2$ (0.4 mmol) *via* cannular at –78ºC, and the resulting solution was stirred for 2 h at 0ºC. To the mixture was added ^{t}BuOOH (109 μL, 0.6 mmol; 5.5 M decane solution) at –78°C, then stirred for 30 min at the same temperature. The reaction was quenched with aqueous NH_4Cl (10 mL) and aqueous $Na_2S_2O_3$ (10 mL), followed by extraction with AcOEt (30 mL × 3). The combined AcOEt layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/3) as an eluent to give the titled compound as a white solid in 94% yield (62.5 mg). ^{1}H and ^{13}C NMR were in agreement with the reference.[6-3] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.39 (d, *J* = 7.0 Hz, 12H), 3.95 (brs, 2H), 6.82-6.85 (m, 1H), 6.99 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.17 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.26-7.30 (m, 1H), 9.25 (s,

1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 21.0, 49.0 (br), 118.0, 118.5, 120.2, 126.8, 131.6, 158.1, 171.1. **EI-MS (% relative intensity):** *m/z*: 221 (M+, 23), 178 (37), 121 (100), 93 (14), 86 (73), 65 (20), 58 (21).

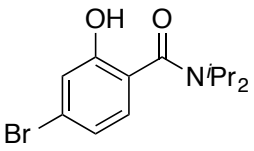
Larger Scale: Following the **General Procedure**, *N,N*-Diisopropylbenzamide (1.44 g, 7 mmol), TMPH (3.1 mL, 18.5 mmol), ^{n}BuLi (2.58 M in ^{n}hexane, 7.2 mL, 18.5 mmol), CuCN (828 mg, 9.2 mmol), and TBHP (5.5 M in ^{n}decane, 2.55 mL, 14 mmol) were used. The reaction was quenched with aqueous NH_4Cl (50 mL) and aqueous $Na_2S_2O_3$ (50 mL), followed by extraction with AcOEt (30 mL × 3). The combined AcOEt layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/3) as an eluent to give the titled compound as a white solid in 91% yield (1.41 g).

4-Chloro-2-hydroxy-*N,N*-diisopropylbenzamide (2b)



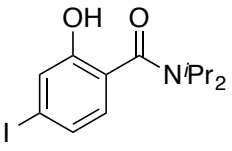
Following the **General Procedure** (The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78°C.; purification: AcOEt/hexane = 1/4), the titled compound was obtained as a white solid in 89% yield (68.0 mg). ^{1}H and ^{13}C NMR were in agreement with the reference.[6-3] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.39 (d, *J* = 6.6 Hz, 12H), 3.91 (brs, 2H), 6.82 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 9.62 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.9, 49.1 (br), 118.2, 118.9, 119.2, 127.6, 136.8, 158.7, 170.4. **EI-MS (% relative intensity):** *m/z*: 255 (M+, 12), 212 (29), 155 (61), 86 (100), 58 (28).

4-Bromo-2-hydroxy-*N,N*-diisopropylbenzamide (2c)



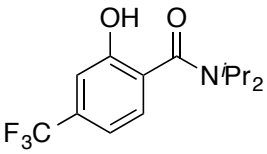
Following the **General Procedure** (The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78ºC.; purification: AcOEt/hexane = 1/4), the titled compound was obtained as a white solid in 88% yield (79.0 mg). ^{1}H and ^{13}C NMR were in agreement with the reference.[6-3] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.37 (d, *J* = 6.5 Hz, 12H), 3.87 (brs, 2H), 6.97 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 9.55 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.8, 49.0 (br), 120.8, 121.0, 121.9, 124.4, 127.5, 157.6, 170.4. **EI-MS (% relative intensity):** *m/z*: 299 (M+, 6), 256 (13), 213 (9), 199 (30), 86 (100), 58 (30).

2-Hydroxy-4-iodo-*N,N*-diisopropylbenzamide (2d)



Following the **General Procedure** (The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78ºC.; purification: AcOEt/hexane = 1/4), the titled compound was obtained as colorless crystals in 92% yield (95.7 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-3] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.34 (d, *J* = 6.0 Hz, 12H), 3.78 (brs, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.20 (d, *J* = 1.5 Hz, 1H), 9.48 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.8, 49.0 (br), 96.1, 122.2, 126.9, 127.5, 128.0, 156.7, 170.4. **EI-MS (% relative intensity):** *m/z*: 347 (M+, 11), 320 (48), 304 (27), 261 (42), 247 (31), 86 (100), 58 (25).

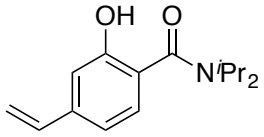
2-Hydroxy-4-(trifluoromethyl)-*N,N*-diisopropylbenzamide (2e)



Following the **General Procedure** (purification: AcOEt/hexane = 1/3), the titled compound was obtained as a white solid in 92% yield (79.9 mg). ^{1}H and ^{13}C NMR were in agreement with the reference.[6-3] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.37 (d, *J* = 6.0 Hz, 12H), 3.81 (brs, 2H), 7.06 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.14 (d, *J* = 1.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 9.42 (s, 1H). **^{13}C NMR (125 MHz,**

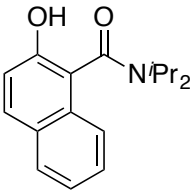
CDCl$_3$): δ 20.8, 49.1 (br), 114.9 (q, *J* = 3.8 Hz), 115.5 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 271.3 Hz), 125.2, 126.9, 132.7 (q, *J* = 32.5 Hz), 156.7, 169.8. **EI-MS (% relative intensity):** *m/z*: 289 (M+, 9), 246 (20), 189 (60), 161 (16), 113 (9), 86 (100), 58 (36).

2-Hydroxy-4-vinyl-*N,N*-diisopropylbenzamide (2f)



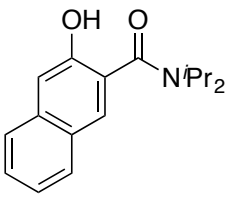
Following the **General Procedure** (1 mmol scale, 1.2 mmol of TBHP was used.; purification: AcOEt/hexane = 1/9), the titled compound was obtained as colorless crystals in 71% yield (176.7 mg). **^{1}H NMR (500 MHz, CDCl$_3$):** δ 1.38 (d, *J* = 6.0 Hz, 12H), 3.93 (brs, 2H), 5.30 (dd, *J* = 0.5, 11.0 Hz, 1H), 5.77 (dd, *J* = 0.5, 17.5 Hz, 1H), 6.63 (dd, *J* = 11.0, 17.5 Hz, 1H), 6.88 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 9.40 (s, 1H). **^{13}C NMR (125 MHz, CDCl$_3$):** δ 19.9, 47.9 (br), 114.2, 114.4, 115.6, 119.1, 125.9, 135.1, 139.7, 156.9, 169.9. **FTIR (ATR):** 3331, 2982, 1328, 1297, 1165, 1110, 1068, 843, 769, 676 cm^{-1}. **mp:** 143.9-144.6ºC (recrystallized from EtOH). **EI-MS (% relative intensity):** *m/z*: 247 (M+, 21), 204 (21), 147 (78), 86 (100), 65 (14), 58 (35). **Anal.:** Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.83; H, 8.37; N, 5.63. **HRMS (pos. ESI):** *m/z*: calcd for $C_{15}H_{21}NO_2$ $[M+H]^+$ 248.1645, found 248.1644.

2-Hydroxy-*N,N*-diisopropyl-1-naphthamide (2g)



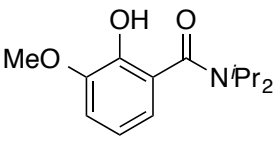
Following the **General Procedure** (The substrate was added as a solution in 1 mL of THF.; purification: AcOEt/hexane = 2/3), the titled compound was obtained as a white solid in 89% yield (72.9 mg). **^{1}H NMR (500 MHz, DMSO-d6):** δ 1.02 (d, *J* = 6.5 Hz, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.60 (d, *J* = 6.5 Hz, 3H), 3.60 (sep, *J* = 6.8 Hz , 2H), 7.17 (d, *J* = 9.0 Hz, 1H), 7.29 (ddd, *J* = 1.3, 6.8, 8.3 Hz, 1H), 7.44 (ddd, *J* = 1.3, 6.8, 8.3 Hz, 1H), 7.50 (brd, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.80 (brd, *J* = 8.3 Hz, 1H), 9.80 (s, 1H). **^{13}C NMR (125 MHz, DMSO-d6):** δ 21.0, 21.0, 21.1, 21.3, 45.3, 51.1, 118.6, 119.3, 123.4, 123.5, 127.1, 128.0, 128.5, 129.4, 131.5, 150.6, 167.4. **FTIR (ATR):** 3053, 2999, 2973, 2932, 2873, 1623, 1579, 1509, 1470, 1348, 1307, 1275, 1249, 1208, 1161, 1122, 1051, 1021, 968, 821, 750, 714, 617 cm^{-1}. **mp:** 234.7-236.7ºC (recrystallized from MeOH). **Anal.:** Calcd: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.10; H, 7.94; N, 5.12. **HRMS (pos. ESI):** *m/z*: calcd for $C_{17}H_{21}NO_2$ $[M+H]^+$ 272.1645, found 272.1646.

3-Hydroxy-*N,N*-diisopropyl-2-naphthamide (2h)



Following the **General Procedure** (The substrate was added as a solution in 1 mL of THF.; purification: AcOEt/hexane = 1/3), the titled compound was obtained as a white solid in 76% yield (61.8 mg). ^{1}H and ^{13}C NMR were in agreement with the reference.[6-3] **^{1}H NMR (500 MHz, CDCl$_3$):** δ 1.43 (d, *J* = 6.5 Hz, 12H), 4.00 (brs, 2H), 7.31-7.34 (m, 2H), 7.45 (ddd, *J* = 1.3, 7.0, 8.3 Hz, 1H), 7.67-7.68 (m, 2H), 7.73 (d, *J* = 8.5 Hz, 1H), 8.60 (s, 1H). **^{13}C NMR (125 MHz, CDCl$_3$):** δ 21.0, 49.2, 112.2, 123.2, 123.9, 126.4, 126.7, 127.1, 127.6, 128.2, 135.3, 153.8, 170.5. **EI-MS (% relative intensity):** *m/z*: 271 (M+, 45), 228 (25), 170 (100), 142 (38), 115 (48), 86 (26).

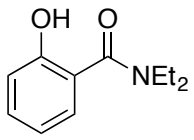
2-Hydroxy-3-methoxy-*N,N*-diisopropylbenzamide (2i)



Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 1/4), the titled compound was obtained as a white solid in 79% yield (198.9 mg). **^{1}H NMR (500 MHz, CDCl$_3$):** δ 1.36 (d, *J* = 4.5 Hz, 12H), 3.76 (brs, 2H), 3.90 (s, 3H), 6.78 (dd, *J* = 1.9, 7.5 Hz, 1H), 6.78 (dd, *J* = 7.5, 8.0 Hz 1H), 6.86 (dd, *J* = 1.9, 8.0 Hz, 1H), 7.08 (s, 1H). **^{13}C NMR (125 MHz, CDCl$_3$):** δ 20.8, 48.6 (br), 56.1, 111.5, 118.8, 119.4, 123.8, 144.0, 147.5, 169.0. **FTIR (ATR):** 3153, 2999, 2966, 2931,

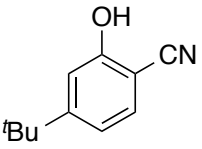
2845, 1736, 1599, 1487, 1439, 1369, 1344, 1290, 1265, 1231, 1124, 1065, 1035, 941, 841, 806, 776, 744, 607, 553, 511 cm^{-1}. **mp:** 126.6-127.7ºC (recrystallized from EtOH). **EI-MS (% relative intensity):** *m/z*: 251 (M+, 28), 208 (26), 151 (100), 122 (41), 108 (15), 86 (48). **Anal.:** Calcd: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.86; H, 8.24; N, 5.54. **HRMS (pos. ESI):** *m/z*: calcd for $C_{14}H_{21}NO_3$ $[M+H]^+$ 252.1594, found 252.1595.

2-Hydroxy-*N,N*-diethylbenzamide (2j)



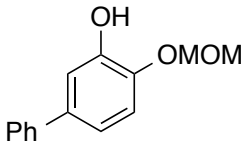
Following the **General Procedure** (0.45 mmol of $(TMP)_2Cu(CN)Li_2$ was used.; purification: AcOEt/hexane = 1/3), the titled compound was obtained as a colorless oil in 90% yield (56.1 mg). ^1H and ^{13}C NMR were in agreement with the reference.[6-4] **^1H NMR (500 MHz, $CDCl_3$):** δ 1.28 (t, *J* = 7.0 Hz, 6H), 3.78 (q, *J* = 7.0 Hz, 4H), 6.84 (ddd, *J* = 1.1, 7.2, 7.5 Hz, 1H), 7.00 (brd, *J* = 8.1 Hz, 1H), 7.26-7.28 (m, 1H), 7.30-7.33 (m, 1H) 9.75 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 13.4, 42.2 (br), 118.0, 118.1, 118.4, 127.3, 132.3, 158.8, 171.4. **EI-MS (% relative intensity):** *m/z*: 192 (M+, 43), 121 (100), 93 (14), 72 (36), 65 (21), 58 (41).

4-*tert*-Butyl-2-hydroxybenzonitrile (2k)



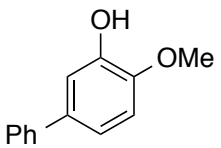
Following the **General Procedure** (1 mmol scale. 1.5 mmol of $(TMP)_2Cu(CN)Li_2$ and 1.4 mmol of TBHP were used.; purification: AcOEt/hexane = 1/19), the titled compound was obtained as a white solid in 87% yield (152.8 mg). **^1H NMR (500 MHz, $CDCl_3$):** δ 1.30 (s, 9H), 5.88 (brs, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 7.03 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 30.8, 35.3, 96.4, 113.7, 116.5, 118.8, 132.2, 158.1, 159.5. **FTIR (ATR):** 3244, 2954, 2232, 1739, 1611, 1584, 1424, 1362, 1310, 1279, 1236, 1204, 1130, 1089, 1025, 939, 871, 819, 748, 739, 688, 655, 622, 526 cm^{-1}. **mp:** 128.4-129.1ºC (recrystallized from CH_2Cl_2). **EI-MS (% relative intensity):** *m/z*: 175 (M+, 30), 160 (100), 132 (44), 120 (16). **Anal.:** Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.35; H, 7.61; N, 8.02. **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{13}NO$ $[M+H]^+$ 176.1070, found 176.1068.

3-Hydroxy-4-methoxymethoxybiphenyl (2l)



Following the **General Procedure** (1 mmol scale, 1.5 mmol of $(TMP)_2Cu(CN)Li_2$ and 1.4 mmol of TBHP were used.; purification: AcOEt/hexane = 1/19), the titled compound was obtained as a colorless oil in 82% yield (188.6 mg). **^1H NMR (500 MHz, $CDCl_3$):** δ 3.55 (s, 3H), 5.24 (s, 2H), 5.98-5.99 (m, 1H), 7.07 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.41 (dd, *J* = 7.4, 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 56.5, 96.1, 114.2, 115.8, 119.0, 126.9, 127.0, 128.7, 136.6, 140.6, 144.0, 146.5. **FTIR (ATR):** 3404, 2951, 2902, 2849, 2827, 1737, 1591, 1573, 1519, 1487, 1299, 1287, 1247, 1191, 1152, 1126, 1077, 1043, 981, 922, 900, 872, 814, 757, 696, 586 cm^{-1}. **EI-MS (% relative intensity):** *m/z*: 230 (M+, 100), 198 (56), 185 (30), 157 (43), 139 (26), 128 (45). **HRMS (pos. ESI):** *m/z*: calcd for $C_{14}H_{14}O_3$ $[M+Na]^+$ 253.0835, found 253.0828.

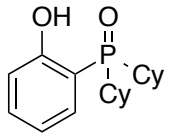
3-Hydroxy-4-methoxybiphenyl (2m)



Following the **General Procedure** (1 mmol scale, 2.2 mmol of $(TMP)_2Cu(CN)Li_2$ and 2.0 mmol of TBHP were used.; purification: AcOEt/hexane = 1/19), the titled compound was obtained as a white solid in 83% yield (166.2 mg). ^1H NMR spectrum was in agreement with the reference.[6-5] **^1H NMR (500 MHz, $CDCl_3$):** δ 3.92 (s, 3H), 5.65 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 7.09 (dd, *J* = 2.2, 8.5 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.30 (tt, *J* = 1.4, 7.5 Hz, 1H), 7.39-7.42 (m, 2H), 7.53-7.55 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 56.1, 110.9, 113.4, 118.8, 126.8, 126.8, 128.7, 134.8, 140.8, 145.8, 146.2.

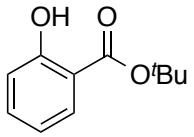
EI-MS (% relative intensity): *m/z*: 200 (M+, 100), 185 (93), 157 (79), 139 (9), 128 (39), 115 (9), 102 (11), 77 (10), 63 (8), 51 (10).

Dicyclohexyl(2-hydroxyphenyl)phosphine oxide (2n)



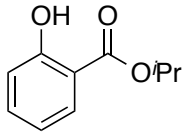
Following the **General Procedure** (0.45 mmol of $(TMP)_2Cu(CN)Li_2$ was used.; purification: AcOEt/hexane = 1/3), the titled compound was obtained as a white solid in 86% yield (78.9 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.13-1.47 (m, 10H), 1.69-1.72 (m, 4H), 1.78-1.87 (m, 4H), 1.98-2.07 (m, 4H), 6.83-6.88 (m, 1H), 6.90 (dd, *J* = 3.9, 8.3 Hz, 1H), 6.96-7.01 (m, 1H), 7.36-7.40 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 24.1 (d, J_{C-P} = 2.9 Hz), 25.2 (d, J_{C-P} = 2.2 Hz), 25.7, 26.2 (d, J_{C-P} = 13.2 Hz), 26.3 (d, J_{C-P} = 13.2 Hz), 35.7 (d, J_{C-P} = 66.0 Hz), 108.4 (d, J_{C-P} = 85.8 Hz), 118.4 (d, J_{C-P} = 6.6 Hz), 118.6 (d, J_{C-P} = 11.0 Hz), 129.5 (d, J_{C-P} = 9.5 Hz), 133.7, 165.4. **FTIR (ATR):** 2927, 2852, 2690, 2660, 2588, 2549, 1591, 1444, 1391, 1297, 1123, 1070, 910, 889, 851, 757, 732, 573 cm^{-1}. **mp**: 215.9-218.0°C (recrystallized from EtOH). **HRMS (pos. ESI):** *m/z*: calcd for $C_{18}H_{27}O_2P$ $[M+Na]^+$ 329.1641, found 329.1654. **Anal.:** Calcd: C, 70.56; H, 8.88. Found: C, 70.30; H, 8.82.

***tert*-Butyl 2-hydroxybenzoate (2o)**



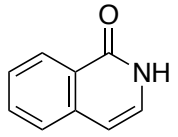
Following the **General Procedure** (1 mmol scale, 2.2 mmol of $(TMP)_2Cu(CN)Li_2$ and 2.0 mmol of cumene hydroperoxide instead of TBHP were used.; purification: AcOEt/hexane = 1/9), the titled compound was obtained as a brown oil in 82% yield (189.1 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.61 (s, 9H), 6.82-6.85 (m, 1H), 6.94 (dd, *J* = 1.0, 8.5 Hz, 1H), 7.41 (ddd, *J* = 1.5, 7.3, 8.5 Hz, 1H), 7.78 (dd, *J* = 1.5, 8.0 Hz, 1H), 11.04 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 28.2, 82.8, 113.9, 117.5, 118.8, 130.1, 135.1, 161.8, 169.8. **EI-MS (% relative intensity):** *m/z*: 194 (M+, 3), 138 (51), 120 (100), 92 (20), 65 (10), 57 (11). **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{14}O_3$ $[M+H]^+$ 195.1016, found 195.1015.

Isopropyl 2-hydroxybenzoate (2p)



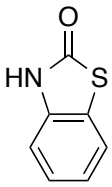
Following the **General Procedure** (1 mmol scale, 2.2 mmol of $(TMP)_2Cu(CN)Li_2$ and 2.0 mmol of cumene hydroperoxide instead of TBHP were used.; purification: AcOEt/hexane = 1/9), the titled compound was obtained as a colorless oil in 82% yield (189.1 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-6] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.39 (d, *J* = 6.3 Hz, 6H), 5.29 (sep, *J* = 6.3 Hz, 1H), 6.87 (ddd, *J* = 1.0, 7.1, 8.0 Hz, 1H), 6.97 (dd, *J* = 1.0, 8.3 Hz, 1H), 7.44 (ddd, *J* = 1.7, 7.1, 8.3 Hz, 1H), 7.84 (dd, *J* = 1.7, 8.0 Hz, 1H), 10.93 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.8, 68.2, 111.9, 116.5, 118.0, 128.9, 134.4, 160.7, 168.7. **EI-MS (% relative intensity):** *m/z*: 180 (M+, 14), 138 (26), 120 (100), 92 (30), 65 (9).

1(2*H*)-Isoquinolinone (2r)



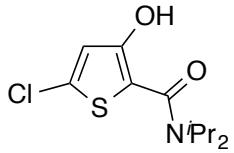
Following the **General Procedure** (1 mmol scale, 1.5 mmol of $(TMP)_2Cu(CN)Li_2$ and 1.4 mmol of TBHP were used.; purification: AcOEt/hexane = 1/4), the titled compound was obtained as a white solid in 86% yield (125.3 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-7] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.58 (d, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.52 (ddd, *J* = 1.0, 7.0, 8.0 Hz, 1H), 7.57 (brd, *J* = 8.0 Hz, 1H), 7.68 (ddd, *J* = 1.4, 7.0, 8.1 Hz, 1H), 8.44 (m, 1H), 11.48 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 106.7, 126.1, 126.2, 126.8, 127.3, 127.7, 132.6, 138.2, 164.4. **EI-MS (% relative intensity):** *m/z*: 145 (M+, 100), 118 (33), 90 (36), 63 (16).

2(3*H*)-Benzothiazolone (2s)



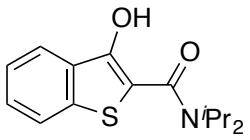
Following the **General Procedure** (purification: AcOEt/hexane = 1/3), the titled compound was obtained as a white solid in 64% yield (29.0 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-8] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.14-7.18 (m, 2H), 7.26-7.30 (m, 1H), 7.41 (brd, *J* = 8.1 Hz, 1H), 8.81 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 111.8, 122.6, 123.3, 123.9, 126.5, 135.4, 173.1. **EI-MS (% relative intensity):** *m/z*: 151 (M+, 100), 123 (53), 96 (60), 69 (12), 63 (6).

5-Chloro-3-hydroxy-*N*,*N*-diisopropylthiophene-2-carboxamide (2t)



Following the **General Procedure** (The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78ºC.; purification: AcOEt/hexane = 1/10), the titled compound was obtained as a colorless oil in 81% (63.7 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.40 (d, *J* = 5.4 Hz, 12H), 4.02 (brs, 2H), 6.66 (s, 1H), 13.33 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.0, 48.5 (br), 101.9, 119.7, 134.5, 165.6, 166.6. **FTIR (ATR):** 2972, 2931, 1584, 1550, 1458, 1369, 1343, 1253, 1145, 1083, 1026, 990, 874, 823, 748, 707, 657, 625, 580, 539 cm^{-1}. **HRMS (neg. ESI):** *m/z*: calcd for $C_{11}H_{16}ClNO_2S$ $[M–H]^-$ 260.0518, found 260.0527. **Anal.:** Calcd: N, 5.06; C, 52.07; H, 6.92. Found: N, 5.25; C, 50.49; H, 6.11.

3-Hydroxy-*N*,*N*-diisopropylbenzo[*b*]thiophene-2-carboxamide (2u)



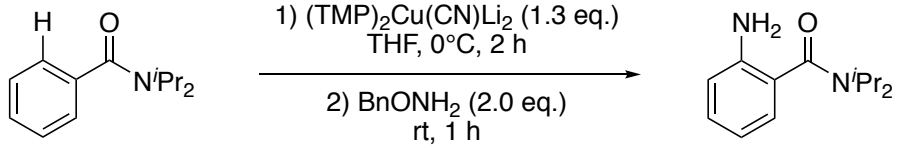
Following the **General Proceedure** (1 mmol scale; purification: AcOEt/hexane = 1/49), the titled compound was obtained as a white solid in 81% (224.9 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.45 (d, *J* = 6.0 Hz, 12H), 4.25 (brs, 2H), 7.39 (ddd, *J* = 0.9, 7.0, 7.9 Hz, 1H), 7,46 (ddd, *J* = 1.2, 7.0, 8.2 Hz, 1H), 7.68 (ddd, *J* = 0.6, 0.9, 8.2 Hz, 1H), 7.97 (ddd, *J* = 0.9, 1.2, 7.9 Hz, 1H), 13.63 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 21.3, 48.5 (br), 101.3, 122.1, 122.9, 124.4, 128.3, 131.3, 137.1, 161.9, 168.2. **FTIR (ATR):** 3001, 2970, 2932, 2873, 1574, 1523, 1473, 1441, 1379, 1346, 1322, 1264, 1238, 1156, 1127, 1062, 1022, 930, 864, 784, 748, 734, 715, 638, 616, 546, 509 cm^{-1}. **mp**: 97.4-98.4°C (recrystallized from EtOH). **HRMS (pos. ESI):** *m/z*: calcd for $C_{15}H_{19}NO_2S$ $[M+H]^+$ 278.1209, found 278.1214. **Anal.:** Calcd: N, 5.05; C, 64.95; H, 6.90. Found: N, 5.00; C, 64.89; H, 6.75.

***ortho* Amination of Aromatics (Table 2-4)**

General Procedure:

Unless otherwise noted, the reaction was performed on 0.3 mmol scale.

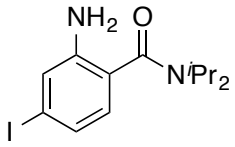
2-Amino-*N*,*N*-diisopropylbenzamide (3a)



N,N-Diisopropylbenzamide (205.5 mg, 1 mmol) and dry THF (1 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Cu(CN)Li_2$ (1.3 mmol) *via* cannula at –78ºC, and the resulting solution was stirred for 2 h at 0ºC. To the mixture was added *O*-benzylhydroxylamine (233 μL, 2.0 mmol) at –78ºC, then stirred for 30 min at room temperature. The reaction was quenched with aqueous NH_4Cl (10 mL) and aqueous $Na_2S_2O_3$ (10 mL), followed by extraction with AcOEt (30 mL × 3). The combined AcOEt layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/3) as an eluent to

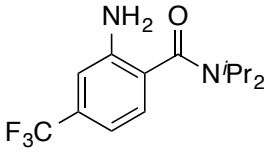
give the titled compound as a colorless solid in 93% yield (205.1 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-9] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.35 (brs, 12H), 3.74 (brs, 2H), 4.03 (brs, 2H), 6.69-6.73 (m, 2H), 7.00 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.12 (ddd, *J* = 1.5, 7.7, 7.8 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.9, 48.3 (br), 116.5, 117.6, 123.8, 125.9, 129.4, 144.4, 170.3. **EI-MS (% relative intensity):** *m/z*: 220 (M+, 11), 120 (100), 100 (10), 92 (16), 65 (10).

2-Amino-4-iodo-*N*,*N*-diisopropylbenzamide (3d)



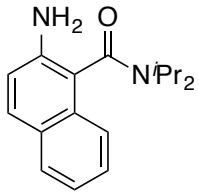
Following the **General Procedure** (The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78ºC.; purification: AcOEt/hexane = 1/9), the titled compound was obtained as a white solid in 84% yield (86.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.34 (brs, 12H), 3.71 (brs, 2H), 4.04-4,06 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.08 (d, *J* = 1.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.9, 48.6 (br), 95.0, 123.1, 125.0, 126.6, 127.3, 145.7, 169.5. **FTIR (ATR):** 3422, 3332, 3231, 2971, 2929, 2869, 1737, 1717, 1594, 1581, 1561, 1455, 1406, 1378, 1369, 1345, 1210, 1187, 1154, 1135, 1033, 916, 863, 795, 619, 555, 542, 522 cm^{-1}. **mp:** 142.6-144.1ºC (recrystallized from EtOH). **EI-MS (% relative intensity):** *m/z*: 346 (M+, 8), 331 (4), 303 (7), 246 (100), 218 (7), 119 (8), 100 (11), 91 (8). **HRMS (pos. ESI):** *m/z*: calcd for $C_{13}H_{20}IN_2O$ $[M+H]^+$ 347.0615, found 347.0615. **Anal.:** Calcd: C, 45.10; H, 5.53; N, 8.09. Found: C, 45.40; H, 5.53; N, 8.08.

2-Amino-4-(trifluoromethyl)-*N*,*N*-diisopropylbenzamide (3e)



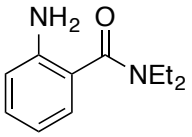
Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 1/9 followed by further purification with a preparative TLC developed with toluene/acetone = 6/1), the titled compound was obtained as a white solid in 70% yield (203.1 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.35 (brs, 12H), 3.69 (brs, 2H), 4.20 (brs, 2H), 6.93 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.8, 47.3 (br), 50.6 (br), 113.0 (q, *J* = 3.8 Hz), 114.3, 123.9 (q, *J* = 271.3 Hz), 126.3, 126.6, 131.5 (q, *J* = 31.3 Hz), 144.5, 169.0. **FTIR (ATR):** 3475, 3344, 3227, 2979, 2939, 2874, 1736, 1610, 1514, 1435, 1371, 1334, 1259, 1211, 1171, 1108, 1051, 1035, 928, 885, 804, 765, 744, 684, 666, 622, 563, 530 cm^{-1}. **mp:** 109.6-111.1ºC (recrystallized from EtOH). **EI-MS (% relative intensity):** *m/z*: 288 (M+, 7), 273 (4), 245 (6), 188 (100), 160 (18), 140 (5), 100 (6), 86 (14). **HRMS (pos. ESI):** *m/z*: calcd for $C_{14}H_{20}F_3N_2O_3$ $[M+H]^+$ 289.1522, found 289.1525. **Anal.:** Calcd: C, 58.32; H, 6.64; N, 9.72. Found: C, 58.33; H, 6.63; N, 9.74.

2-Amino-*N*,*N*-diisopropyl-1-naphthamide (3g)



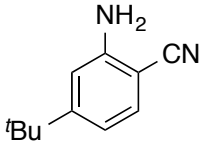
Following the **General Procedure** (1 mmol scale, the substrate was added as a solution in 5 mL of THF.; purification: AcOEt/hexane = 1/3), the titled compound was obtained as a white solid in 76% yield (205.9 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.02 (d, *J* = 6.7 Hz 3H), 1.12 (d, *J* = 6.8 Hz 3H), 1.68 (d, *J* = 7.0 Hz 3H), 1.73 (d, *J* = 7.0 Hz 3H), 3.59 (sep, *J* = 6.8 Hz 1H), 3.69 (sep, *J* = 6.7 Hz 1H), 3.92 (brs, 2H), 6.93 (d, *J* = 8.5 Hz 1H), 7.22-7.26 (m, 1H), 7.39 (ddd, *J* = 1.4, 6.9, 8.4 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.6, 20.9, 21.0, 21.6, 46.1, 51.3, 117.1, 118.5, 122.7, 122.9, 127.0, 127.6, 128.1, 129.1, 130.8, 140.2, 169.2. **FTIR (ATR):** 3432, 3323, 3221, 2969, 2932, 2872, 1739, 1594, 1513, 1447, 1371, 1334, 1286, 1263, 1211, 1122, 1047, 822, 746, 690, 616, 588, 532 cm^{-1}. **mp:** 223.4-225.0ºC (recrystallized from EtOH). **EI-MS (% relative intensity):** *m/z*: 270 (M+, 45), 170 (100), 143 (39), 115 (24), 100 (10). **HRMS (pos. ESI):** *m/z*: calcd for $C_{17}H_{22}N_2O$ $[M+H]^+$ 271.1803, found 271.1805. **Anal.:** Calcd: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.59; H, 8.11; N, 10.28.

2-Amino-*N*,*N*-diethylbenzamide (3j)



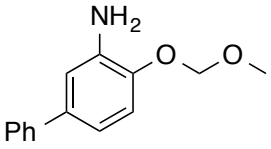
Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 1/5), the titled compound was obtained as a white solid in 92% yield (177.4 mg). ^{1}H and ^{13}C NMR were in agreement with the reference.[6-9] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.19 (brs, 6H), 3.43 (brs, 4H), 4.16 (brs, 2H), 6.70-6.73 (m, 2H), 7.06-7.08 (m, 1H), 7.27 (ddd, *J* = 1.1, 7.1, 7.9 Hz 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 12.5 (br), 38.6 (br), 42.0 (br), 115.5, 116.5, 120.7, 125.9, 129.0, 143.8, 169.6. **EI-MS (% relative intensity):** *m/z*: 192 (M+, 33), 121 (100), 92 (22), 72 (21), 65 (12).

2-Amino-4-*tert*-butylbenzonitrile (3k)



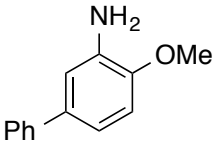
Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 2/9), the titled compound was obtained as a brown oil in 84% yield (146.1 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.27 (s, 9H), 4.34 (brs, 2H), 6.74 (d, *J* = 1.7 Hz, 1H), 6.79 (dd, *J* = 1.7, 8.5 Hz 1H), 7.20 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 30.8, 35.1, 93.3, 112.1, 116.0, 117.9, 132.0, 149.5, 158.1. **FTIR (ATR):** 3474, 3372, 3235, 2963, 2905, 2869, 2211, 1735, 1626, 1562, 1498, 1430, 1364, 1243, 1203, 1151, 1117, 1025, 942, 867, 807, 657, 523 cm^{-1}. **EI-MS (% relative intensity):** *m/z*: 174 (M+, 43), 159 (100), 131 (40), 119 (26), 116 (6). **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{14}N_2$ $[M+H]^+$ 175.1230, found 175.1228.

3-Amino-4-methoxymethoxybiphenyl (3l)



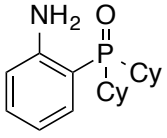
Following the **General Procedure** (1 mmol scale; purification: acetone/toluene = 1/50), the mixture of titled compound and 4-phenyl phenol (1 : 0.026) was obtained as a yellow oil in 81% yield (189.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.53 (s, 3H), 3.89 (brs, 2H), 5.24 (s, 2H), 6.92-6.94 (m, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.30 (m, 1H), 7.38-7.41 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 56.2, 95.2, 114.3, 115.0, 117.4, 126.7, 126.9, 128.6, 135.8, 137.0, 141.2, 144.5. **FTIR (ATR):** 3461, 3371, 3031, 2951, 2899, 2825, 1738, 1614, 1520, 1488, 1422, 1315, 1241, 1188, 1141, 1075, 1041, 988, 920, 864, 808, 758, 697, 651, 586 cm^{-1}. **EI-MS (% relative intensity):** *m/z*: 229 (M+, 39), 198 (56), 184 (71), 156 (54), 128 (16), 115 (7). **HRMS (pos. ESI):** *m/z*: calcd for $C_{14}H_{15}NO_2$ $[M+H]^+$ 230.1176, found 230.1176.

3-Amino-4-methoxybiphenyl (3m)



Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 1/3), the titled compound was obtained as a brown solid in 86% yield (171.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.86-3.89 (m, 5H), 6.85 (dd, *J* = 2.2, 8.3 Hz, 1H), 6.95-6.97 (m, 2H), 7.28 (tt, *J* = 1.3, 7.5 Hz, 1H), 7.37-7.41 (m, 2H), 7.53 (dd, *J* = 1.3, 8.5 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 55.6, 110.6, 113.8, 117.2, 126.6, 126.8, 128.6, 134.4, 136.3, 141.3, 147.0. **FTIR (ATR):** 3438, 3350, 3061, 3035, 2995, 2967, 2946, 2838, 1736, 1608, 1520, 1488, 1460, 1424, 1373, 1364, 1298, 1243, 1212, 1179, 1158, 1045, 1017, 866, 809, 758, 696, 643, 599, 520 cm^{-1}. **mp:** 78.8-80.2ºC (recrystallized from CH_2Cl_2).[8] **EI-MS (% relative intensity):** *m/z*: 199 (M+, 74), 184 (100), 156 (65), 128 (16), 115 (7), 77 (6). **HRMS (pos. ESI):** *m/z*: calcd for $C_{13}H_{13}NO$ $[M+H]^+$ 200.1070, found 200.1079.

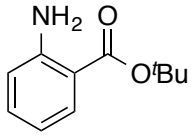
(2-Aminophenyl)dicyclohexylphosphine oxide (3n)



Following the **General Procedure** (0.45 mmol of $(TMP)_2Cu(CN)Li_2$ was used.; purification: AcOEt/hexane = 10/9), the titled compound was obtained as a white foam in 94% yield (86.3 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.16-1.43 (m, 10H), 1.68-1.78 (m,

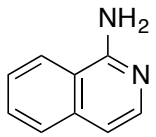
6H), 1.84-1.87 (m, 2H), 1.98-2.10 (m, 4H), 5.61 (brs, 2H), 6.59-6.65 (m, 2H), 6.92 (ddd, J = 1.2, 7.7, 13.4 Hz, 1H), 7.20 (m, 1 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 24.4 (d, $J_{C–P}$ = 2.9 Hz), 25.4 (d, $J_{C–P}$ = 2.2 Hz), 25.9, 26.3 (d, $J_{C–P}$ = 5.1 Hz), 26.5 (d, $J_{C–P}$ = 5.9 Hz), 36.0 (d, $J_{C–P}$ = 67.5 Hz), 107.6 (d, $J_{C–P}$ = 86.6 Hz), 115.9 (d, $J_{C–P}$ = 11.0 Hz), 117.0 (d, $J_{C–P}$ = 7.3 Hz), 130.8 (d, $J_{C–P}$ = 9.5 Hz), 132.3 (d, $J_{C–P}$ = 2.2 Hz), 154.7 (d, $J_{C–P}$ = 2.2 Hz). **FTIR (ATR):** 3406, 3384, 3309, 3199, 2927, 2852, 1611, 1484, 1448, 1326, 1136, 1111, 747, 570, 533 cm^{-1}. **HRMS (pos. ESI):** *m/z*: calcd for $C_{18}H_{28}NOP$ $[M+H]^+$ 306.1981, found 306.1985. **Anal.:** Calcd: N, 4.59; C, 70.79; H, 9.24. Found: N, 4.44; C, 70.28; H, 9.32.

***tert*-Butyl 2-aminobenzoate (3o)**



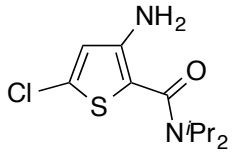
Following the **General Procedure** (purification: CH_2Cl_2/hexane = 1/9), the titled compound was obtained as a brown oil in 79% yield (151.9 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-10] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.58 (s, 9H), 5.68 (brs, 2H), 6.60-6.64 (m, 2H), 7.22 (ddd, J = 1.5, 7.0, 8.3 Hz, 1H), 7.80-7.82 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 28.4, 80.6, 112.6, 116.1, 116.7, 131.5, 133.6, 150.3, 167.7. **EI-MS (% relative intensity):** *m/z*: 193 (M+, 15), 137 (62), 119 (100), 92 (23), 65 (12), 56 (5).

Isoquinolin-1-amine (3r)



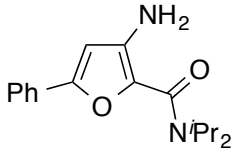
Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 5/1 with 1% Et_3N), the titled compound was obtained as a yellow solid in 87% yield (126.4 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-11] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 5.12 (brs, 2H), 7.06 (d, J = 5.5 Hz, 1H), 7.50 (ddd, J = 1.3, 7.0, 8.3 Hz, 1H), 7.63 (ddd, J = 1.1, 7.0, 8.2 Hz, 1H), 7.72 (apparent brd, J = 8.2 Hz, 1H), 7.80 (m, 1H), 7.96 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 112.7, 117.8, 122.6, 126.1, 127.1, 130.1, 137.4, 141.3, 156.1. **EI-MS (% relative intensity):** *m/z*: 144 (M+, 100), 117 (47), 89 (18), 63 (7).

3-Amino-5-chloro-*N*,*N*-diisopropylthiophene-2-carboxamide (3t)



Following the **General Procedure** (The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78ºC.; purification: AcOEt/hexane = 1/3), the titled compound was obtained as a white solid in 68% yield (53.4 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.37 (d, J = 6.9 Hz, 12H), 4.04 (brs, 2H), 5.24 (brd, 2H), 6.44 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.4, 48.4, 103.0, 120.4, 132.1, 151.2, 165.1. **FTIR (ATR):** 3446, 3341, 3230, 3083, 2968, 2932, 1582, 1538, 1441, 1419, 1368, 1334, 1213, 1162, 1114, 1068, 1028, 984, 823, 748, 707, 623, 548 cm^{-1}. **mp**: 96.6-99.0°C (recrystallized from CH_2Cl_2/hexane). **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{17}ClN_2OS$ $[M+Na]^+$ 283.0642, found 283.0651. **Anal.:** Calcd: N, 10.74; C, 50.66; H, 6.57. Found: N, 10.64; C, 50.65; H, 6.30.

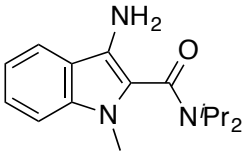
3-Amino-*N*,*N*-diisopropyl-5-phenylfuran-2-carboxamide (3v)



Following the **General Procedure** (The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78ºC.; purification: AcOEt/CH_2Cl_2 = 1/30), the titled compound was obtained as a brown solid in 46% yield (39.7 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.44 (d, J = 6.6 Hz, 12H), 4.26 (brs, 2H), 4.78 (brs, 2H), 6.38 (s, 1H), 7.31 (dd, J = 7.3, 7.6 Hz, 1H), 7.39 (dd, J = 7.3, 7.6 Hz, 2H), 7.61 (brd, J = 7.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.5, 47.4 (br), 100.7, 124.2, 128.4, 128.8, 128.9, 130.1, 144.3, 152.2, 162.2. **FTIR (ATR):** 3460, 3448, 3334, 2967, 2930, 2870, 1624, 1602, 1477, 1349, 1151, 1033, 930, 910, 828, 800, 763, 690, 643, 623 cm^{-1}. **mp**: 124.4-125.3°C (recrystallized from Et_2O/hexane). **HRMS (pos. ESI):** *m/z*: calcd for $C_{17}H_{23}N_2O_2$

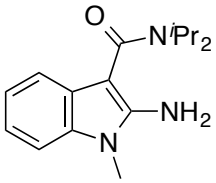
$[M+H]^+$ 287.1754, found 287.1749. **Anal.:** Calcd: N, 9.78; C, 71.30; H, 7.74. Found: N, 9.74; C, 71.36; H, 7.84.

3-Amino-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (3w)



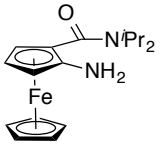
Following the **General Procedure** (purification: AcOEt/hexane = 1/1), the titled compound was obtained as a brown solid in 69% yield (61.1 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.40 (d, *J* = 6.6 Hz, 12H), 3.53 (s, 3H), 4.02 (sep, *J* = 6.6 Hz, 2H), 4.95 (brs, 2H), 7.01-7.12 (m, 3H), 7.26-7.28 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 22.0, 27.9, 47.8, 91.9, 107.9, 117.2, 118.8, 120.3, 125.8, 133.0, 149.1, 169.1. **FTIR (ATR):** 3422, 3309, 3208, 3050, 2965, 2931, 2875, 1579, 1473, 1438, 1364, 1308, 1247, 1207, 1154, 1132, 1098, 1040, 909, 838, 778, 732, 669, 615, 559 cm^{-1}. **mp**: 196.1-196.9°C (recrystallized from CH_2Cl_2/hexane). **HRMS (pos. ESI):** *m/z*: calcd for $C_{16}H_{23}N_3O$ $[M+Na]^+$ 296.1733, found 296.1738. **Anal.:** Calcd: N, 15.37; C, 70.30; H, 8.48. Found: N, 15.23; C, 70.21; H, 8.43.

2-Amino-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-3-carboxamide (3x)



Following the **General Procedure** (purification: AcOEt/hexane = 1/1), the titled compound was obtained as a brown liquid in 69% yield (61.1 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.36 (d, *J* = 6.4 Hz, 6H), 1.44 (d, *J* = 6.4 Hz, 6H), 3.29 (brs, 2H), 3.63 (s, 3H), 3.88 (sep, *J* = 6.6 Hz, 2H), 7.04-7.08 (m, 1H), 7.22-7.26 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.3, 30.7, 48.5, 109.4, 118.1, 118.5, 120.4, 120.9, 121.8, 123.0, 136.0, 163.9. **FTIR (ATR):** 3328, 2966, 2931, 2876, 1607, 1448, 1366, 1340, 1303, 1251, 1209, 1151, 1132, 1035, 923, 735, 611 cm^{-1}. **HRMS (pos. ESI):** *m/z*: calcd for $C_{16}H_{23}N_3O$ $[M+H]^+$ 274.1914, found 274.1913.

1-Amino-*N*,*N*-diisopropyl-ferrocene-2-carboxamide (3y)

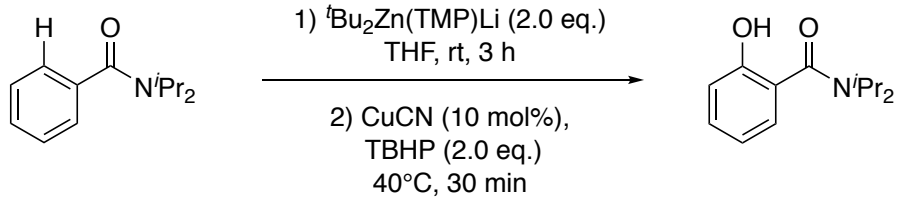


Following the **General Procedure** (1 mmol scale, The THF solution of the substrate was added to the solution of $(TMP)_2Cu(CN)Li_2$ at –78°C, and the resulting solution was stirred for 2 h at –78ºC.; purification: AcOEt/hexane = 3/4), the titled compound was obtained as a brown solid in 63% yield (206.3 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-12] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.42 (brs, 12H), 3.49 (brs, 1H), 3.75 (s, 2H), 3.90 (dd, *J* = 2.5, 2.7 Hz, 1H), 4.08 (m, 1H), 4.12 (m, 5H), 4.18 (m, 1H), 4.61 (brs, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.1, 21.5, 46.7 (br), 49.2 (br) 58.7, 62.4, 62.5, 67.0, 70.6, 111.2, 171.1. **FTIR (ATR):** 3427, 3378, 3326, 3095, 2997, 2964, 2933, 2874, 1575, 1458, 1430, 1367, 1332, 1268, 1200, 1161, 1136, 1101, 1034, 997, 813, 797, 766, 679, 619, 561, 524 cm^{-1}. **mp**: 120.4-122.7°C. **HRMS (pos. ESI):** *m/z*: calcd for $C_{17}H_{24}FeN_2O$ $[M]^+$ 328.1233, found 328.1246. **Anal.:** Calcd: N, 8.57; C, 62.21; H, 7.37. Found: N, 8.42; C, 61.92; H, 7.20.

Catalytic *ortho* Hydroxylation of Aromatics (Table 2-6)

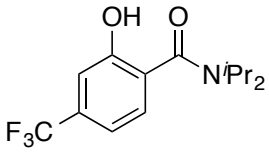
General Procedure:

2-hydroxy-*N,N*-diisopropylbenzamide (2a)



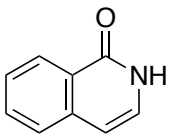
N,N-Diisopropylbenzamide (205.3 mg, 1 mmol) and dry THF (1 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of ^{t}Bu$_2$Zn(TMP)Li (2.0 mmol) *via* cannula at room temperature, and the resulting solution was stirred for 3 h at room temperature. To the mixture was added CuCN (9.0 mg, 0.1 mmol) before addition of ^{t}BuOOH (364 μL, 2.0 mmol; 5.5 M decane solution) at room temperature, then the resultant mixture was stirred for 30 min at 40°C. The reaction was quenched with aqueous NH_4Cl (10 mL) and aqueous $Na_2S_2O_3$ (10 mL), followed by extraction with AcOEt (30 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/3) as an eluent to give the titled compound as a colorless solid in 66% yield (146.5 mg).

2-Hydroxy-4-(trifluoromethyl)-*N,N*-diisopropylbenzamide (2e)



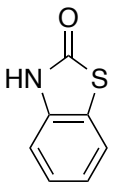
Following the **General Procedure** (1 mmol scale; purification: MeOH/CH_2Cl_2 = 1/50), the titled compound was obtained as a white solid in 63% yield (182.9 mg).

1(2*H*)-Isoquinolinone (2r)



Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 2/1), the titled compound was obtained as a white solid in 66% yield (94.9 mg).

2(3*H*)-Benzothiazolone (2s)

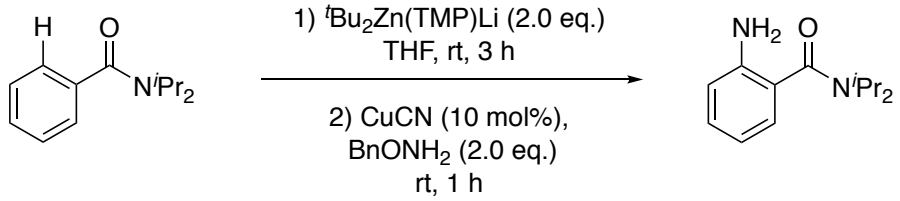


Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 1/3), the titled compound was obtained as a white solid in 53% yield (77.9 mg).

Catalytic *ortho* Amination of Aromatics (Table 2-6)

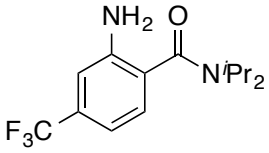
General Procedure:

2-Amino-*N,N*-diisopropylbenzamide (3a)



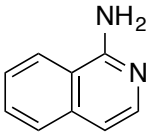
N,N-Diisopropylbenzamide (205.4 mg, 1 mmol) and dry THF (1 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of ^{t}Bu$_2$Zn(TMP)Li (2.0 mmol) *via* cannula at room temperature, and the resulting solution was stirred for 3 h at room temperature. To the mixture was added CuCN (9.0 mg, 0.1 mmol) before *O*-benzylhydroxylamine (233 μL, 2.0 mmol) at room temperature, then the resultant mixture was stirred for 1 h at room temperature. The reaction was quenched with aqueous NH_4Cl (10 mL) and aqueous $Na_2S_2O_3$ (10 mL), followed by extraction with AcOEt (30 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/3) as an eluent to give the titled compound as a colorless solid in 62% yield (136.5 mg).

2-Amino-4-(trifluoromethyl)-*N,N*-diisopropylbenzamide (3e)



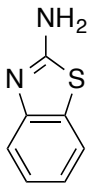
Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 1/9 followed by further purification with a preparative TLC by toluene/acetone = 6/1), the titled compound was obtained as a white solid in 67% yield (194.1 mg).

Isoquinolin-1-amine (3r)



Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 5/1 with 1% Et_3N), the titled compound was obtained as a yellow solid in 71% yield (102.2 mg).

Benzo[*d*]thiazol-2-amine (3s)



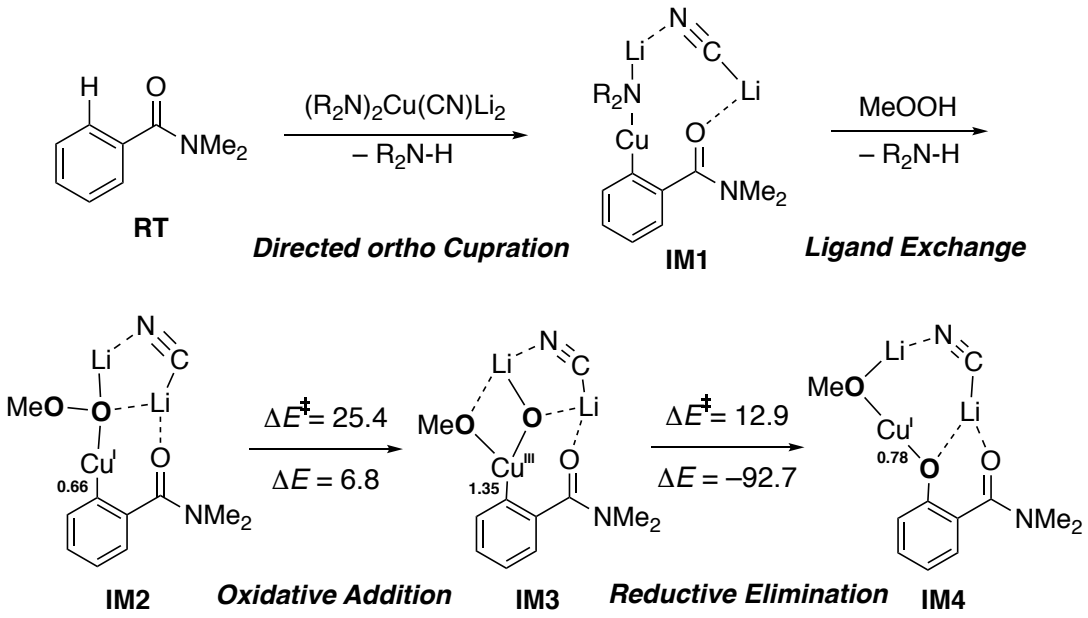
Following the **General Procedure** (1 mmol scale; purification: AcOEt/hexane = 1/1, then triturated in hexane), the titled compound was obtained as a yellow solid in 56% yield (83.5 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-13] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.24 (brs, 2H), 7.14 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.32 (dd, *J* = 1.0, 7.8 Hz, 1H), 7,56 (d, *J* =7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 119.4, 120.9, 122.4, 126.0, 131.7, 152.1, 165.5. **FTIR (ATR):** 3392, 3269, 3055, 3032, 2925, 2728, 1738, 1636, 1522, 1442, 1367, 1306, 1281, 1103, 919, 887, 740, 717, 685, 623, 561 cm^{-1}. **mp**: 127.4-128.5°C (recrystallized from AcOEt/hexane). **HRMS (pos. ESI):** *m/z*: calcd for $C_7H_6N_2S$ $[M+H]^+$ 151.0324, found 151.0331. **Anal.:** Calcd: N, 18.65; C, 55.98; H, 4.03. Found: N, 18.35; C, 56.09; H, 4.33.

Computational Details

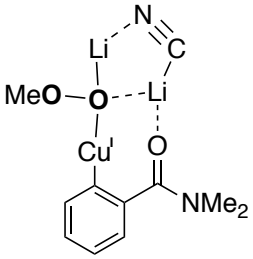
All calculations were carried with the Gaussian 09 program package[6-14] with the help of the development version of the GRRM (The Global Reaction Route Mapping, version 1.22) program[6-15,16] utilizing the energies and energy derivatives from Gaussian 09. The molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functional method based on M06 functional[6-17]. We used Ahlrichs' SVP[6-18] all–electron basis set for Cu atom and 6–31+G* for the other atoms. Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without any symmetry assumptions, and characterized by normal coordinate analysis at the same level of theory (number of imaginary frequencies, NIMAG, 0 for minima and 1 for TSs). The intrinsic reaction coordinate (IRC) method was used to track minimum energy paths from transition structures to the corresponding local minima.[6-19]

Oxidation of Aryl-Cu-ate (Figure 2-4)

Energy Profile for Oxidation of Lipshutz-type Aryl-Cu-ate ArCu(CN)(OOMe)Li$_2$ (Ar = [2-[[dimethylamino]carbonyl]phenyl]-) (M06 / 6-31+G* & SVP (Cu); energy: kcal/mol)



IM2

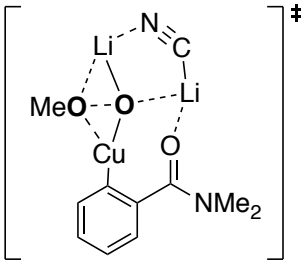


Energy (RB3LYP) = -2417.070579464762 A.U.

Li	-3.203130960087	-1.546336693483	0.988614459724
Li	-0.413586401568	-0.595412706922	1.625683484350
C	-1.819297757469	-1.559493167089	2.874989773460
N	-2.902688325826	-2.020278819417	2.865547011679
Cu	-0.605986601284	0.420024928804	-0.915891454230
C	3.278573930572	1.952378085598	-0.683574155230
C	3.249597389450	3.150522340026	-1.385082252422
C	2.073689640012	3.530446114785	-2.032059494943
C	0.937119052797	2.728331404729	-1.952728501182
C	0.909426054540	1.526282646281	-1.224586674000

C	2.126575929116	1.156609095417	-0.609580218370
C	2.174548610959	-0.103610544821	0.182110079963
O	1.335471400090	-0.353464616514	1.072328362492
N	3.169343266088	-0.993781031991	-0.057131252392
C	3.286594278558	-2.166690290152	0.790969800110
C	3.989968321437	-1.020041685687	-1.256439817625
H	4.193649829232	1.643920954249	-0.173241915554
H	4.135095483109	3.783541158282	-1.426222503373
H	2.043782686343	4.463030162384	-2.596599289765
H	0.034981426484	3.060349589022	-2.469238658101
H	2.701909293980	-3.008410192258	0.388576536492
H	2.925490373188	-1.940235556055	1.796516500304
H	4.340755354842	-2.465359605132	0.838130152622
H	3.918365702635	-2.017510079144	-1.712880158916
H	3.642020792934	-0.280753509269	-1.980471643518
H	5.044790424836	-0.821555568455	-1.019094063445
O	-1.860844214368	-0.718405981531	-0.027302769292
O	-2.109161807708	-2.014507576981	-0.643880673941
C	-0.924301129441	-2.774359794444	-0.601956420105
H	-0.127683386710	-2.276939338336	-1.179244581629
H	-0.585877271155	-2.944692353105	0.433240568410
H	-1.172378351573	-3.735644601268	-1.067178406908

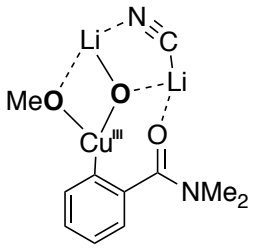
TS1 (between IM2 and IM3)



Energy (RB3LYP) = -2417.030181859679

Li	-2.850233724360	-1.734756259280	0.556864764505
Li	-0.507415116611	-0.604564013923	1.929267194151
C	-1.481322573686	-2.424931937081	2.455220339115
N	-2.398882693756	-3.020676701844	2.019154522296
Cu	-0.750918889218	0.637925299002	-0.561811348298
C	3.258074692976	1.656177511520	-1.090129954568
C	3.287985760033	2.676302344617	-2.030639795795
C	2.097422055386	3.077625154430	-2.637867751588
C	0.890379483282	2.480719988756	-2.280135017110
C	0.810334523748	1.469526906712	-1.310897619377
C	2.038047918734	1.055114378258	-0.744244934546
C	2.010514420015	-0.014011827826	0.290972069962
O	1.122261900910	-0.037281218419	1.170515921039
N	2.964094959985	-0.979302937069	0.293735625257
C	2.977835421317	-1.933409085361	1.391115121079
C	3.756111596290	-1.366331582834	-0.862921918777
H	4.183250709735	1.340643550778	-0.604048264347
H	4.230246909099	3.158697276810	-2.286887219605
H	2.112017109309	3.871036053809	-3.385698786140
H	-0.022619706698	2.828560410409	-2.766511273838
H	2.254725272701	-2.747831782824	1.228313649022
H	2.726375056438	-1.433207091630	2.329580523120
H	3.982831598900	-2.363731758294	1.468504938317
H	3.576948378768	-2.430731461883	-1.074905814960
H	3.471597814796	-0.784758654746	-1.742526732377
H	4.829620565202	-1.226895111164	-0.673437517267
O	-1.909818537330	-0.137421763016	0.572183462373
O	-1.582697171808	-1.347056193130	-0.896315986108
C	-0.442215604723	-2.162298313702	-0.855835099721
H	0.389547004246	-1.737355199620	-1.444032648256
H	-0.093406479114	-2.370058759036	0.169015960922
H	-0.742615494438	-3.134909596381	-1.281976021829

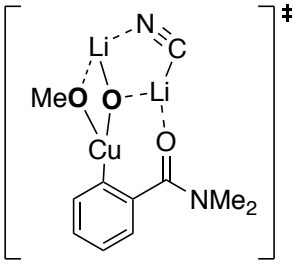
IM3



Energy (RB3LYP) = -2417.059818961372 A.U.

Li	-2.495831056494	-1.288017642431	0.278713876356
Li	-0.530585559489	-0.784452180303	2.230290644736
C	-0.736199868447	-2.760114120962	1.432833993296
N	-1.526847656338	-3.090841943236	0.624838529142
Cu	-0.646800555319	0.480922679343	-0.068593013073
C	3.176678149863	1.257828851177	-1.425984656248
C	3.050131372198	2.014143950858	-2.583825304066
C	1.783487191153	2.282267812477	-3.108810025786
C	0.636857917516	1.815302991926	-2.466473879335
C	0.741065598119	1.084821119032	-1.287542628393
C	2.021231652149	0.784343737070	-0.787813105615
C	1.980056138434	0.052056989232	0.491779257701
O	0.944538064649	0.221460817314	1.210733522664
N	2.944579041480	-0.769983975290	0.923499173149
C	2.797013294189	-1.386219391457	2.238587830507
C	3.981067821976	-1.340999130887	0.074560050877
H	4.166991656044	1.080807181036	-1.005670253292
H	3.939165835555	2.404346598551	-3.076469795428
H	1.692831938750	2.874379230430	-4.019432868409
H	-0.347476277694	2.039130082048	-2.882034850660
H	2.073062110733	-2.213846686254	2.201205193802
H	2.459623786363	-0.642813779808	2.966686093993
H	3.774038653495	-1.766288432647	2.553471598013
H	3.989449163811	-2.427787338871	0.223434320173
H	3.771547203705	-1.144452877744	-0.978817653713
H	4.971786862963	-0.943038045669	0.332547137646
O	-1.777952238407	0.103651575211	1.256976544904
O	-1.832627254260	-0.291764422994	-1.279049188864
C	-1.252286340852	-1.059720210785	-2.300096114298
H	-0.724449410502	-0.445228768246	-3.045796671206
H	-0.559052199238	-1.829480026561	-1.919272086940
H	-2.075550994731	-1.586389878212	-2.811271483686

TS2 (between IM3 and IM4)



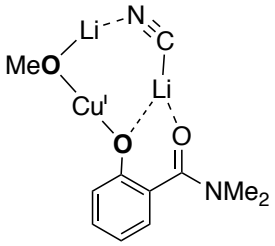
TS2

Energy (RB3LYP) = -2417.039280485563 A.U.

Li	-2.688905844702	-1.303946583646	0.573153952443
Li	-0.489029843383	-0.211771302738	2.021068757190
C	-1.381398727287	-2.112813886493	2.412313802688
N	-2.240963688659	-2.740883010223	1.907788401378
Cu	-0.815612730708	0.391330849290	-0.706945453334
C	3.194921173591	1.733735570968	-1.009114913113
C	3.166573280743	2.787942159794	-1.917818839345
C	1.963223407007	3.136717866179	-2.531037477163
C	0.797456505697	2.441679359288	-2.221480284996

C	0.770042489219	1.385293918978	-1.290042758474
C	2.015279338143	1.051126446016	-0.702171281015
C	2.031973468624	-0.024098604630	0.332266487669
O	1.231153409017	0.008429696532	1.284311820190
N	2.933365559014	-1.030375603983	0.243045808691
C	2.988146436974	-2.009312040419	1.318503813894
C	3.655984832750	-1.390423638913	-0.964724270463
H	4.133733467139	1.459737105734	-0.523822489824
H	4.079220050618	3.337914383017	-2.143750741146
H	1.937635832886	3.958311667333	-3.246756348582
H	-0.127874937913	2.738362823476	-2.717991887163
H	2.239497284375	-2.802653673392	1.177133385655
H	2.790784981614	-1.523039396422	2.276811317907
H	3.987843998304	-2.458353791609	1.332790077620
H	3.425809863855	-2.434611478734	-1.221644839498
H	3.357856383099	-0.754196031355	-1.801158850818
H	4.741180133372	-1.300908404903	-0.815646301035
O	-1.827240931442	0.370940378649	0.732958393038
O	-1.657253582937	-1.206343978084	-1.083071743980
C	-0.656746906876	-2.174368582856	-1.260339170798
H	0.115843090806	-1.848235524160	-1.977063666836
H	-0.189554579222	-2.475729304366	-0.306994316083
H	-1.151979761279	-3.068451661485	-1.674944178877

IM4

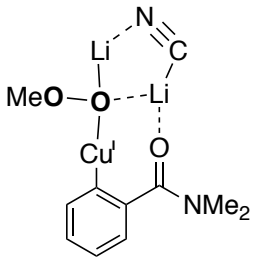


Energy (RB3LYP) = -2417.207595726820 A.U.

Li	-2.145723281106	-2.634474935519	0.303378391679
Li	-0.220854816542	0.746967182126	1.793357798545
C	-1.578116997102	-0.841383627147	2.141716956250
N	-2.184869464872	-1.844093541542	2.039589210389
Cu	-0.865039325346	-0.376072557592	-0.682510142724
C	3.158342403621	1.807415143459	-0.941773602458
C	3.074656416837	2.937484155620	-1.746116536262
C	1.823314190224	3.515204372581	-1.974549261124
C	0.673569121477	2.974729491694	-1.413661279421
C	0.741064905754	1.838497923936	-0.592339388897
C	2.011217268081	1.262605721070	-0.360821928555
C	2.074639224482	0.132737768118	0.600529874056
O	1.629630518195	0.269288074176	1.756390526780
N	2.615657509107	-1.044282382639	0.209314711963
C	2.644539890209	-2.135706754070	1.169265620153
C	2.826507855356	-1.426896869537	-1.175761725295
H	4.127151616862	1.345117644191	-0.742514470290
H	3.972675025758	3.367006759713	-2.186123111612
H	1.745408255236	4.401089374378	-2.604448888426
H	-0.306084583010	3.415701271553	-1.593105156921
H	1.678012275121	-2.663540703437	1.182062769894
H	2.837280000602	-1.747479724132	2.171723484434
H	3.436110002750	-2.837796493704	0.883782475818
H	2.222781998496	-2.319287240599	-1.399616269431
H	2.518370614495	-0.623259816093	-1.849266385684
H	3.883515097552	-1.664686629728	-1.359917623650
O	-0.360161194125	1.322134762713	-0.041768682796
O	-1.376251943554	-2.093575428682	-1.206284977896
C	-1.121989523388	-2.474034262170	-2.523683412715
H	-1.608987725368	-1.806017064447	-3.254811045290
H	-0.040719270105	-2.478560858402	-2.754224820220
H	-1.498612501060	-3.494095505344	-2.713252214454

Transition of Natural Charge through Oxidation of the Aryl-Cu-Ate

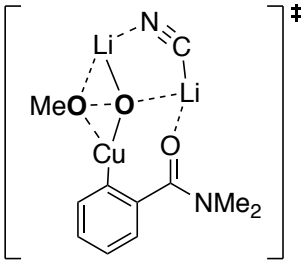
IM2



Summary of Natural Population Analysis:

		Natural	Natural Population			
Atom	No	Charge	Core	Valence	Rydberg	Total
Li	1	0.92078	1.99840	0.00005	0.08076	2.07922
Li	2	0.86306	1.99733	0.12792	0.01169	2.13694
C	3	-0.15400	1.99951	4.09706	0.05743	6.15400
N	4	-0.73568	1.99955	5.70180	0.03433	7.73568
Cu	5	0.65693	17.99632	10.33835	0.00840	28.34307
C	6	-0.23591	1.99887	4.21988	0.01715	6.23591
C	7	-0.26412	1.99894	4.24728	0.01789	6.26412
C	8	-0.23075	1.99893	4.21537	0.01644	6.23075
C	9	-0.27411	1.99896	4.25390	0.02124	6.27411
C	10	-0.41188	1.99899	4.37458	0.03830	6.41188
C	11	-0.20452	1.99876	4.18518	0.02058	6.20452
C	12	0.76315	1.99902	3.19516	0.04268	5.23685
O	13	-0.81068	1.99971	6.79076	0.02021	8.81068
N	14	-0.50974	1.99916	5.49136	0.01923	7.50974
C	15	-0.48468	1.99943	4.47272	0.01253	6.48468
C	16	-0.48082	1.99942	4.47009	0.01131	6.48082
H	17	0.23963	0.00000	0.75923	0.00114	0.76037
H	18	0.24338	0.00000	0.75563	0.00099	0.75662
H	19	0.24266	0.00000	0.75654	0.00081	0.75734
H	20	0.23908	0.00000	0.75983	0.00109	0.76092
H	21	0.23323	0.00000	0.76580	0.00097	0.76677
H	22	0.26940	0.00000	0.72976	0.00084	0.73060
H	23	0.24093	0.00000	0.75848	0.00059	0.75907
H	24	0.23830	0.00000	0.76088	0.00082	0.76170
H	25	0.26796	0.00000	0.73143	0.00060	0.73204
H	26	0.23772	0.00000	0.76142	0.00086	0.76228
O	27	-0.77734	1.99993	6.75914	0.01827	8.77734
O	28	-0.40750	1.99976	6.37953	0.02821	8.40750
C	29	-0.32825	1.99941	4.31099	0.01786	6.32825
H	30	0.20593	0.00000	0.79154	0.00253	0.79407
H	31	0.20660	0.00000	0.79195	0.00145	0.79340
H	32	0.24124	0.00000	0.75817	0.00060	0.75876
* Total *		0.00000	53.98040	97.51178	0.50782	152.00000

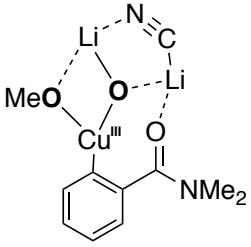
TS1 (between IM2 and IM3)



Summary of Natural Population Analysis:

		Natural	Natural Population			
Atom	No	Charge	Core	Valence	Rydberg	Total
Li	1	0.93182	1.99817	0.00007	0.06994	2.06818
Li	2	0.88052	1.99745	0.11227	0.00976	2.11948
C	3	-0.15394	1.99950	4.09748	0.05696	6.15394
N	4	-0.73639	1.99955	5.70263	0.03421	7.73639
Cu	5	0.96704	17.99538	10.02494	0.01264	28.03296
C	6	-0.22894	1.99889	4.21333	0.01673	6.22894
C	7	-0.26517	1.99894	4.24866	0.01757	6.26517
C	8	-0.22233	1.99893	4.20728	0.01612	6.22233
C	9	-0.27350	1.99896	4.25363	0.02090	6.27350
C	10	-0.42142	1.99897	4.38303	0.03942	6.42142
C	11	-0.20859	1.99876	4.19029	0.01954	6.20859
C	12	0.75909	1.99903	3.20149	0.04039	5.24091
O	13	-0.80914	1.99971	6.78994	0.01949	8.80914
N	14	-0.51156	1.99916	5.49300	0.01940	7.51156
C	15	-0.48473	1.99943	4.47240	0.01290	6.48473
C	16	-0.48270	1.99941	4.47187	0.01142	6.48270
H	17	0.24004	0.00000	0.75876	0.00120	0.75996
H	18	0.24461	0.00000	0.75442	0.00097	0.75539
H	19	0.24374	0.00000	0.75545	0.00080	0.75626
H	20	0.24102	0.00000	0.75802	0.00096	0.75898
H	21	0.23923	0.00000	0.75980	0.00097	0.76077
H	22	0.26471	0.00000	0.73450	0.00079	0.73529
H	23	0.24284	0.00000	0.75663	0.00053	0.75716
H	24	0.23974	0.00000	0.75941	0.00085	0.76026
H	25	0.26485	0.00000	0.73447	0.00067	0.73515
H	26	0.24020	0.00000	0.75898	0.00082	0.75980
O	27	-0.89129	1.99996	6.88416	0.00716	8.89129
O	28	-0.61621	1.99982	6.59797	0.01842	8.61621
C	29	-0.34010	1.99937	4.32157	0.01915	6.34010
H	30	0.19721	0.00000	0.80082	0.00197	0.80279
H	31	0.21182	0.00000	0.78592	0.00225	0.78818
H	32	0.23751	0.00000	0.76120	0.00129	0.76249
* Total *		0.00000	53.97940	97.54439	0.47621	152.00000

IM3

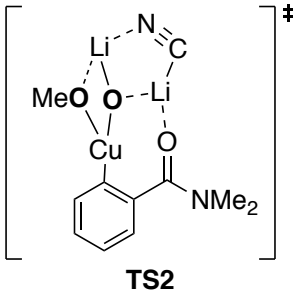


Summary of Natural Population Analysis:

		Natural	Natural Population			
Atom	No	Charge	Core	Valence	Rydberg	Total
Li	1	0.92849	1.99792	0.00005	0.07354	2.07151
Li	2	0.89524	1.99790	0.09498	0.01188	2.10476
C	3	-0.17901	1.99951	4.11967	0.05984	6.17901
N	4	-0.72419	1.99955	5.68960	0.03503	7.72419
Cu	5	1.34633	17.99325	9.63729	0.02313	27.65367
C	6	-0.21466	1.99891	4.20013	0.01562	6.21466
C	7	-0.25663	1.99897	4.24065	0.01701	6.25663
C	8	-0.20557	1.99895	4.19096	0.01566	6.20557
C	9	-0.27430	1.99890	4.25438	0.02101	6.27430
C	10	-0.30502	1.99873	4.26608	0.04021	6.30502
C	11	-0.21220	1.99874	4.19623	0.01724	6.21220
C	12	0.75169	1.99901	3.21187	0.03743	5.24831
O	13	-0.78426	1.99971	6.76438	0.02017	8.78426
N	14	-0.48011	1.99913	5.46304	0.01794	7.48011

C 15	-0.49376	1.99943	4.48155	0.01279	6.49376
C 16	-0.48276	1.99942	4.47236	0.01098	6.48276
H 17	0.24234	0.00000	0.75656	0.00110	0.75766
H 18	0.25018	0.00000	0.74896	0.00087	0.74982
H 19	0.25054	0.00000	0.74872	0.00074	0.74946
H 20	0.25987	0.00000	0.73931	0.00082	0.74013
H 21	0.26200	0.00000	0.73700	0.00100	0.73800
H 22	0.25851	0.00000	0.74071	0.00077	0.74149
H 23	0.24767	0.00000	0.75187	0.00046	0.75233
H 24	0.25388	0.00000	0.74551	0.00061	0.74612
H 25	0.26147	0.00000	0.73771	0.00082	0.73853
H 26	0.24261	0.00000	0.75664	0.00074	0.75739
O 27	-1.29407	1.99998	7.28633	0.00776	9.29407
O 28	-0.82535	1.99984	6.80712	0.01839	8.82535
C 29	-0.33365	1.99939	4.31532	0.01894	6.33365
H 30	0.18795	0.00000	0.80990	0.00215	0.81205
H 31	0.20876	0.00000	0.78955	0.00169	0.79124
H 32	0.21802	0.00000	0.78052	0.00146	0.78198
* Total *	0.00000	53.97722	97.53497	0.48781	152.00000

TS2 (between IM3 and IM4)



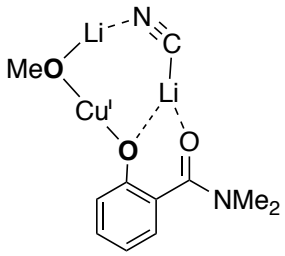
TS2

Summary of Natural Population Analysis:

		Natural Population			
Atom No	Natural Charge	Core	Valence	Rydberg	Total
Li 1	0.92175	1.99844	0.00005	0.07976	2.07825
Li 2	0.89194	1.99754	0.10143	0.00909	2.10806
C 3	-0.16166	1.99951	4.10418	0.05797	6.16166
N 4	-0.73366	1.99956	5.69935	0.03475	7.73366
Cu 5	1.22167	17.99511	9.76415	0.01907	27.77833
C 6	-0.23336	1.99877	4.21821	0.01638	6.23336
C 7	-0.23326	1.99897	4.21671	0.01757	6.23326
C 8	-0.23978	1.99893	4.22472	0.01613	6.23978
C 9	-0.23935	1.99897	4.21975	0.02063	6.23935
C 10	-0.51770	1.99905	4.47602	0.04263	6.51770
C 11	-0.16703	1.99879	4.14700	0.02124	6.16703
C 12	0.75089	1.99904	3.20866	0.04142	5.24911
O 13	-0.78150	1.99971	6.76296	0.01883	8.78150
N 14	-0.50748	1.99916	5.48877	0.01955	7.50748
C 15	-0.48688	1.99943	4.47483	0.01263	6.48688
C 16	-0.48088	1.99942	4.47026	0.01121	6.48088
H 17	0.24325	0.00000	0.75547	0.00129	0.75675
H 18	0.24709	0.00000	0.75200	0.00091	0.75291
H 19	0.24712	0.00000	0.75207	0.00081	0.75288
H 20	0.24319	0.00000	0.75592	0.00089	0.75681
H 21	0.24568	0.00000	0.75336	0.00096	0.75432
H 22	0.26893	0.00000	0.73028	0.00079	0.73107
H 23	0.24005	0.00000	0.75940	0.00054	0.75995
H 24	0.24102	0.00000	0.75812	0.00086	0.75898
H 25	0.26197	0.00000	0.73732	0.00072	0.73803
H 26	0.23966	0.00000	0.75951	0.00083	0.76034
O 27	-1.01480	1.99997	7.00812	0.00670	9.01480
O 28	-0.77137	1.99985	6.75237	0.01915	8.77137
C 29	-0.35548	1.99940	4.33669	0.01939	6.35548
H 30	0.19906	0.00000	0.79896	0.00198	0.80094

H 31	0.21552	0.00000	0.78260	0.00188	0.78448
H 32	0.24541	0.00000	0.75329	0.00130	0.75459
* Total *	0.00001	53.97961	97.52252	0.49786	151.99999

IM4



Summary of Natural Population Analysis:

	Natural	Natural Population			
Atom No	Charge	Core	Valence	Rydberg	Total
Li 1	0.94054	1.99686	0.04996	0.01263	2.05946
Li 2	0.88877	1.99785	0.10306	0.01032	2.11123
C 3	-0.11596	1.99954	4.05278	0.06364	6.11596
N 4	-0.78914	1.99954	5.75124	0.03836	7.78914
Cu 5	0.77530	17.99783	10.21436	0.01252	28.22470
C 6	-0.20094	1.99880	4.18593	0.01621	6.20094
C 7	-0.29013	1.99898	4.27343	0.01773	6.29013
C 8	-0.21360	1.99899	4.19883	0.01579	6.21360
C 9	-0.30204	1.99886	4.28592	0.01726	6.30204
C 10	0.36904	1.99861	3.59758	0.03477	5.63096
C 11	-0.23999	1.99869	4.22160	0.01970	6.23999
C 12	0.73996	1.99905	3.21398	0.04702	5.26004
O 13	-0.75961	1.99973	6.74095	0.01894	8.75961
N 14	-0.50476	1.99915	5.48362	0.02200	7.50476
C 15	-0.48723	1.99943	4.47492	0.01288	6.48723
C 16	-0.48234	1.99941	4.47043	0.01249	6.48234
H 17	0.24243	0.00000	0.75619	0.00138	0.75757
H 18	0.24576	0.00000	0.75342	0.00082	0.75424
H 19	0.24520	0.00000	0.75396	0.00085	0.75480
H 20	0.25176	0.00000	0.74697	0.00127	0.74824
H 21	0.24182	0.00000	0.75695	0.00122	0.75818
H 22	0.27162	0.00000	0.72750	0.00088	0.72838
H 23	0.23776	0.00000	0.76169	0.00055	0.76224
H 24	0.23987	0.00000	0.75919	0.00094	0.76013
H 25	0.26078	0.00000	0.73825	0.00097	0.73922
H 26	0.23924	0.00000	0.75994	0.00082	0.76076
O 27	-0.96117	1.99978	6.94244	0.01896	8.96117
O 28	-1.09278	1.99984	7.07428	0.01866	9.09278
C 29	-0.30803	1.99946	4.28824	0.02033	6.30803
H 30	0.19157	0.00000	0.80638	0.00205	0.80843
H 31	0.17945	0.00000	0.81841	0.00214	0.82055
H 32	0.18684	0.00000	0.81121	0.00195	0.81316
* Total *	0.00000	53.98038	97.57359	0.44604	152.00000

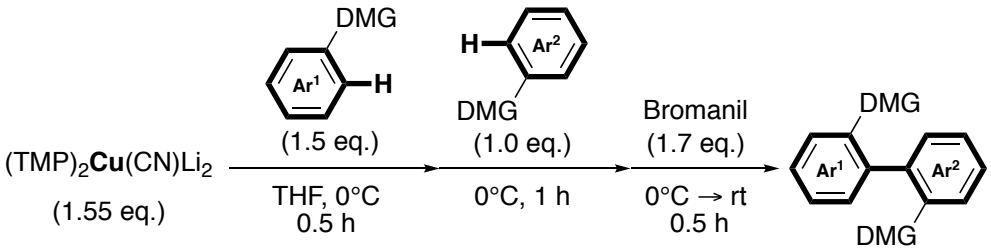
Preparation of Substrates

N,*N*-Diisopropylbenzamide and 4-methoxy-1,1'-biphenyl were prepared with the same protocol as chapter 2. *N*,*N*-diethylbenzenesulfonamide,[6-20] (Methoxymethoxy)benzene[6-21] and dicyclohexyl(phenyl)phosphine oxide[6-22] were prepared according to the literatures.

Formal Cross-Dehydrogenative Coupling *via* Sequential D*o*M and Oxidation

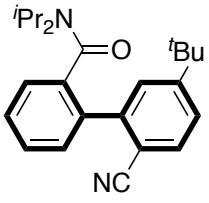
General Procedure:

Unless otherwise noted, the reactions were performed on 0.2 mmol scale.



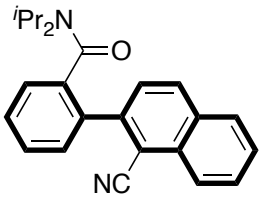
To a solution of 2,2,6,6-tetramethylpiperidine (105 μL, 0.62 mmol) in 0.62 mL of anhydrous THF was added ^{n}BuLi (1.57 M ^{n}hexane solution, 395 μL, 0.62 mmol) at –78°C. The solution was stirred at 0°C for 15 min and transferred to a suspension of copper cyanide (27.8 mg, 0.31 mmol) in 0.62 mL of THF *via* cannula at –78°C. The mixture was stirred at 0°C for 15 min to give the slightly yellow solution of $(TMP)_2Cu(CN)Li_2$ in THF. To this cuprate solution was added the first arene to be deprotonated (Ar^1H, 0.3 mmol) dissolved in 0.3 mL of THF *via* cannula at –78°C and the mixture was stirred at 0°C for 30 min. The second arene (Ar^2H, 0.2 mmol) in 0.2 mL of THF was then transferred to the mixture *via* cannula at –78°C and the resultant solution was stirred at 0°C for 1 h. To the reaction mixture was added bromanil (144.1 mg, 0.34 mmol) at 0°C in one portion and stirred at room temperature for 30 min. The reaction was quenched with saturated NH_4Cl aq. (10 mL), followed by extraction with AcOEt (10 mL × 3). The combined organic layer was washed with 10 wt% Na_2CO_3 aq. (10 mL × 2) and brine (10 mL × 1), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by MPLC and/or PTLC.

5'-(*tert*-Butyl)-2'-cyano-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide (4a)



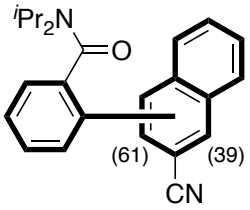
Following the **General Procedure** (83% NMR yield based on mesitylene as an internal standard; purification: MPLC with AcOEt/hexane 0/100 → 10/90, PTLC with acetone/toluene 10/90), the titled compound was obtained as a white solid in 76% (54.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.66 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.32 (s, 9H), 1.48 (d, *J* = 6.8 Hz, 3H), 3.21 (sep, *J* = 6.8 Hz, 1H), 3.57 (sep, *J* = 6.6 Hz, 1H), 7.30-7.34 (m, 1H), 7.43-7.48 (m, 4H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.76 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.3, 20.5, 20.6, 20.7, 31.0, 35.5, 45.5, 50.7, 109.3, 118.7, 125.6, 126.1, 128.4, 129.1, 129.5, 130.6, 132.7, 134.5, 138.4, 143.0, 156.4, 169.3. **FTIR (ATR):** 2965, 2224, 1627, 1337, 768, 731. **mp:** 150.6°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{24}H_{30}N_2O$: C, 79.52; H, 8.34; N, 7.73. Found: C, 79.42; H, 8.15; N, 7.75. **HRMS (pos. ESI):** *m/z*: calcd for $C_{24}H_{30}N_2NaO$ $[M+Na]^+$ 385.2250, found 385.2256.

2-(1-Cyanonaphthalen-2-yl)-*N*,*N*-diisopropylbenzamide (4b)



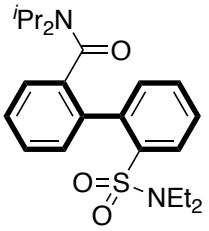
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 10/90, PTLC with acetone/toluene 10/90), the titled compound was obtained as a white solid in 70% (50.1 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.48 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 3.16 (sep, *J* = 6.8 Hz, 1H), 3.67 (sep, *J* = 6.6 Hz, 1H), 7.37-7.41 (m, 1H), 7.50-7.54 (m, 2H), 7.58-7.62 (m, 1H), 7.64 (ddd, *J* = 1.1, 7.0, 8.1 Hz, 1H), 7.73 (ddd, *J* = 1.2, 7.0, 8.3 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.8, 20.1, 20.8, 21.0, 45.7, 50.9, 109.4, 117.3, 125.6, 126.4, 127.7, 128.6, 128.70, 128.74, 129.0, 129.6, 130.9, 132.1, 132.3, 132.8, 134.4, 138.6, 144.4, 169.3. **FTIR (ATR):** 2971, 2221, 1625, 1342, 770, 455. **mp:** 172.8°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{24}H_{24}N_2O$ + 1/10·H_2O: C, 80.46; H, 6.81; N, 7.82. Found: C, 80.45; H, 6.74; N, 7.78. **HRMS (pos. ESI):** *m/z*: calcd for $C_{24}H_{24}N_2NaO$ $[M+Na]^+$ 379.1781, found 379.1784.

2-(3-Cyanonaphthalen-2-yl)-*N*,*N*-diisopropylbenzamide (4c$_{major}$) and 2-(2-cyanonaphthalen-1-yl)-*N*,*N*-diisopropylbenzamide (4c$_{minor}$) (61 : 39)



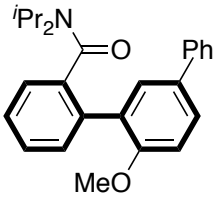
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 20/80, PTLC with acetone/toluene 10/90), the mixture of the titled compounds (61 : 39) were obtained as a slightly pink solid in 73% (52.2 mg). **[4c$_{major}$] ^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.48 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 3.12 (sep, *J* = 6.8 Hz, 1H), 3.63 (sep, *J* = 6.6 Hz, 1H), 7.38-7.40 (m, 1H), 7.42-7.66 (m, 5H), 7.88-7.92 (m, 2H), 8.23 (s, 1H), 8.35 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.7, 20.0, 20.8, 20.9, 45.6, 50.7, 110.3, 118.7, 126.4, 127.9, 128.0, 128.4, 128.7, 129.1, 129.6, 130.8, 131.0, 131.3, 131.4, 133.6, 134.3, 135.5, 138.8, 169.5. **[4c$_{minor}$] ^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.48 (overlapped with **4c$_{major}$**, 3H), 0.82 (brd, *J* = 5.3 Hz, 3H), 1.04 (brd, *J* = 5.3 Hz, 3H), 1.32 (brd, *J* = 5.3 Hz, 3H), 3.10-3.16 (overlapped with **4c$_{major}$**, 1H), 3.85 (brs, 1H), 7.42-7.66 (m, 7H), 7.76 (brd, *J* = 8.3 Hz, 1H), 7.85 (brd, *J* = 8.0 Hz, 1H), 7.88-7.92 (overlapped with **4c$_{major}$**, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.2, 20.4, 20.8 (overlapped with **4c$_{major}$**), 21.4, 45.4, 50.5, 110.0, 118.9, 126.0, 126.3, 127.3, 127.4, 128.8, 129.2, 129.3, 129.5, 129.6 (overlapped with **4c$_{major}$**), 132.0, 133.1, 134.5, 136.7, 139.0, 145.0, 168.7. **HRMS (pos. ESI):** *m/z*: calcd for $C_{24}H_{24}N_2NaO$ $[M+Na]^+$ 379.1781, found 379.1794.

2'-(*N*,*N*-Diethylsulfamoyl)-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide (4d)



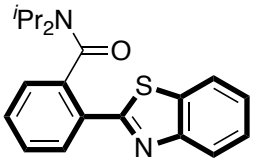
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 15/85, PTLC with MeOH/CH_2Cl_2 2/98, GPC), the titled compound was obtained with inseparable contaminates as a colorless oil in 49% yield (46.6 mg, purity = 87 wt%) determined by ^{1}H NMR using mesitylene (3.9 mg) as an internal standard (mesitylene : **4d** = 1 : 1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.65 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 6H), 1.48 (d, *J* = 6.8 Hz, 3H), 3.19-3.28 (m, 3H), 3.38-3.47 (m, 2H), 4.04 (sep, *J* = 6.6 Hz, 1H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.33-7.45 (m, 3H), 7.51-7.55 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 14.1, 19.9, 20.7, 21.0, 21.1, 41.4, 45.5, 50.3, 126.0, 127.0, 127.6, 128.2, 128.5, 130.7, 131.6, 135.0, 135.1, 138.3, 138.7, 139.4, 169.6. **HRMS (pos. ESI):** *m/z*: calcd for $C_{23}H_{32}N_2NaO_3S$ $[M+Na]^+$ 439.2026, found 439.2026.

***N*,*N*-Diisopropyl-6'-methoxy-[1,1':3',1''-terphenyl]-2-carboxamide (4e)**



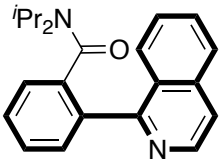
Following the **General Procedure** (Cuprate **1** (2.0 eq.), *N*,*N*-diisopropylbenzamide (**2a**, 2.0 eq.) and pentafluoronitrobenzene (2.5 eq.) were used.; 73% NMR yield based on mesitylene as an internal standard; purification: MPLC with AcOEt/hexane 2/98 → 25/75, GPC), the titled compound was obtained as a white solid in 51% (40.5 mg; 12% of inseparable CH_2Cl_2 was subtracted). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.56 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.47 (d, *J* = 6.8 Hz, 3H), 3.17 (sep, *J* = 6.8 Hz, 1H), 3.62 (sep, *J* = 6.6 Hz, 1H), 3.81 (s, 3H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.25-7.28 (m, 1H), 7.32-7.40 (m, 5H), 7.42-7.45 (m, 1H), 7.56 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.59-7.61 (m, 2H), 7.73 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.0 (overlapped), 20.8, 21.1, 45.5, 50.5, 55.5, 110.8, 126.4, 126.8 (overlapped), 127.3, 127.4, 127.7, 128.6, 128.8, 131.2, 131.3, 133.2, 134.2, 139.0, 140.4, 156.1, 170.2. **FTIR (ATR):** 2965, 1621, 1476, 1338, 1254, 760, 730. **mp:** 178.2°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{26}H_{29}NO_2$ + 1/4·H_2O: C, 79.66; H, 7.59; N, 3.57. Found: C, 79.63; H, 7.40; N, 3.69. **HRMS (pos. ESI):** *m/z*: calcd for $C_{26}H_{29}NNaO_2$ $[M+Na]^+$ 410.2091, found 410.2092.

2-(Benzo[*d*]thiazol-2-yl)-*N*,*N*-diisopropylbenzamide (4f)



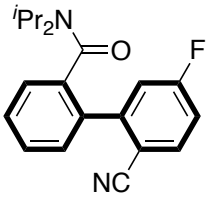
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 20/80), the titled compound was obtained as a slightly brown solid in 66% (44.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.97 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 3.50 (sep, *J* = 6.8 Hz, 1H), 3.74 (sep, *J* = 6.7 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.38 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.45-7.51 (m, 3H), 7.89-7.91 (m, 2H), 8.01 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.9, 20.0, 20.8, 20.9, 45.9, 51.2, 121.7, 123.5, 125.4, 126.3, 126.9, 128.7, 130.1, 130.2, 130.6, 135.8, 138.5, 154.0, 165.9, 169.8. **FTIR (ATR):** 2968, 1631, 1434, 1338, 761. **mp:** 182.7°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.28. Found: C, 71.24; H, 6.55; N, 8.28. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{22}N_2NaOS$ $[M+Na]^+$ 361.1345, found 361.1352.

***N*,*N*-Diisopropyl-2-(isoquinolin-1-yl)benzamide (4g)**



Following the **General Procedure** (purification: MPLC with AcOEt/hexane 10/90 → 25/75), the titled compound was obtained as a brown oil in 60% (39.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.81 (brs, 3H), 0.85 (brs, 3H), 1.04 (brs, 3H), 1.38 (brs, 3H), 3.20 (sep, *J* = 6.8 Hz, 1H), 3.94 (sep, *J* = 6.6 Hz, 1H), 7.40-7.42 (m, 1H), 7.48-7.55 (m, 4H), 7.63-7.67 (m, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 8.52 (d, *J* = 5.6 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.5, 20.2, 20.6, 21.1, 45.4, 51.1, 120.5, 126.4, 126.6, 127.3, 127.5, 128.1, 128.4, 128.6, 130.4, 130.6, 136.5, 136.7, 139.6, 141.6, 159.8, 169.9. **FTIR (ATR):** 2965, 1625, 1338, 730. **HRMS (pos. ESI):** *m/z*: calcd for $C_{22}H_{24}N_2NaO$ $[M+Na]^+$ 355.1781, found 355.1788.

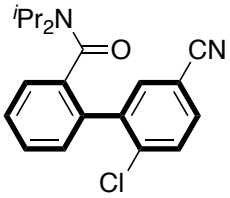
2'-Cyano-5'-fluoro-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide (4h)

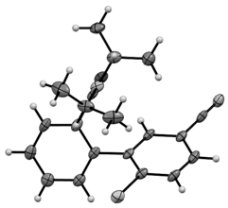


Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 20/80, PTLC with acetone/toluene 10/90), the titled compound was obtained as a white solid in 55% (35.7 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.72 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.50 (d, *J* = 6.7 Hz, 3H), 3.30 (sep, *J* = 6.7 Hz, 1H), 3.63 (sep, *J* = 6.6 Hz, 1H), 7.23 (dd, *J* = 8.8, 9.1 Hz, 1H), 7.34-7.36 (m, 1H), 7.37-7.41 (m, 1H), 7.42-7.47 (m, 2H), 7.64 (ddd, *J* = 2.2, 4.6, 8.5 Hz, 1H), 7.89 (dd, *J* = 2.2, 6.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.8, 20.1, 20.7, 21.1, 45.9, 50.8, 108.7 (d, *J* = 4 Hz), 117.0, (d, *J* = 24 Hz), 117.8, 126.4, 128.4, 129.1, 129.3 (d, *J* =

16 Hz), 129.6, 130.8 (d, *J* = 3 Hz), 133.8 (d, *J* = 9 Hz), 136.8 (d, *J* = 4 Hz), 138.7, 162.1 (d, *J* = 257 Hz), 169.0. **^{19}F NMR (470 MHz, $CDCl_3$):** δ –106.7. **FTIR (ATR):** 2968, 2231, 1623, 1436, 1338, 1032, 701, 618. **mp:** 100.1°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{20}H_{21}FN_2O$: C, 74.05; H, 6.53; N, 8.64. Found: C, 73.82; H, 6.54; N, 8.60. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{21}FN_2NaO$ $[M+Na]^+$ 347.1530, found 347.1534.

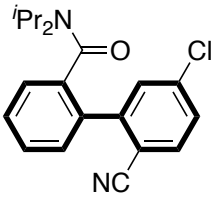
2'-Chloro-5'-cyano-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide ($4i_{major}$)

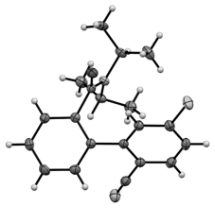




Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 10/90, trituration with hexane), the titled compound was obtained as a white solid in 37% yield (26.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.68 (brs, 3H), 1.02 (brs, 3H), 1.12 (brd, *J* = 6.2 Hz, 3H), 1.49 (brd, *J* = 6.2 Hz, 3H), 3.26 (brs, 1H), 3.62 (brs, 1H), 7.34 (brd, *J* = 7.6 Hz, 1H), 7.38 (brd, *J* = 7.0 Hz, 1H), 7.41-7.47 (m, 2H), 7.57 (brs, 2H), 7.93 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.7, 20.2, 20.5, 21.0, 45.7, 50.6, 110.8, 117.6, 126.0, 127.8, 129.0, 130.6, 130.8, 132.2, 132.4, 136.4, 138.1, 138.5, 139.3, 168.7. **FTIR (ATR):** 2969, 2231, 1624, 1339, 1073, 1032, 764, 613. **mp:** 141.4°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{20}H_{21}ClN_2O$: C, 70.48; H, 6.21; N, 8.22. Found: C, 70.37; H, 6.25; N, 8.19. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{21}ClN_2NaO$ $[M+Na]^+$ 363.1235, found 363.1244. **Crystal structure:** CCDC 1959875.

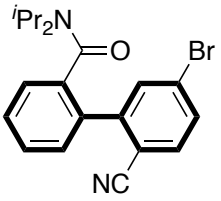
5'-Chloro-2'-cyano-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide ($4i_{minor}$)

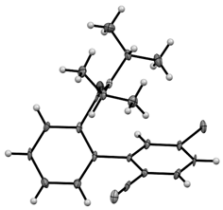




Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 10/90, PTLC with acetone/toluene 10/90), the titled compound was obtained as a white solid in 27% yield (18.3 mg; 7% of isomer was subtracted). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.65 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.51 (d, *J* = 6.8 Hz, 3H), 3.26 (sep, *J* = 6.8 Hz, 1H), 3.57 (sep, *J* = 6.6 Hz, 1H), 7.35-7.38 (m, 1H), 7.44 (dd, *J* = 1.0, 7.3 Hz, 1H), 7.48-7.51 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.8, 20.2, 20.8, 21.0, 45.9, 50.9, 110.9, 117.7, 126.4, 128.6, 128.7, 129.8, 130.3, 132.2, 132.5, 134.2, 138.4, 139.3, 144.9, 168.9. **FTIR (ATR):** 2970, 2227, 1625, 1436, 1338, 1096, 768. **mp:** 148.1°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{20}H_{21}ClN_2O$ + 1/3·H_2O + 1/12·heaxne: C, 69.55; H, 6.50; N, 7.91. Found: C, 69.58; H, 6.67; N, 8.12. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{21}ClN_2NaO$ $[M+Na]^+$ 363.1235, found 363.1241. **Crystal structure:** CCDC 1959872.

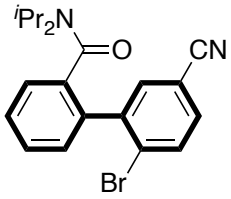
5'-Bromo-2'-cyano-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide ($4j_{major}$)





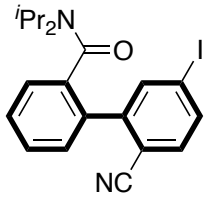
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 15/85, PTLC with acetone/toluene 10/90), the titled compound was obtained as a colorless solid in 34% (26.3 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.66 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.51 (d, *J* = 6.8 Hz, 3H), 3.27 (sep, *J* = 6.8 Hz, 1H), 3.58 (sep, *J* = 6.6 Hz, 1H), 7.34-7.37 (m, 1H), 7.48-7.51 (m, 3H), 7.60 (m, 2H), 7.94 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.9, 20.2, 20.7, 21.0, 45.9, 50.8, 111.3, 117.8, 126.4, 127.7, 128.7, 129.8, 130.3, 131.5, 132.4, 134.2, 134.9, 138.4, 144.9, 168.9. **FTIR (ATR):** 2969, 2228, 1625, 1339, 768. **mp:** 150.9°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{20}H_{21}BrN_2O$: C, 62.35; H, 5.49; N, 7.27. Found: C, 62.51; H, 5.49; N, 7.23. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{21}BrN_2NaO$ $[M+Na]^+$ 407.0729, found 407.0730. **Crystal structure:** CCDC 1959876.

2'-Bromo-5'-cyano-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide ($4j_{minor}$)



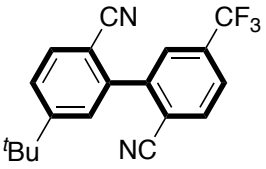
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 15/85, PTLC with acetone/toluene 10/90, GPC), the titled compound was obtained with inseparable contaminates as a colorless solid in 14% yield (13.2 mg, purity = 84 wt%) determined by ^{1}H NMR using mesitylene (3.4 mg) as an internal standard (mesitylene : $\mathbf{4j_{minor}}$ = 2.95 : 1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.68 (brd, *J* = 5.8 Hz, 3H), 1.00 (brd, *J* = 5.8 Hz, 3H), 1.11 (brd, *J* = 6.7 Hz, 3H), 1.49 (brd, *J* = 6.7 Hz, 3H), 3.25 (brs, 1H), 3.61 (brs, 1H), 7.32-7.48 (m, 5H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.94 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 19.8, 20.5, 20.7, 21.0, 45.8, 50.6, 111.6, 117.8, 126.2, 127.8, 128.9, 129.2, 131.1, 132.2, 133.9 (overlapped), 136.3, 138.5, 141.1, 168.8. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{21}BrN_2NaO$ $[M+Na]^+$ 407.0729, found 407.0732.

2'-Cyano-5'-iodo-*N*,*N*-diisopropyl-[1,1'-biphenyl]-2-carboxamide (4k)



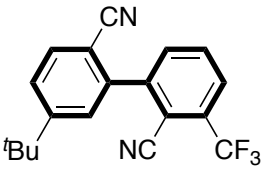
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 5/95, PTLC with CH_2Cl_2/hexane 5/1, GPC), the titled compound was obtained as a white solid in 44% (37.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.67 (brd, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.51 (d, *J* = 6.7 Hz, 3H), 3.27 (sep, *J* = 6.7 Hz, 1H), 3.58 (sep, *J* = 6.7 Hz, 1H), 7.34-7.36 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.47-7.51 (m, 3H), 7.82 (dd, *J* =1.8, 8.2 Hz, 1H), 8.13 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.1, 20.2, 20.7, 21.0, 46.0, 50.8, 100.1, 111.9, 117.9, 126.4, 128.7, 129.8, 130.3, 132.3, 133.9, 137.4, 138.4, 140.7, 144.5, 168.9. **FTIR (ATR):** 2968, 2226, 1620, 1338, 729. **mp:** 154.0°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{20}H_{21}IN_2O$: C, 55.57; H, 4.90; N, 6.48. Found: C, 55.42; H, 4.91; N, 6.49. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{21}IN_2NaO$ $[M+Na]^+$ 455.0591, found 455.0600.

5-(*tert*-Butyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-2,2'-dicarbonitrile (4l)



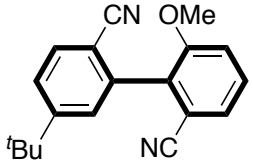
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 15/85, GPC), the titled compound was obtained as a colorless oil in 54% (35.6 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.39 (s, 9H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.63 (dd, *J* = 1.8, 8.2 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.86 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 31.0, 35.8, 109.4, 116.2, 116.6, 117.6, 123.0 (q, *J* = 273 Hz), 126.9 (q, *J* = 4 Hz), 127.1, 127.7 (q, *J* = 4 Hz), 128.1, 133.7, 134.3, 134.8 (q, *J* = 34 Hz), 139.9, 143.2, 157.4. **^{19}F NMR (376 MHz, $CDCl_3$):** δ –63.4. **FTIR (ATR):** 2964, 2221, 1602, 1466, 1326, 1154, 578. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{15}F_3N_2Na$ $[M+Na]^+$ 351.1080, found 351.1081.

5'-(*tert*-Butyl)-3-(trifluoromethyl)-[1,1'-biphenyl]-2,2'-dicarbonitrile (4m)



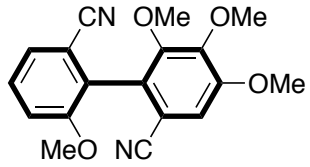
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 10/90), the titled compound was obtained as a slightly brown solid in 55% (36.2 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.39 (s, 9H), 7.61-7.63 (m, 2H), 7.78-7.81 (m, 2H), 7.84 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 31.0, 35.8, 109.4, 110.3 (q, *J* = 2 Hz), 114.2, 117.7, 122.4 (q, *J* = 274 Hz), 126.8 (q, *J* = 5 Hz), 127.0, 128.4, 132.7, 133.7, 133.9, 134.3 (q, *J* = 33 Hz), 140.1, 144.9, 157.3. **^{19}F NMR (470 MHz, $CDCl_3$):** δ –61.8. **FTIR (ATR):** 2967, 2226, 1603, 1330, 1137, 816, 755. **mp:** 126.7°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{19}H_{15}F_3N_2$ + 1/6·H_2O: C, 68.87; H, 4.66; N, 8.45. Found: C, 68.91; H, 4.79; N, 8.44. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{15}F_3N_2Na$ $[M+Na]^+$ 351.1080, found 351.1085.

5-(*tert*-Butyl)-6'-methoxy-[1,1'-biphenyl]-2,2'-dicarbonitrile (4n)



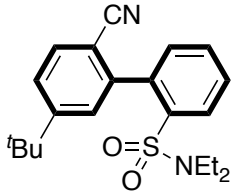
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 20/80), the titled compound was obtained as a slightly brown oil in 41% (23.7 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.38 (s, 9H), 3.87 (s, 3H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H). 7.49-7.54 (m, 3H), 7.71 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 31.0, 35.6, 56.2, 110.9, 114.3, 115.9, 117.6, 118.3, 125.3, 126.0, 128.8, 130.8, 131.3, 132.9, 137.8, 156.8, 157.2. **FTIR (ATR):** 2964, 2226, 1603, 1577, 1468, 1271, 1067, 795. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{18}N_2NaO$ $[M+Na]^+$ 313.1311, found 313.1315.

4,5,6,6'-Tetramethoxy-[1,1'-biphenyl]-2,2'-dicarbonitrile (4o)



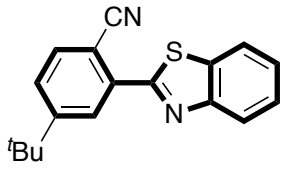
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 25/75 → 35/65, GPC), the titled compound was obtained as a slightly brown oil in 42% (27.3 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.74 (s, 3H), 3.84 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 7.04 (s, 1H), 7.24 (dd, *J* = 0.9, 8.4 Hz, 1H), 7.38 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 8.4 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 56.3, 56.5, 61.4, 61.5, 108.4, 111.5, 115.3, 115.8, 117.5 117.6, 124.8, 126.2, 127.5, 130.7, 146.7, 152.3, 154.3, 157.6. **FTIR (ATR):** 2943, 2842, 2228, 1578, 1466, 1335, 1270, 1103, 730. **HRMS (pos. ESI):** *m/z*: calcd for $C_{18}H_{16}N_2NaO_4$ $[M+Na]^+$ 347.1002, found 347.1003.

5'-(*tert*-Butyl)-2'-cyano-*N*,*N*-diethyl-[1,1'-biphenyl]-2-sulfonamide (4p)



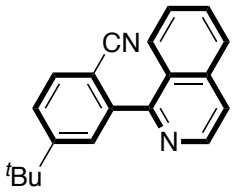
Following the **General Procedure** (62% NMR yield based on mesitylene as an internal standard; purification: MPLC with AcOEt/hexane 5/95 → 15/85, MPLC with CH_2Cl_2 100%), the titled compound was obtained as a white solid in 53% (39.0 mg). For the inverse order of sequential D*o*M, following the **General Procedure** (purification: MPLC with AcOEt/hexane 5/95 → 15/85, washed with 10 wt% Na_2CO_3 aq. once), the titled compound was obtained as a white solid in 35% with a trace amount of inseparable contaminate (25.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.00 (t, *J* = 7.2 Hz, 6H), 1.36 (s, 9H), 2.84 (q, *J* = 7.2 Hz, 4H), 7.37 (dd, *J* = 1.3, 7.5 Hz, 1H), 7.49 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.56 (ddd, *J* = 1.3, 7.5, 7.5 Hz, 1H), 7.63 (ddd, *J* = 1.3, 7.5, 7.5 Hz, 1H), 7.66-7.67 (m, 2H), 8.14 (dd, *J* = 1.3, 7.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 14.4, 31.0, 35.6, 41.5, 109.8, 118.4, 125.5, 128.9, 129.8, 130.3, 132.2, 132.3, 132.8, 137.7, 139.5, 142.6, 155.6. **FTIR (ATR):** 2964, 2221, 1602, 1466, 1326, 1154, 578. **mp:** 102.9°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{21}H_{26}N_2O_2S$: C, 68.08; H, 7.07; N, 7.56. Found: C, 68.17; H, 6.97; N, 7.53. **HRMS (pos. ESI):** *m/z*: calcd for $C_{21}H_{26}N_2NaO_2S$ $[M+Na]^+$ 393.1607, found 393.1612.

2-(Benzo[*d*]thiazol-2-yl)-4-(*tert*-butyl)benzonitrile (4q)



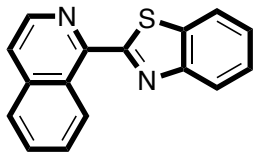
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 0/100 → 5/95, PTLC with CH_2Cl_2/hexane 50/50), the titled compound was obtained as a white solid in 50% (29.3 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.41 (s, 9H), 7.46 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.55 (dd, *J* = 7.2, 8.2 Hz, 1H), 7.60 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 1.9 Hz, 1H) 8.19 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 31.0, 35.6, 108.2, 118.5, 121.8, 124.2, 126.1, 126.8, 127.6, 127.9, 134.9, 135.9, 136.2, 153.7, 157.3, 164.0. **FTIR (ATR):** 2962, 2224, 1221, 986, 835, 759, 728. **mp:** 92.0°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58. Found: C, 73.90; H, 5.49; N, 9.53. **HRMS (pos. ESI):** *m/z*: calcd for $C_{18}H_{16}N_2NaS$ $[M+Na]^+$ 315.0926, found 315.0930.

1-(5-(*tert*-Butyl)-2-isocyanophenyl)isoquinoline (4r)



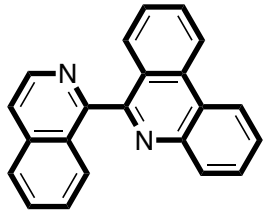
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 10/90 → 20/80, washed with 10 wt% Na_2CO_3 aq. once), the titled compound was obtained as a brown oil in 43% (24.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.38 (s, 9H), 7.57 (ddd, *J* = 1.0, 7.2, 8.1 Hz, 1H), 7.62 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 7.71-7.77 (m, 3H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.94 (dd, *J* = 1.6, 8.1 Hz, 1H), 8.68 (d, *J* = 5.7 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 31.1, 35.6, 110.3, 118.2, 121.3, 126.2, 126.8, 127.1, 127.4, 127.9, 128.2, 130.6, 133.4, 136.9, 142.4, 142.9, 156.5, 157.8. **FTIR (ATR):** 2962, 2225, 1378, 1262, 829, 731. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{18}N_2Na$ $[M+Na]^+$ 309.1362, found 309.1366.

2-(Isoquinolin-1-yl)benzo[*d*]thiazole (4s)



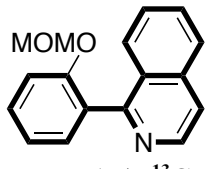
Following the **General Procedure** (44% NMR yield based on mesitylene as an internal standard; purification: MPLC with AcOEt/hexane 0/100 → 10/90, PTLC with acetone/toluene 0.1/99.9, GPC), the titled compound was obtained as a white solid in 30% (15.7 mg). ^{1}H and ^{13}C NMR spectra were in agreement with the reference.[6-23] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.46 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.54 (dd, *J* = 7.6, 8.1 Hz, 1H), 7.75-7.81 (m, 3H), 7.90 (d, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.64 (brs, 1H), 10.00 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 121.8, 123.2, 124.2, 126.0, 126.2 (overlapped), 127.1, 128.0, 129.2, 130.6, 136.2, 137.4, 141.9, 149.5, 155.0, 170.9. **HRMS (pos. ESI):** *m/z*: calcd for $C_{16}H_{10}N_2NaS$ $[M+Na]^+$ 285.0457, found 285.0447.

6-(Isoquinolin-1-yl)phenanthridine (4t)



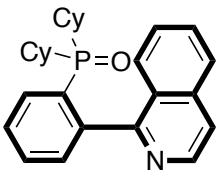
Following the **General Procedure** (1.0 mmol scale; purification: MPLC with AcOEt/hexane 0/100 → 50/50), the titled compound was obtained as a brown oil in 50% (154.2 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.42 (ddd, *J* = 1.2, 7.0, 8.4 Hz, 1H), 7.51 (ddd, *J* = 1.1, 7.0, 8.2 Hz, 1H), 7.66-7.85 (m, 7H), 7.93 (d, *J* = 8.3 Hz, 1H), 8.28 (dd, *J* = 1.3, 8.1 Hz, 1H), 8.68 (dd, *J* = 1.4, 8.1 Hz, 1H), 8.72-8.75 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 121.3, 122.20, 122.23, 124.3, 125.9, 127.1, 127.2, 127.5, 127.6, 127.7, 127.9, 128.5, 129.0, 130.5, 130.6, 131.0, 133.5, 136.9, 142.2, 143.6, 158.3, 158.7. **FTIR (ATR):** 3059, 2962, 1308, 1146, 945, 827, 744, 725, 665. **HRMS (pos. ESI):** *m/z*: calcd for $C_{22}H_{14}N_2Na$ $[M+Na]^+$ 329.1049, found 329.1055.

1-(2-(Methoxymethoxy)phenyl)isoquinoline (4u)



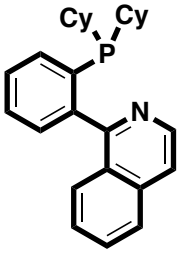
Following the **General Procedure** (purification: MPLC with AcOEt/hexane 5/95 → 20/80), the titled compound was obtained as a brown oil in 34% (18.0 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.21 (s, 3H), 4.93 (d, *J* = 6.8 Hz, 1H), 5.06 (d, *J* = 6.8 Hz, 1H), 7.17 (ddd, *J* = 0.5, 7.4, 6.9 Hz, 1H), 7.28 (dd, *J* = 0.7, 8.3 Hz, 1H), 7.40-7.50 (m, 3H), 7.65-7.69 (m, 2H), 7.76 (dd, *J* = 0.8, 8.5 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.62 (d, *J* = 5.7 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 56.2, 94.9, 115.2, 120.3, 122.3, 126.9, 127.0, 127.9, 128.1, 129.8, 130.1, 130.2, 131.3, 136.3, 142.3, 155.0, 159.1. **FTIR (ATR):** 2928, 1152, 995, 753. **HRMS (pos. ESI):** *m/z*: calcd for $C_{17}H_{15}NNaO_2$ $[M+Na]^+$ 288.0995, found 288.0999.

Dicyclohexyl(2-(isoquinolin-1-yl)phenyl)phosphine oxide (4v)



Following the **General Procedure** (70% NMR yield based on mesitylene as an internal standard; purification: MPLC with AcOEt/hexane 50/50 → 80/20 then MeOH/$CHCl_3$ 5/95 → 10/90, GPC, trituration with hexane), the titled compound was obtained as a white solid in 58% (48.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.61-2.04 (m, 22H), 7.42-7.44 (m, 1H), 7.49 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.58-7.71 (m, 4H), 7.73 (d, *J* = 5.7 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 8.15 (m, 1H), 8.56 (d, *J* = 5.7 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 25.8, 26.4 (brs), 26.6 (d, *J* = 13 Hz), 38.0 (d, *J* = 64 Hz), 120.9, 127.1, 127.4, 127.5, 128.0, 128.2 (d, *J* = 10 Hz), 130.2 (d, *J* = 2 Hz), 130.3, 131.0 (d, *J* = 9 Hz), 132.0 (d, *J* = 80 Hz), 134.4 (d, *J* = 7 Hz), 136.5, 141.3 (d, *J* = 8 Hz), 141.5, 160.9 (d, *J* = 3 Hz). **^{31}P NMR (202 MHz, $CDCl_3$):** δ 48.3. **FTIR (ATR):** 2927, 2850, 1448, 1161, 727, 567. **mp:** 178.4°C (recrystallized from Et_2O). **Anal.:** calcd for $C_{27}H_{32}NOP$: C, 77.67; H, 7.73; N, 3.35. Found: C, 77.77; H, 7.76; N, 3.37. **HRMS (pos. ESI):** *m/z*: calcd for $C_{27}H_{32}NNaOP$ $[M+Na]^+$ 440.2114, found 440.2114.

1-(2-(Dicyclohexylphosphaneyl)phenyl)isoquinoline (5)



The reduction of phosphine oxide was performed directly on the crude mixture of D*o*M/oxidation process based on the previously reported procedure.[6-24] Following the **General Procedure**, the obtained crude mixture containing **4v** was loaded on a short pad of silica gel and eluted with 50 mL of MeOH/CH_2Cl_2 (5/95). All the volatiles were removed *in vacuo* for 30 min and the mixture was transferred to a heat gun-dried Schlenk tube with dry toluene (6 mL). To the solution were added trichlorosilane (221 μL, 2.25 mmol) and *N*,*N*-diisopropylethylamine (481 μL, 2.85 mmol) and the resulting reaction mixture was stirred at 70 °C for 10 h. Then, the mixture was cooled with ice and diluted with CH_2Cl_2. 2M NaOH aq. (20 mL) was carefully added and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by MPLC with AcOEt/hexane (0/100 → 20/80) and the titled compound was obtained as a white solid in 45% (36.0 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.93-1.27 (m, 10H), 1.55-1.69 (m, 11H), 2.03-2.07 (m, 1H), 7.37-7.51 (m, 5H), 7.62-7.70 (m, 3H), 7.85 (d, *J* = 8.2 Hz, 1H), 8.57 (d, *J* = 5.7 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 26.4, 26.5, 27.1 (d, *J* = 11 Hz), 27.2 (d, *J* = 10 Hz), 27.6 (d, *J* = 6 Hz), 27.7 (d, *J* = 13 Hz), 28.8 (d, *J* = 4 Hz), 29.9 (d, *J* = 18 Hz), 30.0 (d, *J* = 13 Hz), 30.7 (d, *J* = 15 Hz), 32.8 (d, *J* = 12 Hz), 35.2 (d, *J* = 15 Hz), 120.2, 126.8, 126.9, 127.7, 128.2, 128.3 (d, *J* = 3 Hz), 128.7, 129.8, 129.9, 130.0, 132.8 (d, *J* = 3 Hz), 135.6 (d, *J* = 21 Hz), 136.0, 141.5, 162.4. **^{31}P NMR (202 MHz, $CDCl_3$):** δ –10.7. **FTIR (ATR):** 2922, 2847, 1445, 822, 729, 681. **mp:** 139.8°C (recrystallized from $CHCl_3$/hexane). **Anal.:** calcd for $C_{27}H_{32}NP$: C, 80.76; H, 8.03; N, 3.49. Found: C, 80.64; H, 8.02; N, 3.51. **HRMS (pos. ESI):** *m/z*: calcd for $C_{27}H_{33}NP$ $[M+H]^+$ 402.2345, found 402.2352.

Preparation of Argentates

The protocols below were scaled up on demand ranging from 0.12 mmol to 1.2 mmol.

Preparation of TMPLi in THF (0.24 mmol scale)*

To a solution of 2,2,6,6-tetramethylpiperidine (40.5 μL, 0.24 mmol) in 0.24 mL of anhydrous THF was added ^{n}BuLi (1.54 M ^{n}hexane solution, 156 μL, 0.24 mmol) at –78°C under Ar. The mixture was stirred for 15–30 min at 0°C to give a slightly yellow solution of TMPLi (lithium 2,2,6,6-tetramethylpiperidide) in THF.

* When 1,4-dioxane was employed as a solvent, ^{n}BuLi was added to solid state TMPH in 1,4-dioxane at –78°C. The mixture gradually transformed into a deep red solution with a small amount of precipitate upon warming to room temperature. This was stirred for 15 min to give TMPLi in dioxane.

* When benzene was employed as a solvent, ^{n}BuLi was added to a solid mixture of TMPH and benzene at –78°C. The mixture gradually gave a yellowish viscous solution upon warming to 0°C, which was stirred for 30 min to give TMPLi in benzene.

General Procedure for Preparation of mono-TMP silvers (TMP)Ag(X)Li in THF (0.12 mmol scale)

To a suspension of silver source (0.12 mmol) in 0.24 mL of anhydrous THF was added the solution of TMPLi in THF (0.12 mmol) *via* cannula at –78°C under Ar. The mixture was stirred at 0°C for 15–30 min to give a solution of (TMP)Ag(X)Li in THF.

1. (TMP)Ag(NO_3)Li: $AgNO_3$ (20.8 mg, 0.12 mmol) was used.
2. (TMP)Ag(CN)Li: AgCN (16.1 mg, 0.12 mmol) was used.

General Procedure for Preparation of bis-TMP argentate $(TMP)_2Ag(X)Li_2$ in THF (0.12 mmol scale)

To a suspension of silver source (0.12 mmol) in 0.12 mL of anhydrous THF was added the solution of TMPLi in THF (0.24 mmol) *via* cannula at –78°C under Ar. The mixture was stirred at 0 °C for 15–30 min to give a solution of $(TMP)_2Ag(X)Li_2$ in THF.*

3. $(TMP)_2Ag(NO_3)Li_2$: $AgNO_3$ (20.5 mg, 0.12 mmol) was used.
4. $(TMP)_2Ag(1/2•CO_3)Li_2$: Ag_2CO_3 (16.5 mg, 0.06 mmol) was used.
5. $(TMP)_2Ag(OTf)Li_2$: AgOTf (30.9 mg, 0.12 mmol) was used.
6. $(TMP)_2Ag(CN)Li_2$: AgCN (16.3 mg, 0.12 mmol) was used.

* When 1,4-dioxane was employed as a solvent, TMPLi in 1,4-dioxane was added to the solid mixture of AgCN and 1,4-dioxane at –78°C. The mixture gradually formed a dark brown solution with a small amount of precipitate upon warming to room temperature and was stirred for 15 min to give $(TMP)_2Ag(CN)Li_2$ in 1,4-dioxane.

* When benzene was employed as a solvent, TMPLi in benzene was added to the solid AgCN in benzene at –78°C. The mixture gradually turned to be the black solution upon warming to 0°C and was stirred for 30 min to give $(TMP)_2Ag(CN)Li_2$ in benzene.

Preparation of $(Cy_2N)_2Ag(CN)Li_2$ in THF (0.12 mmol scale)

To a solution of dicyclohexylamine (47.8 μL, 0.24 mmol) in 0.24 mL of anhydrous THF was added ^{n}BuLi (1.54 M ^{n}hexane solution, 156 μL, 0.24 mmol) at –78°C under Ar. The mixture was stirred for 30 min at 0°C to give a solution of Cy_2NLi (lithium dicyclohexylamide) in THF. To a suspension of silver cyanide (16.2 mg, 0.12 mmol) in 1.2 mL of anhydrous THF was added the solution of Cy_2NLi in THF (0.24 mmol) *via* cannula at –78°C under Ar, and the reaction mixture was stirred at 0°C for 30 min to give a brown suspension of $(Cy_2N)_2Ag(CN)Li_2$ in THF.

Preparation of $(^{i}Pr_2N)_2Ag(CN)Li_2$ in THF (0.12 mmol scale)

To a solution of diisopropylamine (33.9 μL, 0.24 mmol) in 0.24 mL of anhydrous THF was added ^{n}BuLi (1.54 M ^{n}hexane solution, 156 μL, 0.24 mmol) at –78°C under Ar. The mixture was stirred for 30 min at 0°C to give the solution of $^{i}Pr_2NLi$ (lithium diisopropylamide) in THF. To a suspension of silver cyanide (16.2 mg, 0.12 mmol) in 1.2 mL of anhydrous THF was added the solution of $^{i}Pr_2NLi$ in THF (0.24 mmol) *via* cannula at –78°C under Ar, and the reaction mixture was stirred at 0°C for 30 min to give a yellowish brown solution of $(^{i}Pr_2N)_2Ag(CN)Li_2$ in THF.

Preparation of $(HMDS)_2Ag(CN)Li_2$ in THF (0.12 mmol scale)

To a suspension of silver cyanide (16.2 mg, 0.12 mmol) in 0.24 mL of anhydrous THF was added LHMDS (1.0 M THF solution, 240 μL, 0.24 mmol) at –78°C under Ar. The mixture was stirred at 0°C for 30 min to give a yellow solution of $(HMDS)_2Ag(CN)Li_2$ in THF.

Preparation of Me(TMP)Ag(CN)Li_2 in THF (0.12 mmol scale)

To a suspension of silver cyanide (16.3 mg, 0.12 mmol) in 0.24 mL of anhydrous THF was added MeLi (1.00 M diethylether solution, 120 μL, 0.12 mmol) at –78°C under Ar. The mixture was stirred at 0°C for 30 min to give a solution of MeAg(CN)Li in THF. To the solution was added the TMPLi solution (0.12 mmol) at –78°C, and the reaction mixture was stirred at 0°C for 30 min to give a dark brown solution of Me(TMP)Ag(CN)Li_2 in THF.

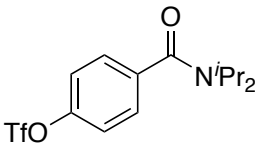
Preparation of $(TMP)_2Cu(CN)Li_2$ in THF (0.24 mmol scale)

To a suspension of copper cyanide (21.5 mg, 0.24 mmol) in 0.24 mL of anhydrous THF was added the solution of TMPLi in THF (0.48 mmol) *via* cannula at –78°C under Ar. The mixture was stirred at 0°C for 15–30 min to give the slightly yellow solution of $(TMP)_2Cu(CN)Li_2$ in THF.

Preparation of Substrates

N,*N*-Diisopropylbenzamide was prepared according to the same protocol as chapter 2.

4-(Diisopropylcarbamoyl)phenyl trifluoromethanesulfonate



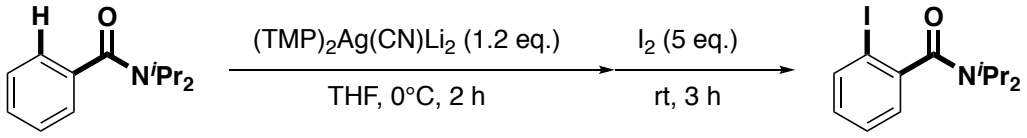
Trifluoromethanesulfonic anhydride (2.3 mL, 8.6 mmol) was added in 3 portions to the vigorously stirred suspension of 4-hydroxy-*N*,*N*-diisopropylbenzamide (1.59 g, 7.2 mmol, synthesized following General Procedure B in chapter 2) in a mixture of CH_2Cl_2 (30 mL) and 30% aq. K_3PO_4 (30 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was washed with water 3 times, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/4) as an eluent to give the titled compound as a white solid in 43% yield (1.103 g). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.35 (brd, 12H), 3.58 (brs, 1H), 3.72 (brs, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.8, 46.4 (brs), 51.2 (brs), 118.9 (CF_3, q, J = 321 Hz), 121.8, 128.0, 139.3, 149.5, 169.1. **^{19}F NMR (376 MHz, $CDCl_3$):** δ –72.9. **FTIR (ATR):** 2975, 1618, 1423, 1346, 1120, 1138, 888, 603. **mp:** 107.9°C (recrystallized from hexane). **Anal.:** Calcd for $C_{14}H_{18}F_3NO_4S$: C, 47.59; H, 5.13; N, 3.96. Found: C, 47.78; H, 5.20; N, 4.00. **HRMS (pos. ESI):** *m/z*: calcd for $C_{14}H_{18}F_3NNaO_4S$ $[M+Na]^+$ 376.0801, found 376.0810.

ortho Iodination of Aromatics (Table 4-2)

General Procedure:

Unless otherwise noted, the reactions were performed on 0.5 mmol scale.

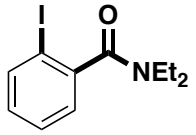
2-Iodo-*N*,*N*-diisopropylbenzamide (6a)



N,*N*-Diisopropylbenzamide (102.7 mg, 0.5 mmol) and dry THF (0.5 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.6 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 2 h at 0°C. To the mixture was added iodine (634.5 mg, 2.5 mmol) at –78°C, then stirred for 3 h at room temperature. The reaction was quenched with aqueous NH_4Cl (5 mL)

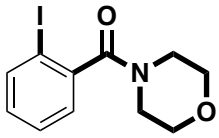
and aqueous $Na_2S_2O_3$ (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/4) as an eluent to give the titled compound **6a** as a white solid in 92% yield (141.8 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-25] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.07 (d, *J* = 6.9 Hz, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.60 (d, *J* = 6.9 Hz, 3H), 3.52 (sep, *J* = 6.9 Hz, 1H), 3.58 (sep, *J* = 6.7 Hz, 1H), 7.03 (dd, *J* = 7.6, 8.1 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{13}H_{18}INNaO$ $[M+Na]^+$ 354.0325, found 354.0341.

_N_,_N_-diethyl-2-iodobenzamide (6b)



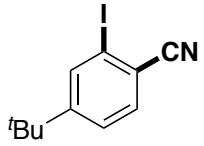
Following the **General Procedure** (purification: AcOEt/hexane = 1/3), the titled compound was obtained as a pale yellow oil in 98% yield (146.0 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-26] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.07 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 3.12 (q, *J* = 7.1 Hz, 1H), 3.15 (q, *J* = 7.1 Hz, 1H), 3.29 (brq, *J* = 7.1 Hz, 1H), 3.87 (brq, *J* = 7.1 Hz, 1H), 7.06 (ddd, *J* = 1.7, 7.6, 7.7 Hz, 1H), 7.21 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.38 (ddd, *J* = 1.7, 7.6, 7.6 Hz, 1H), 7.82 (dd, *J* = 1.7, 7.7 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{14}INNaO$ $[M+Na]^+$ 326.0012, found 326.0016.

(2-Iodophenyl)(morpholino)methanone (6c)



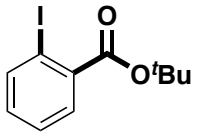
Following the **General Procedure** (purification: AcOEt/hexane = 1/3), the titled compound was obtained as a brown solid in 48% yield (81.9 mg, 6% starting material was included). ^{1}H NMR spectrum was in agreement with the reference.[6-27] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.15-3.21 (m, 1H), 3.26-3.32 (m, 1H), 3.56-3.62 (m, 1H), 3.75-3.90 (m, 5H), 7.09 (ddd, *J* = 1.5, 7.6, 7.7 Hz, 1H), 7.20 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.40 (ddd, *J* = 1.0, 7.6, 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{12}INNaO_2$ $[M+Na]^+$ 339.9805, found 339.9816.

4-(*tert*-butyl)-2-iodobenzonitrile (6d)



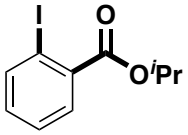
Following the **General Procedure** (purification: AcOEt/hexane = 1/60), the titled compound was obtained as a white solid in 95% yield (135.5 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.31 (s, 9H), 7.45 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 1.7 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 31.0, 35.4, 98.7, 117.8, 119.7, 125.8, 134.0, 136.9, 158.2. **FTIR (ATR):** 2963, 2225, 1589, 1478, 1380, 1256, 1035, 831, 670, 609. **mp:** 30.0°C (recrystallized from hexane). **Anal.:** Calcd for $C_{11}H_{12}IN$: C, 46.34; H, 4.24; N, 4.91. Found: C, 46.15; H, 4.22; N, 4.84. **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{12}INNa$ $[M+Na]^+$ 307.9907, found 307.9908.

***tert*-Butyl 2-iodobenzoate (6e)**



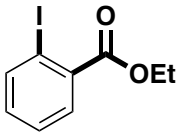
Following the **General Procedure** (purification: AcOEt/hexane = 1/50 followed by distillation with Kugelrohr), the titled compound was obtained as a colorless oil in 92% yield (139.3 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-28] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.62 (s, 9H), 7.10 (ddd, *J* = 1.7, 7.6, 7.8 Hz, 1H), 7.37 (ddd, *J* = 1.0, 7.6, 7.8 Hz, 1H), 7.68 (dd, *J* = 1.7, 7.8 Hz, 1H), 7.94 (dd, *J* = 1.0, 7.8 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{13}INaO_2$ $[M+Na]^+$ 326.9852, found 326.9862.

Isopropyl 2-iodobenzoate (6f)



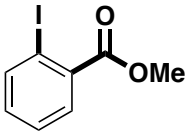
Following the **General Procedure** (purification: AcOEt/hexane = 1/50), the titled compound was obtained as a colorless oil in 90% yield (130.0 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-29] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.40 (d, *J* = 6.4 Hz, 6H), 5.28 (sep, *J* = 6.4 Hz, 2H), 7.13 (dd, *J* = 7.6, 7.7 Hz, 1H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{10}H_{11}INaO_2$ $[M+Na]^+$ 312.9696, found 312.9698.

Ethyl 2-iodobenzoate (6g)



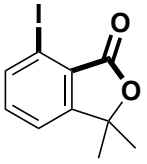
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/50), the titled compound was obtained as a colorless oil in 93% yield (130.5 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-30] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.42 (t, *J* = 7.2 Hz, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 7.15 (ddd, *J* = 1.7, 7.6, 7.8 Hz, 1H), 7.40 (ddd, *J* = 1.2, 7.6, 7.8 Hz, 1H), 7.79 (dd, *J* = 1.7, 7.8 Hz, 1H), 7.99 (dd, *J* = 1.2, 7.8 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_9H_9INaO_2$ $[M+Na]^+$ 298.9539, found 298.9536.

Methyl 2-iodobenzoate (6h)



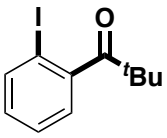
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/50), the titled compound was obtained as a pale yellow oil in 86% yield (112.9 mg). ^{1}H was in agreement with the reference.[6-31] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.94 (s, 3H), 7.15 (ddd, *J* = 1.7, 7.6, 7.7 Hz, 1H), 7.40 (ddd, *J* = 1.2, 7.6, 7.7 Hz, 1H), 7.80 (dd, *J* = 1.7, 7.7 Hz, 1H), 8.00 (dd, *J* = 1.2, 7.7 Hz, 1H). **EI-MS (% relative intensity):** *m/z*: 262 (M+, 78), 231 (100), 203 (31), 127 (29), 76 (30).

7-Iodo-3,3-dimethylisobenzofuran-1(3*H*)-one (6i)



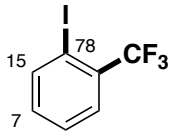
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/4), the titled compound was obtained as a white solid in 99% yield (146.6 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.65 (s, 6H), 7.33 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 27.4, 83.1, 92.4, 120.7, 126.5, 135.0, 140.5, 157.2, 167.9. **FTIR (ATR):** 2978, 1753, 1591, 1451, 1234, 1037, 689. **mp:** 139.1°C (recrystallized from hexane). **Anal.:** Calcd for $C_{10}H_9IO_2$: C, 41.69; H, 3.15. Found: C, 41.66; H, 3.34. **HRMS (pos. ESI):** *m/z*: calcd for $C_{10}H_9INaO_2$ $[M+Na]^+$ 310.9539, found 310.9552.

1-(2-iodophenyl)-2,2-dimethylpropan-1-one (6j)



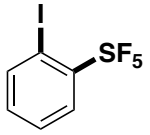
Following the **General Procedure** (0.2 mmol scale; purification: AcOEt/hexane = 0/100 → 1/20; 96% NMR yield determined by ^{1}H NMR spectroscopy using mesitylene), the titled compound was obtained as a colorless oil in 85% yield (48.8 mg). ^{1}H NMR spectroscopy was in agreement with the literature.[6-32] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.31 (s, 9H), 7.07 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H) **HRMS (pos. ESI):** *m/z*: calcd for $C_{11}H_{13}INaO$ $[M+Na]^+$ 310.9903, found 310.9909.

Iodo α,α,α -trifluorotoluene (*ortho* : *meta* : *para* = 78 : 15 : 7) (6k)



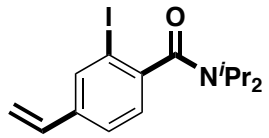
Following the **General Procedure** (0.2 mmol scale; careful evaporation due to high volatility of the products)**,** the titled compound was obtained as a brown oil. The argentation proceeded at *ortho*, *meta* and *para* position in 43%, 8% and 4% yield, respectively, determined by ^{1}H NMR using mesitylene (8.2 mg) as an internal standard (mesitylene : *ortho* : *meta* : *para* = 1 : 0.42 : 0.08 : 0.04). ^{1}H NMR spectrum was in agreement with the reference.[6-33] 2-Iodo α,α,α-trifluorotoluene **^{1}H NMR (500 MHz, CDCl$_3$):** δ 7.20 (dd, *J* = 7.6, 7.9 Hz, 1H), 7.45 (dd, *J* = 7.6, 7.9 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H). 3-iodo α,α,α-trifluorotoluene **^{1}H NMR (500 MHz, CDCl$_3$):** δ 7.23 (dd, *J* = 7.6, 7.9 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.96 (s, 1H). 4-iodo α,α,α-trifluorotoluene **^{1}H NMR (500 MHz, CDCl$_3$):** δ 7.35 (d, *J* = 7.9 Hz, 2H), 7.85 (d, *J* = 7.9 Hz, 2H). **EI-MS (% relative intensity, All isomers are separately detected): Peak (A):** *m/z*: 272 (M+, 36), 145 (100), 127 (32). **Peak (B):** 272 (M+, 100), 253 (14), 145 (65), 127 (15). **Peak (C):** 272 (M+, 100), 253 (5), 145 (50), 127 (18).

Pentafluoro(2-iodophenyl)-λ^6-sulfane (6l)



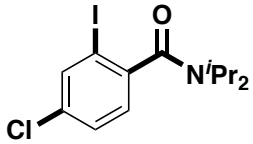
Following the **General Procedure** (careful evaporation due to high volatility of the product)**,** the titled compound was obtained as a brown oil. The titled compound was obtained in 14% yield determined by ^{1}H NMR using mesitylene (19.1 mg) as an internal standard (mesitylene : **2k** = 1 : 0.14). ^{1}H NMR spectrum was in agreement with the reference.[6-34] **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.13 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.45 (m, 1H), 7.82 (dd, *J* = 1.5, 8.6 Hz, 1H), 8.15 (d, *J* = 7.3 Hz, 1H). **EI-MS (% relative intensity):** *m/z*: 330 (M+, 100), 203 (21), 127 (55), 89 (51), 76 (34).

2-Iodo-*N*,*N*-diisopropyl-4-vinylbenzamide (6m)



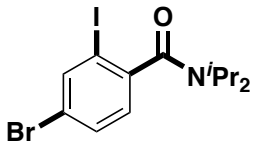
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/8), the titled compound was obtained as a white solid in 86% yield (154.0 mg). **^{1}H NMR (500 MHz, CDCl$_3$):** δ 1.07 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.59 (d, *J* = 6.7 Hz, 3H), 3.51 (sep, *J* = 6.7 Hz, 1H), 3.60 (sep, *J* = 6.7 Hz, 1H), 5.31 (d, *J* = 11.0 Hz, 1H), 5.75 (d, *J* = 17.7 Hz, 1H), 6.61 (dd, *J* = 11.0, 17.7 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.85 (d, *J* = 1.5 Hz, 1H). **^{13}C NMR (125 MHz, CDCl$_3$):** δ 20.2, 20.7, 20.8, 20.9, 46.1, 51.4, 92.7, 115.9, 126.0, 126.1, 134.9, 137.1, 139.1, 143.5, 169.8. **FTIR (ATR):** 2968, 1631, 1437, 1336. **mp:** 118.4°C (recrystallized from hexane). **Anal.:** Calcd for $C_{15}H_{20}INO + 1/8 \cdot H_2O$: C, 50.12; H, 5.68; N, 3.90. Found: C, 50.11; H, 5.56; N, 3.90. **HRMS (pos. ESI):** *m/z*: calcd for $C_{15}H_{20}INNaO$ $[M+Na]^+$ 380.0482, found 380.0496.

4-Chloro-2-iodo-*N*,*N*-diisopropylbenzamide (6n)



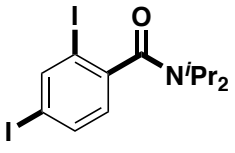
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/6), the titled compound was obtained as a white solid in 95% yield (173.1 mg, 3% of 3-iodo isomer included). ^{1}H NMR spectrum was in agreement with the reference.[6-26] **^{1}H NMR (400 MHz, CDCl$_3$):** δ 1.07 (d, *J* = 6.9 Hz, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.55 (d, *J* = 6.9 Hz, 3H), 1.59 (d, *J* = 6.9 Hz, 3H), 3.52 (sep, *J* = 6.9 Hz, 1H), 3.55 (sep, *J* = 6.9 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.34 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{13}H_{17}ClINNaO$ $[M+Na]^+$ 387.9936, found 387.9941.

4-Bromo-2-iodo-*N*,*N*-diisopropylbenzamide (6o)



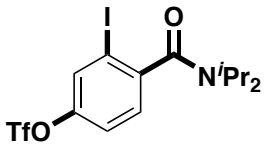
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/8), the titled compound was obtained as a white solid in 98% yield (201.3 mg, 3% of 3-iodo isomer included). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.07 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.59 (d, *J* = 6.7 Hz, 3H), 3.51 (sep, *J* = 6.7 Hz, 1H), 3.55 (sep, *J* = 6.7 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 7.49 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.2, 20.8, 20.9 (overlapped), 46.3, 51.4, 93.0, 122.3, 127.0, 131.6, 141.5, 143.3, 169.1. **FTIR (ATR):** 2929, 1631, 1435, 1335, 1020, 820. **mp:** 104.8°C (26 : 1 mixture with isomer; recrystallized from hexane). **Anal.:** Calcd for $C_{13}H_{17}BrINO$: C, 38.07; H, 4.18; N, 3.42. Found: C, 38.16; H, 4.24; N, 3.46. **HRMS (pos. ESI):** *m/z*: calcd for $C_{13}H_{17}BrINNaO$ $[M+Na]^+$ 431.9430, found 431.9434.

2,4-Diiodo-*N*,*N*-diisopropylbenzamide (6p)



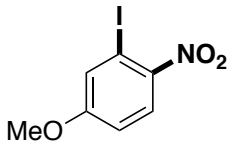
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/8), the titled compound was obtained as a pale yellow solid in 97% yield (220.8 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-25] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.07 (d, *J* = 6.9 Hz, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.55 (d, *J* = 6.9 Hz, 3H), 1.58 (d, *J* = 6.9 Hz, 3H), 3.51 (sep, *J* = 6.9 Hz, 1H), 3.55 (sep, *J* = 6.9 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 7.68 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.17 (d, *J* = 1.5 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{13}H_{17}I_2NNaO$ $[M+Na]^+$ 479.9292, found 479.9297.

4-(Diisopropylcarbamoyl)-3-iodophenyl trifluoromethanesulfonate (6q)



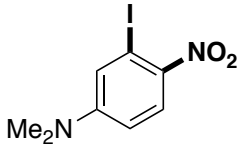
Following the **General Procedure** (argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/10), the titled compound was obtained as a pale yellow oil in 43% yield (108.9 mg, the yield was determined after subtraction of 15% of CH_2Cl_2.; 6% of 2-iodo isomer included). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.09 (d, *J* = 6.9 Hz, 3H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.59 (d, *J* = 6.9 Hz, 3H), 3.51 (sep, *J* = 6.9 Hz, 1H), 3.54 (sep, *J* = 6.9 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 2.5, 8.3 Hz, 1H), 7.73 (d, *J* = 2.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.1, 20.7, 20.9, 21.0, 46.4, 51.5, 92.4, 118.8 (CF_3, q, *J* = 320 Hz), 121.5, 127.0, 132.2, 144.7, 148.2, 168.3. **^{19}F NMR (376 MHz, $CDCl_3$):** δ –72.7. Metalated position (*ortho* to amide group) was determined by HMBC, which shows only one correlation between ^{13}C(C<u>O</u>N^{i}Pr$_2$) and ^{1}H(aromatic). **FTIR (ATR):** 2976, 1632, 1426, 1209, 1138, 895, 729, 607. **HRMS (pos. ESI):** *m/z*: calcd for $C_{14}H_{17}F_3INNaO_4S$ $[M+Na]^+$ 501.9767, found 501.9783.

2-Iodo-4-methoxy-1-nitrobenzene (6r)



Following the **General Procedure** (0.2 mmol scale; argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 0/100 → 1/3), the titled compound was obtained as a yellow solid in 80% yield (44.6 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-35] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.89 (s, 3H), 6.95 (dd, *J* = 2.7, 9.1 Hz, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 1H). **EI-MS (% relative intensity):** *m/z*: 279 (M+, 100), 263 (5), 249 (60), 233 (8).

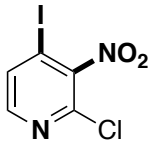
3-Iodo-*N*,*N*-dimethyl-4-nitroaniline (6s)



Following the **General Procedure** (0.2 mmol scale; argentation reaction was performed at –40°C.; purification: PTLC with CH_2Cl_2/hexane = 2/1), the titled compound was obtained as a yellow solid in 81% yield (47.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.08 (s, 6H), 6.60 (dd, *J* = 2.8, 9.5 Hz, 1H), 7.22 (d, *J* = 2.8 Hz,

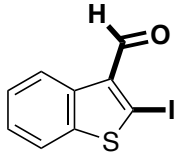
1H), 8.05 (d, *J* = 9.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 40.3, 90.1, 110.5, 142.0, 128.1, 139.7, 153.2. **FTIR (ATR):** 1594, 1547, 1297, 1271, 1011, 829, 741. **mp:** 122.7°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_8H_9IN_2O_2$: C, 32.90; H, 3.11; N, 9.59. Found: C, 32.82; H, 3.17; N, 9.49. **HRMS (pos. ESI):** *m/z*: calcd for $C_8H_9IN_2NaO_$ $[M+Na]^+$ 314.9601, found 314.9600.

2-Chloro-4-iodo-3-nitropyridine (6t)



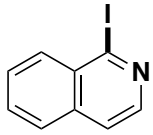
Following the **General Procedure** (0.2 mmol scale; argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 0/100 → 1/4), the titled compound was obtained as a white solid in 90% yield (51.3 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.81 (d, *J* = 5.2 Hz, 1H), 8.13 (d, *J* = 5.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 98.6, 134.0, 141.8, 150.1, 150.9. **FTIR (ATR):** 1550, 1535, 1352, 777. **mp:** 126.0°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_5H_2ClIN_2O_2$: C, 21.11; H, 0.71; N, 9.85. Found: C, 21.18; H, 0.95; N, 9.74. **EI-MS (% relative intensity):** *m/z*: 284 (M+, 100), 238 (84), 127 (52).

2-Iodobenzo[*b*]thiophene-3-carbaldehyde (6u)



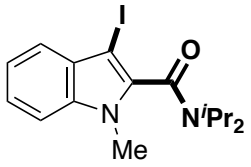
Following the **General Procedure** (0.2 mmol scale; argentation reaction was performed at –40°C.; purification: AcOEt/hexane = 1/19 → 3/17), the titled compound was obtained as a slightly yellow solid in 87% yield (50.1 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-36] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 (m, 2H), 7.76 (d, *J* = 7.1 Hz, 1H), 8.74 (d, *J* = 7.6 Hz, 1H), 10.0 (s, 1H). **EI-MS (% relative intensity):** *m/z*: 288 (M+, 100), 259 (9), 160 (23), 132 (41).

1-Iodoisoquinoline (6v)



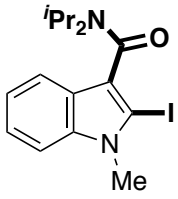
Following the **General Procedure** (purification: AcOEt/hexane = 1/20), the titled compound was obtained as a yellow solid in 81% yield (59.8 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-37] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.59 (d, *J* = 5.6 Hz, 1H), 7.67-7.76 (m, 3H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H). **HRMS (pos. ESI):** *m/z*: calcd for C_9H_7IN $[M+H]^+$ 255.9618, found 255.9616.

3-Iodo-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (6w)



Following the **General Procedure** (0.2 mmol scale; purification: AcOEt/hexane = 1/10), the titled compound was obtained as a white solid in 79% yield (60.8 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.11 (d, *J* = 6.9 Hz, 3H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.63 (d, *J* = 6.9 Hz, 3H), 1.67 (d, *J* = 6.6 Hz, 3H), 3.59 (sep, *J* = 6.6 Hz, 1H), 3.76 (s, 3H), 3.79 (sep, *J* = 6.9 Hz, 1H), 7.20-7.24 (m, 1H), 7.28-7.33 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.3, 20.7, 21.4, 21.6, 31.6, 46.5, 51.8, 54.2, 109.9, 121.0, 121.6, 123.3, 129.7, 136.6, 137.9, 162.9. **FTIR (ATR):** 2970, 1633, 1307, 741. **mp:** 143.3°C (decomp. started at 100°C; recrystallized from hexane). **Anal.:** Calcd for $C_{16}H_{21}IN_2O$ + 1/23·H_2O: C, 50.34; H, 5.61; N, 7.22. Found: C, 50.35; H, 5.57; N, 7.20. **HRMS (pos. ESI):** *m/z*: calcd for $C_{16}H_{21}IN_2NaO$ $[M+Na]^+$ 407.0591, found 407.0595.

2-Iodo-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-3-carboxamide (6x)



Following the **General Procedure** (purification: AcOEt/hexane = 1/3), the titled compound was obtained as a pale yellow solid in 99% yield (190.2 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.27-1.53 (brd, 12H), 3.62-3.90 (br, 2H), 3.77 (brs, 2H), 3.77 (s, 3H), 7.08 (dd, *J* = 7.6, 8.2 Hz, 1H), 7.17 (dd, *J* = 7.6, 7.9 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H),

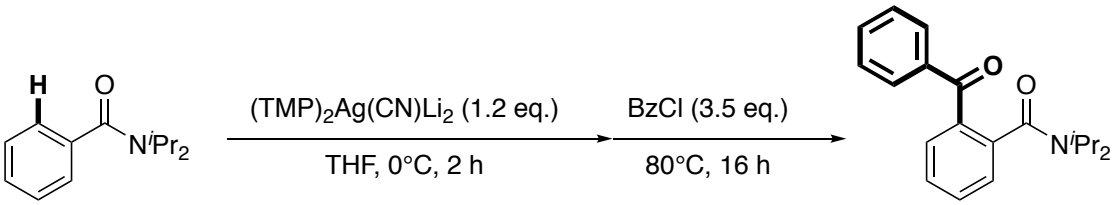
7.45 (d, J = 7.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 21.3, 34.2, 46.2 (brs), 51.3 (brs), 84.0, 109.9, 118.7, 120.4, 121.5, 122.6, 126.6, 137.8, 166.4. **FTIR (ATR):** 2968, 1613, 1459, 1366, 1304, 737. **mp:** 211.1°C (decomp. started at 100°C; recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{16}H_{21}IN_2O$ + 1/4·H_2O: C, 49.43; H, 5.57; N, 7.21. Found: C, 49.49; H, 5.45; N, 7.16. **HRMS (pos. ESI):** *m/z*: calcd for $C_{16}H_{21}IN_2NaO$ $[M+Na]^+$ 407.0591, found 407.0610.

Procedure for Scheme 4-1[6-38]:

To a suspension of silver bromide (37.6 mg, 0.2 mmol) in dry THF (0.4 mL) in a heat gun-dried brown Schlenck tube was added TMPLi in THF (0.2 mmol) *via* cannula at –78°C under Ar. The mixture was covered with aluminum foil to exclude light and stirred at room temperature for 30 min during which time the block-shaped solid of silver bromide disappeared (= mixture **A**). Meanwhile, to a solution of 2-iodo-*N,N*-diisopropylbenzamide (66.2 mg, 0.2 mmol) in dry THF (2.0 mL) was added ^{t}BuLi (1.48M ^{n}pentane solution, 270 μL, 0.4 mmol) at –78°C, and the resulting suspension was stirred for 15 min at the same temperature (= mixture **B**). Following the completion of halogen-metal exchange (confirmed by ESI-MS), mixture **B** was added to the mixture **A** *via* cannula at –78°C, and the resultant mixture was stirred for 1 h at 0°C. Iodine (253.8 mg, 1.0 mmol) was added and the mixture was stirred for 16 h at room temperature. The aluminum foil was removed after the addition of iodine. The reaction was quenched with aqueous NH_4Cl (5 mL) and aqueous $Na_2S_2O_3$ (5 mL) followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yields were determined by NMR spectroscopy using mesitylene as an internal standard.

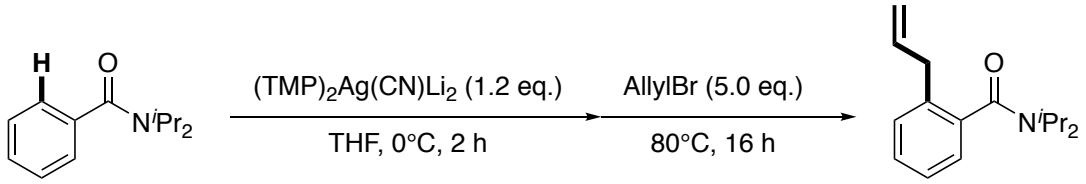
Reactions of Arylargentate with Electrophiles (Scheme 4-3)

2-Benzoyl-*N,N*-diisopropylbenzamide (8)



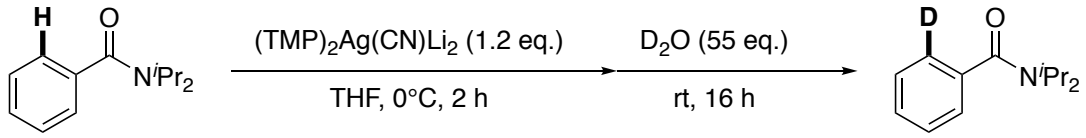
N,N-Diisopropylbenzamide (102.8 mg, 0.5 mmol) and dry THF (0.5 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.6 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 2 h at 0°C. To the mixture was added benzoyl chloride (203.8 μL, 1.75 mmol) at –78°C, then the Schlenk tube was immersed in pre-heated 80°C oil bath and stirred for 16 h. The reaction was cooled to room temperature and quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/1) and PTLC using AcOEt/CH_2Cl_2 (1/6) to give the titled compound **5** as a pale pink solid in 82% yield (127.7 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-25] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.20 (d, J = 6.6 Hz, 6H), 1.43 (d, J = 6.6 Hz, 6H), 3.45 (sep, J = 6.6 Hz, 1H), 3.84 (d, J = 6.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.37-7.58 (m, 6H), 7.80-7.82 (m, 2H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{23}NNaO_2$ $[M+Na]^+$ 332.1621, found 332.1621.

2-Allyl-*N,N*-diisopropylbenzamide (9)



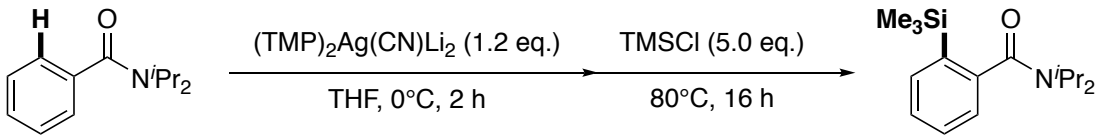
N,N-Diisopropylbenzamide (102.6 mg, 0.5 mmol) and dry THF (0.5 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.6 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 2 h at 0°C. To the mixture was added allyl bromide (213 μL, 2.5 mmol) at –78°C, then the Schlenk tube was immersed in pre-heated 80°C oil bath and stirred for 16 h. The reaction was cooled to room temperature and quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Desired product **6** was obtained in 88% yield determined by ^{1}H NMR using mesitylene (20.8 mg) as an internal standard. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/7) and GPC to give the titled compound **6** as a white solid in 56% yield (68.1 mg). ^{1}H NMR spectra was in agreement with the reference.[6-25] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.10 (d, *J* = 6.6 Hz, 6H), 1.57 (d, *J* = 6.6 Hz, 6H), 3.42 (d, *J* = 6.6 Hz, 2H), 3.50 (sep, *J* = 6.6 Hz, 1H), 3.68 (sep, *J* = 6.6 Hz, 1H), 5.07-5.12 (m, 2H), 5.96 (ddt, *J* = 6.6, 10.0, 16.8 Hz 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 7.18-7.30 (m, 3H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{16}H_{23}NNaO$ $[M+Na]^+$ 268.1672, found 268.1677.

2-Deuterio-*N,N*-diisopropylbenzamide (10)



N,N-Diisopropylbenzamide (102.6 mg, 0.5 mmol) and dry THF (0.5 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.6 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 2 h at 0°C. To the mixture was added D_2O (500 μL, 27.7 mmol), then the mixture was stirred for 16 h at room temperature. The reaction was quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/3) to give the titled compound **7** as a white solid in 96% yield (99.4 mg, D/H = 97/3). ^{1}H NMR spectrum was in agreement with the reference.[6-25] **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.16-1.52 (brd, 12H), 3.52-3.83 (brd, 2H), 7.30-7.32 (m, 1H), 7.36-7.38 (m 3H). **EI-MS (% relative intensity):** *m/z*: 206 (M+, 9), 191 (4), 163 (20), 106 (100), 78 (24).

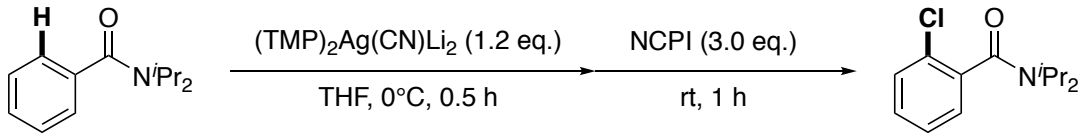
***N,N*-Diisopropyl-2-(trimethylsilyl)benzamide (11)**



N,N-Diisopropylbenzamide (102.6 mg, 0.5 mmol) and dry THF (0.5 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.6 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 2 h at 0°C. To the mixtutre was added chlorotrimethylsilane (316 μL, 2.5 mmol), then the Schlenk tube was immersed in pre-heated 80 °C oil bath and stirred for 16 h. The reaction was cooled to the room temperature and quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/10) to give the titled compound **9** as a white solid in 62% yield (85.5 mg). ^{1}H NMR spectrum was in agreement with the reference.[6-25] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.32 (s, 9H), 1.15 (d, *J* = 5.9 Hz, 6H), 1.56 (d, *J* = 5.6 Hz, 6H), 3.46-3.53 (brq, 1H), 3.77-3.84 (brq, 1H), 7.14-7.16 (m, 1H), 7.29-7.34 (m, 2H), 7.58-7.61 (m, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{16}H_{27}NNaOSi$ $[M+Na]^+$ 300.1754, found 300.1765.

2-Chloro-*N,N*-diisopropylbenzamide (12)



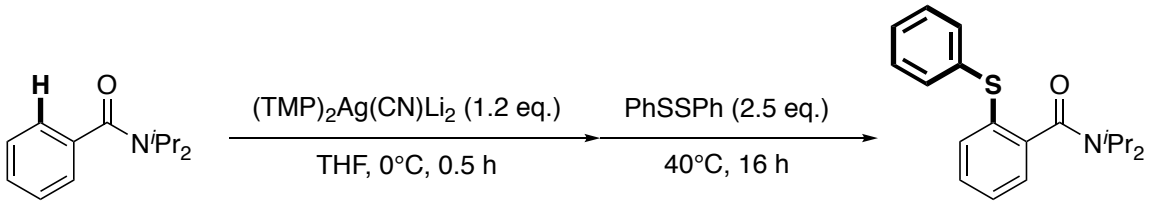
N,N-Diisopropylbenzamide (41.1 mg, 0.20 mmol) and dry THF (0.2 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.24 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 0.5 h at 0°C. To the mixture was added *N*-chlorophthalimide (109.0 mg, 0.60 mmol), then the mixture was stirred for 1 h at room temperature. The reaction was quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (3 mL × 3). The combined AcOEt layer was concentrated under reduced pressure and dissolved in Et_2O. The Et_2O solution was washed with 1M NaOH aq. (3 mL × 3) and brine (3 mL × 1), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/9 → 1/4) to give the titled compound **9** as a white solid in 92% yield (45.9 mg, 4% of *N,N*-Diisopropylbenzamide included). ^{1}H NMR spectrum was in agreement with the reference.[6-39] **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.07 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.58 (d, *J* = 6.9 Hz, 3H), 3.53 (sep, *J* = 6.7 Hz, 1H), 3.61 (sep, *J* = 6.7 Hz, 1H), 7.18-7.22 (m, 1H), 7.25-7.30 (m, 2H), 7.36-7.40 (m, 1H). **HRMS (pos. ESI):** *m/z*: calcd for $C_{13}H_{18}ClNNaO$ $[M+Na]^+$ 262.0969, found 262.0973.

<u>Chalcogen Installation (Table 4-4)</u>

General Procedure:

The reactions were performed on 0.2 mmol scale.

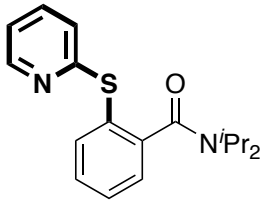
***N,N*-Diisopropyl-2-(phenylthio)benzamide (13a)**



N,N-Diisopropylbenzamide (41.1 mg, 0.2 mmol) and dry THF (0.2 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.24 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 0.5 h at 0°C. To the mixture was added diphenyldisulfide (109.2 mg, 0.5 mmol) at –78°C, then the sealed Schlenk tube was immersed in pre-heated 40°C oil bath and stirred for 16 h. The reaction was quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/6) to give the titled compound **10a** as a colorless oil in 99% yield (63.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.09 (d, *J* = 6.7 Hz, 3H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.57-1.58 (brd, 6H), 3.51 (sep, *J* = 6.7 Hz, 1H), 3.71 (sep, *J* = 6.7 Hz, 1H), 7.17 (m, 5H), 7.27-7.31 (m, 2H), 7.35-7.39 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.4,

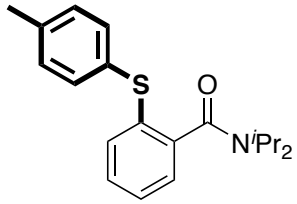
20.8, 20.9, 21.0, 46.1, 51.2, 125.8, 127.2, 127.4, 128.9, 129.3, 131.8, 132.1, 132.8, 135.3, 140.6, 168.9. **FTIR (ATR):** 2969, 1629, 1438, 1337, 1032, 739. **mp:** 86.4°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47. Found: C, 72.69; H, 7.35; N, 4.42. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{23}NNaOS$ $[M+Na]^+$ 336.1393, found 336.1395.

_N_,_N_-Diisopropyl-2-(pyridin-2-ylthio)benzamide (13b)



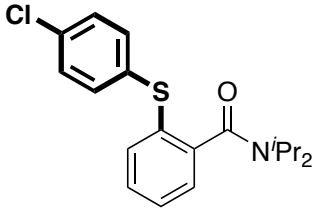
Following the **General Procedure** (purification: AcOEt/hexane = 1/10 → 1/3), the titled compound was obtained as a colorless oil in 99% yield (62.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.04 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.53 (d, *J* = 6.7 Hz, 3H), 3.47 (sep, *J* = 6.7 Hz, 1H), 3.65 (sep, *J* = 6.7 Hz, 1H), 6.96-6.99 (m, 2H), 7.29 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.38 (ddd, *J* = 1.5, 7.3, 7.5 Hz, 1H), 7.42-7,47 (m, 2H), 7.61 (dd, *J* = 1.2, 7.5 Hz, 1H), 8.37 (dd, *J* = 1.5, 5.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.2, 20.4, 20.7, 20.9, 46.0, 51.1, 120.1, 122.2, 126.3, 127.3, 129.2, 129.7, 136.8, 136.9, 144.1, 149.3, 160.9, 168.5. **FTIR (ATR):** 2968, 1627, 1338, 1119, 1032, 752, 723. **mp:** 117.5°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{18}H_{22}N_2OS$: C, 68.75; H, 7.05; N, 8.91. Found: C, 68.73; H, 7.10; N, 8.85. **HRMS (pos. ESI):** *m/z*: calcd for $C_{18}H_{22}N_2NaOS$ $[M+Na]^+$ 337.1345, found 337.1360.

_N_,_N_-Diisopropyl-2-(*p*-tolylthio)benzamide (13c)



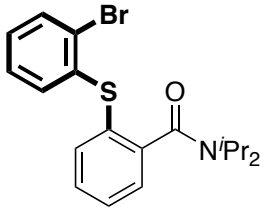
Following the **General Procedure** (sulfide formation was run at room temperature.; purification: AcOEt/hexane = 1/10 → 3/17), the titled compound was obtained as a white solid in 95% yield (61.9 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.09 (d, *J* = 6.7 Hz, 3H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.59 (d, *J* = 6.7 Hz, 3H), 2.34 (s, 3H), 3.52 (sep, *J* = 6.7 Hz, 1H), 3.72 (sep, *J* = 6.7 Hz, 1H), 7.06-7.08 (m, 1H), 7.12-7.20 (m, 5H), 7.32 (d, *J* = 7.9 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.4, 20.9, 21.3, 46.0, 51.2, 125.6, 126.5, 128.7, 130.2, 130.7, 130.9, 132.9, 134.1, 137.9, 139.6, 169.0. **FTIR (ATR):** 2970, 1629, 1337, 1033, 730. **mp:** 106.3°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{20}H_{25}NOS$: C, 73.35; H, 7.69; N, 4.28. Found: C, 73.11; H, 7.62; N, 4.23. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{25}N_2NaOS$ $[M+Na]^+$ 350.1549, found 350.1554.

2-((4-Chlorophenyl)thio)-_N_,_N_-diisopropylbenzamide (13d)



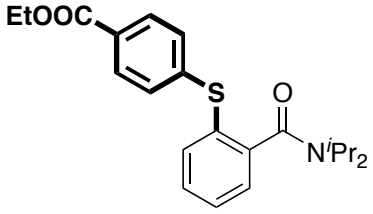
Following the **General Procedure** (sulfide formation was run at room temperature.; purification: AcOEt/hexane = 1/10 → 1/4 and GPC), the titled compound was obtained as a colorless oil in 81% yield (56.4 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.09 (d, *J* = 6.7 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.56 (d, *J* = 6.7 Hz, 6H), 3.51 (sep, *J* = 6.7 Hz, 1H), 3.67 (sep, *J* = 6.7 Hz, 1H), 7.19-7.30 (m, 8H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.4, 20.8 (overlapped), 20.9, 46.1, 51.2, 126.0, 127.9, 129.1, 129.5, 131.8, 132.6, 132.7, 133.3, 134.3, 141.3, 168.7. **FTIR (ATR):** 2971, 1628, 1474, 1338, 1092, 733. **mp:** 93.5°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{22}ClNOS$: C, 65.60; H, 6.37; N, 4.03. Found: C, 65.44; H, 6.40; N, 3.98. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{22}ClNNaOS$ $[M+Na]^+$ 370.1003, found 370.1017.

2-((2-Bromophenyl)thio)-*N*,*N*-diisopropylbenzamide (13e)



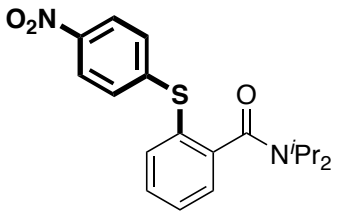
Following the **General Procedure** (purification: AcOEt/hexane = 7/93 → 1/4), the titled compound was obtained as a pale yellow oil in 99% yield (78.5 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.08 (d, *J* = 6.7 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.53 (d, *J* = 6.7 Hz, 3H), 1.54 (d, *J* = 6.7 Hz, 3H), 3.49 (sep, *J* = 6.7 Hz, 1H), 3.67 (sep, *J* = 6.7 Hz, 1H), 7.03 (ddd, *J* = 1.8, 7.3, 7.9 Hz, 1H), 7.07 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.17 (ddd, *J* = 1.2, 7.3, 7.9 Hz, 1H), 7.26 (ddd, *J* = 0.9, 1.2, 7.3 Hz, 1H), 7.29-7.32 (m, 2H), 7.32-7.38 (m, 1H), 7.54 (dd, *J* = 1.2, 7.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.3, 20.7, 20.8, 21.0, 46.1, 51.2, 123.6, 126.4, 127.7, 128.0, 128.7, 129.2, 129.8, 131.1, 133.1, 134.2, 137.7, 142.5, 168.5. **FTIR (ATR):** 2969, 1630, 1444, 1338, 1018, 747. **mp:** 69.4°C (decomp.; recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{22}BrNOS$: C, 58.16; H, 5.65; N, 3.57. Found: C, 58.09; H, 5.67; N, 3.51. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{22}BrNNaOS$ $[M+Na]^+$ 414.0498, found 414.0504.

Ethyl 4-((2-(diisopropylcarbamoyl)phenyl)thio)benzoate (13f)



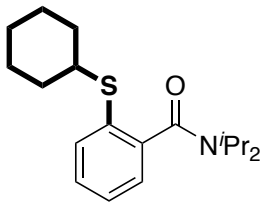
Following the **General Procedure** (sulfide formation was run at room temperature.; purification: AcOEt/hexane = 1/10 → 1/4 and PTLC with AcOEt/hexane = 1/4), the titled compound was obtained as a pale yellow solid in 93% yield (71.5 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.06 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.54(d, *J* = 6.7 Hz, 3H), 3.49 (sep, *J* = 6.7 Hz, 1H), 3.65 (sep, *J* = 6.7 Hz, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 7.25-7.27 (m, 3H), 7.32 (ddd, *J* = 1.5, 7.3, 7.6 Hz, 1H), 7.37 (ddd, *J* = 1.2, 7.3, 7.6 Hz, 1H), 7.41 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 14.5, 20.4, 20.7, 20.8, 20.9, 46.1, 51.2, 61.1, 126.3, 128.3, 128.4, 129.0, 129.2, 129.3, 130.2, 135.0, 142.9, 143.5, 166.3, 168.5. **FTIR (ATR):** 2975, 1713, 1631, 1338, 1270, 1105, 761. **mp:** 92.7°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{22}H_{27}NO_3S + 1/4 \cdot H_2O$: C, 67.75; H, 7.11; N, 3.59. Found: C, 67.79; H, 7.06; N, 3.54. **HRMS (pos. ESI):** *m/z*: calcd for $C_{22}H_{27}NNaO_3S$ $[M+Na]^+$ 408.1604, found 408.1613.

***N*,*N*-Diisopropyl-2-((4-nitrophenyl)thio)benzamide (13g)**



Following the **General Procedure** (sulfide formation was run at room temperature.; purification: AcOEt/hexane = 1/10 → 1/4 and GPC), the titled compound was obtained as a pale yellow solid in 86% yield (61.4 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.08 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 1,47 (d, *J* = 6.7 Hz, 3H), 1.53 (d, *J* = 6.7 Hz, 3H), 3.49 (sep, *J* = 6.7 Hz, 1H), 3.61 (sep, *J* = 6.7 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 2H), 7.32 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.41 (ddd, *J* = 1.5, 7.6, 7.6 Hz, 1H), 7.48 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.54 (dd, *J* = 1.2, 7.6 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.3, 20.6, 20.7, 20.9, 46.1, 51.2, 124.1, 126.6, 127.0, 127.4, 129.6, 130.3, 136.5, 144.2, 145.6, 147.8, 168.1. **FTIR (ATR):** 2971, 1630, 1512, 1335, 852, 741. **mp:** 158.0°C (decomp.; recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{22}N_2O_3S + 1/3 \cdot H_2O$: C, 63.03; H, 6.24; N, 7.74. Found: C, 63.10; H, 6.23; N, 7.74. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{22}N_2NaO_3S$ $[M+Na]^+$ 381.1243, found 381.1252.

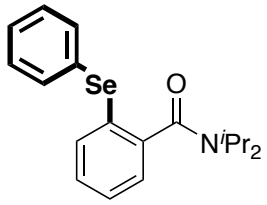
2-(Cyclohexylthio)-*N*,*N*-diisopropylbenzamide (13h)



Following the **General Procedure** (sulfide formation was run at room temperature.; purification: AcOEt/hexane = 1/10 → 1/5), the titled compound was obtained as a colorless oil in 54% yield (34.7 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.03 (d, *J* = 6.7 Hz, 3H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.21-1.41 (m, 6H),

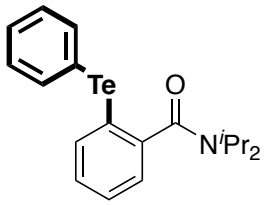
1.56 (d, J = 6.7 Hz, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.71-1.77 (m, 2H), 1.91-1.98 (m, 2H), 3.21-3.26 (m, 1H), 3.50 (sep, J = 6.7 Hz, 1H), 3.56 (sep, J = 6.7 Hz, 1H), 7.13-7.15 (m, 1H), 7.22-7.27 (m, 2H), 7.42-7.46 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.1, 20.6, 20.7, 20.8, 25.8 (2C, overlaped), 26.1, 33.0, 33.7, 45.7, 47.1, 50.9, 125.7, 127.3, 128.1, 131.1, 133.7, 142.7, 169.1. **FTIR (ATR):** 2927, 1629, 1439, 1337, 1032, 769. **mp:** 47.6°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{29}NOS$: C, 71.43; H, 9.15; N, 4.38. Found: C, 71.68; H, 9.24; N, 4.56. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{29}NNaOS$ $[M+Na]^+$ 342.1862, found 342.1861.

_N_,_N_-Diisopropyl-2-(phenylselanyl)benzamide (13i)



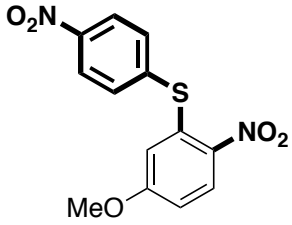
Following the **General Procedure** (selenide formation was run at 80°C.; purification: AcOEt/hexane = 1/9 → 1/4), the titled compound was obtained as a pale yellow solid in 95% yield (56.2 mg, the yield was determined after subtraction of 5% of CH_2Cl_2). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.14 (brs, 6H), 1.59 (brs, 6H), 3.53 (brs, 1H), 3.75 (brs, 1H), 7.13-7.17 (m, 2H), 7.21-7.30 (m, 5H), 7.50-7.54 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.7, 20.9, 46.1, 51.3, 125.5, 127.2, 127.8, 129.0, 129.2, 129.5, 130.7, 133.6, 134.1, 141.3, 169.5. **FTIR (ATR):** 2968, 1627, 1437, 1336, 1031, 734, 691. **mp:** 85.6°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{23}NOSe$: C, 63.33; H, 6.43; N, 3.89. Found: C, 63.08; H, 6.48; N, 3.94. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{23}NNaOSe$ $[M+Na]^+$ 384.0837, found 384.0844.

_N_,_N_-Diisopropyl-2-(phenyltellanyl)benzamide (13j)



Following the **General Procedure** (telluride formation was run at 80°C.; purification: AcOEt/hexane = 1/49 → 1/4), the titled compound was obtained as a pale yellow oil in 97% yield (83.4 mg, the yield was determined after subtraction of 25% of AcOEt, which remained after high vaccum for 16 h.; AcOEt could be removed by iterative azeotropic evaporation with hexane). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.38 (br, 12H), 3.74 (br, 2H), 7.05 (ddd, J = 1.8, 7.0, 7.6 Hz, 1H), 7.14-7.20 (m, 2H), 7.25 (dd, J = 7.3, 7.3 Hz, 2H), 7.35 (ddd, J = 1.2, 6.7, 7.3 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.83 (d, J = 7.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.9, 46.4 (brs), 51.2(brs), 115.4, 116.8, 125.2, 126.7, 128.4, 129.2, 129.6, 136.8, 139.9, 142.9, 171.3. **FTIR (ATR):** 2967, 1614, 1434, 1337, 1017, 731, 691. **Anal.:** Calcd for $C_{19}H_{23}NOTe$ + 1/3·H_2O: C, 54.99; H, 5.75; N, 3.38. Found: C, 54.84; H, 5.58; N, 3.33. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{23}NNaOTe$ $[M+Na]^+$ 434.0734, found 434.0740.

(5-Methoxy-2-nitrophenyl)(4-nitrophenyl)sulfane (10k)



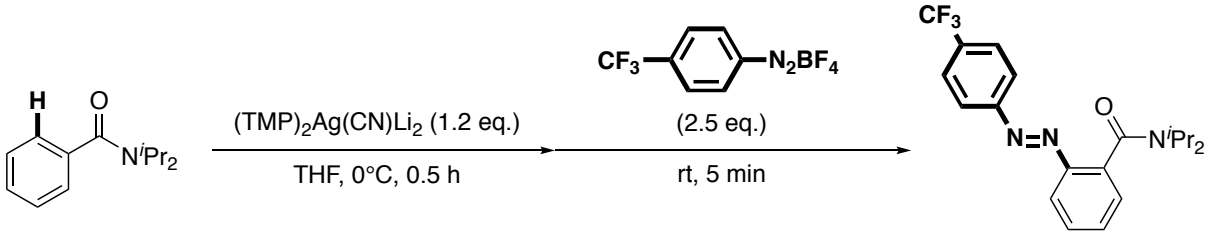
Following the **General Procedure** (argentation reaction was performed at –40°C for 2 h; purification: AcOEt/hexane = 0/100 → 25/75), the titled compound was obtained as a yellow solid in 89% yield (54.4 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 3.72 (s, 3H), 6.36 (d, J = 2.8 Hz, 1H), 6.79 (dd, J = 2.8, 9.2 Hz, 1H), 7.74 (d, J = 8.9 Hz, 2H), 8.28 (d, J = 9.2 Hz, 1H), 8.30 (d, J = 8.9 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 56.0, 111.5, 114.3, 125.0, 128.6, 135.6, 138.9, 139.6, 140.8, 148.5, 163.6. **FTIR (ATR):** 3095, 2919, 2849, 1574, 1519, 1335, 1243, 1044, 852. **mp:** 158.1°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{13}H_{10}N_2O_5S$ + 1/3·H_2O: C, 50.00; H, 3.44; N, 8.97. Found: C, 49.92; H, 3.38; N, 8.91. **EI-MS (% relative intensity):** *m/z*: 306 (M+, 22), 259 (18), 196 (100), 181 (92), 153 (49).

Synthesis of Azo Compounds (Table 4-5)

General Procedure:

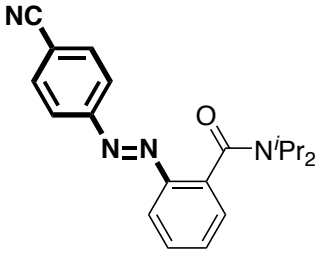
The reactions were performed on 0.2 mmol scale.

(*E*)-*N*,*N*-Diisopropyl-2-((4-(trifluoromethyl)phenyl)diazenyl)benzamide (14a)



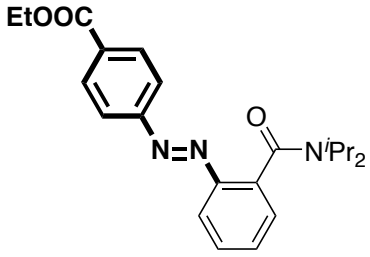
N,N-Diisopropylbenzamide (41.1 mg, 0.2 mmol) and dry THF (0.2 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.24 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 0.5 h at 0°C. The mixture was transferred to a heat gun-dried Schlenk tube containing 4-(trifluoromethyl)benzenediazonium tetrafluoroborate (130.0 mg, 0.5 mmol, pre-dried for 1 h under high vacuum). Azo formation (mixture of *cis*- and *trans*-forms) completed within 5 min with a vigorous stirring at room temperature. The Schlenk tube was immersed in a pre-heated 80°C oil bath and stirred for 16 h in order to obtain the *trans*-form. The reaction was cooled to the room temperature and quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using AcOEt/hexane (1/10 → 1/4) and PTLC using AcOEt/hexane (1/4) to give the titled compound as an orange solid in 68% yield (51.5 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.94 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.64 (d, *J* = 6.7 Hz, 3H), 3.54 (sep, *J* = 6.7 Hz, 1H), 3.73 (sep, *J* = 6.7 Hz, 1H), 7,41 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.47 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.54 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.2, 20.6, 20.8, 21.0, 46.1, 51.2, 116.6, 123.4, 124.0 (CF_3, q, *J* = 272 Hz), 126.4 ($\underline{C_{Ar}}$–C_{Ar}–CF_3, q, *J* = 4 Hz), 126.6, 129.0, 132.4, 132.6 ($\underline{C_{Ar}}$–CF_3, q, *J* = 35 Hz), 139.7, 147.9, 154.3, 168.8. **^{19}F NMR (470 MHz, $CDCl_3$):** δ –62.6. **FTIR (ATR):** 2970, 1632, 1440, 1319, 1125, 1063, 850, 764. **mp:** 158.7°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{20}H_{22}F_3N_3O$: C, 63.65; H, 5.88; N, 11.13. Found: C, 63.34; H, 5.98; N, 11.10. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{22}F_3N_3NaO$ $[M+Na]^+$ 400.1607, found 400.1620.

(*E*)-2-((4-Cyanophenyl)diazenyl)-*N*,*N*-diisopropylbenzamide (14b)



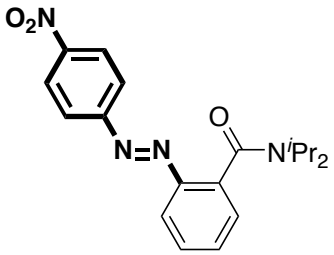
Following the **General Procedure** (purification: AcOEt/hexane = 7/93 → 1/4), the titled compound was obtained as a brown solid in 74% yield (49.8 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.93 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.62 (d, *J* = 6.7 Hz, 3H), 3.54 (sep, *J* = 6.7 Hz, 1H), 3.72 (sep, *J* = 6.7 Hz, 1H), 7.41 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.47 (ddd, *J* = 1.2, 7.6, 8.2 Hz, 1H), 7.55 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.84 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.3, 20.6, 20.8, 20.9, 46.1, 51.2, 114.4, 116.7, 118.5, 123.7, 126.7, 129.1, 132.8, 133.4, 139.9, 147.9, 154.4, 168.6. **FTIR (ATR):** 2970, 2227, 1630, 1441, 1339, 848, 768, 734, 565. **mp:** 159.3°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{20}H_{22}N_4O$ + H_2O: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.23; H, 6.37; N, 15.82. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{22}N_4NaO$ $[M+Na]^+$ 357.1686, found 357.1690.

Ethyl (*E*)-4-((2-(diisopropylcarbamoyl)phenyl)diazenyl)benzoate (14c)



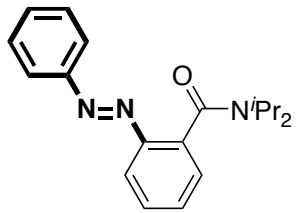
Following the **General Procedure** (purification: AcOEt/hexane = 7/93 → 1/4), the titled compound was obtained as a brown solid in 69% yield (53.0 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.93 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.64 (d, *J* = 6.7 Hz, 3H), 3.54 (sep, *J* = 6.7 Hz, 1H), 3.72 (sep, *J* = 6.7 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 7.41 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.47 (ddd, *J* = 1.5, 7.3, 7.9 Hz, 1H), 7.53 (ddd, *J* = 1.2, 7.3, 7.3 Hz, 1H), 7.84 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.93 (d, *J* = 8.9 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.5, 20.2, 20.5, 20.9, 21.0, 46.1, 51.1, 61.4, 116.5, 123.1, 126.6, 129.0, 130.7, 132.3, 132.6, 139.7, 148.0, 155.0, 166.1, 168.8. **FTIR (ATR):** 2971, 1714, 1626, 1442, 1339, 1269, 769. **mp:** 149.5°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 68.96; H, 7.09; N, 10.88. **HRMS (pos. ESI):** *m/z*: calcd for $C_{22}H_{27}N_3NaO_3$ $[M+Na]^+$ 404.1945, found 404.1953.

(*E*)-*N*,*N*-Diisopropyl-2-((4-nitrophenyl)diazenyl)benzamide (14d)



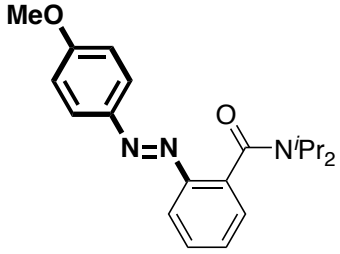
Following the **General Procedure** (purification: AcOEt/hexane = 7/93 → 1/4), the titled compound was obtained as a red solid in 72% yield (51.0 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.94 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.63 (d, *J* = 6.7 Hz, 3H) 1.64 (d, *J* = 6.7 Hz, 3H), 3.55 (sep, *J* = 6.7 Hz, 1H), 3.73 (sep, *J* = 6.7 Hz, 1H), 7.43 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.49 (ddd, *J* = 1.2, 7.6, 7.9 Hz, 1H), 7.57 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.86 (dd, *J* = 1.2, 7.9 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 2H), 8.37 (d, *J* = 9.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.3, 20.6, 20.8, 20.9, 46.1, 51.2, 116.6, 123.8, 124.9, 126.7, 129.1, 133.1, 140.1, 147.9, 149.0, 155.6, 168.6. **FTIR (ATR):** 2969, 1629, 1526, 1440,1339, 858, 765. **mp:** 153.6°C (decomp.; recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{22}N_4O_3$ + 1/10·hexane + 1/5·H_2O: C, 64.21; H, 6.54; N, 15.28. Found: C, 64.14; H, 6.37; N, 15.39. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{22}N_4NaO_3$ $[M+Na]^+$ 377.1584, found 377.1591.

(*E*)-*N*,*N*-Diisopropyl-2-(phenyldiazenyl)benzamide (14e)



Following the **General Procedure** (purification: AcOEt/hexane = 1/10 → 1/4), the titled compound was obtained as an orange solid in 52% yield (32.3 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 0.94 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.64 (d, *J* = 6.7 Hz, 3H), 3.53 (sep, *J* = 6.7 Hz, 1H), 3.73 (sep, *J* = 6.7 Hz, 1H), 7.39 (dd, *J* = 1.2, 7.0 Hz, 1H), 7.43-7.51 (m, 5H), 7.82 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.2, 20.5, 20.9, 21.0, 46.0, 51.1, 116.5, 123.4, 126.5, 128.9, 129.2, 131.4, 131.6, 139.1, 148.1, 152.6, 169.1. **FTIR (ATR):** 2968, 1631, 1440, 1338, 776, 688. **mp:** 111.9°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{19}H_{23}N_3O$ + 1/16·hexane + 1/8·H_2O: C, 73.40; H, 7.67; N, 13.25. Found: C, 73.35; H, 8.00; N, 13.54. **HRMS (pos. ESI):** *m/z*: calcd for $C_{19}H_{23}N_3NaO$ $[M+Na]^+$ 332.1733, found 332.1748.

(*E*)-*N*,*N*-Diisopropyl-2-((4-methoxyphenyl)diazenyl)benzamide (14f)



Following the **General Procedure** (purification: AcOEt/hexane = 7/93 → 1/4 and PTLC with AcOEt/hexane = 1/3), the titled compound was obtained as an orange solid in 34% yield (23.2 mg). **^{1}H NMR (500 MHz,**

$CDCl_3$): δ 0.93 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.65 (d, *J* = 6.7 Hz, 3H), 3.52 (sep, *J* = 6.7 Hz, 1H), 3.71 (sep, *J* = 6.7 Hz, 1H), 3.88 (s, 3H), 6.98 (d, *J* = 8.9 Hz, 2H), 7.36-7.38 (m, 1H), 7.41-7.46 (m, 2H), 7.77-7.80 (m, 1H), 7.90 (d, *J* = 8.9 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 20.1, 20.6, 20.9, 21.0, 45.9, 51.1, 55.7, 114.3, 116.4, 125.3, 126.5, 128.9, 130.9, 138.7, 147.1, 148.2, 162.4, 169.3. **FTIR (ATR):** 2967, 1627, 1599, 1501, 1441, 1338, 1251, 1142, 1029, 839, 729, 549. **mp:** 124.8°C (recrystallized from $CHCl_3$/hexane). **Anal.:** Calcd for $C_{20}H_{25}N_3O_2$ + 1/10·H_2O: C, 70.40; H, 7.44; N, 12.31. Found: C, 70.39; H, 7.44; N, 12.23. **HRMS (pos. ESI):** *m/z*: calcd for $C_{20}H_{25}N_3NaO_2$ $[M+Na]^+$ 362.1839, found 362.1850.

General Procedure for Scheme 4-6:

N,N-Diisopropylbenzamide (41.1 mg, 0.2 mmol) and dry THF (0.2 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Cu(CN)Li_2$ (0.24 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 2 h at 0°C. The mixture was transferred to a heat gun-dried Schlenk tube containing diazonium tetrafluoroborate (0.5 mmol, pre-dried for 1 h under high vacuum). Azo formation (mixture of *cis*- and *trans*-forms) completed within 5 min with a vigorous stirring at room temperature. The Schlenk tube was immersed in a pre-heated 80°C oil bath and stirred for 16 h in order to obtain the *trans*-form. The reaction was cooled to the room temperature and quenched with aqueous NH_4Cl (5 mL), followed by extraction with AcOEt (10 mL × 3). The combined AcOEt layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. NMR yields were determined using mesitylene as an internal standard (The yield of SM-dimer was calculated based on the reference).[1]

Crystal and Computational Details

Synthesis and Characterization of Cyanoargentate $(TMP)_2Ag(CN)Li_2(THF)$ (Figure 4-4)

To a solution of TMPH (0.34 mL, 2 mmol) in toluene (4 mL) at –78°C was added ^{n}BuLi (1.25 mL, 2 mmol). The solution was warmed to room temperature whereupon it was transferred to a slurry of AgCN (0.13 g, 1 mmol) in toluene (2 mL) at –78°C. The suspension was warmed to 0°C and stirred for 10 min, and then stirred at room temperature for a further 10 min. During this time, the solution darkened. After no further darkening occurred, the solvent was removed *in vacuo* and THF (3 mL) was added. This was subsequently removed *in vacuo* and the residue digested in hexane (6 mL) and toluene (6 mL). Filtration gave an orange-yellow solution, which was concentrated until precipitation occurred. The precipitate was dissolved with gentle warming and the solution was stored at 5°C for 24 h, after which time a crop of block-like crystals formed. **Yield:** 13% wrt. AgCN (65 mg). **^{1}H NMR (500 MHz, 298 K, C_6D_6):** δ 1.06 (s, 1.5H, TMPH-Me), 1.31 (br, m, 4H, THF), 1.46 (br, s, 16H, TMP-Me + TMP-3,5)*, 1.53 (s, 1.5H, unidentified), 1.61–1.64 (br, 2H, TMP-4), 1.67 (s, 12H, TMP-Me), 1.81 (m, 4H, TMP-3,5), 2.01 (m, 2H, TMP-4), 3.54 (m, 4H, THF). *Integration and COSY suggest one set of TMP-3,5 hydrogens lie beneath the broad TMP-Me resonance at δ 1.46 ppm. **^{13}C NMR (125 MHz, 298 K, C_6D_6):** δ 18.4 (TMPH-4), 19.7 (TMP-4), 24.9 (THF), 31.6 (TMPH-Me), 35.2 (TMP-Me), 38.2 (TMPH-3,5), 38.4 (TMP-Me), 39.8 (br, TMP-3,5), 49.1 (TMPH-2,6), 54.1 (d, $^2J_{Ag\text{-}C}$ = 3 Hz, TMP-2,6), 68.2 (THF), 168.2 (CN). **^{7}Li NMR (194 MHz, 298 K, C_6D_6):** δ 0.29 (s, 1Li, CA), 1.09 (s, 0.07Li, A). CA = cyanoargentate, A = argentate. **IR (nujol)** $\bar{\nu}$ (CN) = 2150 (br, w), 2102 (s). **m.p.**: 115°C (decomp.). **Anal.:** Calcd for $C_{23}H_{44}AgLi_2N_3O$: C, 55.21; H, 8.86; N, 8.40. Found: C, 54.49; H, 8.57; N, 8.43. **X-ray:** $C_{46}H_{88}Ag_2Li_4N_6O_2$, M = 1000.72, triclinic, space group $P\bar{1}$, *a* = 8.3861(3), *b* = 11.5994(4), *c* = 14.0500(5) Å, α = 86.881(2), β = 79.282(2), γ = 83.876(2) °, *V* = 1334.35(8) Å^3, *Z* = 1, ρ_{calcd} = 1.245 g cm^{-3}, Cu-K$_\alpha$ radiation, λ = 1.54184 Å, μ = 6.615 mm^{-1}, *T* = 180(2) K. 14620 data (4655 unique, R_{int} = 0.0325, θ < 66.637 °) were collected. *wR*2 = $\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ = 0.0673, conventional *R* = 0.0272 on *F* values of 4220 reflections with $F^2 > 2\sigma(F^2)$, *S* = 1.077, 307 parameters. Residual electron density extrema ±0.486 eÅ^{-3}.

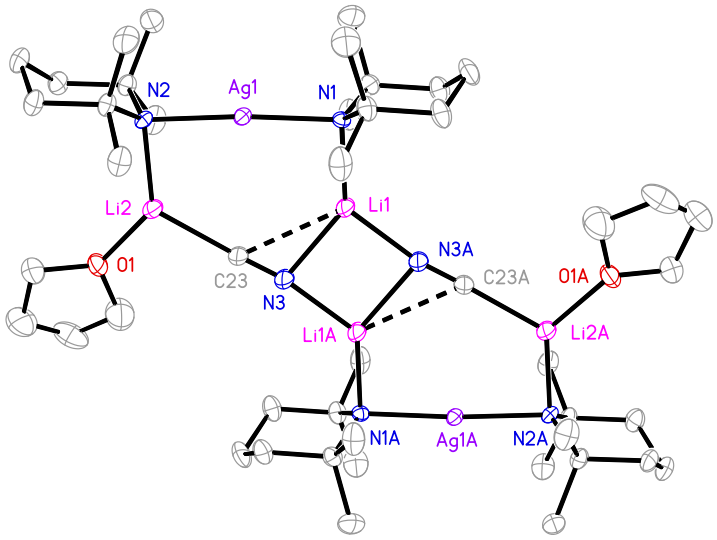


Figure S1. Molecular structure of the dimer of $(TMP)_2Ag(CN)Li_2(THF)$ at 30% probability

Crystal Structures of Arylargentates (Figre 4-4)

• Arylargentate from the 1 : 1 Reaction of *N,N*-Diisopropylbenzamide and $(TMP)_2Ag(CN)Li_2$

N,N-Diisopropylbenzamide (49.3 mg, 0.24 mmol) and dry THF (0.2 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.24 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 30 min at 0°C. Then, the solvent was removed *in vacuo* and dry hexane (3 mL) was added. This was vigorously stirred and the volatiles were removed *in vacuo* to give a slightly yellow solid. The residue was dissolved in dry benzene (1 mL) and the solution was stored at 4°C for a week to give a few colorless tiny solid.

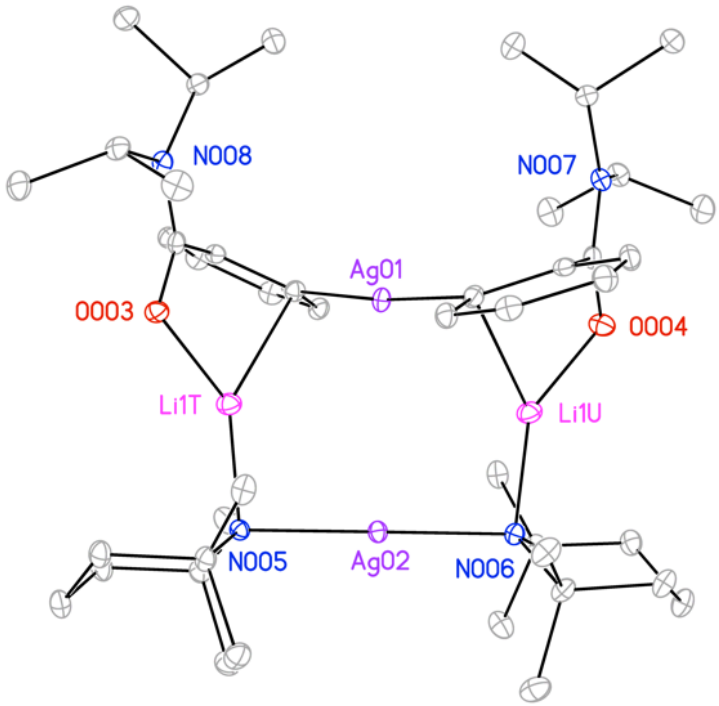


Fig. S2. Molecular structure of arylargentate from 1 : 1 reaction of *N,N*-Diisopropylbenzamide and $(TMP)_2Ag(CN)Li_2$ at 30% probability

• Arylargentate from the 2 : 1 Reaction of *N,N*-Diisopropylbenzamide and $(TMP)_2Ag(CN)Li_2$

N,N-Diisopropylbenzamide (205.3 mg, 1.0 mmol) and dry THF (1.0 mL) were added to a heat gun-dried Schlenk tube. The mixture was added to a solution of $(TMP)_2Ag(CN)Li_2$ (0.5 mmol) *via* cannula at –78°C, and the resulting solution was stirred for 2 hours at 0°C. During which time, white precipitates appeared. The solvent was removed *via* cannula and the resulted white solids were washed with dry THF. Then, all the volatiles were removed *in vacuo* and dry benzene was added. This was filtered over cotton in the glovebox. The filterate was stored at 4°C for a week to give a few colorless tiny solid.

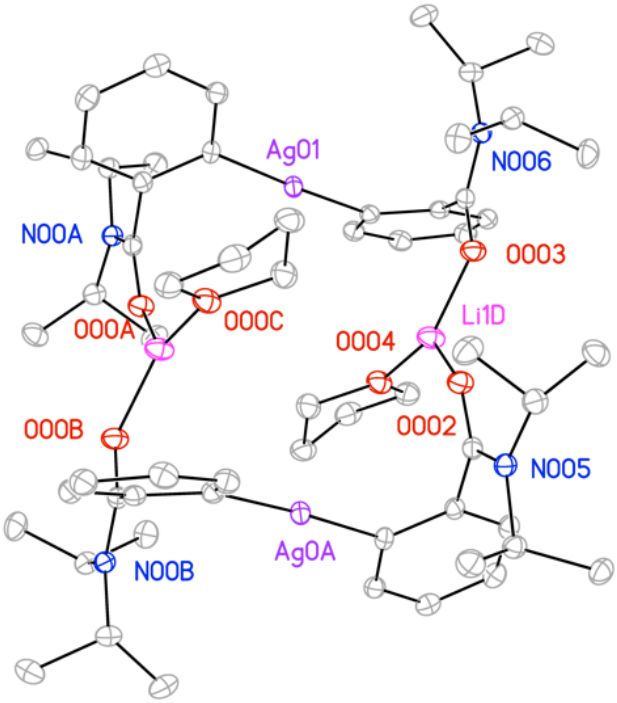
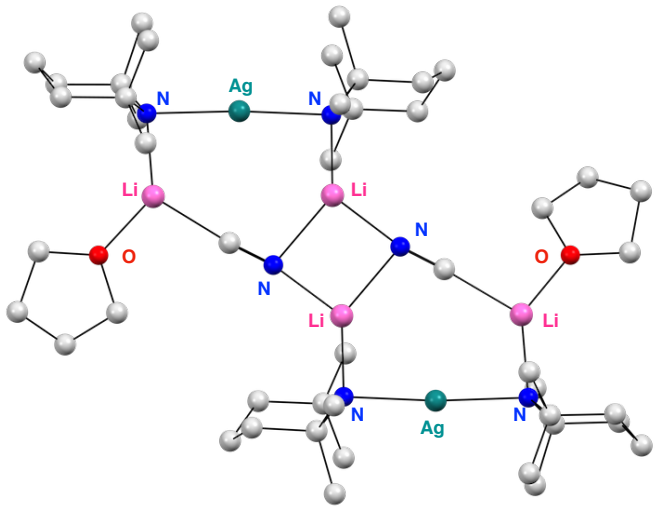


Fig. S3. Molecular structure of arylargentate from 2 : 1 reaction of *N,N*-Diisopropylbenzamide and $(TMP)_2Ag(CN)Li_2$ at 30% probability

DFT Calculations

Generals:
All calculations were carried with the Gaussian 16 program package[6-40]. The molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functional method based on M06 functional[6-17]. We used LanL2DZ[6-41] for Ag atom and 6–31+G* for the other atoms. Geometry optimization and vibrational analysis were performed at the same level. All the optimizations were calculated without any symmetry assumptions, and characterized by normal coordinate analysis at the same level of theory (number of imaginary frequencies, NIMAG, 0 for minima).

• DFT Calculation on $(TMP)_2Ag(CN)Li_2(THF)$ (Figure 4-4)



The structure of $[(TMP)_2Ag(CN)Li_2(THF))]_2$ calculated at M06/6-31+G*&LanL2DZ(Ag). H atoms were omitted for clarity.

Cartesian Coordinates

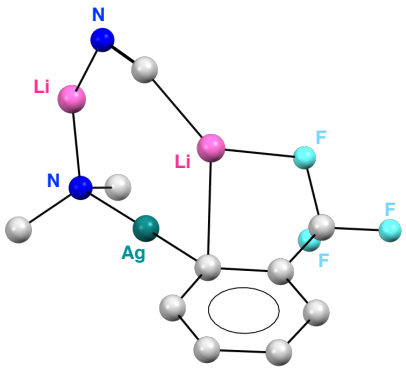
Li	-4.37844800	-1.36886800	0.30063700	O	-4.52244900	-3.20586100	-0.38403600
Ag	-3.88714700	1.45597300	0.17102600	C	-5.63937300	-4.07213900	-0.60516700
C	-1.75351700	2.99877700	-1.39998700	H	-6.25595800	-4.06946000	0.30207000
C	-1.99095800	3.69140100	1.02082100	H	-6.24331800	-3.67866400	-1.44150100
Li	-0.91464900	1.10839800	0.53700300	C	-3.34445100	-3.74948000	-1.01464500
N	-2.05196100	2.62662200	-0.00120800	H	-2.90554300	-2.97773400	-1.66255400
C	-2.26897800	-1.18457800	0.62754600	H	-2.61665900	-3.98727700	-0.22371600
N	-1.10903800	-1.01739200	0.71989200	C	4.05152400	5.37151000	-1.30000400
N	-5.63943800	0.13923900	0.33163500	H	4.16834700	5.32247700	-2.39215800
C	-6.29480800	0.22837100	1.65172600	H	3.41889100	6.23540800	-1.06620500
C	-6.49271700	0.25971200	-0.86678700	C	5.41827200	5.41328200	-0.62404700
Li	4.35580200	1.35236900	0.02160500	H	5.31995500	5.73479500	0.42270800
Ag	3.84403000	-1.46273900	0.17206600	H	6.13481000	6.07772100	-1.12021700
C	1.67783600	-3.08894100	-1.27603300	C	-3.81195000	-4.98556700	-1.76561000
C	1.98143300	-3.65662900	1.17007500	H	-3.02919900	-5.75056000	-1.83016800
Li	0.89854900	-1.09244900	0.56284300	H	-4.11549400	-4.72495800	-2.78974600
N	2.01097300	-2.64603900	0.09330100	C	-5.02828100	-5.41610600	-0.95091600
C	2.24690400	1.22520400	0.36042100	H	-5.71743500	-6.06651100	-1.50147800
N	1.09943500	1.05775200	0.55280100	H	-4.71580700	-5.93992600	-0.03630300
N	5.60906500	-0.15498700	0.24612900	C	-7.72561500	-0.65612000	-0.76063300
C	6.23212200	-0.13828600	1.58470200	H	-8.38467100	-0.48934200	-1.62881100
C	6.48536800	-0.40608500	-0.91513600	H	-7.38546300	-1.70644500	-0.81901900
O	4.61293700	3.21320900	-0.53917300	C	-7.53693700	-0.68041600	1.71090800
C	5.82932800	3.95482600	-0.69290500	H	-7.19686500	-1.73253200	1.69536200
H	6.52329700	3.64150300	0.09798100	H	-8.05571300	-0.53397600	2.67257800
H	6.27772100	3.70647500	-1.66956400	C	-8.48459500	-0.46776300	0.54265400
C	3.47588500	4.07174400	-0.76562200	H	-9.32603400	-1.17442700	0.60056900
H	2.79195700	3.56616400	-1.45899800	H	-8.93264200	0.53794600	0.58757300
H	2.95211500	4.21061400	0.19291900	C	-5.66346800	-0.21416200	-2.06367200

H	-6.26436300	-0.22135800	-2.98518100	C	8.46627000	0.39167400	0.47340700
H	-4.80011700	0.44880800	-2.23585100	H	9.32709500	1.07706600	0.48743600
H	-5.28349900	-1.23874000	-1.90972300	H	8.88292900	-0.61739300	0.62320800
C	-6.96197500	1.69005000	-1.19614700	C	5.22918800	0.50217800	2.54668400
H	-6.11394800	2.39119100	-1.15317200	H	4.28728800	-0.06773200	2.58296700
H	-7.38980900	1.73554900	-2.20996800	H	5.63294000	0.54954500	3.56852100
H	-7.72923300	2.06220200	-0.50713100	H	4.98668200	1.53772000	2.25156200
C	-5.30165000	-0.29399200	2.69233800	C	6.57216300	-1.52406000	2.16223500
H	-5.03384300	-1.34933400	2.50940900	H	6.90304100	-1.44174900	3.20944000
H	-4.37134000	0.29550500	2.69125000	H	5.68346700	-2.17377900	2.13970700
H	-5.72734000	-0.24896100	3.70526000	H	7.36677300	-2.03750100	1.60923400
C	-6.68121300	1.65193800	2.09081900	C	5.69718100	-0.01197400	-2.16647000
H	-7.46849200	2.09466700	1.47031700	H	4.80653900	-0.64865500	-2.29282900
H	-7.04233500	1.65709200	3.13120600	H	5.36334500	1.03851500	-2.11658500
H	-5.80495600	2.31669600	2.03481900	H	6.31044600	-0.11576300	-3.07377200
C	-0.45845100	3.83090900	-1.48209800	C	6.91630300	-1.87316400	-1.10616100
H	-0.30440100	4.16750500	-2.52128500	H	7.37460600	-2.01870600	-2.09698100
H	0.38901600	3.16944600	-1.22956600	H	7.64798000	-2.20761700	-0.36129100
C	-0.68787300	4.50392300	0.89359900	H	6.04489600	-2.54278600	-1.03344200
H	-0.70690800	5.34031100	1.61207500	C	0.38451000	-3.92759200	-1.27908200
H	0.15822000	3.85451900	1.18095500	H	0.19668800	-4.31145000	-2.29668300
C	-0.45037800	5.00828700	-0.52105700	H	-0.45446100	-3.25475100	-1.02888500
H	0.51337700	5.54006100	-0.57850500	C	0.68232600	-4.48340100	1.11747200
H	-1.21639700	5.74825500	-0.80538200	H	0.72732700	-5.28336900	1.87497700
C	-1.50681300	1.70304500	-2.17773000	H	-0.16108100	-3.82709700	1.39614500
H	-0.62888200	1.15903600	-1.79301400	C	0.41080500	-5.05808800	-0.26378800
H	-2.37846300	1.03050200	-2.12113400	H	-0.55012400	-5.59833100	-0.26750800
H	-1.31051900	1.91093500	-3.23979300	H	1.17442200	-5.80572300	-0.53381400
C	-1.97374000	3.00296100	2.38804300	C	1.40399700	-1.83390800	-2.10886300
H	-2.90003800	2.42958900	2.55544900	H	0.53992200	-1.26874000	-1.72112100
H	-1.11861800	2.31332400	2.49014700	H	2.27635100	-1.16059900	-2.11652000
H	-1.88450800	3.73706200	3.20211200	H	1.17018000	-2.09364100	-3.15178100
C	-3.19026400	4.65779200	1.03081500	C	2.79462900	-3.86426900	-1.99617400
H	-4.13616400	4.09400500	1.00937100	H	3.72922900	-3.28207500	-1.98417600
H	-3.18411800	5.27749300	1.94126600	H	3.00856100	-4.83626700	-1.53736900
H	-3.19869900	5.34343200	0.17556800	H	2.52675100	-4.05036000	-3.04825100
C	-2.88711400	3.74270900	-2.12757300	C	1.98925300	-2.89722400	2.49926500
H	-2.64975900	3.86931000	-3.19566200	H	2.91488600	-2.31079300	2.61719600
H	-3.82464900	3.16938900	-2.05604700	H	1.13157500	-2.20794600	2.58079900
H	-3.08102600	4.74013800	-1.71694500	H	1.92132400	-3.58750400	3.35277400
C	7.74456200	0.47827400	-0.86126800	C	3.18769500	-4.61426000	1.19978300
H	8.41828800	0.21024100	-1.69190400	H	3.21119100	-5.18258800	2.14284900
H	7.44110300	1.52770600	-1.02879200	H	3.17638600	-5.34649100	0.38381600
C	7.49845300	0.73827200	1.59197600	H	4.12942400	-4.04840700	1.12011800
H	7.99015700	0.66738500	2.57615000				
H	7.18963900	1.79334200	1.47257000				

Modeled DFT Calculations on Arylargentates Derived from Ph–CF_3 and Ph–SF_5

Me_2N^- was used as a model for TMP^-.

• Arylargentates of Ph–CF_3



The structure of modeled arylargentate derived from Ph–CF_3 calculated at M06/6-31+G*&LanL2DZ(Ag). H atoms were omitted for clarity.

Cartesian Coordinates for Ph–CF_3

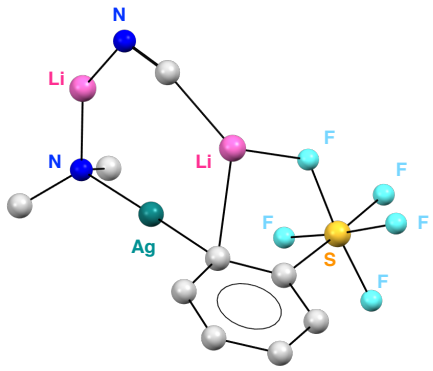
C	3.85464500	-1.69092100	0.09805700	N	-3.07331000	-0.13954600	-0.51398500
C	3.55638400	-0.36579700	-0.19882500	C	-3.72950400	-1.38062300	-0.89481900
C	2.22622200	0.06076400	-0.16385700	H	-4.82260600	-1.23791000	-1.02101700
C	1.14562800	-0.78721300	0.16149200	H	-3.35797500	-1.79195400	-1.85504100
C	1.50504000	-2.11176100	0.47183000	H	-3.58093700	-2.15618400	-0.12856000
C	2.82510200	-2.56283200	0.43984800	C	-3.30005900	0.84264700	-1.56445600
H	4.88678200	-2.03613900	0.06968000	H	-2.91148200	0.52066400	-2.55144500
H	4.35330000	0.32950600	-0.45614600	H	-4.38255800	1.04077500	-1.70599400
H	0.72616000	-2.82635000	0.74413300	H	-2.81389900	1.79926000	-1.32042500
H	3.05045800	-3.60131000	0.68233500	Li	-3.31732200	0.49146800	1.28460600
F	1.09147200	1.70292100	-1.46009000	C	-1.29431600	0.94428800	2.80963800
F	1.29653800	2.06717300	0.66168900	N	-2.45902300	1.02660500	2.94143800
F	3.00577500	2.25535000	-0.65229100	Li	0.50919700	0.60708800	1.89384300
Ag	-0.95397500	-0.43572400	-0.21787900	C	1.92689400	1.50221200	-0.44032800

NBO analysis on F(12)–Li(27) interaction in arylargentate derived from Ph–CF_3:

Interactions	kcal/mol
LP (1) F 12 /LP*(1)Li 27	6.08
LP (2) F 12 /LP*(1)Li 27	4.82
LP (2) F 12 /RY*(2)Li 27	0.39
LP (2) F 12 /RY*(3)Li 27	0.19
LP (2) F 12 /RY*(4)Li 27	0.11
LP (3) F 12 /LP*(1)Li 27	0.77
LP (3) F 12 /RY*(2)Li 27	0.10
LP (3) F 12 /RY*(3)Li 27	0.27

LP: Lone pair. RY: Rydberg orbital. " * " refers to vacant orbital.

• Arylargentates of Ph–SF_5



The structure of modeled arylargentate derived from Ph–SF_5 calculated at M06/6-31+G*&LanL2DZ(Ag). H atoms were omitted for clarity.

Cartesian Coordinates for Arylargentate of Ph–SF_5

C	-2.92743600	2.82257000	-0.19639300	F	-1.11800300	-1.32783000	1.26906200
C	-3.01500100	1.43706700	-0.24030400	F	-3.37607300	-1.04082300	0.87081100
C	-1.83751900	0.70292200	-0.09126200	F	-3.03364100	-1.11572100	-1.40669000
C	-0.56260200	1.23382100	0.09190700	Ag	1.41292900	0.38816900	-0.27653900
C	-0.54770000	2.64613300	0.15373000	N	3.41342800	-0.35621300	-0.58274600
C	-1.69081400	3.42769700	0.01101700	C	4.23625700	0.60556300	-1.30045300
H	-3.82915600	3.42099100	-0.31315400	H	5.27057700	0.22822300	-1.43644600
H	-3.97857500	0.95654600	-0.38355800	H	3.85351200	0.83381300	-2.31532900
H	0.40468100	3.15464200	0.31293500	H	4.29769500	1.55776300	-0.75266800
H	-1.61721200	4.51364300	0.05982700	C	3.36570000	-1.59023600	-1.35528000
S	-2.07832200	-1.13400000	-0.10816400	H	2.95120100	-1.44915500	-2.37334400
F	-0.78635300	-1.41803700	-1.03881400	H	4.37900700	-2.02151200	-1.48839200
F	-2.26918800	-2.72881500	-0.04665800	H	2.74325400	-2.34555200	-0.85250500

```
Li   3.71428500   -0.54936200    1.30707200     N    2.88871800   -0.43742200    3.05493800
C    1.74341300   -0.20349300    2.93590600
-----------------------------------------------------------------------------------------------------------------------
```

NBO analysis on F(14)–Li(30) interaction in arylargentate derived from Ph–SF_5:

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-----------------------------------------------------------------------------------------------------------------------
            Interactions              kcal/mol
CR (1) F 14      /LP*(1)Li 30          1.34
LP (1) F 14      /LP*(1)Li 30          4.26
LP (2) F 14      /LP*(1)Li 30          0.25
LP (2) F 14      /RY*(3)Li 30          0.07
LP (3) F 14      /LP*(1)Li 30         10.17
LP (3) F 14      /RY*(2)Li 30          0.47
LP (3) F 14      /RY*(3)Li 30          0.14
LP (3) F 14      /RY*(4)Li 30          0.13
LP (4) F 14      /LP*(1)Li 30          1.34
LP (4) F 14      /RY*(2)Li 30          0.17
LP (4) F 14      /RY*(3)Li 30          0.12
LP (4) F 14      /RY*(5)Li 30          0.08
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```

LP: Lone pair. RY: Rydberg orbital. “ * ” refers to vacant orbital.

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