博士論文

論文題目　基質－配位子間の水素結合を利用した芳香族化合物C–Hボリル化反応の位置選択性、反応性および化学選択性の向上

氏　　名　井田　悠

博　士　論　文

基質－配位子間の水素結合を利用した芳香族化合物C–Hボリル化反応の位置選択性、反応性および化学選択性の向上

Improvement of Site-selectivity, Reactivity, and Chemoselectivity of C-H Borylation of Aromatic Compounds Using Hydrogen Bond between Substrates and Ligand

井　田　悠

目次

略語表

便宜上、本論文の全般において以下に示す略語及び略称を用いた。

Ac	acetyl
acac	acetylacetonate
Ar	aryl
^{i}Bu	iso butyl
^{n}Bu	normal butyl
^{t}Bu	tertiary butyl
cod	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
DCE	dichloroethane
dioxane	1,4-dioxacyclohexane
DMF	dimethylformamide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dtbpy	4,4’-di-*tert*-butyl-2,2’-dipyridyl
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl
EWG	electron-withdrawng group
h	hour
hex	*n*-hexyl
Me	methyl
Mes	mesityl
MS	mass spectrometry
NMR	nuclearmagnetic resonance
Ph	phenyl
pin	pinacole
Piv	pivaloyl
ppm	parts per million
^{i}Pr	isopropyl
quant.	quantitative
recov.	recovoery
rt	room temperature

SM	starting material
temp	temperature
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
tol	tolyl

序論

現代の医療、とりわけ治療においては、低分子医薬、バイオ医薬および再生医療医薬品の進展が重要である。バイオ医薬や再生医療では、低分子医薬に比べ副作用の低減や治療可能な疾患対象の拡大などが期待できる。その一方で低分子医薬は、安定かつ低コストでの供給や、患者の QOL を害さない治療を可能としている。また日本の医薬品市場 9.6 兆円規模のうち、低分子医薬はその 50%以上を担い、超高齢化社会である日本において低分子医薬の重要性は増す一方である。[1] さらに日本の貿易において医薬品は輸入超過であり、国内における医薬品の需要の高まりやアジア諸国における人件費の高騰化の潮流を鑑みると、低分子医薬の国産化、これを目標とした医薬品の開発および生産の効率化は喫緊の課題である。

低分子医薬の開発研究では、精密に制御できる有機反応の利用が必須である。加えて近年は環境負荷の小さい有機合成の重要性も叫ばれているが、今回、精密有機合成および環境調和型の有機合成のいずれも実現しうる炭素－水素結合（C－H 結合）の直截的な変換反応に着目した。

C－H 結合は有機化合物に遍在しているが、この結合は非常に安定で、長い間官能基とはみなされてこなかった。[2] しかし 1950 年代に日本で、C－H 結合を効率的に目的の結合に変換する有機反応、C－H 結合変換反応が発見された。[3] 以来、世界中の研究者が C－H 結合変換反応の開発研究を行い、この二十年超で一定の成果を挙げてきた。[4] だがその適用可能範囲は未だ限定的で、さらなる汎用性の向上が必須である。

C－H 結合変換反応の抱える課題のうち、本論文では、特に反応の位置選択性に関する問題の解決を第一の目標とした。従来法では、反応基質の構造に工夫を加えることで位置選択性の問題を解決してきたが、基質ではなく触媒により制御することが可能となれば、上に挙げた基質適用範囲の大幅な拡張が可能になると考えた。

本論文の第 1 章では、メタ位選択的な C－H 結合ボリル化反応について記す。第 2 章では、第 1 章で開発した触媒を基に、反応性の向上を意図した配位子の構造改変について、第 3 章では、化学選択的な C－H 結合変換反応について述べる。

本研究により得られた知見が世界中の研究者に活用され、革新的新薬の開発やより安定・安価な医薬品供給に貢献できれば幸いである。

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[1] 厚生労働省「平成 26 年薬事工業生産動態統計年報」

[2] Kerr, J. A. “*CRC Handbook of Chemistry and Physics”* 71st ed. by Lide, D. R. CRC Inc., Boston, pp1990, 9-95-9-96.

[3] Murahashi, S. *J. Am. Chem. Soc.***1955**, *77*, 6403.

[4] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

本論

第 1 章 芳香族化合物のメタ位選択的炭素－水素結合ボリル化反応の開発研究

炭素－水素結合（C－H 結合）変換反応は、従来の有機合成反応と比べて反応工程数を削減することができるため、医薬品をはじめとする複雑有機化合物の合成効率を大きく高めることが期待される。それゆえに近年精力的にその開発研究がなされ、多様な変換反応が報告されている。以下、その変遷から現代に残される課題、そしてその課題解決に向けた本研究の内容を詳述する。

1-1 背景

炭素－水素結合変換反応の発見

現代有機化学は、天然物をはじめとする入手容易な原料に対し、官能基の導入・変換・除去、さらに必要に応じ保護・脱保護等の変換を施すことで、さまざまな有機化合物を生み出してきた。変換反応としては、反応性の高い炭素－ヘテロ原子単結合に対する置換反応や、アルデヒド、ケトンおよびエステル等のカルボニル基に代表される炭素－ヘテロ原子多重結合に対する付加反応が汎用されている。これらの官能基はその反応性の違いから、限られた位置で反応を進行させることができる。また保護基は、官能基の反応性や化合物の溶解性などの制御を目的に用いられる。しかし、多様な合成手法を組み合わせた有機化合物の合成では複数の変換工程を必要とするため、反応工程数や廃棄物の観点から、より直截的・効率的な反応の実現が求められている。

炭素－水素結合（C－H 結合）は、その結合解離エネルギーが約 100 kcal/mol[2] と大きく不活性であり、多くの場合官能基とはみなされない。しかし、1955 年に村橋らが $Co_2(CO)_8$ を触媒とした芳香族イミンのカルボニル化反応を報告し（Scheme1-1）、[3] 続けて 1963 年に Kleiman、Dubeck が $NiCp_2$ を用いてアゾベンゼンの C－H 結合活性化を報告して以来（Scheme 1-2）、[5] C－H 結合の切断を経る結合形成反応は、有機化学者の新たな興味の対象となった。しかし、当初は藤原－守谷反応（Scheme 1-3）[6] に代表されるように、ベンゼンやトルエンなど、単純な構造の化合物を溶媒量用いて反応を行う例が多くを占めていた。これらの反応の反応効率は低く、また反応位置の制御ができないことから、C－H 結合変換反応は精密有機合成には利用しにくい反応であった。

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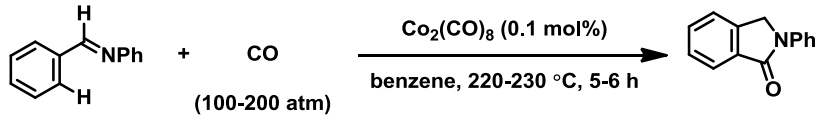
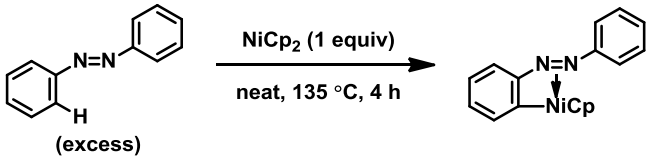
[5] (a) Chatt, J.; Watson, H. R. *J. Chem. Soc.* **1962**, 2545. (b) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544. (c) Chatt, J.; Davidson J. M. *J. Chem. Soc.* **1965**, 843.

[6] Fujiwara, Y.; Moritani, I.; Matsuda, M; Teraniahi, S. *Tetrahedron Lett.* **1968**, *9*, 3863.

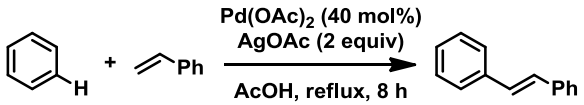
Scheme 1-1 | Carobonylation-annulation of aromatic imines



Scheme 1-2 | C-H nickelation

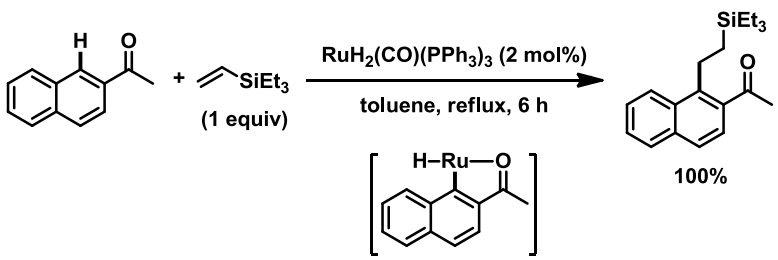


Scheme 1-3 | Fujiwara-Moritani reaction



しかし、村井らがヘテロ原子による金属へのキレーションを利用した C−H 結合官能基化反応を報告したときから状況は一変した。彼らはルテニウム触媒存在下、芳香族ケトンのオルト位選択的にアルケニル化反応が進行することを見出した（Scheme 1-4）。[4] 本反応では、反応基質を過剰量用いる必要がなく、定量的に新たな炭素－炭素結合形成が進行する。反応効率および反応位置の制御いずれの観点からも C−H 結合官能基化反応を実用に大きく近づけた。実際にこの論文が発表されてからキレーションを利用した C−H 結合変換反応は盛んに研究が行われるようになり、さまざまな配向基を利用できることが明らかとなった（Figure 1-1）。Scheme 1-5 には、Scheme 1-4 に加えて、代表的な配向基を用いた C−H 結合変換反応の例として、2-フェニルピリジン窒素原子によるロジウムへの配位を利用した炭素－炭素結合形成反応[7]およびアミド酸素原子によるパラジウムへの配位を利用した炭素－炭素結合形成反応[8]を示した。

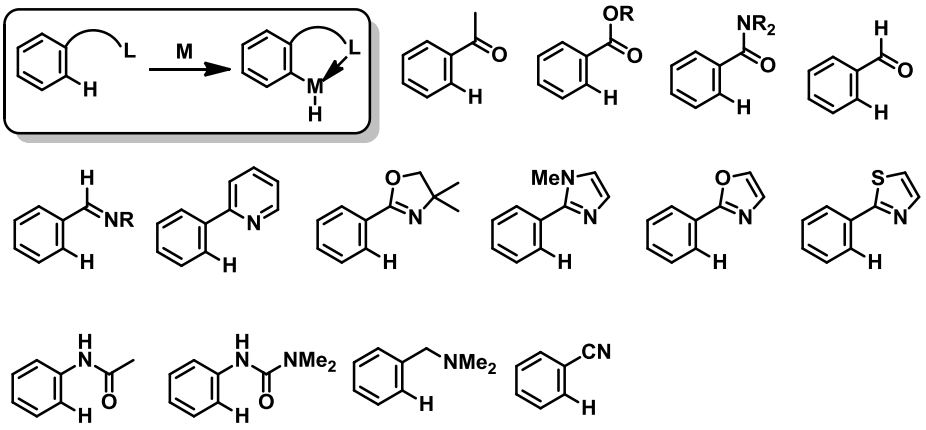
Scheme 1-4 | Ruthenium-catalyzed C-C bond formation



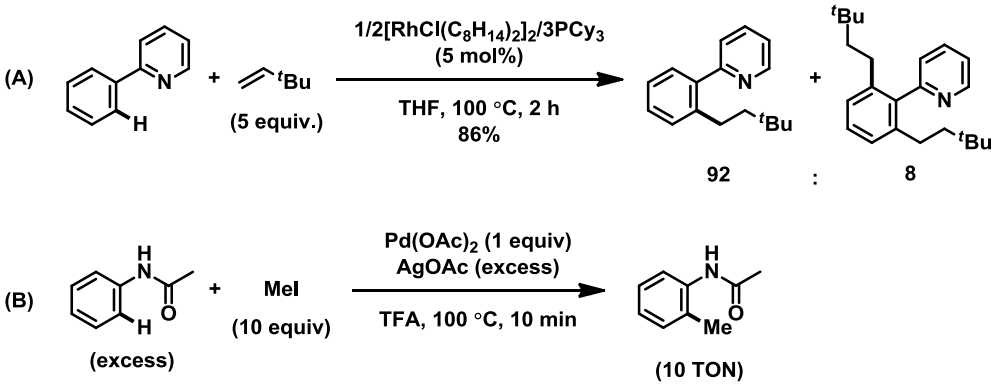
[7] Lim, Y. G.; Kim, Y. H.; Kang, J. B. *J. Chem. Soc., Chem. Commun*. **1994**, 2267.

[8] Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759.

Figure 1-1 Representative directing groups



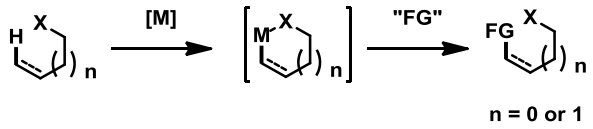
Scheme 1-5 | *ortho*-Selective C-H functionalization using a directing group



さまざまな配向基の利用により、ベンゼン環をはじめとする芳香環オルト位選択的な C－H 結合変換反応は大きく発展した。[9] しかし、配向基に依存する C－H 結合活性化を伴う変換反応では、次に挙げる主として二つの問題点が残されている。一つは、配向基は基質と共有結合を形成しているため、反応後に除去する工程が必要な点であり、反応工程数、原子効率の観点から、C－H 結合の利点を活用できていないことになる。また、配向基によっては、生成物から除去できないという問題点もある。二点目は、五員環または六員環遷移状態を経て C－H 結合の切断が起こる（Scheme 1-6）ため、反応点が配向基近傍（ベンゼン誘導体ではオルト位）に限られていることであり、より遠隔位における位置選択的な C－H 結合切断は困難である。

[9] Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

Scheme 1-6 | C-H transformations via the formation of 5- or 6-membered metallacyclic intermediate



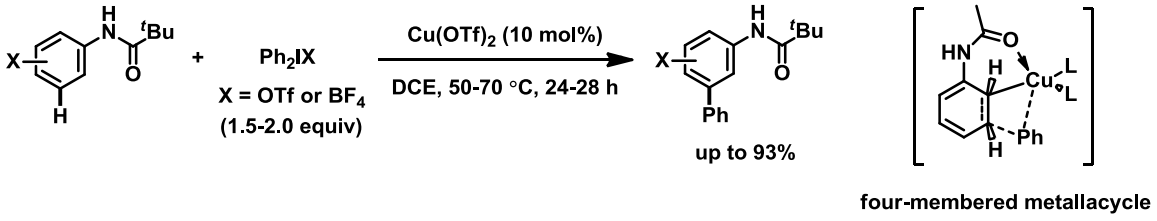
二点目の反応位置の制限に関しては、近年新たにその解決法が示されつつある。

メタ位選択的 C－H 結合変換反応

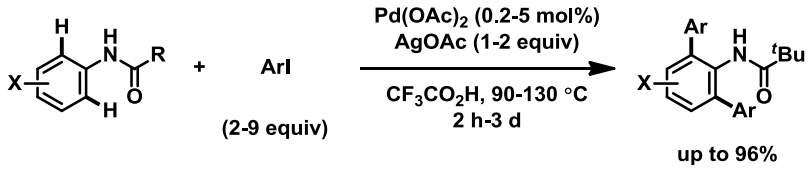
配向基を用いた芳香族 C－H 結合変換反応では、その機構上、オルト位選択的な反応が報告例の多くを占めている。近年では、いくつかの反応形式でベンゼン環メタ位選択的変換反応の成功例が増えつつあり、それらは主に次の五例に集約される。

Gaunt らは酸化的条件下、触媒量の銅触媒 $Cu(OTf)_2$ を用いることで、アニリド誘導体のメタ位選択的なアリール化反応を実現した（Scheme 1-7）。[10] $Cu(OTf)_2$ ではなく $Pd(OAc)_2$ を用いた触媒反応では、アニリド酸素がパラジウムに配位し、オルト位選択的な C－H アリール化反応が進行することとは対照的である（Scheme 1-8）。[11] 一方で、$Cu(OTf)_2$ による反応では C－H 結合切断が遅く、かわりに Heck 反応で見られるような四員環遷移状態（Scheme 1-7、右図）を経るために、オルト位ではなくメタ位でアリール化が起こる。[12] 本反応は配向基を利用したメタ位選択的な C－H 結合変換反応である。

Scheme 1-7 | Cu-Catalyzed *meta*-Arylation



Scheme 1-8 | Pd-Catalyzed *ortho*-Arylation



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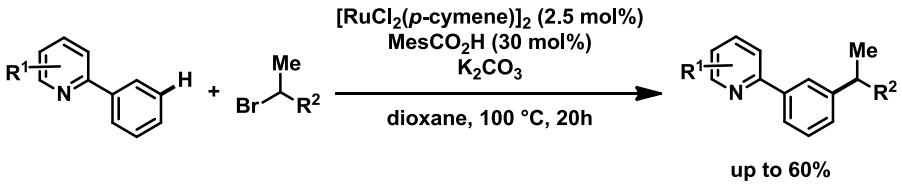
[10] Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

[11] Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046.

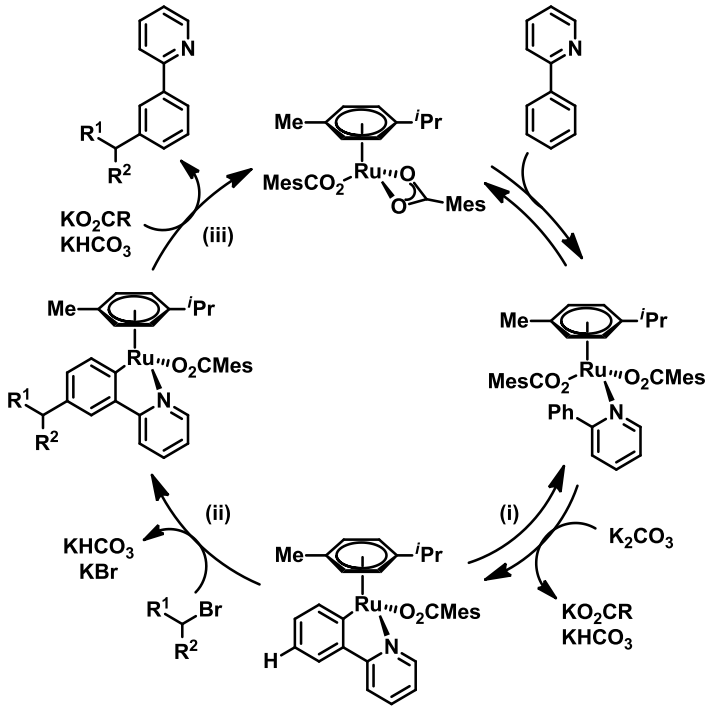
[12] Chen, B.; Hou, X.-L.; Li, Y.-X, Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 7668.

Ackermann らは、ルテニウム(II)触媒を用いることで、2-フェニルピリジンのメタ位アルキル化反応を実現した（Scheme 1-9)。[13] 本反応では、以下に示す反応機構が提唱されている：（ｉ）ピリジル基を配向基としてベンゼン環 C－H 結合のオルトメタル化が起こることで鍵中間体を生じ、（ii）電子豊富なルテニウムからの電子押し出しにより芳香環が電子豊富になるため、C－Ru 結合のオルト位またはパラ位でのフリーデル・クラフツアルキル化反応が進行し、（iii）生じるアリールルテニウム中間体がプロトン化を受けることで、結果としてメタ位がアルキル化された生成物が得られる（Scheme 1-10)。本反応では、基質が 2-フェニルピリジンをはじめとする、2 位にベンゼン環を有する含窒素ヘテロ芳香族化合物に限られている。さらに除去が不可能なピリジン配向基を用いているため、一般性の高い有機合成反応としての利用は難しい。

Scheme 1-9 ｜ Ru-catalyzed C-C bond formation at *meta*-position



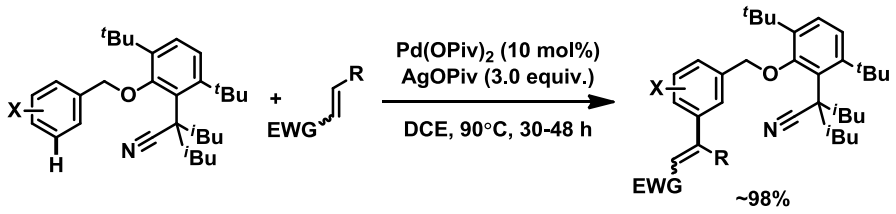
Scheme 1-10 ｜ Proposed catalytic cycle



[13] Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 587.

Yu らは、パラジウム触媒による、メタ位選択的な C－H アルケニル化反応を報告した（Scheme 1-11）。[14] 末端にシアノ基を有する複雑な構造をもつ配向基をもつ芳香族化合物を基質として用いることにより、シアノ基の窒素原子が触媒金属に配位し、触媒金属中心がメタ位 C－H 結合に接近することで、位置選択性を発現することに成功している。本報告では、基質の調製に多段階を要する点、C－H 結合変換反応ののちに不要となった配向基を除去する必要がある点に改善の余地を残す。

Scheme 1-11 | Pd-Catalyzed C-C bond Formation at *meta*-Position using directing group



さらに Yu らは、ノルボルネンを添加することにより、フェニル酢酸誘導体のメタ位選択的な C－C 結合形成反応を実現した（Scheme 1-12）。[15] 本反応では、アミド窒素のパラジウムへの配位により、オルト位選択的な C－H 結合活性化が起こり、その結果生じるアリールパラジウム中間体のパラジウム－炭素結合にノルボルネンが挿入することで、パラジウムのメタ位への接近が可能になる（Scheme 1-13）。Scheme 1-11 の場合とは異なり短工程で基質の調製が可能となり、フェノールやアニリン誘導体に対して配向基を導入するだけで、本反応系が適用可能となる。[16] ただし、反応の第一段階でオルト位の C－H 結合を足掛かりとするため、オルト位に置換基をもつ基質に対して本反応は適用できない。

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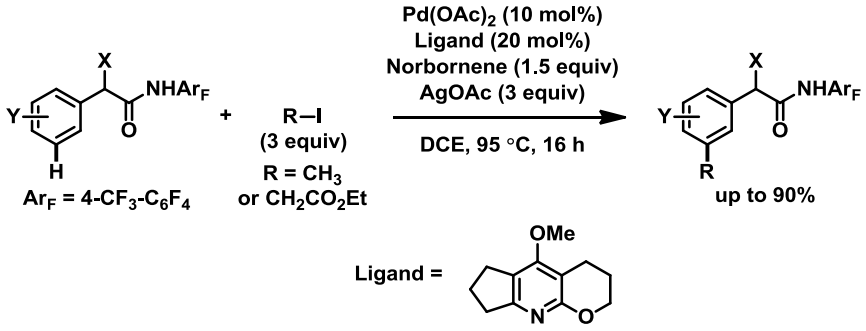
[14] Leow, D.; Li, G.; Mei, T. S.; Yu, J. Q. *Nature* **2012**, *486*, 518.

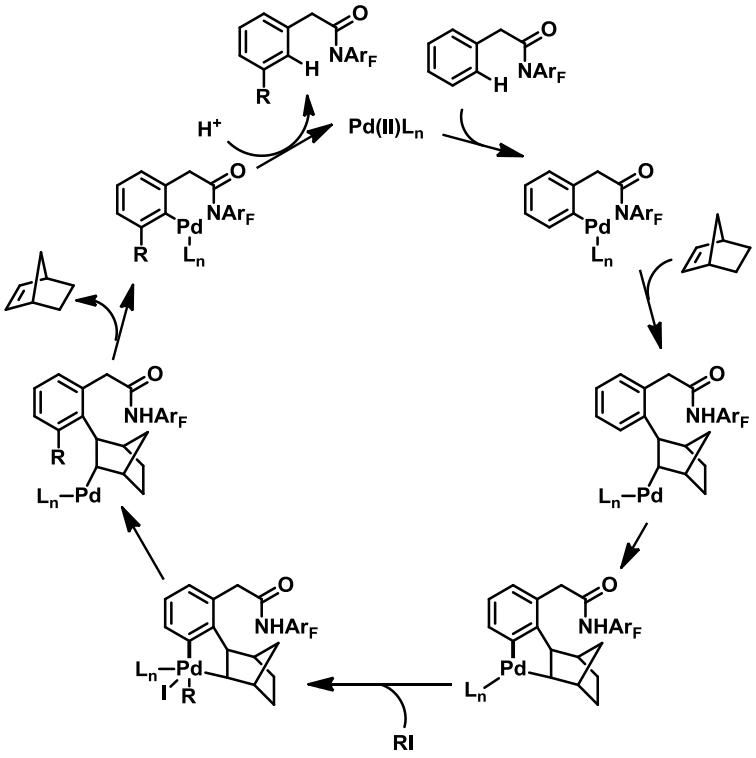
[15] Wang, X. C.; Gong, W.; Fang, L. Z.; Zhu, R. Y.; Li, S.; Engle, K. M.; Yu, J. Q. *Nature* **2015**, *519*, 334.

[16] (a) Shen, P. X.; Wang, X. C.; Wang, P.; Zhu, R. Y.; Yu, J. Q. *J. Am. Chem. Soc.* **2015**, *137*, 11574. (b) Wang, P.; Farmer, M. E.; Huo, X.; Jain, P.; Shen, P. X.; Ishoey, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. D.; Yu, J. Q. *J. Am. Chem. Soc.* **2016**, *138*, 9269. (c) Wang, P.; Li, G. C.; Jain, P.; Farmer, M. E. He, J.; Shen, P. X.; Yu, J. Q. *J. Am. Chem. Soc.* **2016**, *138* 14092.

Scheme 1-12 | Pd-Catalyzed C-C bond Formation at *meta*-Position with norbornene



Scheme 1-13 | Plausible catalytic cycle for norbornene-mediated meta-C-H alkylation

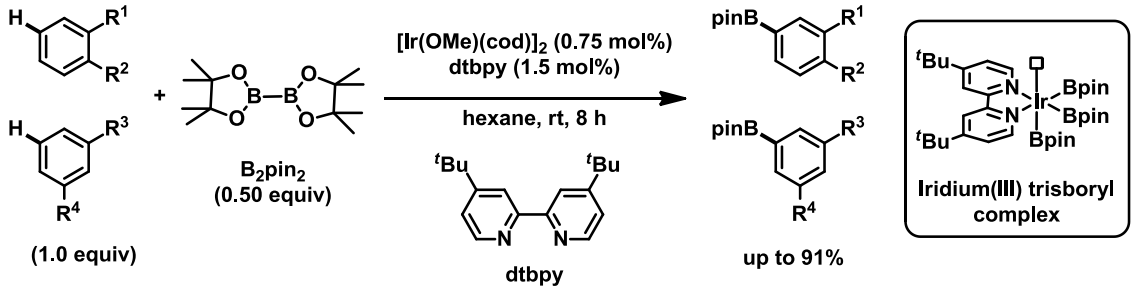


石山、宮浦、Hartwigらは、イリジウム触媒を用いるベンゼン環のメタ位選択的なC－Hボリル化反応を報告している（Scheme 1-14）。[17] 一般に、C－H結合の切断には高温を要する場合が多いが、本反応は活性の高いイリジウム(III)トリスボリル錯体（Scheme 1-14、右図）を用いることで室温にて反応が進行する点が、数あるC－H結合変換反応の中で秀でている点の１つである。しかし、一般的な基質では、メタ体およびパラ体の混合物が得られる。その位置選択性は立体障害に依存するため、メタ体のみに収束させるためには1,2-二置換も

[17] Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056.

しくは1,3-二置換ベンゼン誘導体を用いる必要がある。

Scheme 1-14 | Ir-catalyzed borylation at *meta*-position

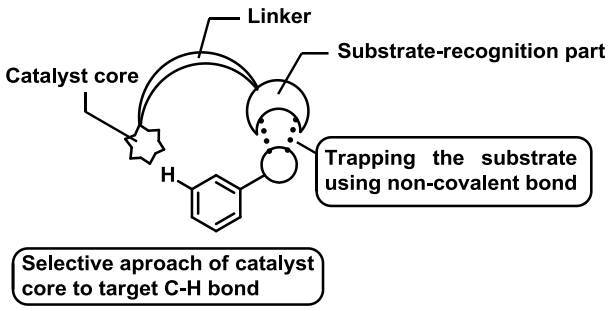


これらのベンゼン誘導体のメタ位選択的な官能基化反応では、いまだに適用基質に制限があることがわかる。そこで私は、一般的な基質に対するメタ位選択的なC－H変換反応を実現すべく、触媒配位子が非共有結合性相互作用により基質を認識することのできる分子認識触媒の開発に着手した。

1-2 課題設定：非共有結合型分子認識触媒の設計

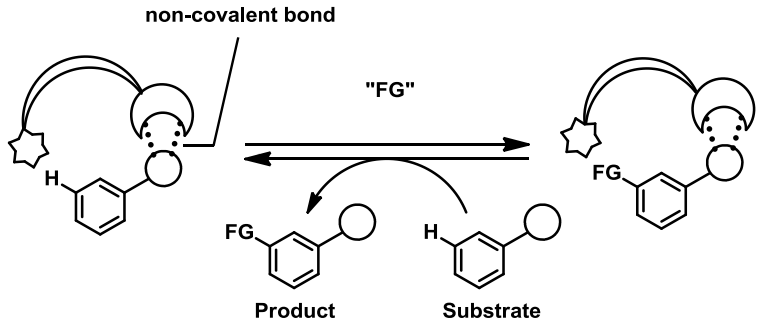
1-1 項で述べた反応例を受け、現在の C－H 結合活性化反応開発において解決すべき最重要課題は、共有結合型配向基使用からの脱却および基質一般性・化学選択性の拡充であると考えた。ここで、直截的かつ位置選択的な C－H 結合官能基化反応を達成しうる非共有結合型分子認識触媒の開発に着手した（Figure 1-2）。すなわち、触媒配位子に基質認識部位を導入し、基質との間の非共有結合性相互作用により、目的の C－H 結合のみを触媒部位に接近させることで、位置選択的な C－H 結合変換反応が進行すると考えた。非共有結合を介して触媒的に反応点の制御ができれば、配向基を用いた場合とは異なり、触媒設計次第でさまざまな位置の C－H 結合を反応点として選択することが可能となり、また同時に配向基の脱着工程が不要となる。

Figure 1-2 | Concept of recognition system



水素結合や静電相互作用に代表される非共有結合は、不斉有機触媒反応に見られるように、反応基質を捕捉するのに十分な強さをもっている一方で、それほど強い結合ではないため、生成物と基質との交換反応が進行し、触媒サイクル（Scheme 1-15）を実現できるため、触媒反応を制御するのに適した分子間相互作用だと考えられる。さらに後で Figure 1-5 に示すように、電荷を持たないさまざまな官能基が水素結合供与体および受容体となることが知られているため、水素結合を用いれば多様な基質に適用することが可能となると考え、水素結合を位置選択性発現のための触媒－基質間の非共有結合性相互作用として選択した。

Scheme 1-15 | Catalytic cycle of non-covalent bond-controlled regioselective C-H transformations



水素結合とその生体内における利用

水素結合の発見を報告した最初の論文は特定されていないが、20 世紀初頭にはその存在が示されており、1920 年代には Latimer や Rodebush、Huggins、Pauling によって明確にその存在が示された。[18] 水素結合は、電気陰性な原子（X)、おもに酸素、窒素、フッ素原子などに結合する水素原子（H） と電気陰性な原子（A） との間に起こる分子間または分子内相互作用であり、IUPAC Technical Report では以下ように定義されている。[19]

“The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.”

水素結合の結合エネルギーは強いもので 40 kcal/mol、弱いものでは 0.4 kcal/mol 程度であり、N－H－N 間に見られる水素結合は最も強い部類に入り、フッ素原子の関わる水素結合は 5-6 kcal/mol であるとされている（共有結合：500 kJ/mol 程度、ファンデルワールス力：1 kJ/mol 程度）。[20]また水素結合の強さは X－H－A のなす角度によっても異なり、180 度に近いほど強くなることが知られている。

水素結合は、生体内で大きな役割を果たしており、触媒反応やイオンの運搬に関わっている。セリンプロテアーゼはセリン残基による特徴的なペプチド加水分解を行う酵素一群であるが、活性中心において Ser195 が基質となるペプチドを活性化したのち、生じるオキシアニオンを同 Ser195 と Gly193 が水素結合により安定化することで反応を促進している

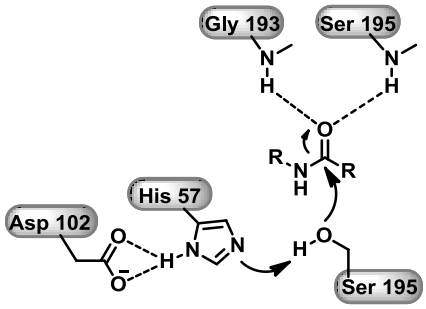
[18] Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48.

[19] Arunan, E.; Desiraju, G. R.; Klein R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. IUPAC Technical Report (http://media.iupac.org/reports/provisional/abstract11/arunan_tr.pdf).

[20] Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

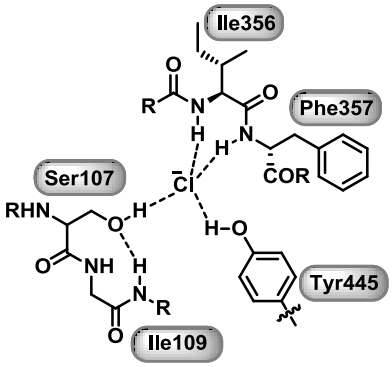
（Figure 1-3）。[21] また Ser195 付近に存在するアミノ酸残基がポケットを形成することで、基質を捕捉し、反応位置を規定している。

Figure 1-3 | Mechanism for serine protease



水素結合を利用したチャネルとしては CIC クロライドチャネルが知られており、細胞の膜電位を司る塩化物イオンの移動を制限するこのチャネルは水素結合により塩化物イオンを捕捉している（Figure 1-4）。[22]

Figure 1-4 | Mechanism for CIC chrolide channel



イソペニシリン *N* シンターゼ（IPNS）は C－H 結合変換反応を触媒する酵素として知られている（Scheme 1-16）。[23] イソペニシリンはペニシリンの生合成における前駆体である。原料のトリペプチドが IPNS の四アミノ酸残基により認識されることで、二度の閉環反応を立体・位置選択的に進行させている。

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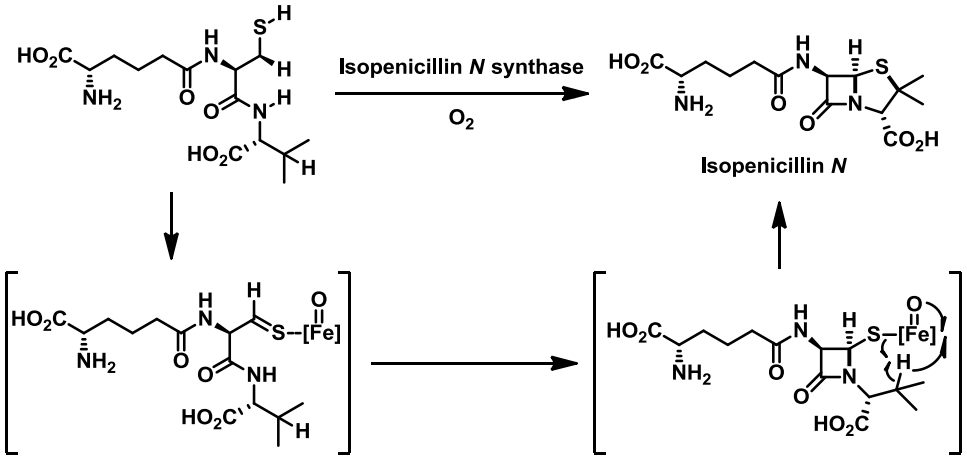
[21] Hedstrom, L *Chem Rev.* **2002**, *102*, 4501.

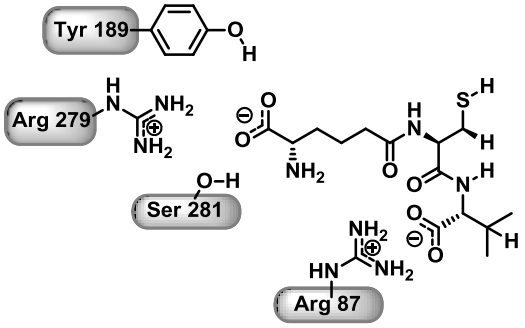
[22] Dutzler, R.; Campbell, E. B.; Cadene, M.;, Chait, B. T.; MacKinnon, R. *Nature* **2002**, *415*, 287.

[23] (a) Burzlaff, N. I.; Rutledge, P. J.; Clifton, I. J.; Hensgens, C. M. H.; Pickford, M.; Adlington, R. M.; Roach, P. L.; Baldwin, J. E. *Nature* **1999**, *401*, 721. (b) Lundberg, M.; Kawatsu, T.; Vreven, T.; Frisch, M. J.; Morokuma, K. *et al. J. Chem. Theory Comput.* **2009**, *5*, 222.

Scheme 1-16 | Enantio- and site-selective C-H functionalization controlled by enzyme



Recognition of substrate with non-covalent bonds by isopenicillin *N* synthase



水素結合を利用した有機合成反応の制御

有機合成化学者もまた水素結合によって反応を制御してきた。近年飛躍的に成長を見せた不斉触媒に関して以下に例を示す。不斉触媒としては、Corey らのグアニジン誘導体、[24] 戸田らのジオール、[25] 秋山、寺田らのリン酸誘導体、[26] Bach らのラクタム、[27] Jørgensen らのビススルホンアミド誘導体[28]など多種報告があるが（Figure 1-6）、非共有結合型分子認識触媒としての Brønsted 酸の地位を確立した Wynberg ら、向山らおよび Jacobsen らにより開発された有機触媒反応を下に示す。

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[24] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

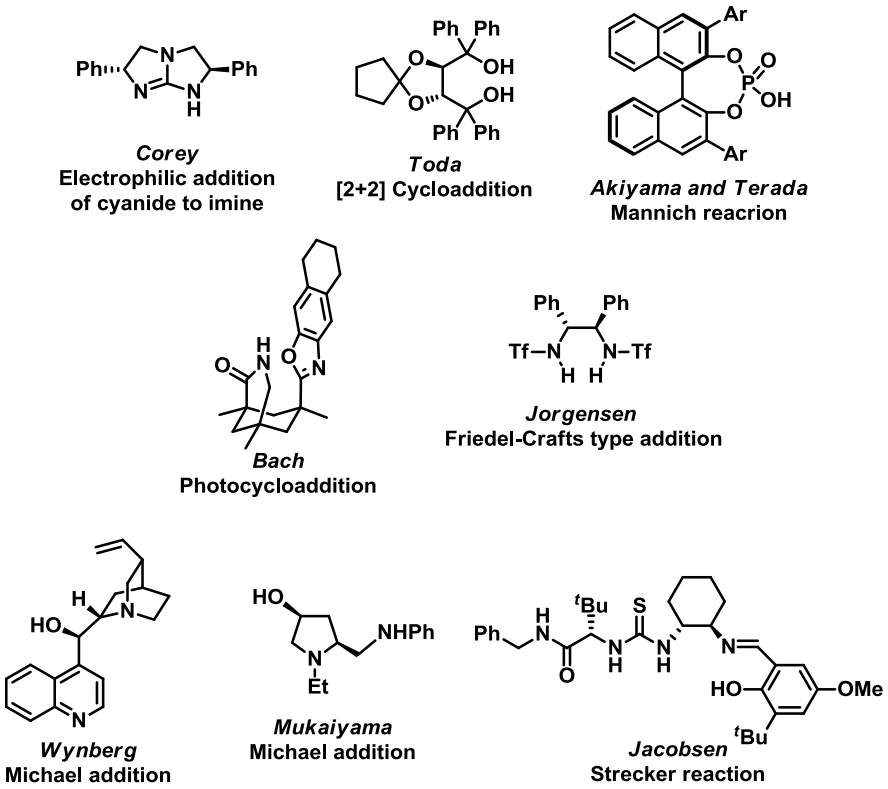
[25] Tanaka, K.; Toda, F. *J. Chem. Soc., Chem. Commun.* **1983**, 593.

[26] (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5357.

[27] Back, T.; Bergmann, H. Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2302.

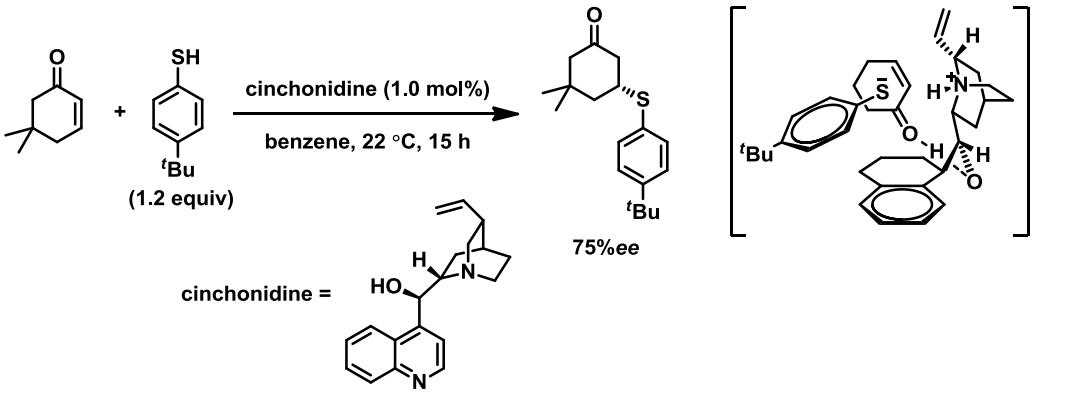
[28] Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2566.

Figure 1-6 | Representative organocatalysts for assymmetric reactions



Wynberg らは触媒量のシンコニジンを用いることで、芳香族チオールのシクロアルケノンに対する不斉共役付加反応を実現した（Scheme 1-17）。[29] 本反応では、キヌクリジン部位がチオールと、ヒドロキシ基がエノンと水素結合を形成し、シンコニジンが共役付加反応の促進および不斉場の構築に関与している（Scheme 1-17、右図）。シンコナアルカロイドとしては他にもキニジン、キニーネ、シンコニン等が不斉有機触媒として使われており、共役付加反応のほかにも森田-Baylis–Hillman 反応、[30] ニトロアルドール反応、[31] 求電子的アミノ化反応[32]の不斉触媒化を実現している。

Scheme 1-17 | Cinchona alkaloid-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones



[29] Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057.

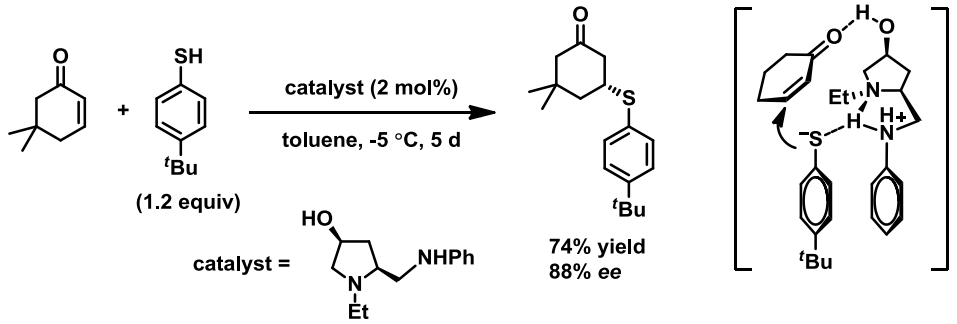
[30] Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

[31] Misumi, Y.; Bulman, R. A.; Matsumoto, K. *Heterocycles* **2002**, *56*, 599.

[32] Brandes, S.; Bella, M.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 114.

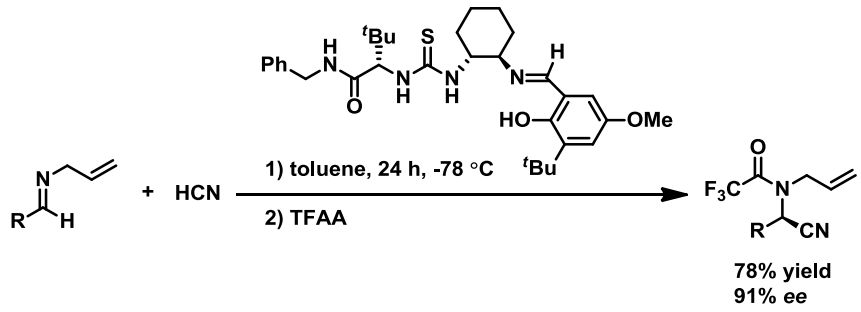
また向山らは、ピロリジン誘導体を用いることで触媒的に不斉共役付加反応を行うことが可能であることを示した（Scheme 1-18）。[33] シンコニジンによる触媒反応と同様、触媒中の窒素原子がチオールと、触媒中のヒドロキシ基がカルボニルと相互作用することでScheme 1-18、右図に示すような遷移状態を経て、74%収率、88% *ee* にて目的物を得ている。

Scheme 1-16 | Pyrolidine-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones



Jacobsen らは不斉中心を有するチオ尿素誘導体を触媒とした不斉 Strecker 反応を報告し（Scheme 1-19）。[34] チオ尿素部位が水素結合供与体として反応剤であるシアニドを活性化し、またアミド部位で基質のイミンを認識し、不斉を発現している。尿素およびチオ尿素構造はイミンのほかにカルボニル基、[35] ニトロ基、[36] スルホン酸[37]を認識することが知られている。

Scheme 1-19 | Schiff base-catalyzed asymmetric Strecker reaction



水素結合は、位置選択的なC－H結合変換反応にも用いられている（Scheme 1-20）。[38]この触媒系では、イブプロフェンのもつ二つのベンジル位のうち一方を選択的に酸化するこ

[33] Mukaiyama, T.; Ikegawa, A.; Suzuki, K. *Chem. Lett.* **1981**, 165.

[34] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

[35] Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603.

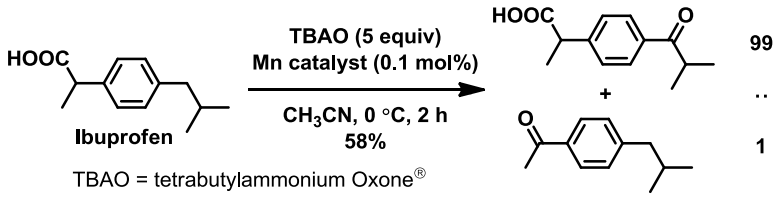
[36] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[37] Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986.

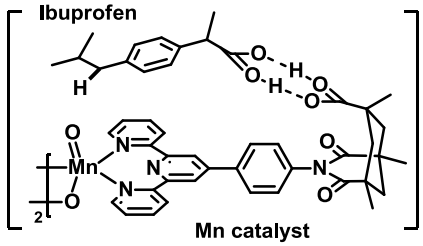
[38] Das, S.; Incarvito, C. D.; Crabtree, R. H. Brudvig, G. W. *Science* **2006**, *312*, 1941.

とが可能となった。基質および触媒分子のもつカルボキシル基間の水素結合を用いることで、高い位置選択性を実現している。

Scheme 1-20 | Site-selective C-H oxidation controlled by hydrogen bond



TBAO = tetrabutylammonium Oxone®

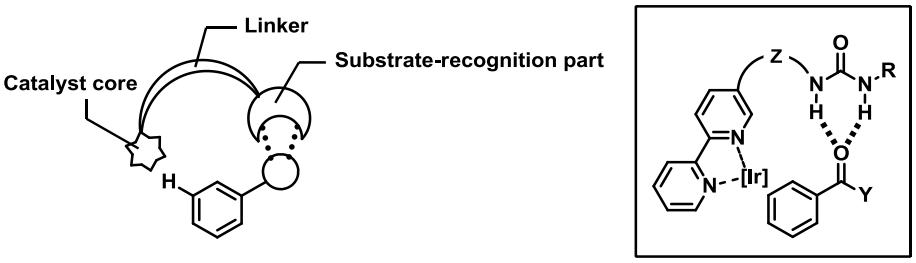


上記のいくつかの例から、反応及び触媒の構成について次の特徴を抽出できる。反応の特徴としては、高選択的に目的物を得るために、比較的弱い分子間相互作用である水素結合の形成効率を高めるよう、室温以下の温度条件下反応が行われていることが挙げられる。また、触媒構造に関しては、①反応の活性化を担う触媒活性中心と②不斉制御を行うための反応剤捕捉部位すなわち水素結合供与体を同一分子内にもたせ、さらに③これらをつなぐリンカー構造を最適化することで、最大の触媒活性を引き出している点である。

触媒設計

上記例を鑑み、①触媒活性中心、②分子認識部位、③リンカー構造、から成る触媒分子を設計した（Figure 1-6）。すなわち、水素結合は低温下ほど形成効率が高いため、触媒活性部位としては、室温下で C－H 結合を官能基化できるイリジウム／ビピリジル錯体を選択した（Scheme 2-1-8）。[17] 基質認識部位としては、尿素・チオ尿素構造を選択した。尿素およびチオ尿素は二点の水素結合供与部位をもつため、水素結合の中でも比較的強い分子間力を発揮するからである。また二点で基質を認識するため、水素結合による触媒活性中心と基質の位置関係を規定しやすいことも期待した。ここで、リンカー構造の異なる触媒を合成し、その反応性への影響を検討することとした。

Figure 1-6｜Design of catalyst for *meta*-selective C-H borylation

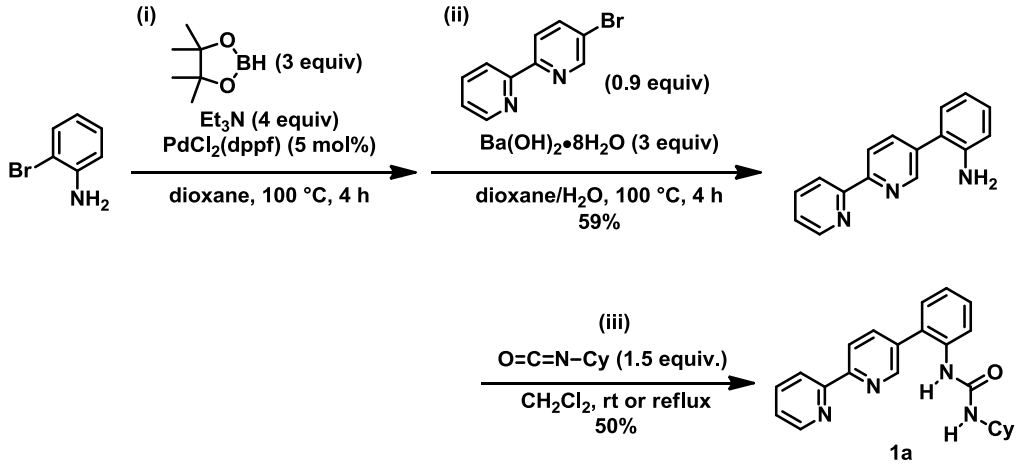


1-3 触媒分子の合成と検討

触媒活性部位としてビピリジル配位子、基質認識部位として尿素・チオ尿素構造を有し、リンカー部位の異なる配位子 **1a**、**2** および **3** を合成した（Scheme 1-21, 1-22, 1-23）。

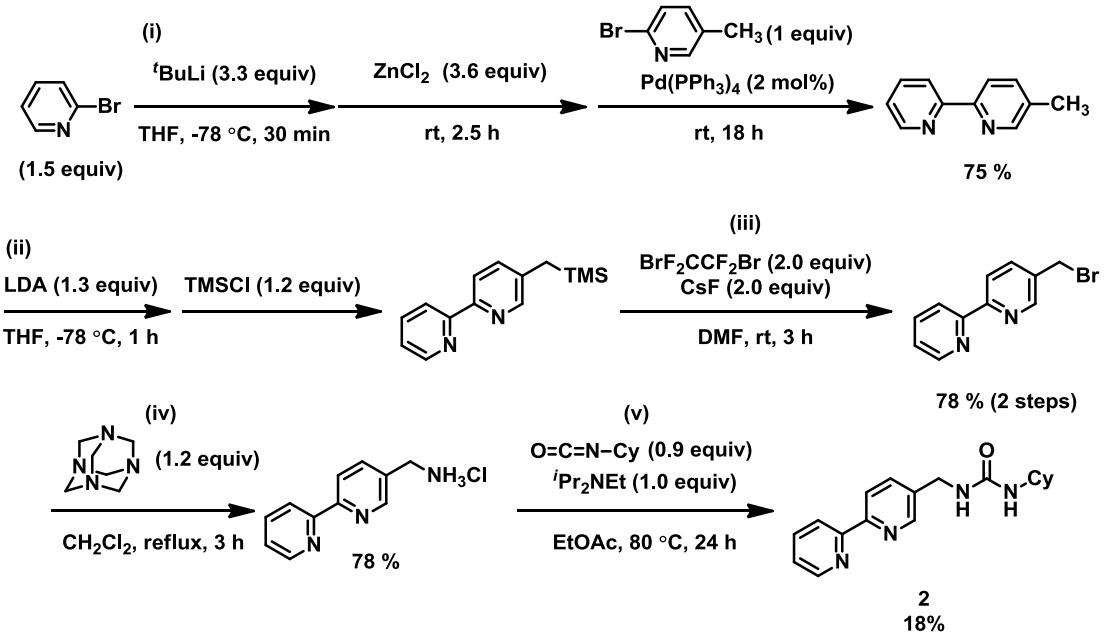
配位子 **1a** およびその類縁体の合成は以下のとおりである：（ⅰ）触媒量の $PdCl_2$(dppf) およびトリエチルアミン存在下、2-ブロモアニリンにピナコールボランを作用させることで、アリールボランを系中で発生させた。（ⅱ）そこに、5-ブロモビピリジンおよび水酸化バリウム八水和物を加えることで、鈴木－宮浦クロスカップリングによりアニリン誘導体を得て、（ⅲ）この化合物にイソシアネートを作用させることで、尿素部位をもつビピリジル配位子 **1a** およびその類縁体を得た。

Scheme 1-21 | Synthesis of 1a



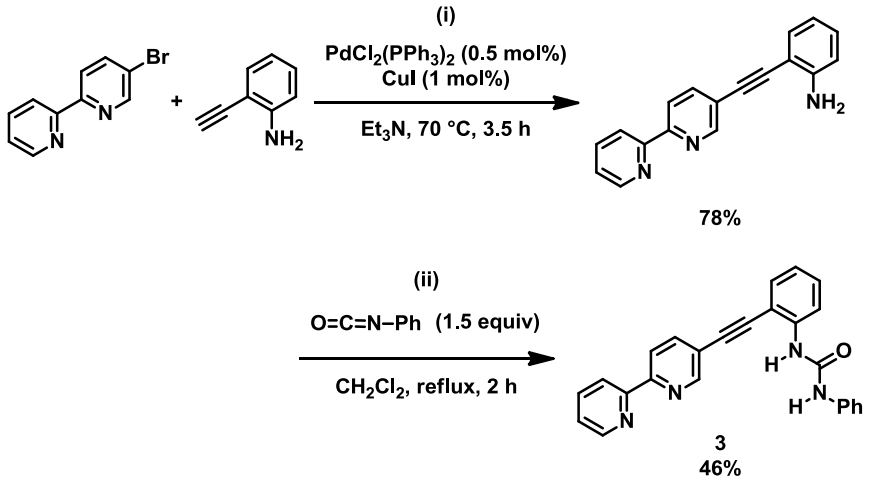
リンカー構造にメチレンをもつビピリジル配位子 **2** は、（ⅰ）2-ブロモピリジンを根岸カップリングにより 5-メチル-2,2′-ビピリジルとし、（ⅱ）ベンジル位のリチオ化、シリル化、（ⅲ）ブロモ化を経て、（ⅳ）ヘキサメチレンテトラミンとの反応によりアミン誘導体を得、（ⅴ）これをシクロヘキシルイソシアネートと反応させることで合成した（Scheme 1-22）。

Scheme 1-22 | Synthesis of 2



リンカー部位にフェニルエチニレン構造をもつビピリジル配位子 **3** は、（ｉ）5-ブロモビピリジンと 2-エチニルアニリンとの薗頭カップリングにより得られたアニリン誘導体に対し、（ii）フェニルイソシアネートを作用させることで、合成した（Scheme 1-23）。

Scheme 1-23 | Synthesis of 3

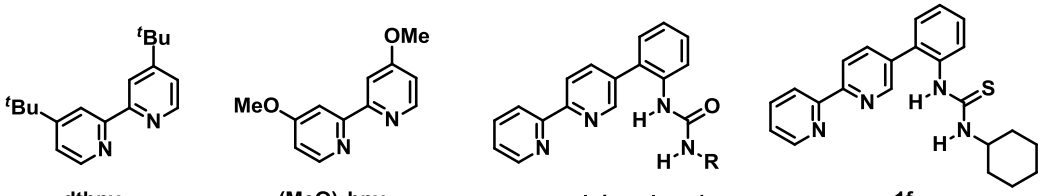


ベンズアミド誘導体 **4a** を基質に、ボリル化反応の位置選択性を比較した（Table 1-1）。まず、既知の C－H ボリル化条件で用いられている電子豊富なビピリジル配位子（4,4′-ジ-*tert*-ブチル-2,2′-ビピリジン [dtbpy]および 4,4′-ジメトキシ-2,2′-ビピリジン [$(MeO)_2$bpy]）を用いたところ、中程度の収率で C－H ホウ素化反応が進行したものの、位置選択性は低く、メタ位およびパラ位ボリル化体の混合物が得られた（*meta*/*para* = 1.9 and 1.4, entries 1 and 2）。メタ位選択性は、尿素部位をもつビピリジル配位子 **1a** を用いた際に大幅に向上した（収率 50%、*meta*/*para* = 8.3, entry 3）。^{1}H NMR および GC MS によりオルト位ボリル化体が生成していないことを確認した。電子・立体効果の異なるアリール基を検討したが、位置選択性の改善にはつながらなかった（entries 4-7）。チオ尿素部位を有するビピリジル配位子 **1f** ではボリル化生成物は得られなかった（entry 8）。

Table 1-1 | Application of 1 to iridium-catalyzed borylation

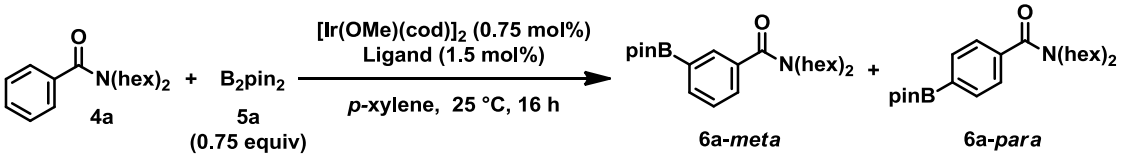
Entry	Ligand	Yield (%)[a] (*meta*+*para*)	Ratio of *meta* to *para*[a]
1	dtbpy	67	1.9
2	$(MeO)_2$bpy	52	1.4
3	1a	50	8.3
4	1b	22	1.4
5	1c	31	7.2
6	1d	40	3.9
7	1e	32	3.6
8	1f	0	—

[a]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.



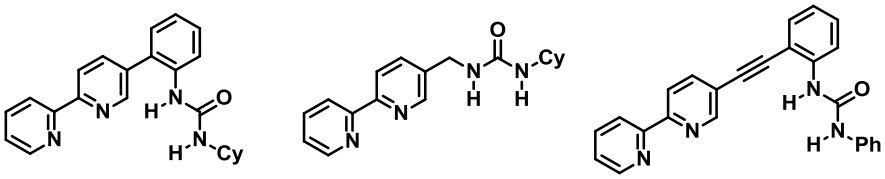
溶媒として *p*-キシレンを用いた際に、メタ位およびパラ位ボリル化生成物の生成比が 27 まで向上した（Table 1-2, entry 1）。メチレンリンカーを有するビピリジル配位子 **2** では、メタ位選択性は大幅に低下し、dtbpy や$(MeO)_2$bpy と同程度の値しか示さなかった（entry 2）。フェニルエチニレンリンカーを有するビピリジル配位子 **3** ではボリル化反応はまったく進行しなかった（entry 3）。アルキン部位がイリジウムに配位することで、触媒が失活したためだと考えている。

Table 1-2 | Application of 1 to 3 to iridium-catalyzed borylation



Entry	Ligand	Yield (%)[a] (mono)	Ratio of *meta* to *para*[a]
1	1a	44	27
2	2	47	2.0
3	3	0	—
4[b]	1a	51 (48)[c]	17 (19)[d]

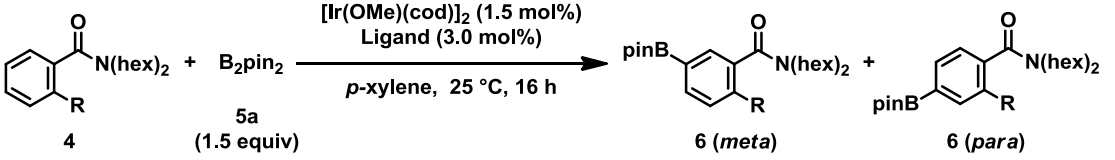
[a]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]5a (1.0 equiv), $[Ir(OMe)(cod)]_2$ (1.5 mol%), 3a (3.0 mol%). [c]Isolated yield. [d]Ratio of *meta* to *para* in the isolated product.

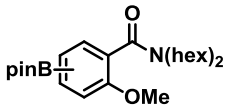


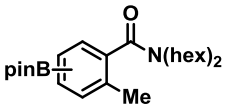
1-4 基質一般性の検討

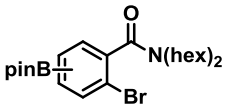
オルト位に電子供与性・電子求引性の置換基をもついずれのベンズアミドにおいても、目的のC－Hボリル化体は中程度から良好な収率で進行し、dtbpyを用いた場合に比較して、尿素部位をもつビピリジル配位子**1a**を用いた際にメタ位選択性が大幅に向上した（Table 1-3）。

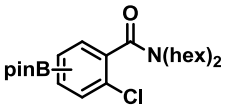
Table 1-3 | Substrate scope of benzamide with substituents on benzene ring

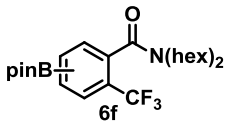


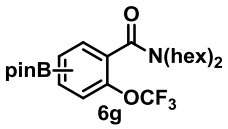


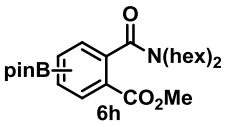


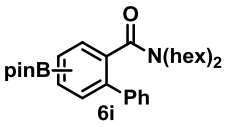








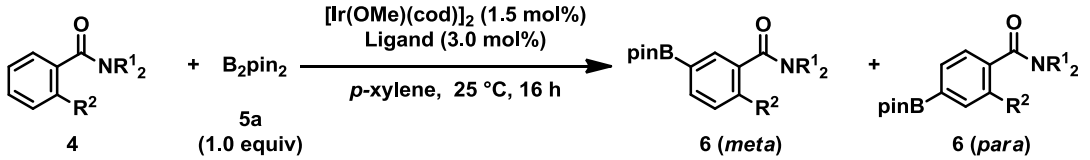


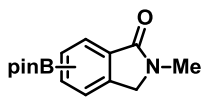


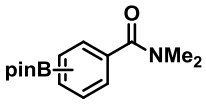
^{1}H NMR yield of mono-borylated products (as a mixture of *meta*- and *para*-products) with the *meta*/*para* ratio described in parentheses. ^{a}35 °C, 24 h. ^{b}5a (1.5 equiv).

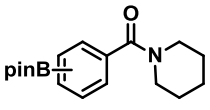
N,N-ジヘキシルアミドのかわりに、より立体障害の小さい*N,N*-ジメチルアミド、ピロリジンアミド、モルホリンアミドおよびアゼパンアミドを基質とした際にも、メタ位選択的にC－Hボリル化反応が進行した（Table 1-4）。モルホリンアミドでは位置選択性のみならず、収率も向上した。

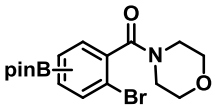
Table 1-4 | Substrate scope of benzamide with substituents on nitrogen atom of amide group

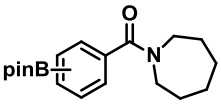



6j[ab]
1a: 51% (3.3)
dtbpy: 54% (1.1)


6k
1a: 44% (27)
dtbpy: 49% (1.5)


6l
1a: 46% (>30)
dtbpy: 40% (1.5)

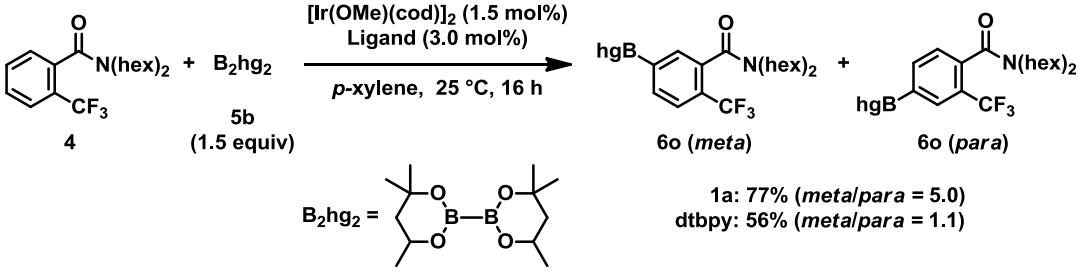

6m[b]
1a: 95% (3.3)
dtbpy: 5% (0.67)


6n
1a: 46% (17)
dtbpy: 45% (2.3)

[1]H NMR yield of mono-borylated products (as a mixture of *meta*- and *para*-products) with the *meta*/*para* ratio described in parentheses. [a]35 °C, 24 h. [b]5a (1.5 equiv).

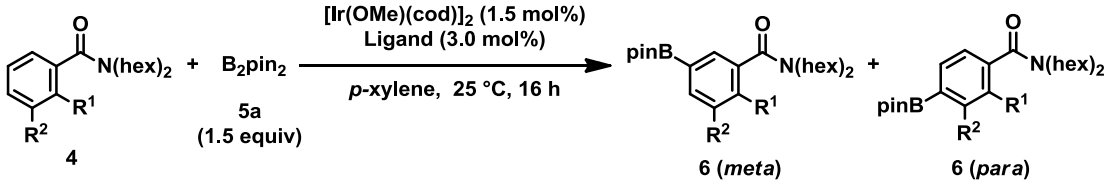
ビスピナコールジボロンの代わりにビスヘキシレングリコラートジボロンを用いてもボリル化反応は進行したが、収率・メタ位選択性ともに低下した（Scheme 1-24）。

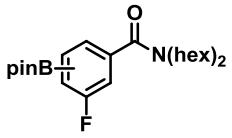
Scheme 1-24 | Substrate scope of benzamide with substituents on nitrogen atom of amide group



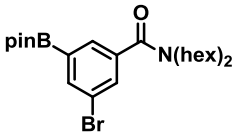
メタ位にフルオロ基またはシアノ基を有するベンズアミド**4p**および**4s**を基質とした場合は、アミドのメタ位またはパラ位ボリル化体の混合物が得られたが、**1a**を配位子に用いた場合にメタ位選択性が向上した（Table 1-5）。メタ位、またはオルト位とメタ位に置換基を有するベンズアミド**4q**、**4r**、**4t**および**4u**では、**1a**、dtbpyいずれの配位子を用いても、単一の生成物が得られた。

Table 1-5 | Substrate scope of benzamide with substituents at 3-position or 2,3-positions

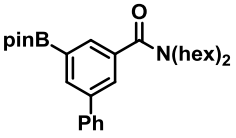




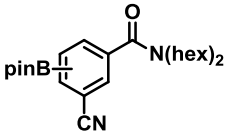
6p
1a: >99% (9.1)
dtbpy: >99% (1.0)



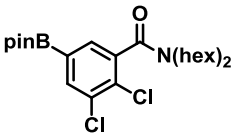
6q
1a: 85%
dtbpy: >99%



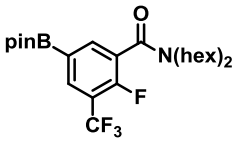
6r
1a: >99%
dtbpy: >99%



6s
1a: 92% (20)
dtbpy: 75% (12)



6t
1a: >99%
dtbpy: >99%

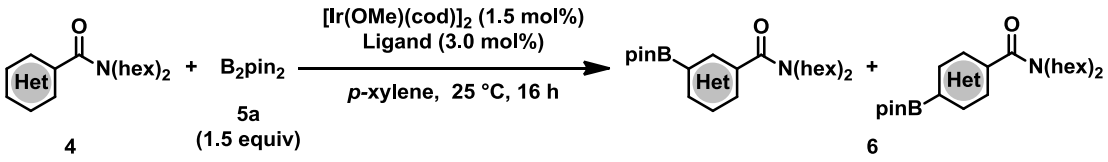


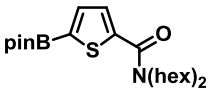
6u
1a: >99%
dtbpy: >99%

^{1}H NMR yield of mono-borylated products (as a mixture of *meta*- and *para*-products) with the *meta*/*para* ratio described in parentheses.

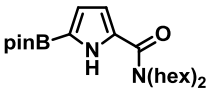
チオフェン、ピロール、インドールおよびピリジン等、ヘテロ芳香環をもつ基質においてもボリル化反応は進行した（Table 1-6, **6v**-**6bb**）。*N*-メチルピロール誘導体では５位ボリル化体の生成が促進され（**6x**）、ピコリン酸アミドでは４位選択性が向上した（**6z**）。

Table 1-6 | Substrate scope of heteroaromatics

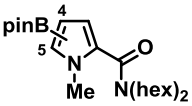




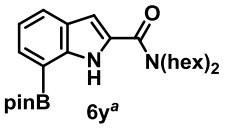
6v
1a: 86%
dtbpy: 90%



6w
1a: 94%
dtbpy: 96%

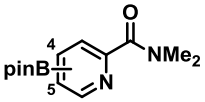


6x
1a: 84% (6.6)
dtbpy: 95% (2.3)
Ratio: 5-position/4-position

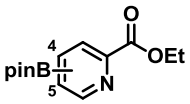


6y[a]
1a: 86% (>30)
dtbpy: 89% (>30)

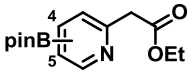
(Ratio: 4-position/5-position for pyridine derivatives)



6z[b]
1a: 86% (6.4)
dtbpy: 88% (1.9)



6aa[b]
1a: >99% (4.3)
dtbpy: 92% (1.3)

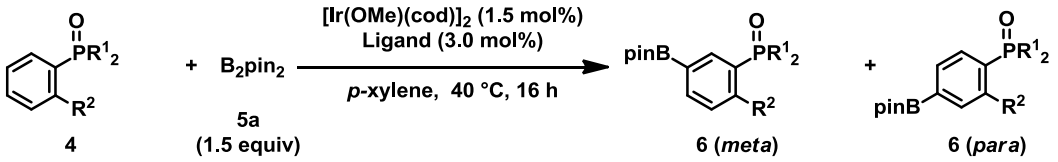


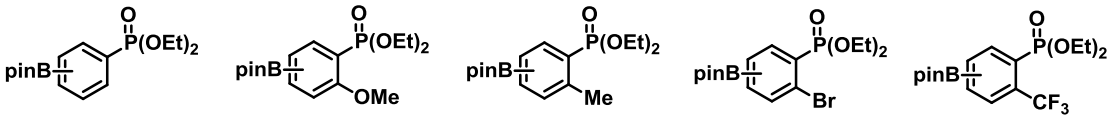
6bb[b]
1a: 99% (1.5)
dtbpy: 89% (0.48)

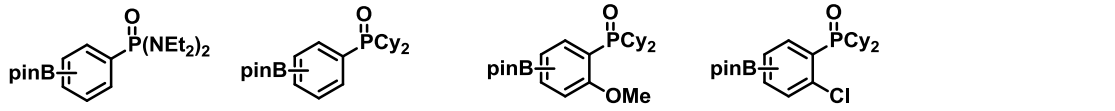
[1]H NMR yield mono-borylated products (as a mixture of *meta*- and *para*-products) with the *meta*/*para* ratio described in parentheses. [a] [Ir(OMe)(cod)]2 (2.0 mol%), 1a (4.0 mol%), 24 h. [b] 1d was used as a ligand.

また、リン酸エステル、リン酸アミドおよびホスフィンオキシドなどのリン含有化合物についても、対応するボリル化体生成物が良好な収率で得られ、配位子として**1a**を用いた場合にのみ、高いメタ位選択性が見られた（Table 1-7）。

Table 1-7 | Substrate scope of phosphorous cmpounds





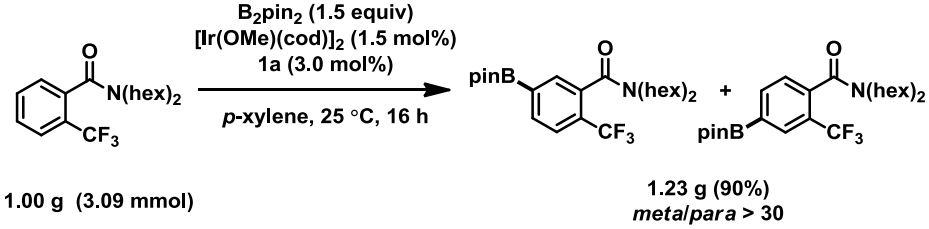


[1]H NMR yield of mono-borylated products (as a mixture of *meta*- and *para*-products) with the *meta*/*para* ratio described in parentheses. [a] 5a (1.0 equiv), 6 h. [b] 25 °C.

1-5 グラムスケールでの反応

1.00 g の *N*,*N*-ジヘキシル-2-トリフルオロメチルベンズアミドを用いてボリル化反応を行ったところ、89.4 mg（0.250 mmol）スケールと同等の収率・メタ位選択性でボリル化生成物が得られた（1.23 g, *meta*/*para*>30）。

Scheme 1-25 | Scale-up operation study

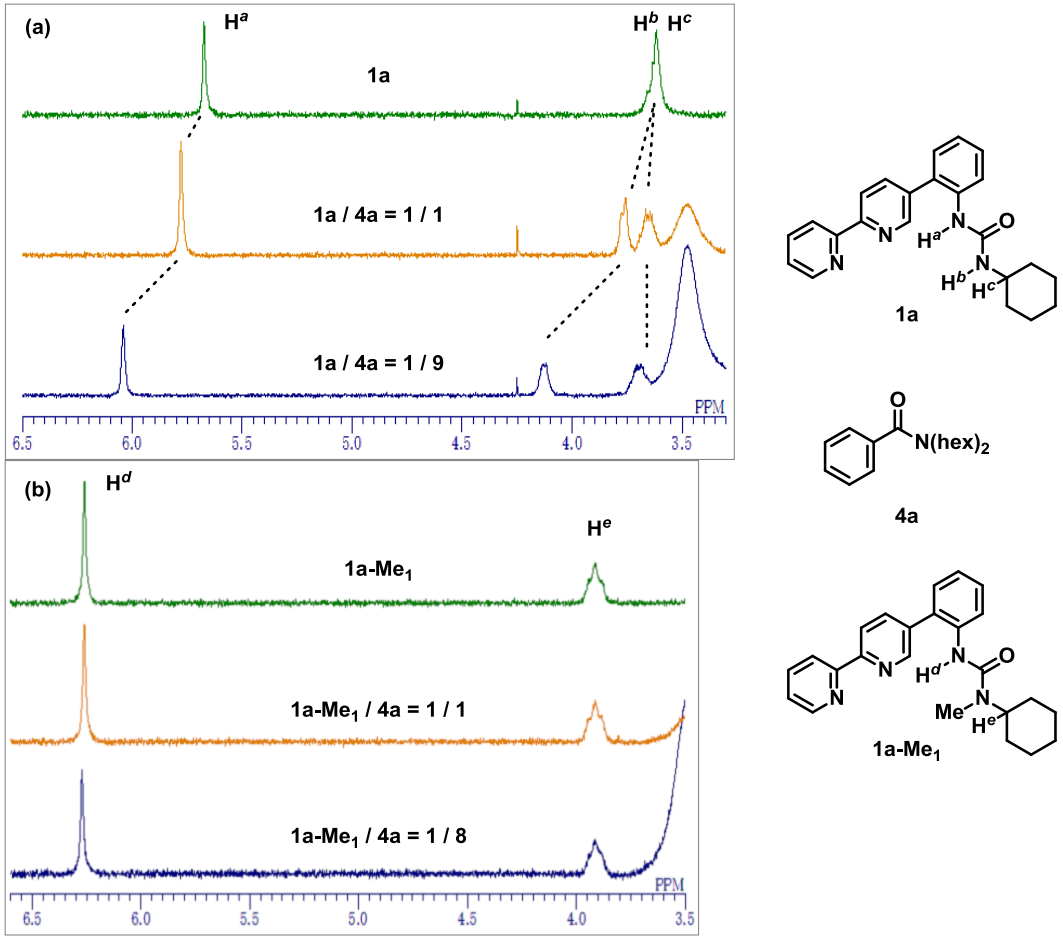


1-6 水素結合の重要性の検証

C−H ボリル化反応の機構はすでに報告されており、[39] 本反応でも同様のメカニズムで進行していると考えている。位置選択性の制御に、基質－配位子間の水素結合の関与が重要であることを確認するために、以下の実験を行った。

まず、^{1}H NMR において、基質を共存させることで、**1a** の尿素部位の NH プロトンの低磁場シフトが観測された（Figure 1-7a）。一方、尿素部位の窒素原子をメチル基によって保護した配位子 **1a-Me$_1$** では、ベンズアミド存在下においても NH プロトンのシフトは起こらなかった（Figure 1-7 b）。これにより、配位子の無保護の尿素部位と基質との間の水素結合形成の存在が強く示唆された。

Figure 1-7 | Confirmation of hydrogen bond

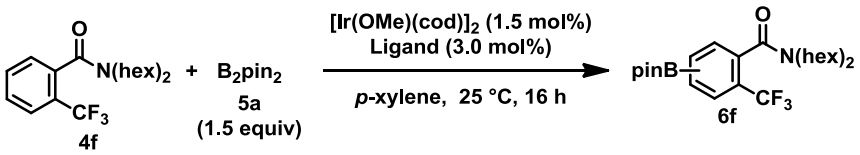


(a) Spectra of solution of 1a and 4a in C_6D_6. (b) Spectra of solution of 1a-Me$_1$ and 4a in C_6D_6.

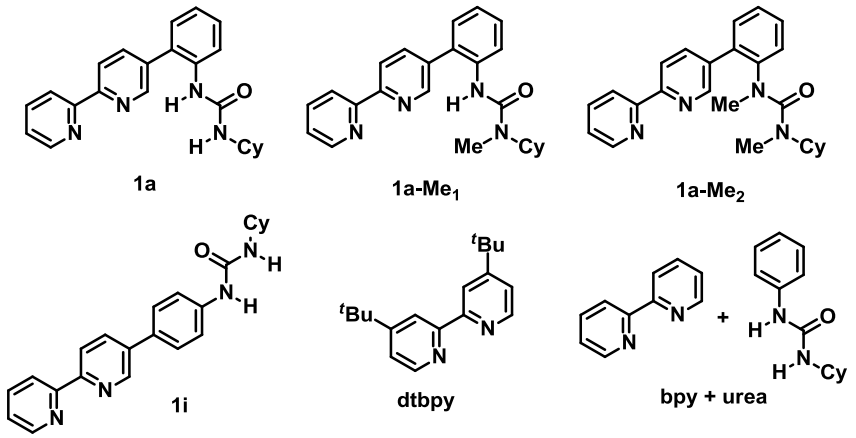
[39] Timothy M. Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.

また、尿素部位の窒素原子の一方または両方をメチル化した配位子 **1a-Me$_1$** および **1a-Me$_2$** を用いてボリル化反応を行った。その結果、いずれの配位子とも十分な反応性を示すものの、メタ位選択性は大幅に低下した（Table 1-8, entries 2 and 3）。**1a-Me$_1$** を用いた場合にはわずかながらメタ位選択性が発現した（*meta*/*para* = 1.6, entry 2）が、**1a-Me$_2$** では尿素構造をもたないビピリジル配位子 dtbpy と同程度の位置選択性を示すのみだった（*meta*/*para* = 0.84, entry 3）。Figure 1-7b において **1a-Me$_1$** と **4a** を混合した際に尿素部位の NH プロトンがシフトしなかったことと一貫する結果である。ビピリジル部位と尿素部位がパラ位に置換された配位子 **1i** を用いてボリル化反応を行った場合も同様に、**1a** を用いた場合と比較してメタ位選択性は大幅に低下した（entry 4）。ビピリジンと尿素が共有結合で結ばれていて適切な位置関係にあることも、メタ位選択性の発現に必須である。2,2'-bipyridine とシクロヘキシルフェニル尿素の混合物を用いて反応を行った場合に、dtbpy の場合と同程度の位置選択性を示すのみだった（Table 1-3, entry 6）。以上の対照実験の結果より、ビピリジル部位と尿素部位の三次元的な位置関係が重要であることが示唆された。

Table 1-8 | Comparison of product *meta*/*para* ratios between target reaction and control experiment

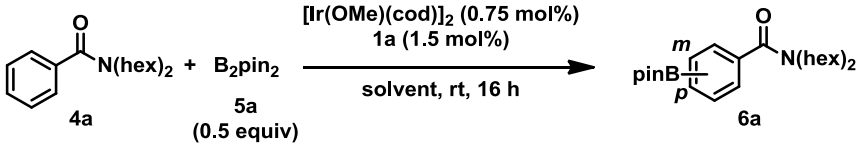


Entry	Ligand	Yield (%)	*meta*/*para*
1	1a	95	18
2	1a-Me$_1$	90	1.6
3	1a-Me$_2$	90	0.84
4	1i	99	1.0
5	dtbpy	98	0.96
6	bpy + urea	99	1.1



低極性溶媒でメタ位選択性が向上した（Table 1-9）ことも、基質のアミド部位と配位子の尿素部位の間で形成される水素結合の重要性を示唆している。

Table 1-9 | Effect of solvents



Entry	Solvent	Yield (%)[a]	Ratio[b] (*meta*/*para*)
1	*p*-xylene	42	30
2	cyclohexane	43	29
3	THF	27	3.5
4	NMP	15	2.8

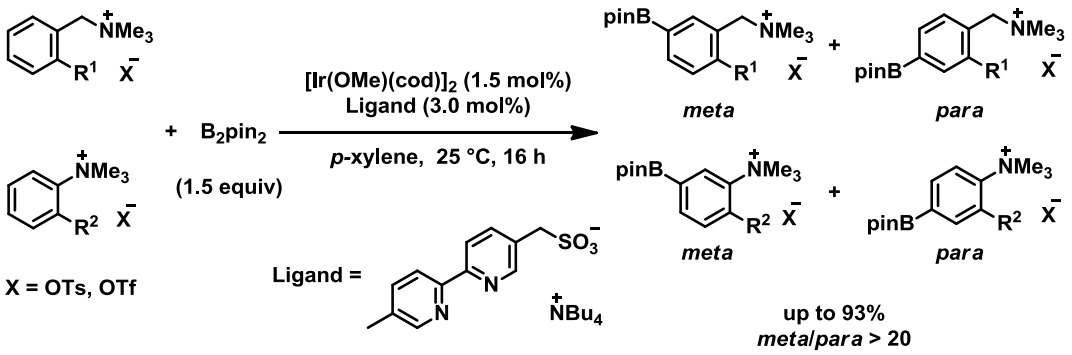
[a]Detemined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]Detemined by GC-MS.

1-7 小括

尿素部位を有するビピリジル配位子をもったイリジウム触媒を設計、合成した。その触媒を用いることで、芳香族化合物の C－H ボリル化反応を高収率および高いメタ位選択性にて達成した。1-5 項の実験結果より、基質－触媒配位子間での可逆な水素結合形成を利用することで、高い位置選択性が発現していることが示唆された。本反応は、触媒配位子と基質の間での非共有結合性相互作用を利用する位置選択的 C－H 結合変換反応の初めての例である。本触媒系は、触媒分子のもつ基質認識部位の構造（Figure 1-2、本論文では尿素構造を採用した）を置換することで、原理的には他の官能基の認識を行うことも可能であり、C－H 結合変換の反応形式および基質適用範囲の大幅な拡張に貢献し、C－H 結合変換反応の発展に大きく資するものと期待される。例えば、ごく最近、Phipps らによって、スルホン酸塩を基質認識部位とした、ベンジルアミン誘導体のメタ位選択的なボリル化反応が報告された。[40]

[40] Davis, H. J.; Mihai, M. T. Philips, R. J. *J. Am. Chem. Soc.* **2016**, *138*, 12759.

Scheme 1-26 | *meta*-Selective C-H borylation of amino compounds controlled by ion-pair interaction



実験項

General.

All reactions were carried out in a dry solvent under an argon atmosphere. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. 4-([2,2'-Bipyridin]-5-yl)aniline[41,42], [2,2'-bipyridin]-5-ylmethanamine[43], benzamides **4a**[44], **4j**[45,46], **4l**[47], and **4z**[48], phenylphosphates **4dd**[49], **4ee**[50], and **4ff**[49], phosphinic diamide **4hh**[51], phosphine oxides **4ii**[52], and **4jj**[53], and dicyclohexylphosphine[54] were prepared according to the literature methods and identified by comparing the spectroscopic data with those of reported data. Amide **4k**, esters **4aa** and **4bb**, and phosphate **4cc** were purchased from Tokyo Kasei Kogyo Co. Cyclohexylphenylurea was synthesized according to the literature method from aniline and cyclohexylisocyanate[55]. Column chromatography was performed with silica gel (230-400 mesh ASTM). Recycling preparative HPLC (LC-9210NEXT; column, JAIGEL-1H and JAIGEL-2H; solvent, $CHCl_3$) was used for isolation of phosphates **4dd** and **4ee**, ligand **1a-Me$_1$**, and borylated products **6** (as mixtures of *meta* and *para* isomers except **6a**, **6c**, and **6e**) and **7** after removing metal wastes through a short pad of silica gel. Melting point was measured on simultaneous DTA-TC apparatus (DTA-60). NMR spectra were recorded on 500 MHz (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) and 400 MHz (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 368 MHz for ^{19}F NMR, 125 MHz for ^{11}B NMR, and 158 MHz

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41 Saifuddin M. *et al. Eur. J. Org. Chem.* 5108-5117 (2010).

42 Mahata K., Frischmann P. D. & Würthner F. *J. Am. Chem. Soc.* **135**, 15656-15661 (2013).

43 (a) Kiehne, U.; Bunzen, J.; Staats, J.; Lützen, A. *Synthesis* **2007**, 1061. (b) Custelcean, R.; Bosano, J.; Bonnesen, P. V.; Kertesz, V.; Hay, B. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 4025.

44 Kardon F., Mőrtl M. & Magyarfalvi G. *Synth. Commun.* **38**, 192-199 (2008).

45 Duan X.-H. *et al. Bioorg. Med. Chem.* **18**, 1337-1343 (2010).

46 Das S. *et al. Angew. Chem. Int. Ed.* **50**, 9180-9184 (2011).

47 Guo Z., Dowdy E. D., Li W.-S., Polniaszek R. & Delaney E. *Tetrahedron Lett.* **42**, 1843-1845 (2001).

48 Zhou S., Junge K., Addis D., Das S. & Beller M. *Angew. Chem. Int. Ed.* **48**, 9507-9510 (2009).

49 Bonnaventure I. & Charette A. B. *J. Org. Chem.* **73**, 6330-6340 (2008).

50 Hirao T., Masunaga T., Yamada N., Ohshiro Y. & Agawa T. *Bull. Chem. Soc. Jpn.* **55**, 909-913 (1982).

51 Ogawa T., Usuki N. & Ono N. *J. Chem. Soc., Perkin Trans. 1* 2953-2958 (1998).

52 Unoh Y. *et al. Org. Lett.* **15**, 3258-3261 (2013).

53 Ishikawa S. & Manabe K. *Chem. Lett.* **36**, 1302-1303 (2007).

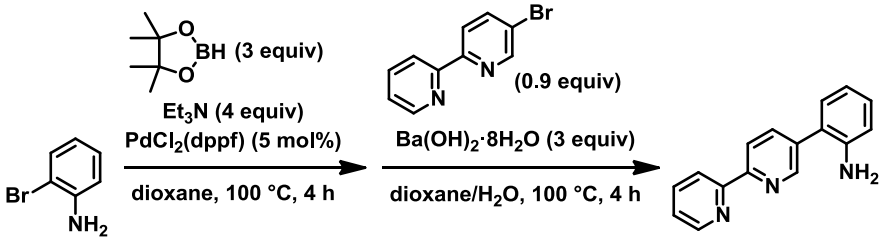
54 Montel S., Jia T. & Walsh P. J. *Org. Lett.* **16**, 130-133 (2014).

55 Kotecki B. J., Fernando D. P., Haight A. R. & Lukin K. A. *Org. Lett.* **11**, 947-950 (2009).

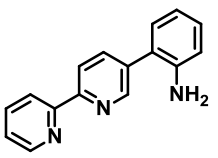
for ^{31}P NMR) spectrometers. Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference. Fluorine, boron, and phosphorus chemical shifts are reported relative to trifluoroacetic acid (δ -76.55 ppm), $BF_3 \cdot OEt_2$ (δ 0.00 ppm), and triphenylphosphine (δ 5.60 ppm) as an external reference, respectively. Infrared (IR) spectra were recorded on Fourier transform infrared spectrophotometer. ESI-MS spectra were measured on a spectrometer for HRMS.

Synthesis and Characterisation of Ligands

Synthesis of 2-([2,2'-bipyridin]-5-yl)aniline[56].



To a solution of 2-bromoaniline (0.86 g, 5.0 mmol, 1.0 equiv) in dioxane (10 mL) were added Et_3N (2.02 g, 20.0 mmol, 4.0 equiv), $PdCl_2$(dppf) (183 mg, 0.250 mmol, 5 mol%), and pinacolborane (1.92 g, 15.0 mmol, 3.0 equiv) dropwise. The mixture was stirred at 100 °C for 4 h, then cooled to room temperature, and water (2.2 mL), $Ba(OH)_2 \cdot 8H_2O$ (4.73 g, 15.0 mmol, 3.0 equiv), and 5'-bromo-2,2'-bipyridine (1.08 g, 4.60 mmol, 0.92 equiv) were successively added. The mixture was stirred at 100 °C for 4 h before addition of water (50 mL) at room temperature. The mixture was filtered through Celite. The eluent was extracted with ethyl acetate and the organic layer was dried over Na_2SO_4. The solvent was removed and the residue was purified by column chromatography (hexane/ethyl acetate = 3/1) using silica gel deactivated with 20% Et_3N in hexane. 2-([2,2'-bipyridin]-5-yl)aniline was isolated as white solid (672 mg, 59% yield).

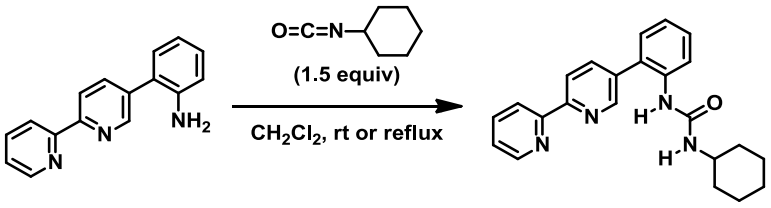


2-([2,2'-Bipyridin]-5-yl)aniline. 59% yield; white solid; R_f = 0.50 (hexane/ethyl acetate = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.22 (dd, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.8, 5.2 Hz, 1H), 7.84 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.71 (d, *J* = 5.2 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.0, 119.0, 121.0, 121.1, 123.6, 123.8, 129.5, 130.6, 135.3, 137.0, 137.5, 143.9, 149.3, 149.5, 154.9, 156.0; IR (KBr, ν / cm^{-1}) 3346, 3219, 1459, 1357, 1240, 1094, 994, 858, 751, 644; HRMS (ESI^+) Calcd for $C_{16}H_{13}N_3Na$ ($[M+Na]^+$) 270.1002, Found

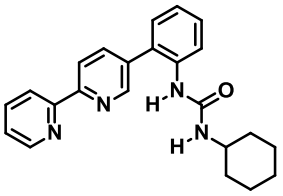
[56] Rebstock A.-S., Mongin F., Trécourt F. & Quéguiner G. *Org. Biomol. Chem.* **1**, 3064-3068 (2003).

270.1007.

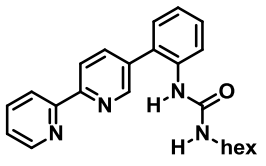
Typical procedure for synthesis of 1.



The mixture of 2-([2,2'-bipyridin]-5-yl)aniline (371 mg, 1.50 mmol, 1.0 equiv) and cyclohexylisocyanate (282 mg, 2.25 mmol, 1.5 equiv) in dichloromethane (5.0 mL) was stirred at room temperature for 24 h. The solvent was removed and the residue was purified by recrystallization with dichloromethane and hexane to give **1a** (281 mg, 50% yield).

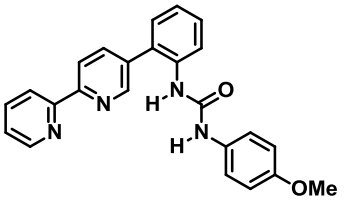


1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-cyclohexylurea (1a). 50% yield; white solid; R_f = 0.53 (hexane/ethyl acetate = 1/2); melting point, 236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98-1.13 (m, 4H), 1.25-1.34 (m, 2H), 1.62-1.66 (m, 2H), 1.87-1.89 (m, 2H), 3.54-3.56 (m, 1H), 4.59-4.60 (m, 1H), 6.08 (s, 1H), 7.20 (dd, *J* = 7.2, 6.3 Hz, 1H), 7.29 (d, *J* = 6.3 Hz, 1H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.42 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.81-7.87 (m, 2H), 7.95 (d, *J* = 8.6 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 8.67-8.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 25.6, 33.7, 49.2, 121.1, 121.3, 122.5, 123.8, 124.1, 129.0, 129.6, 130.4, 134.8, 136.6, 137.2, 137.9, 149.4, 149.5, 154.8, 155.1, 155.5; IR (KBr, ν / cm^{-1}) 3245, 3219, 1458, 1367, 1240, 1094, 994, 858, 751, 644; HRMS (ESI$^+$) Calcd for $C_{23}H_{24}N_4NaO$ ([M+Na]$^+$) 395.1842, Found 395.1850.

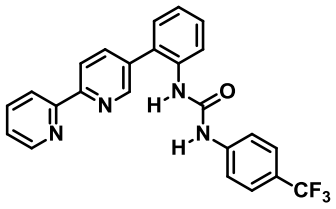


1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-hexylurea (1b). 62% yield; white solid; R_f = 0.32 (hexane/ethyl acetate = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, *J* = 6.9 Hz, 3H), 1.16-1.22 (m, 6H), 1.33-1.38 (m, 2H), 3.14 (td, *J* = 7.2, 7.2 Hz, 2H), 5.48 (brs, 1H), 6,70 (s, 1H), 7.12-7.20 (m, 2H), 7.32 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.39 (ddd, *J* = 6.3, 4.8, 1.1 Hz, 1H), 7.69 (ddd, *J* = 8.5, 7.6, 2.2 Hz, 1H), 7.81 (ddd, *J* = 7.7, 7.6, 1.6 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.56 (d, *J* = 2.2 Hz, 1H), 8.64 (dd, *J* = 4.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 26.6, 30.0, 31.5, 40.2, 120.9, 121.1, 122.3, 123.2, 124.0, 128.4, 129.4, 130.1, 135.1, 136.9, 137.1, 137.1, 149.1, 149.4, 154.3, 155.2, 156.1; IR (KBr, ν / cm^{-1}) 3292, 2922, 2855, 1626, 1457, 1371, 1266, 1090, 856, 649; HRMS (ESI$^+$) Calcd for $C_{23}H_{26}N_4NaO$ ([M+Na]$^+$) 397.1999,

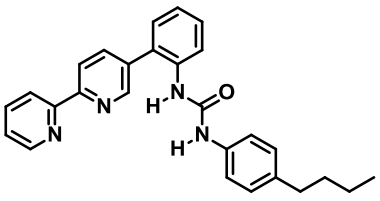
Found 397.1997.

1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-(4-methoxyphenyl)urea (1c). 

6.5% yield; white solid; R_f = 0.50 (hexane/ethyl acetate = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.20-7.22 (m, 1H), 7.36-7.38 (m, 3H), 7.46-7.49 (m, 1H), 7.54 (s, 1H), 7.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.89 (ddd, *J* = 8.0, 7.7, 1.7 Hz, 1H), 7.94-7.96 (m, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.63 (d, *J* = 1.7 Hz, 1H), 8.73 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.6, 114.1, 120.4, 121.0, 124.7, 126.8, 127.8, 129.2, 130.2, 130.6, 132.0, 135.5, 135.7, 137.1, 137.6, 137.9, 149.3, 149.8, 154.2, 155.3, 157.2, 181.4; IR (KBr, ν / cm^{-1}) 3278, 1636, 1509, 1458, 1370, 1244, 1111, 855, 756, 649; HRMS (ESI^+) Calcd for $C_{24}H_{20}N_4NaO_2$ ($[M+Na]^+$) 419.1478, Found 419.1458.

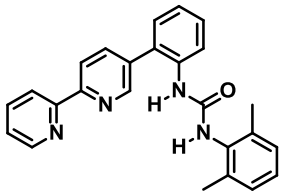
1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-(4-(trifluoromethyl)phenyl) urea (1d). 

50% yield; pale yellow solid; R_f = 0.63 (hexane/ethyl acetate = 1/2); melting point, 198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.16 (m, 2H), 7.35-7.53 (m, 7H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.84-7.85 (m, 2H), 8.22 (brs, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 8.52 (d, *J* = 1.3 Hz, 1H), 8.57 (d, *J* = 3.1 Hz, 1H), 9.35 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.1, 118.7, 121.1, 121.3, 123.2, 123.6 (q, *J* = 33.6 Hz), 124.3 (q, *J* = 271 Hz), 124.5, 126.1 (q, *J* = 3.6 Hz), 127.2, 129.9, 130.3, 135.8, 136.9, 137.7, 138.6, 143.0, 149.5, 150.1, 153.2, 153.5, 154.3; ^{19}F NMR (368 MHz, $CDCl_3$) δ -63.8 (s, 3F); IR (KBr, ν / cm^{-1}) 3331, 3058, 1716, 1654, 1449, 1329, 1165, 1014, 842, 759; HRMS (ESI^+) Calcd for $C_{24}H_{17}F_3N_4NaO$ ($[M+Na]^+$) 457.1247, Found 457.1252.

1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-(4-butylphenyl)urea (1e). 

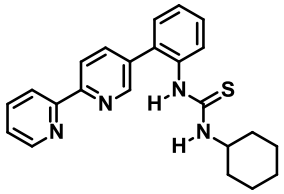
27% yield; white solid; R_f = 0.64 (hexane/ethyl acetate = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.5 Hz, 3H), 1.20-1.28 (m, 2H), 1.38-1.46 (m, 2H), 2.38 (t, *J* = 7.7 Hz, 2H), 6.94 (d, *J* = 1.9 Hz, 2H), 7.05-7.15 (m, 4H), 7.34 (dd, *J* = 7.2, 4.9 Hz, 1H), 7.41 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 7.2, 7.2 Hz, 1H), 8.01-8.03 (m, 1H), 8.15-8.16 (m, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.52 (s, 1H), 8.65 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 33.7, 35.0, 120.6, 121.0, 121.3, 121.4, 123.2, 124.2, 127.8, 129.0, 129.6, 130.2, 135.1, 136.2, 136.8, 137.3, 138.1, 138.3, 149.4, 149.7, 153.6, 154.4, 155.0; IR (KBr, ν / cm^{-1}) 3293, 1637, 1546, 1509, 1458, 1372, 1246, 1122, 799, 757; HRMS (ESI^+) Calcd for $C_{27}H_{26}N_4NaO$ ($[M+Na]^+$) 445.1999, Found 445.1989.

1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-(2,6-dimethylphenyl)urea (1f).



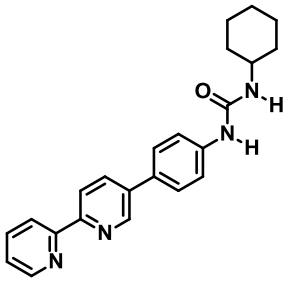
58% yield; white solid; R_f = 0.30 (hexane/ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 6H), 5.73 (s, 1H), 6.19 (s, 1H), 6.78-6.80 (m, 1H), 6.84 (d, *J* = 6.7 Hz, 2H), 7.13-7.18 (m, 2H), 7.36-7.44 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.89 (ddd, *J* = 7.6, 7.6, 1.8 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.39 (s, 1H), 8.43 (d, *J* = 8.1 Hz, 1H), 8.75 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 120.9, 121.1, 124.1, 128.4, 128.5, 129.0, 129.6, 130.0, 132.8, 133.8, 136.1, 137.0, 137.1, 137.3, 149.1, 149.5, 154.1, 155.3, 155.6, 155.7, 157.0; IR (KBr, ν / cm^{-1}) 3265, 1632, 1550, 1457, 1371, 1240, 1002, 855, 797, 717; HRMS (ESI^+) Calcd for $C_{25}H_{22}N_4NaO$ ($[M+Na]^+$) 417.1686, Found 417.1679.

1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-cyclohexylthiourea (1g).



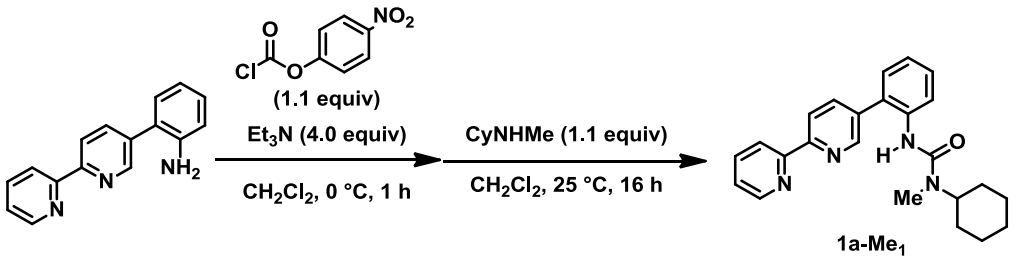
Prepared by the same method as ligand **1** using 2-([2,2'-bipyridin]-5-yl)aniline (124 mg, 0.500 mmol, 1.0 equiv) and cyclohexylisothiocyanate (106 mg, 0.750 mmol, 1.5 equiv). 51% yield; white solid; R_f = 0.36 (hexane/ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96-1.12 (m, 3H), 1.24-1.37 (m, 2H), 1.55-1.63 (m, 4H), 1.90-1.93 (m, 2H), 4.14 (s, 1H), 5.71 (s, 1H), 7.30-7.34 (m, 2H), 7.41-7.54 (m, 3H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.85 (ddd, *J* = 8.1, 8.1, 2.2 Hz, 1H), 8.40 (d, *J* = 8.1 Hz, 1H), 8.47 (d, *J* = 9.0 Hz, 1H), 8.68-8.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.5, 32.7, 54.1, 121.1, 121.4, 124.0, 127.9 (2C), 128.6, 130.0, 131.6, 133.6, 135.3, 137.0 (2C), 148.9, 149.4, 155.7, 155.8, 179.5; IR (KBr, ν / cm^{-1}) 3293, 2931, 2857, 1637, 1458, 1373, 1229, 1001, 841, 656; HRMS (ESI^+) Calcd for $C_{23}H_{24}N_4NaS$ ($[M+Na]^+$) 411.1619, Found 411.1611.

1-(4-([2,2'-Bipyridin]-5-yl)phenyl)-3-cyclohexylurea (1h). Prepared by the same method as ligand **3** using 4-([2,2'-bipyridin]-5-yl)aniline (346 mg, 1.4 mmol, 1.0 equiv) and cyclohexylisocyanate (526 mg, 4.2 mmol, 3.0 equiv). 24% yield; pale yellow solid; R_f = 0.40 (ethyl acetate/Et_3N = 20/1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.05-1.25 (m, 3H), 1.25-1.40 (m, 2H), 1.45-1.58 (m, 1H), 1.58-1.70 (m, 2H), 1.70-1.80 (m, 2H), 3.40-3.53 (m, 1H), 6.10-6.16 (m, 1H), 7.40-7.47 (m, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.94 (td, *J* = 7.6, 1.3 Hz, 1H), 8.17 (dd, *J* = 8.1, 2.2 Hz, 1H), 8.36-8.45 (m, 2H), 8.49 (s, 1H), 8.69 (d, *J* = 4.0 Hz, 1H), 8.97 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.4, 25.3, 33.0, 47.7, 118.0, 120.3, 120.5, 124.1, 127.2, 128.9, 134.2, 135.5, 137.4, 141.1, 146.7, 149.4, 153.4, 154.3, 155.1; IR (KBr, ν / cm^{-1}) 3315, 3047, 3006, 2930, 2852,

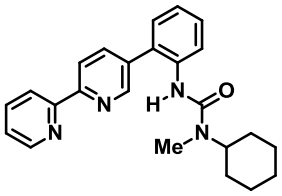


1635, 1589, 1570, 1529, 1458, 1435, 1412, 1319, 1245, 1227, 834, 794, 747; HRMS (ESI^+) Calcd for $C_{23}H_{24}N_4NaO$ ($[M+Na]^+$) 395.1848, Found 395.1862.

Synthesis of ligand 1a-Me_1[57].



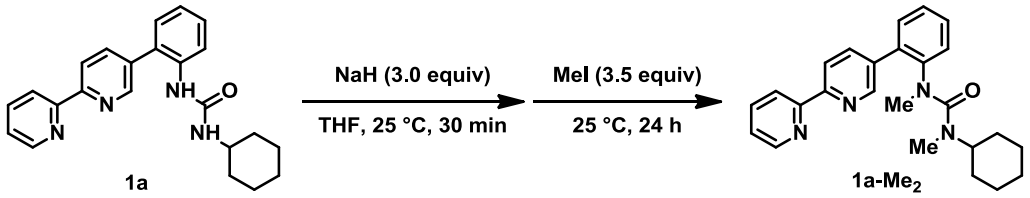
2-([2,2'-Bipyridin]-5-yl)aniline (326 mg, 1.32 mmol, 1.0 equiv) and 4-nitorophenyl chloroformate (292 mg, 1.45 mmol, 1.1 equiv) were dissolved in anhydrous dichloromethane (5.0 mL). Et_3N (534 mg, 5.28 mmol, 4.0 equiv) was added under 0 °C and stirred for 1 h. Cyclohexylmethylamine (164 mg, 1.45 mmol, 1.1 equiv) was added and stirred at room temperature. After 16 h, the reaction mixture was extracted with water (5.0 mL) and ethyl acetate (2×5.0 mL). Organic phase was dried with Na_2SO_4. After removing the solvent in vacuo, the product was isolated by recycling preparative HPLC to give **1a-Me_1** (19.0 mg, 4% yield).

1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-cyclohexyl-3-methylurea (1a-Me_1). 

4% yield; white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (qt, *J* = 12.6, 3.5 Hz, 1H), 1.18-1.35 (m, 4H), 1.52-1.65 (m, 3H), 1.66-1.75 (m, 2H), 2.62 (s, 3H), 3.86 (brs, 1H), 6.30 (brs, 1H), 7.14 (td, *J* = 7.5, 1.2 Hz, 1H), 7.24 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.31-7.37 (m, 1H), 7.39 (td, *J* = 8.6, 1.7 Hz, 1H), 7.86 (td, *J* = 8.6, 1.7 Hz, 1H), 7.86 (dd, *J* = 8.0, 2.3 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.70 (d, *J* = 4.0 Hz, 1H), 8.72 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 25.6, 28.2, 30.5, 54.2, 120.9, 121.1, 121.8, 123.2, 124.0, 128.2, 129.3, 129.8, 134.6, 136.7, 137.0, 137.7, 149.3, 149.5, 155.0, 155.47, 155.54; IR (KBr, ν / cm^{-1}) 3275, 3048, 3005, 2926, 2853, 1647, 1636, 1587, 1542, 1519, 1508, 1490, 1474, 1457, 1446, 1362, 1314, 1259, 1165, 1122, 1030, 1003, 800, 755; HRMS (ESI^+) Calcd for $C_{24}H_{27}N_4O$ ($[M+H]^+$) 387.2185, Found 387.2196.

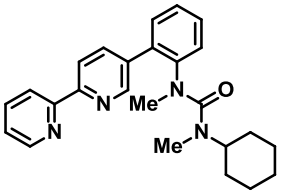
[57] Li Y.-J., Bostrom L. L. & Yao W. PCT WO 2007/130898 A1.

Synthesis of ligand 1a-Me_2[58].

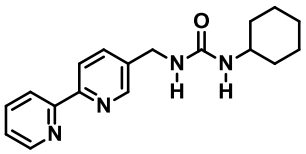


Sodium hydride (60% in oil) (120 mg, 3.00 mmol, 3.0 equiv) was placed to the reaction vessel and washed with anhydrous hexane (2×2.0 mL). THF (3.3 mL) and ligand **3a** (372 mg, 1.00 mmol, 1.0equiv) was added and the mixture was stirred at room temperature in 30 min. Methyl iodide (497 mg, 3.50 mmol, 3.5 equiv) was added to the suspension. After 24 h, the reaction was quenched with aq. NH_4Cl (3.0 mL) and was diluted with ethyl acetate (10.0 mL). Organic layer was washed with brine (3.0 mL) and was dried with $MgSO_4$. After removing the solvent in vacuo, the product was isolated by column chromatography on silica gel (dichloromethane/methanol = 10/1) to give **3a-Me_2** (392 mg, 98% yield).

1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-cyclohexyl-1,3-dimethylurea (1a-Me_2). 98% yield; pale yellow solid; R_f = 0.50 (dichloromethane/methanol = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (qt, *J* = 12.6, 3.5 Hz, 1H), 1.06 (qt, *J* = 12.6, 3.5 Hz, 2H), 1.21 (qd, *J* = 12.1, 3.5 Hz, 2H), 1.38 (d, *J* = 10.9 Hz, 2H), 1.50 (d, *J* = 12.6 Hz, 1H), 1.64 (d, *J* = 13.2 Hz, 2H), 2.34 (s, 3H), 3.08 (s, 3H), 3.50 (td, *J* = 12.0, 3.5 Hz, 1H), 7.26-7.34 (m, 3H), 7.38-7.43 (m, 2H), 7.83 (td, *J* = 8.0, 1.7 Hz, 1H), 7.89 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.70 (d, *J* = 4.0 Hz, 1H), 8.76 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 25.8, 29.79, 29.81, 40.0, 56.7, 120.6, 121.1, 123.7, 126.2, 127.1, 129.5, 131.4, 133.8, 135.1, 136.5, 136.9, 144.8, 148.8, 149.3, 154.9, 155.8, 161.5; IR (KBr, ν / cm^{-1}) 3057, 3008, 2928, 2853, 1647, 1636, 1588, 1542, 1507, 1474, 1457, 1436, 1395, 1363, 1319, 1145, 1104, 1002, 895, 855, 801, 758, 619; HRMS (ESI$^+$) Calcd for $C_{25}H_{29}N_4O$ ($[M+H]^+$) 401.2341, Found 401.2329.



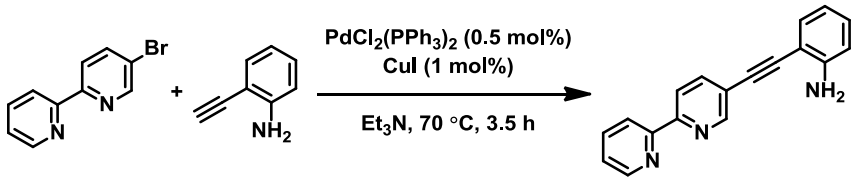
Synthesis of 1-([2,2'-bipyridin]-5-ylmethyl)-3-cyclohexylurea (2). Prepared by the same method as ligand **1** using [2,2'-bipyridin]-5-ylmethanamine (371 mg, 1.50 mmol, 1.0 equiv) and cyclohexylisocyanate (274 mg, 2.3 mmol, 1.5 equiv). 50% yield; white



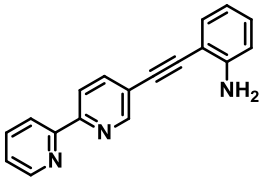
[58] Bach R., Clayden J. & Hennecke U. *Synlett* 421-424 (2009).

solid; R_f = 0.10 (hexane/ethyl acetate = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06-1.17 (m, 3H), 1.30-1.39 (m, 2H), 1.68-1.71 (m, 3H), 1.93-1.96 (m, 2H), 3.52-3.54 (m, 1H), 4.23-4.25 (m, 1H), 4.46 (d, *J* = 5.8 Hz, 2H), 4.60 (brs, 1H), 7.31 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.78-7.84 (m, 2H), 8.34-8.37 (m, 2H), 8.37 (d, *J* = 7.4 Hz, 1H), 8.60 (d, *J* = 1.8 Hz, 1H), 8.67 (dd, *J* = 4.9, 0.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 25.7, 34.0, 41.9, 49.5, 121.1, 121.2, 123.8, 135.4, 136.5, 137.1, 148.6, 149.3, 155.4, 156.1, 157.4; IR (KBr, ν / cm^{-1}) 3308, 3032, 1560, 1458, 1392, 1237, 1054, 844, 750, 694; HRMS (ESI^+) Calcd for $C_{18}H_{22}N_4NaO$ ($[M+Na]^+$) 333.1686, Found 333.1681.

Synthesis of 2-([2,2'-bipyridin]-5-ylethynyl)aniline[59].



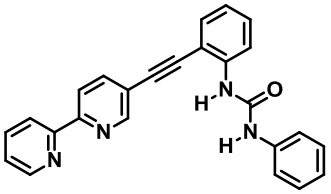
$PdCl_2(PPh_3)_2$ (7.0 mg, 0.010 mmol, 0.5 mol%) and CuI (3.8 mg, 0.02 mmol, 1 mol%) were added to a solution of 5-bromo-2,2'-bipyridine (470 mg, 2.00 mmol, 1.0 equiv) in Et_3N (5.0 mL), and the mixture was stirred at room temperature about 15 min. 2-Ethynylaniline (0.31 mL, 2.40 mmol, 1.2 equiv) was added to the mixture, and the mixture was stirred at the room temperature. The reaction was monitored by TLC. After 3.5 h, white precipitate was filtered through a Celite pad. The filtrate was concentrated at reduced pressure. H_2O (20 mL) was added to the residue and products were extracted with diethyl ether (3×20 mL). The combined organic layer was washed with sat. aq. NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by column chromatography (hexane/ ethyl acetate = 3/1) to give 2-([2,2'-bipyridin]-5-ylethynyl)aniline.



2-([2,2'-Bipyridin]-5-ylethynyl)aniline. 78% yield; R_f = 0.15 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (brs, 2H), 6.72-6.77 (m, 2H), 7.18 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.34 (dd, *J* = 7.6, 4.9 Hz, 1H), 7.40 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.84 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.93 (dd, *J* = 8.1, 2.2 Hz, 1H), 8.41-8.44 (m, 2H), 8.70 (d, *J* = 4.0 Hz, 1H), 8.81 (dd, *J* = 8.2, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 90.4, 91.8, 107.3, 114.6, 118.2, 120.5 (2C), 121.5, 124.0, 130.4, 132.5, 137.1, 139.2, 148.1, 149.4, 151.5, 154.9, 155.6; IR (KBr, ν / cm^{-1}) 3313, 2362, 2206, 1624, 1569, 1488, 1459, 1312, 1093, 739; HRMS (ESI^+) Calcd for $C_{18}H_{13}N_3Na$ ($[M+Na]^+$) 294.1007, Found 294.0999.

[59] Yin Y., Ma W., Chai Z. & Zhao G. *J. Org. Chem.* **72**, 5731-5736 (2007).

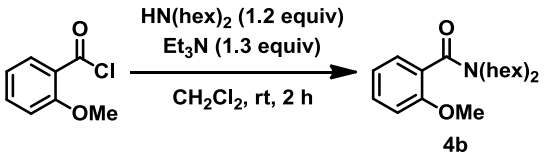
1-(2-([2,2'-Bipyridin]-5-ylethynyl)phenyl)-3-phenylurea (3).



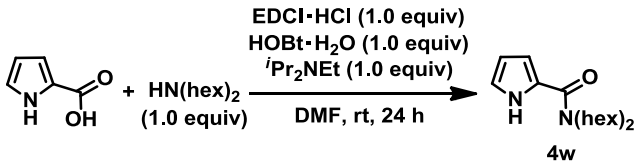
Prepared by the same method as ligand **3** using 2-([2,2'-Bipyridin]-5-ylethynyl)aniline (27.1 mg, 0.100 mmol) and phenylisocyanate (17.9 mg, 0.150 mmol, 1.5 equiv). 46% yield; white solid; R_f = 0.29 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (brs, 1H), 7.04-7.10 (m, 3H), 7.29-7.30 (m, 1H), 7.34-7.41 (m, 4H), 7.47-7.49 (m, 2H), 7.58 (d, *J* = 6.3 Hz, 1H), 7.86 (dd, *J* = 5.8, 5.8 Hz, 1H), 8.30 (d, *J* = 6.7 Hz, 1H), 8.37 (d, *J* = 10.2 Hz, 1H), 8.44 (d, *J* = 6.3 Hz, 1H), 8.56 (s, 1H), 8.72 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 88.8, 92.7, 111.4, 119.4, 134.4, 120.4, 121.6, 122.8, 123.4, 124.3, 125.7, 127.7, 129.8, 130.5, 132.2, 137.2, 139.5, 139.9, 149.5, 151.7, 153.0, 155.3, 155.4; IR (KBr, ν / cm^{-1}) 3299, 1644, 1576, 1552, 1458, 1296, 1091, 794, 743, 692; HRMS (ESI^+) Calcd for $C_{25}H_{18}N_4NaO$ ($[M+Na]^+$) 413.1378, Found 413.1388.

Synthesis and Characterisation of Benzamides, Phosphonates, and Phosphine Oxides

Typical procedures for synthesis of benzamides 4.



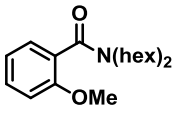
Method A: To a solution of dihexylamine (2.20 g, 12.0 mmol, 1.2 equiv) and Et_3N (1.30 g, 13.0 mmol, 1.3 equiv) in dichloromethane (1.7 mL), 2-methoxybenzoyl chloride (1.60 g, 9.60 mmol, 1.0 equiv) was added at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with dichloromethane (5.0 mL) and washed with aq. 1.0 M HCl (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1) to give **4b** (2.8 g, 90% yield).



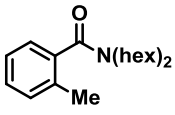
Method B: To a solution of pyrrole-2-carboxylic acid (1.00 g, 9.00 mmol, 1.0 equiv), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) (1.73 g, 9.00 mmol, 1.0

equiv), 1-hydroxybenzotriazole monohydrate ($HOBt{\cdot}H_2O$) (1.38 g, 9 mmol, 1.0 equiv) and ethyldiisopropylamine ($^{i}Pr_2NEt$, 1.16 g, 9.00 mmol, 1.0 equiv) in DMF (70 mL), dihexylamine (1.67 g, 9.00 mmol, 1.0 equiv) was added and the reaction mixture was stirred at room temperature for 24 h. After removing the solvent in vacuo, the residue was diluted with ethyl acetate (50 mL) and washed with H_2O (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The eluent was concentrated under reduced pressure. The product was isolated by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give **4w** (2.33 g, 93% yield).

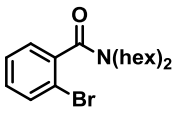
***N*,*N*-Dihexyl-2-methoxybenzamide (4b).** Method A; 90% yield; colorless oil; 0.42 (hexane/ethyl acetate = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 6.3 Hz, 3H), 1.05-1.12 (m, 4H), 1.15-1.21 (m, 2H), 1.33-1.41 (m, 8H), 1.61-1.67 (m, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 3.36-3.37 (m, 1H), 3.62-3.66 (m, 1H), 3.81 (s, 3H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.96 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.17 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.31 (ddd, *J* = 8.5, 8.3, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.2, 22.6, 22.8, 26.3, 26.8, 27.5, 28.4, 31.4, 31.8, 44.3, 48.4, 55.6, 111.0, 120.8, 127.2, 127.8, 129.9, 155.2, 169.3; IR (neat, ν / cm^{-1}) 3421, 2928, 2857, 1635, 1601, 1466, 1376, 1246, 1096, 753; HRMS (ESI^+) Calcd for $C_{20}H_{33}NNaO_2$ ($[M+Na]^+$) 342.2404, Found 342.2389.

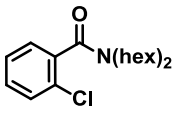


***N*,*N*-Dihexyl-2-methylbenzamide (4c).** Method A; 92% yield; colorless oil; R_f = 0.64 (hexane/ethyl acetate = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.6 Hz, 3H), 1.06-1.08 (m, 4H), 1.17-1.20 (m, 2H), 1.35-1.44 (m, 8H), 1.65-1.67 (m, 2H), 2.28 (s, 3H), 3.02-3.05 (m, 2H), 3.32-3.67 (m, 2H), 7.13 (d, *J* = 9.2 Hz, 1H), 7.16-7.19 (m, 2H), 7.23 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 19.0, 22.5, 22.7, 26.3, 26.9, 27.5, 28.4, 31.3, 31.7, 44.3, 48.3, 125.7, 125.8, 128.5, 130.3, 133.9, 137.3, 171.2; IR (neat, ν / cm^{-1}) 3404, 2929, 2858, 1625, 1425, 1378, 1215, 1095, 754, 665; HRMS (ESI^+) Calcd for $C_{20}H_{33}NNaO$ ($[M+Na]^+$) 326.2454, Found 326.2465.

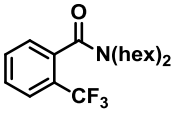


2-Bromo-*N*,*N*-dihexylbenzamide (4d). Method A; 92% yield; colorless oil; R_f = 0.63 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H), 1.09-1.10 (m, 4H), 1.17-1.21 (m, 2H), 1.35-1.40 (m, 8H), 1.68-1.69 (m, 2H), 3.02-3.08 (m, 2H), 3.17-3.24 (m, 1H), 3.73-3.81 (m, 1H), 7.21-7.24 (m, 2H), 7.33 (ddd, *J* = 10.0, 9.2, 1.2 Hz, 1H), 7.55 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.5, 22.8, 26.3, 27.0, 27.2, 28.4, 31.3, 31.8, 44.7, 48.4, 119.4, 127.5, 127.9, 130.0, 132.8, 139.0, 168.9; IR (neat, ν / cm^{-1}) 2929, 2857, 1714, 1643, 1590, 1426, 1302, 1219, 1024, 750; HRMS (ESI^+) Calcd for $C_{19}H_{30}BrNNaO$ ($[M+Na]^+$) 390.1403, Found 390.1405.

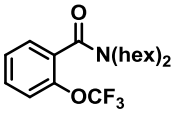


2-Chloro-*N*,*N*-dihexylbenzamide (4e). 

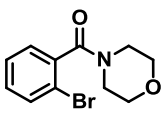
Method A; 89% yield; colorless oil; R_f = 0.53 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 0.89-0.92 (m, 3H), 1.07-1.08 (m, 4H), 1.17-1.20 (m, 2H), 1.35-1.49 (m, 8H), 1.66-1.68 (m, 2H), 3.03-3.09 (m, 2H), 3.20-3.27 (m, 1H), 3.74-3.61 (m, 1H), 7.26-7.33 (m, 3H), 7.36-7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.5, 22.7, 26.3, 26.9, 27.3, 28.4, 31.3, 31.8, 44.6, 48.3, 127.0, 127.9, 129.7, 129.9, 130.4, 136.9, 168.2; IR (neat, ν / cm^{-1}) 2929, 1640, 1593, 1425, 1377, 1302, 1114, 1054, 748, 694; HRMS (ESI^+) Calcd for $C_{19}H_{30}ClNNaO$ ($[M+Na]^+$) 346.1908, Found 346.1897.

***N*,*N*-Dihexyl-2-(trifluoromethyl)benzamide (4f).** 

Method A; 91% yield; colorless oil; R_f = 0.51 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.08-1.22 (m, 6H), 1.34-1.45 (m, 8H), 1.64-1.65 (m, 2H), 2.91-3.03 (m, 2H), 3.14-3.21 (m, 1H), 3.74-3.81 (m, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.57 (dd, *J* = 7.7, 7.6 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 22.5, 22.8, 26.3, 26.87, 26.90, 28.1, 31.3, 31.7, 44.5, 48.8, 123.8 (q, *J* = 275 Hz), 126.6 (q, *J* = 4.8 Hz), 126.7 (q, *J* = 32.4 Hz), 127.5, 128.8, 132.0, 135.9, 168.5; ^{19}F NMR (368 MHz, $CDCl_3$) δ -61.8 (s, 3F); IR (neat, ν / cm^{-1}) 2930, 1644, 1582, 1499, 1378, 1267, 1173, 1055, 769, 667; HRMS (ESI^+) Calcd for $C_{20}H_{30}F_3NNaO$ ($[M+Na]^+$) 380.2172, Found 380.2176.

***N*,*N*-Dihexyl-2-(trifluoromethoxy)benzamide (4g).** 

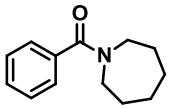
Method A; 96% yield; colorless oil; R_f = 0.64 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H), 1.08-1.09 (m, 4H), 1.17-1.20 (m, 2H), 1.34-1.47 (m, 8H), 1.60-1.66 (m, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 3.12-3.16 (m, 1H), 3.82-3.85 (m, 1H), 7.27-7.36 (m, 3H), 7.39-7.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 22.7, 26.2, 26.7, 27.2, 28.3, 31.3, 31.8, 44.4, 48.3, 120.0 (q, *J* = 1.9 Hz), 120.6 (q, *J* = 259 Hz), 126.9, 128.6, 130.2, 130.9, 144.8 (q, *J* = 19.0 Hz), 166.8; ^{19}F NMR (368 MHz, $CDCl_3$) δ -58.8 (s, 3F); IR (neat, ν / cm^{-1}) 2931, 2859, 1644, 1427, 1377, 1255, 1092, 926, 766, 629; HRMS (ESI^+) Calcd for $C_{20}H_{30}F_3NNaO_2$ ($[M+Na]^+$) 396.2121, Found 396.2105.

(2-Bromophenyl)-4-morpholinyl-methanone (4m). 

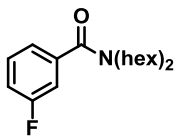
Method A; quant; white solid; R_f = 0.55 (dichloromethane/methanol = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16-3.23 (m, 1H), 3.25-3.32 (m, 1H), 3.55-3.62 (m, 1H), 3.68-3.83 (m, 4H), 3.84-3.92 (m, 1H), 7.23-7.28 (m, 2H), 7.36 (td, *J* = 7.5, 1.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.0, 47.1, 66.6, 66.7, 119.1, 127.7, 127.8, 130.4, 132.8, 137.5, 167.7; IR

(KBr, ν / cm^{-1}) 2865, 1626, 1287, 1250, 1112, 1011, 843, 768, 749; HRMS (ESI^+) Calcd for $C_{11}H_{12}BrNO_2Na$ ($[M+Na]^+$) 291.9949, Found 291.9943.

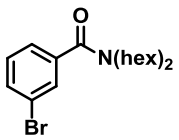
Azepan-1-yl(phenyl)methanone (4n). Method A; 94% yield; colorless oil; R_f = 0.24 (hexane/ethyl acetate = 3/1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.60-1.66 (m, 6H), 1.81-1.87 (m, 2H), 3.36 (t, *J* = 5.6 Hz, 2H), 3.68 (t, *J* = 5.8 Hz, 2H), 7.37-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 27.3, 27.9, 29.5, 46.4, 49.8, 126.5, 128.4, 129.1, 137.4, 171.6; IR (neat, ν / cm^{-1}) 2927, 1631, 1424, 1357, 1220, 1100, 1004, 907, 749, 632; HRMS (ESI^+) Calcd for $C_{13}H_{17}NNaO$ ($[M+Na]^+$) 226.1202, Found 226.1211.



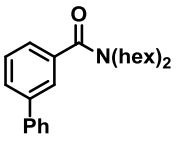
3-Fluoro-*N*,*N*-dihexylbenzamide (4p). Method A; 93% yield; colorless oil; R_f = 0.50 (hexane/ethyl acetate = 3/1); ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.7 Hz, 3H), 0.89-0.92 (m, 3H), 1.12-1.34 (m, 12H), 1.46-1.50 (m, 2H), 1.62-1.64 (m, 2H), 3.16 (t, *J* = 7.2 Hz, 2H), 3.46 (t, *J* = 7.6 Hz, 2H), 7.05-7.10 (m, 2H), 7.12 (ddd, *J* = 7.6, 1.3, 1.3 Hz, 1H), 7.33-7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 22.7, 26.2, 26.8, 27.5, 28.7, 31.3, 31.7, 44.9, 49.0, 113.9 (d, *J* = 22.5 Hz), 116.1 (d, *J* = 20.7 Hz), 122.2 (d, *J* = 3.8 Hz), 130.2 (d, *J* = 8.5 Hz), 139.5 (d, *J* = 7.5 Hz), 162.6 (d, *J* = 248.1 Hz), 170.1; ^{19}F NMR (368 MHz, $CDCl_3$) δ -114.0 (s, 1F); IR (neat, ν / cm^{-1}) 2929, 2857, 1643, 1585, 1466, 1377, 1267, 1101, 879, 751; HRMS (ESI^+) Calcd for $C_{19}H_{30}FNNaO$ ($[M+Na]^+$) 330.2204, Found 330.2195.



3-Bromo-*N*,*N*-dihexylbenzamide (4q). Method A; 93% yield; colorless oil; R_f = 0.59 (hexane/ethyl acetate = 3/1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.5 Hz, 3H), 0.89-0.91 (m, 3H), 1.13-1.34 (m, 12H), 1.49-1.53 (m, 2H), 1.60-1.64 (m, 2H), 3.15 (t, *J* = 7.5 Hz, 2H), 3.46 (t, *J* = 7.4 Hz, 2H), 7.27-7.30 (m, 2H), 7.49 (s, 1H), 7.50-7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 22.7, 26.3, 26.8, 27.5, 28.7, 31.3, 31.7, 44.9, 49.1, 122.6, 125.1, 129.7, 130.1, 132.2, 139.4, 169.9; IR (neat, ν / cm^{-1}) 2928, 1633, 1562, 1426, 1377, 1299, 1111, 887, 746, 680; HRMS (ESI^+) Calcd for $C_{19}H_{30}BrNNaO$ ($[M+Na]^+$) 390.1403, Found 390.1405.

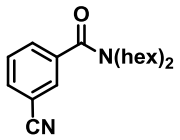


***N*,*N*-Dihexyl-[1,1'-biphenyl]-3-carboxamide (4r).** Method A; 91% yield; colorless oil; R_f = 0.58 (hexane/ethyl acetate = 3/1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, *J* = 6.7 Hz, 3H), 0.89-0.93 (m, 3H), 1.12-1.18 (m, 6H), 1.34-1.38 (m, 6H), 1.50-1.53 (m, 2H), 1.65-1.70 (m, 2H), 3.22 (t, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 7.4 Hz, 2H), 7.30-7.38 (m, 2H), 7.43-7.47 (m, 3H), 7.56-7.62 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 22.5, 22.8, 26.3, 26.9, 27.6, 28.8, 31.4, 31.8, 44.9, 49.2, 125.3, 125.4, 127.2, 127.7, 127.8,

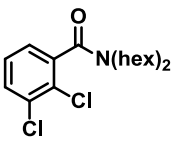


128.92, 128.94, 138.0, 140.6, 141.5, 171.6; IR (neat, ν / cm^{-1}) 2928, 1633, 1426, 1376, 1316, 1257, 1109, 809, 744, 656; HRMS (ESI^+) Calcd for $C_{25}H_{35}NNaO$ ($[M+Na]^+$) 388.2611, Found 388.2616.

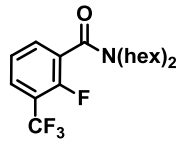
3-Cyano-*N*,*N*-dihexylbenzamide (4s). Method A; 87% yield; colorless oil; R_f = 0.37 (hexane/ethyl acetate = 3/1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.4 Hz, 3H), 0.89-0.90 (m, 3H), 1.11-1.34 (m, 12H), 1.46-1.50 (m, 2H), 1.63-1.64 (m, 2H), 3.13 (t, *J* = 6.9 Hz, 2H), 3.47 (t, *J* = 8.0 Hz, 2H), 7.52 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.64 (s, 1H), 7.69 (dd, *J* = 8.1, 1.6 Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 22.7, 26.2, 26.8, 27.5, 28.7, 31.3, 31.7, 45.1, 49.2, 112.8, 118.2, 129.5, 130.2, 130.9, 132.7, 138.7, 169.2; IR (neat, ν / cm^{-1}) 2928, 2231, 1633, 1464, 1302, 1187, 1108, 808, 747, 633; HRMS (ESI^+) Calcd for $C_{20}H_{30}N_2NaO$ ($[M+Na]^+$) 337.2250, Found 337.2256.



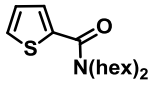
2,3-Dichloro-*N*,*N*-dihexylbenzamide (4t). Method A; 94% yield; colorless oil; R_f = 0.52 (hexane/ethyl acetate = 3/1); ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.09-1.11 (m, 4H), 1.15-1.21 (m, 2H), 1.35-1.54 (m, 8H), 1.61-1.71 (m, 2H), 2.96-3.11 (m, 2H), 3.20-3.27 (m, 1H), 3.71-3.79 (m, 1H), 7.16 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.24 (dd, *J* = 8.1, 7.9 Hz, 1H), 7.46 (dd, *J* = 8.1, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 22.7, 26.3, 26.8, 27.2, 28.4, 31.3, 31.7, 44.7, 48.3, 125.9, 127.9, 128.9, 130.5, 133.6, 138.9, 167.3; IR (neat, ν / cm^{-1}) 2929, 1650, 1559, 1426, 1376, 1194, 1049, 800, 740, 675; HRMS (ESI^+) Calcd for $C_{19}H_{29}Cl_2NNaO$ ($[M+Na]^+$) 380.1518, Found 380.1522.



2-Fluoro-*N*,*N*-dihexyl-3-(trifluoromethyl)benzamide (4u). Method A; 83% yield; colorless oil; R_f = 0.50 (hexane/ethyl acetate = 3/1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.6 Hz, 3H), 1.08-1.11 (m, 4H), 1.14-1.21 (m, 2H), 1.31-1,41 (m, 6H), 1.45-1.48 (m, 2H), 1.60-1.70 (m, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 3.40-3.54 (m, 2H), 7.30 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.52 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 7.64 (ddd, *J* = 7.8, 7.4, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 22.5, 22.7, 26.2, 26.7, 27.4, 28.4, 31.2, 31.7, 44.9, 48.7, 119.0 (dd, *J* = 33.0, 12.6 Hz), 122.4 (q, *J* = 272 Hz), 124.6 (q, *J* = 4.8 Hz), 127.3 (d, *J* = 19.2 Hz), 127.8 (d, *J* = 4.8 Hz), 132.8 (d, *J* = 4.8 Hz), 155.3 (d, *J* = 257 Hz), 165.0; ^{19}F NMR (368 MHz, $CDCl_3$) δ -63.3 (s, 3F), -119.1 (s, 1F); IR (neat, ν / cm^{-1}) 2931, 2859, 1644, 1464, 1333, 1236, 1141, 1075, 753, 666; HRMS (ESI^+) Calcd for $C_{20}H_{29}F_4NNaO$ ($[M+Na]^+$) 398.2077, Found 398.2065.

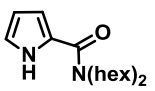


***N*,*N*-Dihexyl-2-thiophenecarboxamide (4v).** Method A; quant; colorless oil; R_f = 0.35 (hexane/ethyl acetate = 5/1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz,

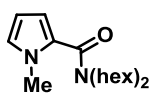


6H), 1.19-1.40 (m, 12H), 1.58-1.69 (m, 4H), 3.42-3.48 (m, 4H), 7.03 (dd, *J* = 5.1, 4.0 Hz, 1H), 7.29 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.41 (dd, *J* = 5.1, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 22.5 (2C), 26.4 (2C), 28.1 (2C), 31.4 (2C), 46.8 (br), 48.9 (br), 126.5, 127.99, 128.01, 138.3, 164.0; IR (neat, ν / cm^{-1}) 3074, 2955, 2928, 2857, 1618, 1523, 1459, 1430, 1377, 1298, 1261, 1233, 1092, 853, 738, 708; HRMS (ESI^+) Calcd for $C_{17}H_{29}NNaOS$ ($[M+Na]^+$) 318.1868, Found 318.1869.

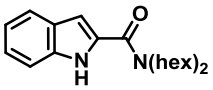
***N*,*N*-Dihexyl-1*H*-pyrrol-2-carboxamide (4w).** Method B; 93% yield; pale yellow solid; R_f = 0.25 (hexane/ethyl acetate = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80-1.00 (m, 6H), 1.25-1.41 (m, 12H), 1.55-1.80 (m, 4H), 3.35-3.65 (m, 4H), 6.20-6.30 (m, 1H), 6.46-6.50 (m, 1H), 6.89-6.93 (m, 1H), 9.49 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 22.5 (2C), 26.5 (2C), 27.8 (br), 28.4 (br), 31.5 (2C), 47.5 (br), 48.5 (br), 109.2, 111.1, 120.7, 125.0, 161.8; IR (neat, ν / cm^{-1}) 3229, 2961, 2931, 2857, 1590, 1549, 1480, 1442, 1417, 1378, 1315, 1309, 1280, 1175, 1129, 1047, 839, 782, 731, 611; HRMS (ESI^+) Calcd for $C_{17}H_{30}N_2NaO$ ($[M+Na]^+$) 301.2256, Found 301.2253.



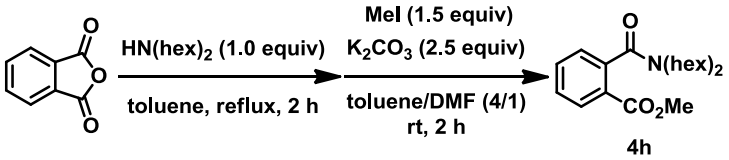
***N*,*N*-Dihexyl-1-methyl-1*H*-pyrrol-2-carboxamide (4x).** Method B; 93% yield; colorless oil; R_f = 0.28 (hexane/ethyl acetate = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.5 Hz, 6H), 1.10-1.35 (m, 12H), 1.52-1.65 (m, 4H), 3.46 (t, *J* = 7.5 Hz, 4H), 3.73 (s, 3H), 6.04-6.08 (m, 1H), 6.25-6.30 (m, 1H), 6.63-6.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 22.5 (2C), 26.4 (2C), 28.1 (br), 31.4 (2C), 35.4, 47.0 (br), 106.5, 111.0, 125.2, 126.1, 164.0; IR (neat, ν / cm^{-1}) 104, 2955, 2928, 2858, 1622, 1534, 1467, 1429, 1257, 1205, 1105, 1376, 1317, 1000, 888, 753, 721; HRMS (ESI^+) Calcd for $C_{18}H_{32}N_2NaO$ ($[M+Na]^+$) 315.2412, Found 315.2421.



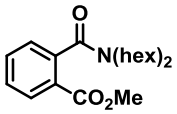
***N*,*N*-Dihexyl-1*H*-indole-2-carboxamide (4y).** Method B; 72% yield; white solid; R_f = 0.38 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.95 (m, 6H), 1.28-1.44 (m, 12H), 1.60-1.85 (m, 4H), 3.35-3.80 (m, 4H), 6.75 (d, *J* = 2.3 Hz, 1H), 7.13 (td, *J* = 8.0, 0.9 Hz, 1H), 7.25-7.30 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 9.46 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 22.6 (2C), 26.7 (2C), 27.5 (br), 28.9 (br), 31.6 (2C), 47.6 (br), 49.0 (br), 104.2, 111.8, 120.2, 121.8, 124.0, 127.8, 129.9, 135.5, 162.5; IR (KBr, ν / cm^{-1}) 3433, 3271, 2958, 2930, 2855, 1600, 1525, 1466, 1407, 1379, 1338, 1317, 1257, 1230, 1189, 1142, 812, 768, 748; HRMS (ESI^+) Calcd for $C_{21}H_{32}N_2NaO$ ($[M+Na]^+$) 351.2412, Found 351.2414.



Synthesis of benzamide 4h[60]**.**

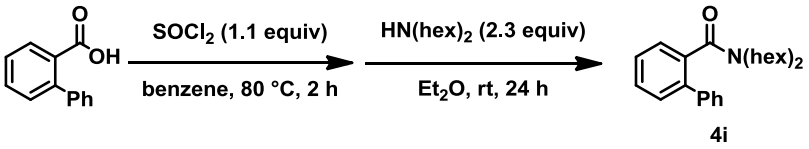


To the solution of phthalic anhydride (320 mg, 2.2 mmol, 1.0 equiv) in toluene (40 mL), dihexylamine (408 mg, 2.20 mmol, 1.0 equiv) was added under 0 °C and the reaction mixture was refluxed. After 2 h the mixture was cooled to room temperature and then DMF, methyl iodide (468 mg, 3.30 mmol, 1.5 equiv) and K_2CO_3 (760 mg, 5.50 mmol, 2.5 equiv) were added. The reaction mixture was stirred at room temperature for 12 h, then diluted with H_2O (50 mL) and extracted with ethyl acetate (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1).



Methyl 2-(dihexylcarbamoyl)benzoate (4h). 91% yield; colorless oil; R_f = 0.34 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 6.5 Hz, 3H), 1.06-1.10 (m, 4H), 1.16-1.21 (m, 2H), 1.34-1.48 (m, 8H), 1.67-1.72 (m, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 3.46-3.50 (m, 2H), 3.87 (s, 3H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 7.9, 7.5 Hz, 1H), 7.55 (dd, *J* = 7.5, 7.4 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 22.5, 22.8, 26.4, 27.0, 27.1, 28.1, 31.3, 31.8, 44.8, 48.8, 52.3, 127.1, 127.2, 128.4, 130.7, 132.7, 139.4, 166.2, 170.6; IR (neat, ν / cm^{-1}) 2929, 2370, 1644, 1575, 1432, 1377, 1292, 1126, 1078, 777; HRMS (ESI^+) Calcd for $C_{21}H_{33}NNaO_3$ ($[M+Na]^+$) 370.2353, Found 370.2360.

Synthesis of benzamide 4i[61]**.**

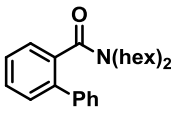


A mixture of [1,1'-biphenyl]-2-carboxylic acid (1.04 g, 5.25 mmol, 1.0 equiv), benzene (2.0 mL), DMF (0.05 mL), and $SOCl_2$ (0.69 g, 5.8 mmol, 1.1 equiv) was stirred at 80 °C for 2 h. Evaporation of the solvent gave brown solid, which was dissolved in diethyl ether (2.0 mL). An ethereal solution

[60] Bischoff A., Subramanya H. S., Sundaresan K., Sammeta S. R. & Vaka A. K. PCT WO 2008/157844 A1.

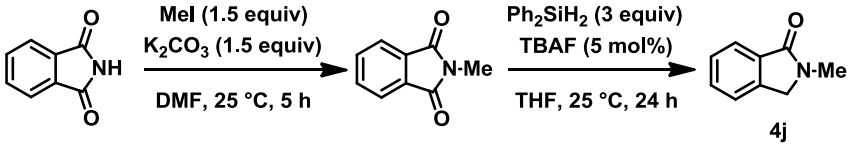
[61] Meca L., Císařová I., Drahoňovský D. & Dvořák D. *Organometallics* **27**, 1850-1858 (2008).

of dihexylamine (2.22 g, 12.0 mmol, 2.3 equiv) was slowly added to the residue at 0 °C and resulting suspension was stirred at room temperature for 24 h. The white solid was removed by filtration and the organic layer was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **4i** (1.06 g, 53% yield).

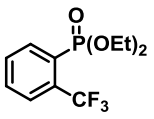


***N*,*N*-Dihexyl-[1,1'-biphenyl]-2-carboxamide (4i).** 53% yield; colorless oil; R_f = 0.51 (hexane/ethyl acetate = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.92-1.27 (m, 16H), 2.46-2.50 (m, 1H), 2.84-2.89 (m, 2H), 3.65-3.70 (m, 1H), 7.33-7.38 (m, 6H), 7.41-7.43 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.1, 22.4, 22.6, 26.2, 26.75, 26.78, 27.9, 31.3, 31.7, 44.3, 48.1, 127.4, 127.55, 127.59, 128.4, 128.9, 129.0, 129.4, 136.6, 138.5, 140.0, 171.0; IR (neat, ν / cm^{-1}) 2928, 2857, 1630, 1465, 1421, 1376, 1098, 775, 700, 629; HRMS (ESI^+) Calcd for $C_{25}H_{35}NNaO$ ($[M+Na]^+$) 388.2611, Found 388.2610.

Synthesis of benzamide 4j[45, 46].



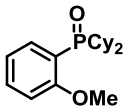
Solution of methyl iodide (2.13 g, 15.0 mmol, 1.5 equiv) in DMF (20 mL) was added dropwise to a mixture of phthalimide (1.47 g, 10.0 mmol, 1.0 equiv), K_2CO_3 (2.07 g, 15.0 mmol, 1.5 equiv), and DMF (100 mL) at room temperature for 5 h. Evaporation of the solvent gave light yellow suspension, which was extracted with water and ethyl acetate. The organic layer was dried with Na_2SO_4, filtered off, and concentrated under reduced pressure. Recrystallization (hexane/ethyl acetate) gave *N*-methylphthalimide as a colorless solid (0.98 g, 61% yield). A mixture of *N*-methylphthalimide (0.79 g, 4.90 mmol, 1.0 equiv), THF (14 mL), diphenylsilane (0.270 g, 14.7 mmol, 3.0 equiv), and tetrabutylammonium fluoride solution (TBAF) (1.0 M in THF, 240 μL, 0.24 mmol, 5 mol%) was stirred at room temperature for 24 h. Dark brown solution was diluted with ethyl acetate and filtered through Celite. The eluent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 40/1) to give **4j** (0.63 g, 87% yield).



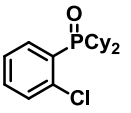
Diethyl (2-trifluoromethylphenyl)phosphonate (4gg)[49]. 4gg was prepared from 1-iodo-2-(trifluoromethyl)benzene and diethyl phosphonate according to the literature method. 39% yield; colorless oil; R_f = 0.55 (ethyl acetate/^{i}PrOH = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, *J* = 6.9 Hz, 6H), 4.06-4.27 (m, 4H), 7.62-7.70 (m, 2H), 7.78-7.85 (m, 1H), 8.20-8.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1 (d, J_{C-P} = 7.2 Hz), 62.7 (d,

J_{C-P} = 6.0 Hz), 123.3 (qd, $J_{C-F, C-P}$ = 275, 4.8 Hz), 127.1 (d, J_{C-P} = 185 Hz), 127.4 (dq, $J_{C-F, C-P}$ = 6.0, 12.0 Hz), 131.3 (d, J_{C-P} = 13.2 Hz), 132.3 (qd, $J_{C-F, C-P}$ = 32.4, 7.2 Hz), 132.3 (d, J_{C-P} = 3.6 Hz), 136.1 (d, J_{C-P} = 7.2 Hz); ^{19}F NMR (368 MHz, $CDCl_3$) δ -60.7 (s, 3F); ^{31}P NMR (158 MHz, $CDCl_3$) δ 25.6; IR (KBr, ν / cm^{-1}) 2987, 1597, 1576, 1480, 1442, 1393, 1370, 1313, 1250, 1179, 1132, 1063, 1026, 967, 776, 741, 894, 648; HRMS (ESI^+) Calcd for $C_{11}H_{14}F_3NaO_3P$ ($[M+Na]^+$) 305.0530, Found 305.0537.

Dicyclohexyl(2-methoxyphenyl)phosphine oxide (4jj)[53]**. 4jj** was prepared by oxidation of dicyclohexyl(2-methoxyphenyl)phosphine according to the literature method. 85% yield; white solid; R_f = 0.27 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14-1.50 (m, 12H), 1.65-1.72 (m, 4H), 1.80-1.84 (m, 2H), 2.03-2.06 (m, 2H), 20.9-2.19 (m, 2H), 3.83 (s, 3H), 6.89 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.09-7.12 (m, 1H), 7.45-7.50 (m, 1H), 7.93 (ddd, *J* = 11.4, 7.4, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (d, J_{C-P} = 3.7 Hz), 25.80, 25.84 (d, J_{C-P} = 3.8 Hz), 26.4 (d, J_{C-P} = 13.2 Hz), 26.7 (d, J_{C-P} = 13.2 Hz), 36.6 (d, J_{C-P} = 67.7 Hz), 54.9, 109.9 (d, J_{C-P} = 11.5 Hz), 118.7 (d, J_{C-P} = 110 Hz), 120.8 (d, J_{C-P} = 10.3 Hz), 132.9 (d, J_{C-P} = 1.9 Hz), 135.7 (d, J_{C-P} = 4.7 Hz), 159.0 (d, J_{C-P} = 110 Hz); ^{31}P NMR (158 MHz, $CDCl_3$) δ 59.6; IR (KBr, ν / cm^{-1}) 2929, 2850, 1191, 1577, 1479, 1463, 1446, 1431, 1278, 1241, 1210, 1159, 1138, 1114, 1075, 1047, 1020, 1002, 893, 850, 822, 802, 763, 745; HRMS (ESI^+) Calcd for $C_{19}H_{29}NaO_2P$ ($[M+Na]^+$) 343.1803, Found 343.1799.



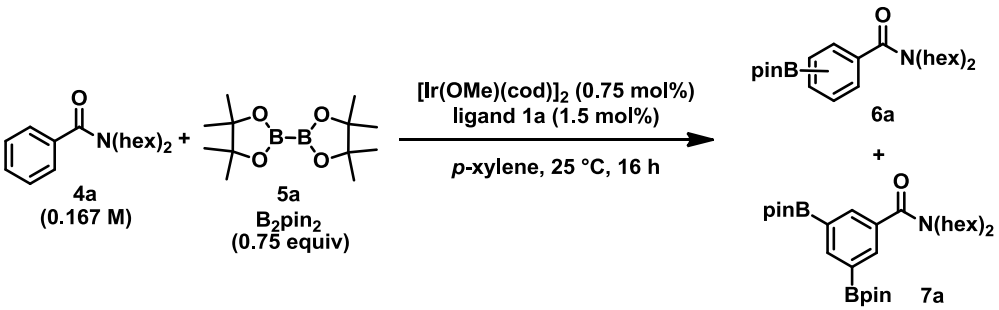
Dicyclohexyl(2-chlorophenyl)phosphine oxide (4kk)[62]**. 4kk** was prepared by coupling reaction between 1-chloro-2-iodobenzene and dicyclohexylphosphine oxide according to the literature method. 39% yield; white solid; R_f = 0.20 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.26 (m, 4H), 1.27-1.45 (m, 6H), 1.55-1.75 (m, 6H), 1.80-1.90 (m, 2H), 2.02-2.13 (m, 2H), 2.28-2.38 (m, 2H), 7.36-7.46 (m, 3H), 8.08-8.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 26.0 (2C), 26.3 (d, J_{C-P} = 13.2 Hz), 26.5 (d, J_{C-P} = 13.2 Hz), 37.0 (d, J_{C-P} = 67.2 Hz), 126.5-127.0 (m), 129.6-130.0 (m), 130.3 (d, J_{C-P} = 81.6 Hz), 132.3-132.7 (m), 134.1 (d, J_{C-P} = 4.8 Hz), 136.5-136.8 (m); ^{31}P NMR (158 MHz, $CDCl_3$) δ 59.5; IR (KBr, ν / cm^{-1}) 2930, 2851, 1581, 1455, 1416, 1276, 1212, 1179, 1152, 1129, 1114, 1044, 1028, 888, 849, 819, 762; HRMS (ESI^+) Calcd for $C_{18}H_{26}ClNaOP$ ($[M+Na]^+$) 347.1307, Found 347.1305.



[62] Stankevič M. & Wlodarczyk A. *Tetrahedron* **69**, 73-81 (2013).

Procedure and Results of C-H Borylation

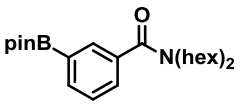
Typical procedure for iridium-catalyzed borylation of (hetero)arenes.



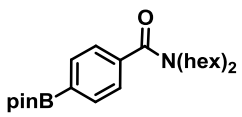
In a sealed tube, a mixture of $[Ir(OMe)(cod)]_2$ (1.2 mg, 1.9 μmol, 0.75 mol%), ligand **1a** (1.2 mg, 3.8 μmol, 1.5 mol%), and bis(pinacolato)diboron (**5a**) (47.6 mg, 0.188 mmol, 0.750 equiv) was added to a solution of *N*,*N*-dihexylbenzamide **4a** (72.4 mg, 0.250 mmol, 1.0 equiv) in *p*-xylene (1.5 mL). The mixture is then stirred at 25 °C for 16 h. The product was isolated from starting material and other byproduct by recycling preparative HPLC to give a mixture of **6a** and **7a** (**6a**: 41.0 mg, 43% yield; **7a**: 4.5 mg, 4% yield).

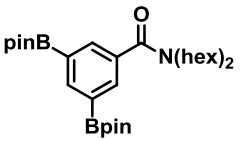
Characterisation of Borylated Products

***N*,*N*-Dihexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6a**, *meta* isomer**).** 40% yield; colorless oil; ^{1}H NMR (500 M Hz, $CDCl_3$) δ 0.82 (t, *J* = 6.9 Hz, 3H), 0.89-0.92 (m, 3H), 1.10-1.21 (m, 6H), 1.30-1.41 (m, 18H), 1.46-1.50 (m, 2H), 1.65-1.66 (m, 2H), 3.15 (t, *J* = 6.9 Hz, 2H), 3.46 (t, *J* = 7.2 Hz, 2H), 7.38 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.43 (ddd, *J* = 8.0, 1.7, 1.7 Hz, 1H), 7.78 (s, 1H), 7.80 (ddd, *J* = 7.2, 1.7, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 22.6, 22.8, 25.0, 26.3, 26.9, 27.6, 28.8, 31.4, 31.8, 45.0, 49.2, 84.1, 127.8, 129.3, 132.7, 135.4, 136.8, 171.8; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.2; IR (neat, ν / cm^{-1}) 2930, 2858, 1626, 1411, 1358, 1319, 1144, 861, 754, 666; HRMS (ESI^+) Calcd for $C_{25}H_{42}BNNaO_3$ ($[M+Na]^+$) 438.3150, Found 438.3151.

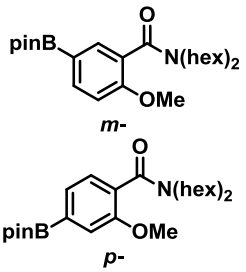


***N*,*N*-Dihexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6a**, *para* isomer**).** 3.3% yield; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3H), 0.89-0.92 (m, 3H), 1.06-1.11 (m, 4H), 1.18-1.25 (m, 2H), 1.35-1.36 (m, 18H), 1.46-1.47 (m, 2H), 1.63-1.66 (m, 2H), 3.13 (t, *J* = 6.9 Hz, 2H), 3.46 (t, *J* = 7.2 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 22.7, 25.0, 26.3, 26.8, 27.6, 28.7, 31.4, 31.7, 44.8, 49.0, 84.1, 125.7, 134.8, 140.1, 171.6; ^{11}B NMR (130 MHz, $CDCl_3$) δ 29.9; IR (neat, ν / cm^{-1}) 2929, 1636, 1511, 1396, 1360, 1322, 1144, 1108, 859, 659; HRMS (ESI^+) Calcd for $C_{25}H_{42}BNNaO_3$ ($[M+Na]^+$) 438.3150, Found 438.3170.

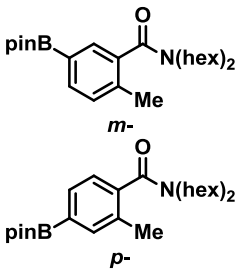




***N*,*N*-Dihexyl-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (7a).** 3.0% yield; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 0.90-0.93 (m, 3H), 1.10-1.27 (m, 10H), 1.31-1.35 (m, 28H), 1.62-1.66 (m, 2H), 3.12 (t, *J* = 6.9 Hz, 2H), 3.44 (t, *J* = 7.2 Hz, 2H), 7.88 (s 2H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 22.5, 22.8, 25.0, 26.3, 27.0, 27.7, 28.9, 31.4, 31.8, 45.0, 49.3, 84.0, 135.5, 136.3, 141.7, 171.7; ^{11}B NMR (130 MHz, $CDCl_3$) δ 32.9; IR (neat, ν / cm^{-1}) 2929, 1628, 1329, 1265, 1142, 967, 889, 801, 755, 718; HRMS (ESI^+) Calcd for $C_{31}H_{53}B_2NNaO_5$ ($[M+Na]^+$) 564.4002, Found 564.4021.

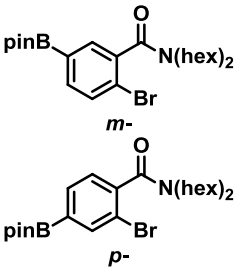


***N*,*N*-Dihexyl-2-methoxy-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6b).** 63% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 0.80 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.06-1.08 (m, 4H), 1.16-1.50 (m, 22H), 1.62-1.64 (m, 2H), 3.01-3.04 (m, 2H), 3.48-3.49 (m, 2H), 3.82 (s, 3H), 6.87 (d, *J* = 8.3 Hz, 1H), 7.63 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), (*para* isomer) 0.80 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 6.7 Hz,, 3H), 1.06-1.08 (m, 4H), 1.18-1.50 (m, 20H), 1.62-1.64 (m, 4H), 3.01-3.04 (m, 2H), 3.48-3.49 (m, 2H), 3.85 (s, 3H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.29 (s, 1H), 7.41 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (*meta* isomer) 14.1, 14.2, 22.5, 22.8, 24.7, 26.3, 26.7, 27.6, 28.4, 31.4, 31.8, 44.4, 48.5, 55.4, 83.7, 110.1, 126.6, 134.4, 137.0, 157.8, 169.2, (*para* isomer) 14.1, 14.2, 22.6, 22.8, 25.0, 26.3, 26.8, 27.5, 28.4, 31.4, 31.8, 44.3, 48.3, 55.6, 84.1, 116.4, 127.1, 127.4, 130.0, 154.6, 169.2; ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.9; IR (neat, ν / cm^{-1}) 2930, 1627, 1410, 1355, 1140, 1027, 965, 851, 754, 683; HRMS (ESI^+) Calcd for $C_{26}H_{44}BNNaO_4$ ($[M+Na]^+$) 468.3256, Found 468.3246.

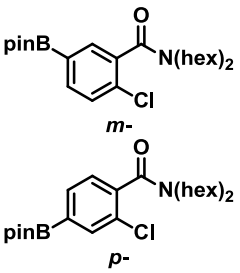


***N*,*N*-Dihexyl-2-methyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6c).** 39% yield; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (*meta* isomer) 0.82 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H), 1.07-1.11 (m, 4H), 1.14-1.21 (m, 2H), 1.25-1.39 (m, 18H), 1.41-1.47 (m, 2H), 1.62-1.70 (m, 2H), 2.29 (s, 3H), 3.01-3.05 (m, 2H), 3.39-3.56 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.59 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), (*para* isomer) 0.81 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.0 Hz, 3H), 1.04-1.11 (m, 4H), 1.14-1.26 (m, 2H), 1.28-1.47 (m, 20H), 1.62-1.67 (m, 2H), 2.27 (s, 3H), 2.85-3.15 (m, 2H), 3.20-3.75 (m, 2H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (*meta* isomer) 14.1, 14.2, 19.4, 22.5, 22.8, 25.0, 26.3, 27.0, 27.7, 28.5, 31.3, 31.8, 44.6, 48.6, 83.9, 129.8, 132.3, 134.9, 136.8, 137.4, 171.3, (*para* isomer) 14.1, 14.2, 18.9, 22.6, 22.8, 25.0, 26.4, 27.0, 27.6, 28.5,

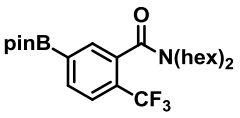
31.4, 31.8, 44.4, 48.4, 84.1, 125.3, 132.2, 133.2, 136.7, 140.1, 171.2; ^{11}B NMR (130 MHz, $CDCl_3$) δ (*meta* isomer) 30.5, (*para* isomer) 31.3; IR (neat, ν / cm^{-1}) 2929, 1634, 1466, 1357, 1145, 1105, 965, 862, 754, 686; HRMS (ESI^+) Calcd for $C_{26}H_{44}BNNaO_3$ ($[M+Na]^+$) 452.3306, Found 452.3306.

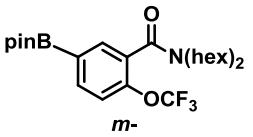
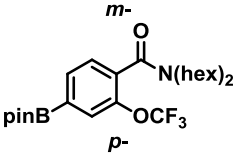


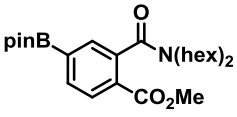
2-Bromo-*N*,*N*-dihexyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benz amide (6d). 91% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 0.80 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.07-1.10 (m, 4H), 1.16-1.20 (m, 2H), 1.32-1.34 (m, 16H), 1.45-1.59 (m, 4H), 1.66-1.68 (m, 2H), 3.01-3.08 (m, 2H), 3.22-3.29 (m, 1H), 3.66-3.73 (m, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.67 (d, *J* = 1.4 Hz, 1H), (*para* isomer) 0.80 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.07-1.10 (m, 4H), 1.16-1.20 (m, 2H), 1.32-1.34 (m, 16H), 1.45-1.59 (m, 4H), 1.66-1.68 (brs, 2H), 3.01-3.08 (m, 2H), 3.22-3.29 (m, 1H), 3.66-3.73 (m, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (*meta* isomer) 14.0, 14.2, 22.4, 22.7, 24.8 (br), 26.2, 26.9, 27.3, 28.3, 31.3, 31.7, 44.6, 48.3, 84.2, 122.8, 132.1, 134.2, 135.9, 138.4, 168.9, (*para* isomer) 14.0, 14.2, 22.5, 22.7, 24.9 (br), 26.3, 26.9, 27.2, 28.3, 31.2, 31.7, 44.7, 48.5, 84.4, 119.1, 127.3, 133.6, 138.7, 141.3, 168.8; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.0; IR (neat, ν / cm^{-1}) 2929, 1640, 1590, 1355, 1144, 1094, 964, 839, 754, 688; HRMS (ESI^+) Calcd for $C_{25}H_{41}BBrNNaO_3$ ($[M+Na]^+$) 516.2255, Found 516.2245.



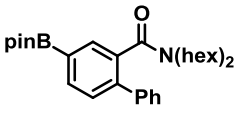
2-Chloro-*N*,*N*-dihexyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benz amide (6e). 84% yield; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 0.80 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.08-1.19 (m, 6H), 1.25-1.61 (m, 20H), 1.63-1.69 (m, 2H), 2.98-3.12 (m, 2H), 3.28-3.34 (m, 1H), 3.64-3.70 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), (*para* isomer) 0.81 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.5 Hz, 3H), 1.07-1.20 (m, 6H), 1.25-1.51 (m, 20H), 1.65-1.67 (m, 2H), 2.98-3.12 (m, 2H), 3.19-3.26 (m, 1H), 3.71-3.79 (m, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*meta* isomer) 14.1, 14.2, 22.5, 22.8, 24.8, 26.3, 26.9, 27.4, 28.4, 31.3, 31.8, 44.7, 48.5, 84.3, 129.0, 133.5, 134.3, 136.0, 136.4, 168.2, (*para* isomer) 14.1, 14.2, 22.5, 22.8, 25.0, 26.4, 26.9, 27.3, 28.4, 31.4, 31.8, 44.6, 48.5, 84.3, 127.4, 132.2, 133.1, 135.7, 139.3, 168.1; ^{11}B NMR (130 MHz, $CDCl_3$) δ (*meta* isomer) 32.1, (*para* isomer) 30.2; IR (neat, ν / cm^{-1}) (*meta* isomer) 2929, 2857, 1645, 1507, 1456, 1387, 1144, 1095, 963, 732, (*para* isomer) 2929, 2857, 1644, 1498, 1456, 1355, 1143, 1096, 1047, 686; HRMS (ESI^+) Calcd for $C_{25}H_{41}BClNNaO_3$ ($[M+Na]^+$) 472.2760, Found 472.2764.

***N*,*N*-Dihexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzamide (6f).**  93% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.07-1.22 (m, 6H), 1.33-1.49 (m, 20H), 1.64-1.65 (m, 2H), 2.88-3.04 (m, 2H), 3.13-3.23 (m, 1H), 3.69-3.79 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.75 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.4, 22.7, 24.9, 26.2, 26.8, 27.0, 28.0, 31.3, 31.7, 44.5, 48.8, 84.5, 123.8 (q, *J* = 275 Hz), 125.6 (q, *J* = 4.8 Hz), 127.1, 128.7 (q, *J* = 31.2 Hz), 133.8, 134.9, 168.6; ^{19}F NMR (368 MHz, $CDCl_3$) δ -62.0; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.5; IR (neat, ν / cm^{-1}) 2930, 2859, 1644, 1505, 1467, 1312, 1102, 1041, 844, 690; HRMS (ESI^+) Calcd for $C_{26}H_{41}BF_3NNaO_3$ ($[M+Na]^+$) 506.3024, Found 506.3018.

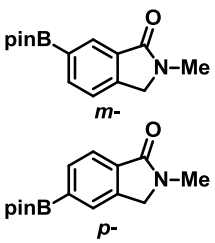
***N*,*N*-Dihexyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)benzamide (6g).**   92% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 0.80 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.7 Hz, 3H), 1.08-1.09 (m, 4H), 1.17-1.20 (m, 2H), 1.32-1.45 (m, 20H), 1.62-1.67 (m, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 3.19-3.26 (m, 1H), 3.72-3.76 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.75 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), (*para* isomer) 0.80 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.7 Hz, 3H), 1.08-1.09 (m, 4H), 1.17-1.20 (m, 2H), 1.32-1.45 (m, 20H), 1.62-1.67 (m, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 3.19-3.26 (m, 1H), 3.72-3.76 (m, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.67 (s, 1H), 7.73 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*meta* isomer) 13.9, 14.1, 22.4, 22.6, 24.9, 26.2, 26.7, 27.2, 28.3, 31.2, 31.7, 44.4, 48.4, 84.3, 118.6 (q, *J* = 1.9 Hz), 123.8 (q, *J* = 258 Hz), 129.8, 135.2, 136.7, 147.1 (q, *J* = 1.9 Hz), 166.8, (*para* isomer) 13.9, 14.1, 22.5, 22.6, 24.8, 26.2, 26.7, 27.2, 28.3, 31.3, 31.7, 44.4, 48.3, 84.4, 123.8 (q, *J* = 258 Hz), 125.9, 127.9, 133.2, 133.3, 144.5 (q, *J* = 1.9 Hz), 166.7; ^{19}F NMR (368 MHz, $CDCl_3$) δ -58.6; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.2; IR (neat, ν / cm^{-1}) 2931, 2859, 1644, 1468, 1359, 1255, 1003, 965, 850, 687; HRMS (ESI^+) Calcd for $C_{26}H_{41}BF_3NNaO_4$ ($[M+Na]^+$) 522.2973, Found 522.2996.

Methyl 2-(dihexylcarbamoyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (6h).  96% yield; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H), 1.05-1.07 (m, 4H), 1.15-1.20 (m, 2H), 1.30-1.47 (m, 20H), 1.69-1.72 (m, 2H), 2.99 (t, *J* = 7.8 Hz, 2H), 3.45-3.49 (m, 2H), 3.86 (s, 3H), 7.70 (d, *J* = 1.0 Hz, 1H), 7.83 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 22.3, 22.7, 24.8, 26.2, 26.9, 27.1, 28.0, 31.2, 31.7, 44.8, 48.8, 52.2, 84.3, 129.1, 129.6, 133.4, 134.5, 138.3, 166.2, 170.6; ^{11}B NMR (130 MHz, $CDCl_3$) δ 29.6; IR (neat, ν / cm^{-1}) 2930, 2858, 1730, 1639,

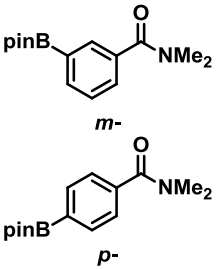
1494, 1359, 1143, 964, 855, 795; HRMS (ESI^+) Calcd for $C_{27}H_{44}BNNaO_5$ ($[M+Na]^+$) 496.3205, Found 496.3186.



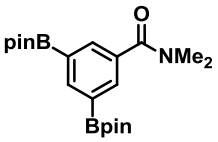
***N*,*N*-Dihexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-carboxamide (6i).** 26% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.92-1.01 (m, 4H), 1.05-1.28 (m, 10H), 1.34 (s, 12H), 1.62-1.66 (m, 2H), 2.48-2.54 (m, 1H), 2.80-2.98 (m, 2H), 3.54-3.61 (m, 1H), 7.30-7.41 (m, 4H), 7.48-7.50 (m, 2H), 7.82 (s, 1H), 7.85 (dd, *J* = 7.9, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 22.5, 22.7, 24.8, 25.1, 26.2, 26.9, 27.9, 31.3, 31.8, 44.4, 48.3, 84.0, 127.8, 128.4, 128.7, 128.9, 134.1, 135.2, 136.0, 140.0, 141.0, 171.1; ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.8; IR (neat, ν / cm^{-1}) 2928, 2857, 1629, 1466, 1387, 1318, 1144, 965, 700, 611; HRMS (ESI^+) Calcd for $C_{31}H_{46}BNNaO_3$ ($[M+Na]^+$) 514.3463, Found 514.3452.



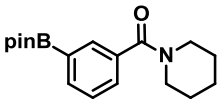
2,3-Dihydro-2-methyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-isoindolin-1-one (6j). 39% yield; pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 1.35 (s, 12H), 3.18 (s, 3H), 4.36 (s, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 8.29 (s, 1H), (*para* isomer) 1.35 (s, 12H), 3.19 (s, 3H), 4.35 (s, 2H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.86 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (*meta* isomer) 24.8, 29.4, 52.1, 84.0, 121.9, 130.1, 132.3, 137.3, 143.8, 168.5, (*para* isomer) 24.9, 29.5, 51.9, 84.2, 122.7, 128.7, 134.3, 135.2, 140.1, 168.6; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.8; IR (KBr, ν / cm^{-1}) 2978, 2932, 1680, 1397, 1355, 1337, 1309, 1258, 1202, 1143, 1115, 967, 863, 849, 714, 655; HRMS (ESI^+) Calcd for $C_{15}H_{20}BNNaO_3$ ($[M+Na]^+$) 296.1434, Found 296.1438.



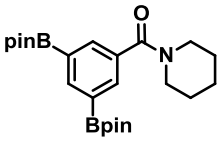
***N*,*N*-Dimethyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6k).** 41% yield; white solid; ^1H NMR (500 MHz, $CDCl_3$) δ (*meta* isomer) 1.34 (s, 12H), 2.96 (s, 3H), 3.10 (s, 3H), 7.40 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.49 (ddd, *J* = 8.1, 1.1, 1.1 Hz, 1H), 7.82-7.84 (m, 2H), (*para* isomer) 1.35 (s, 12H), 2.94 (s, 3H), 3.10 (s, 3H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.83 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*meta* isomer) 25.0, 35.4, 39.7, 84.1, 127.9, 129.8, 133.2, 135.8, 135.9, 171.8, (*para* isomer) 25.0, 35.4, 39.7, 84.1, 126.3, 129.8, 134.8, 171.8; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.6; IR (neat, ν / cm^{-1}) 2978, 1634, 1482, 1356, 1267, 1213, 965, 812, 709, 671; HRMS (ESI^+) Calcd for $C_{15}H_{22}BNNaO_3$ ($[M+Na]^+$) 298.1585, Found 298.1585.

***N*,*N*-Dimethyl-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (7k).** 

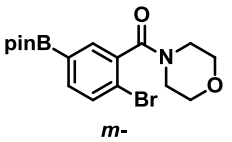
11% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 24H), 2.95 (s, 3H), 3.09 (s, 3H), 7.93 (d, *J* = 1.3 Hz, 2H), 8.28 (t, *J* = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 35.3, 39.8, 84.1, 135.5, 135.9, 142.1, 171.9; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.6; IR (neat, ν / cm^{-1}) 2978, 1636, 1594, 1380, 1330, 1213, 1142, 889, 755, 689; HRMS (ESI^+) Calcd for $C_{21}H_{33}B_2NNaO_5$ ($[M+Na]^+$) 424.2437, Found 424.2455.

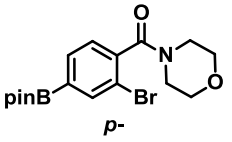
Piperidin-1-yl-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (6l). 

50% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H), 1.48-1.51 (m, 2H), 1.63-1.70 (m, 4H), 3.29-3.37 (m, 2H), 3.67-3.73 (m, 2H), 7.38 (dd, *J* = 7.6, 6.7 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.81-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.0, 25.7, 26.6, 43.1, 48.9, 84.1, 127.8, 129.5, 133.1, 135.7, 136.1, 170.4; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.8; IR (neat, ν / cm^{-1}) 2938, 1714, 1626, 1358, 1271, 1143, 1094, 964, 859, 754, 666; HRMS (ESI^+) Calcd for $C_{18}H_{26}BNNaO_3$ ($[M+Na]^+$) 338.1898, Found 338.1897.

(3,5-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(piperidin-1-yl)methanone (7l). 

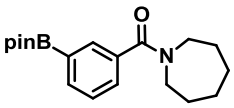
11% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 24H), 1.49-1.65 (m, 6H), 3.32-3.33 (m, 2H), 3.64-3.70 (m, 2H), 7.89 (s, 2H), 8.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.0, 25.7, 26.6, 43.1, 48.9, 84.1, 135.6, 135.8, 142.1, 170.5; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.8; IR (neat, ν / cm^{-1}) 2979, 1624, 1329, 1267, 1142, 966, 889, 755, 716, 666; HRMS (ESI^+) Calcd for $C_{24}H_{37}B_2NNaO_5$ ($[M+Na]^+$) 464.2750, Found 464.2728.

(2-Bromo-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-morpholinylmethanone (6m). 

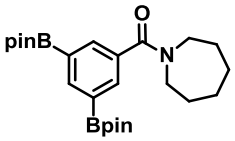
m-


p-
88% yield; pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (*meta* isomer) 1.30 (s, 12H), 3.10-3.29 (m, 2H), 3.50-3.61 (m, 1H), 3.64-3.80 (m, 4H), 3.80-3.89 (m, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), (*para* isomer) 1.28 (s, 12H), 3.10-3.29 (m, 2H), 3.50-3.61 (m, 1H), 3.64-3.80 (m, 4H), 3.80-3.89 (m, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (*meta* isomer) 24.9, 41.8, 47.0, 66.5, 66.6, 84.2, 122.4, 132.0, 133.8, 136.4, 138.7, 167.7, (*para* isomer) 24.5, 41.8, 47.0, 66.5, 66.6, 84.3, 118.8, 127.0, 133.8, 136.9, 139.8, 167.5; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.8; IR (KBr, ν / cm^{-1}) 2977, 2927, 2857, 1645, 1592, 1434, 1386, 1356, 1280, 1248, 1143, 1114, 1094, 1016, 848, 689; HRMS (ESI^+) Calcd for

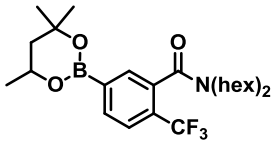
$C_{17}H_{23}BBrNNaO_4$ ([M+Na]$^+$) 418.0801, Found 418.0791.



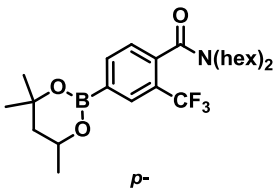
Azepan-1-yl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (6n). 36% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H), 1.59-1.64 (m, 6H), 1.81-1.85 (m, 2H), 3.36 (t, *J* = 5.4 Hz, 2H), 3.67 **(**t, *J* = 5.8 Hz, 2H**)**, 7.38 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.80-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.6, 27.4, 28.0, 29.6, 46.3, 49.9, 84.1, 127.8, 129.2, 132.8, 135.4, 136.9, 171.7; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.6; IR (neat, ν / cm^{-1}) 2977, 2928, 1631, 1409, 1356, 1319, 1216, 1099, 859, 708; HRMS (ESI$^+$) Calcd for $C_{19}H_{28}BNNaO_3$ ([M+Na]$^+$) 352.2054, Found 352.2049.



Azepan-1-yl(3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanone (7n). 12% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 24H), 1.58-1.59 (m, 6H), 1.80-1.86 (m, 2H), 3.36 (t, *J* = 5.4 Hz, 2H), 3.65 **(**t, *J* = 5.4 Hz, 2H**)**, 7.90 (s, 2H), 8.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.7, 27.5, 28.1, 29.6, 46.1, 50.0, 84.1, 135.5, 136.3, 141.8, 171.8; ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.3; IR (neat, ν / cm^{-1}) 2930, 2927, 1628, 1429, 1389, 1270, 1142, 889, 754, 689; HRMS (ESI$^+$) Calcd for $C_{25}H_{39}B_2NNaO_5$ ([M+Na]$^+$) 478.2907, Found 478.2926.



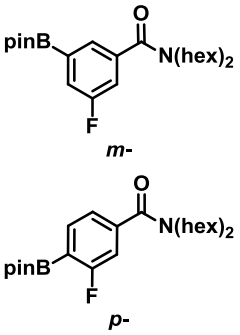
m-



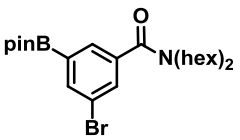
p-

***N*,*N*-dihexyl-2-(trifluoromethyl)-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)benzamide (6o).** 62% yield; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 0.81 (t, *J* = 7.2 Hz, 3H), 0.89-0.92 (m, 3H), 1.08-1.09 (m, 4H), 1.17-1.21 (m, 2H), 1.33-1.47 (m, 18H), 1.61-1.64 (m, 2H), 1.86-1.91 (m, 1H), 2.95-3.00 (m, 2H), 3.12-3.19 (m, 1H), 3.77-3.84 (m, 1H), 4.13-4.37 (m, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.75 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), (*para* isomer) 0.81 (t, *J* = 7.2 Hz, 3H), 0.89-0.92 (m, 3H), 1.08-1.09 (m, 4H), 1.17-1.21 (m, 2H), 1.33-1.47 (m, 18H), 1.61-1.64 (m, 2H), 1.86-1.91 (m, 1H), 2.95-3.00 (m, 2H), 3.12-3.19 (m, 1H), 3.77-3.84 (m, 1H), 4.13-4.37 (m, 1H), 7.26 (d, *J* = 6.7 Hz, 1H), 7.96 (d, *J* = 6.7 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*meta* isomer) 14.0, 14.1, 22.5, 22.7, 23.1, 26.2, 26.4, 26.9, 28.0, 28.2, 31.2, 31.4, 31.7, 44.4, 46.0, 48.7, 65.4, 71.6, 124.0 (q, *J* = 274 Hz), 125.2 (q, *J* = 3.6 Hz), 126.4, 127.6 (q, *J* = 32.3 Hz), 132.9, 133.9, 169.2, (*para* isomer) 14.0, 14.1, 22.4, 22.7, 23.1, 26.2, 26.4, 26.9, 28.0, 28.2, 31.2, 31.3, 31.7, 44.4, 46.0, 48.7, 65.4, 71.6, 124.3 (q, *J* = 296 Hz), 125.7, 127.6 (q, *J* = 32.3 Hz), 131.8 (q, *J* = 4.8 Hz), 134.6, 169.2; ^{19}F NMR (368 MHz, $CDCl_3$) δ (*meta* isomer) -61.9, (*para* isomer) -61.5; ^{11}B NMR (130 MHz, $CDCl_3$) δ 26.2 (*meta* and *para* isomers); IR (neat, ν / cm^{-1}) 2931, 1644, 1502, 1408, 1306, 1170, 1039, 844, 767, 687; HRMS (ESI$^+$) Calcd for

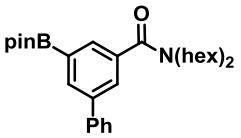
$C_{26}H_{41}BF_3NNaO_3$ ([M+Na]$^+$) 506.3024, Found 506.3013.



3-Fluoro-*N*,*N*-dihexyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benz amide (6p). 99% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 0.82 (t, *J* = 6.7 Hz, 3H), 0.89-0.91 (m, 3H), 1.12-1.17 (m, 4H), 1.21-1.49 (m, 22H), 1.61-1.62 (m, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 3.44 (t, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.55 (s, 1H), (*para* isomer) 0.82 (t, *J* = 6.7 Hz, 3H), 0.89-0.91 (m, 3H), 1.12-1.18 (m, 4H), 1.21-1.49 (m, 22H), 1.61-1.62 (m, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 3.44 (t, *J* = 7.2 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 1H), 7.73-7.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*meta* isomer) 14.0, 14.1, 22.5, 22.7, 24.9, 26.2, 26.8, 27.5, 28.7, 31.3, 31.7, 45.0, 49.1, 84.3, 116.5 (d, *J* = 22.6 Hz), 121.6 (d, *J* = 19.7 Hz), 128.2 (d, *J* = 2.8 Hz), 138.9 (d, *J* = 6.6 Hz), 162.2 (d, *J* = 248 Hz), 170.1, (*para* isomer) 14.0, 14.1, 22.5, 22.7, 24.9, 26.2, 26.8, 27.5, 28.7, 31.3, 31.7, 44.8, 49.0, 84.2, 113.6 (d, *J* = 26.3 Hz), 132.0 (br), 137.1 (d, *J* = 8.4 Hz), 142.4 (d, *J* = 7.5 Hz), 165.4 (d, *J* = 253 Hz), 169.9; ^{19}F NMR (368 MHz, $CDCl_3$) δ (*meta* isomer) -115.3 (s, 1F), (*para* isomer) -103.7 (s, 1F); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.0 (*meta* and *para* isomers); IR (neat, ν / cm^{-1}) 2929, 1633, 1368, 1143, 1099, 968, 923, 854, 756, 676; HRMS (ESI$^+$) Calcd for $C_{25}H_{41}BFNNaO_3$ ([M+Na]$^+$) 456.3056, Found 456.3035.

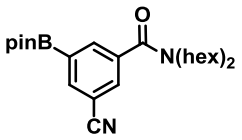


3-Bromo-*N*,*N*-dihexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ben zamide (6q). 86% yield; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.2 Hz, 3H), 0.89-0.91 (m, 3H), 1.12-1.17 (m, 4H), 1.21-1.33 (m, 20H), 1.49-1.63 (m, 4H), 3.13 (t, *J* = 7.6 Hz, 2H), 3.43 (t, *J* = 7.6 Hz, 2H), 7.56 (s, 1H), 7.69 (s, 1H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 22.7, 24.9, 26.2, 26.8, 27.5, 28.7, 31.3, 31.7, 45.0, 49.1, 84.4, 122.4, 131.0, 132.1, 138.0, 138.8, 169.9; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.7; IR (neat, ν / cm^{-1}) 2929, 2857, 1635, 1435, 1348, 1143, 965, 964, 885, 704; HRMS (ESI$^+$) Calcd for $C_{25}H_{41}BBrNNaO_3$ ([M+Na]$^+$) 516.2255, Found 516.2255.

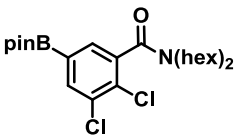


***N*,*N*-Dihexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphe nyl]-3-carboxamide (6r).** 81% yield; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3H), 0.90-0.92 (m, 3H), 1.11-1.19 (m, 6H), 1.23-1.35 (m, 18H), 1.51-1.53 (m, 2H), 1.63-1.66 (m, 2H), 3.20 (t, *J* = 7.6 Hz, 2H), 3.48 (t, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 8.1, 7.4 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.66 (s, 1H), 7.76 (s, 1H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 22.5, 22.8, 25.0, 26.3, 27.0, 27.7, 28.9, 31.4, 31.8, 45.0, 49.3, 84.2, 127.3, 127.6, 128.0, 128.8, 131.6, 134.1, 137.5, 140.6, 140.8, 171.6; ^{11}B NMR (130 MHz, $CDCl_3$) δ 32.5; IR (neat, ν / cm^{-1}) 2929,

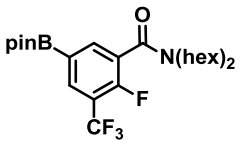
2857, 1634, 1411, 1321, 1144, 966, 894, 756, 698; HRMS (ESI^+) Calcd for $C_{31}H_{46}BNNaO_3$ ($[M+Na]^+$) 514.3463, Found 514.3456.



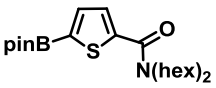
3-Cyano-*N*,*N*-dihexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6s). 87% yield; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3H), 0.88-0.90 (m, 3H), 1.11-1.42 (m, 24H), 1.48-1.52 (m, 2H), 1.65-1.69 (m, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 3.43 (t, *J* = 7.6 Hz, 2H), 7.69 (dd, *J* = 1.6, 1.6 Hz, 1H), 7.97 (dd, *J* = 1.6, 1.4 Hz, 1H), 8.08 (dd, *J* = 1.6, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.4, 22.6, 24.9, 26.2, 26.8, 27.5, 28.7, 31.2, 31.6, 45.1, 49.2, 84.8, 112.4, 118.2, 132.3, 136.6, 137.9, 138.7, 169.2; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.3; IR (neat, ν / cm^{-1}) 2930, 2857, 2231, 1637, 1371, 1265, 1143, 966, 850, 704; HRMS (ESI^+) Calcd for $C_{26}H_{41}BN_2NaO_3$ ($[M+Na]^+$) 463.3102, Found 463.3124.



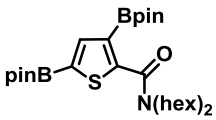
2,3-Dichloro-*N*,*N*-dihexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6t). 94% yield; pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 6.7 Hz, 3H), 1.08-1.11 (m, 4H), 1.18-1.21 (m, 2H), 1.32-1.50 (m, 20H), 1.65-1.70 (m, 2H), 2.98-3.02 (m, 1H), 3.05-3.09 (m, 1H), 3.26-3.31 (m, 1H), 3.64-3.70 (m, 1H), 7.56 (d, *J* = 1.2 Hz, 1H), 7.85 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.4, 22.7, 24.9 (br), 26.2, 26.8, 27.3, 28.3, 31.2, 31.7, 44.7, 48.5, 84.6, 131.6, 131.9, 133.1, 136.3, 138.4, 167.3; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.4; IR (neat, ν / cm^{-1}) 2930, 2858, 1644, 1467, 1350, 1268, 1142, 965, 894, 755; HRMS (ESI^+) Calcd for $C_{25}H_{40}BCl_2NNaO_3$ ($[M+Na]^+$) 506.2371, Found 506.2394.



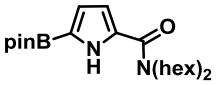
2-Fluoro-*N*,*N*-dihexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzamide (6u). 89% yield; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.7 Hz, 3H), 1.08-1.11 (m, 4H), 1.17-1.22 (m, 2H), 1.33-1.49 (m, 20H), 1.65-1.67 (m, 2H), 3.14 (t, *J* = 7.6 Hz, 2H), 3.40-3.64 (m, 2H), 7.94 (d, *J* = 6.3 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 22.4, 22.6, 24.9, 26.1, 26.7, 27.4, 28.4, 31.2, 31.7, 44.9, 48.8, 84.7, 118.4 (qd, *J* = 33.6, 12.0 Hz), 122.5 (q, *J* = 272 Hz), 126.6 (d, *J* = 18.0 Hz), 134.1 (d, *J* = 3.6 Hz), 139.2 (d, *J* = 4.8 Hz), 157.3 (d, *J* = 260 Hz), 165.0; ^{19}F NMR (368 MHz, $CDCl_3$) δ -115.4 (s, 1F), -63.1 (s, 3F); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.1; IR (neat, ν / cm^{-1}) 2931, 1644, 1468, 1385, 1302, 1239, 1197, 914, 756, 672; HRMS (ESI^+) Calcd for $C_{26}H_{40}BF_4NNaO_3$ ($[M+Na]^+$) 524.2930, Found 524.2939.

***N*,*N*-Dihexyl-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene)carboxamide (6v).** 

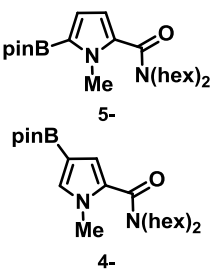
51% yield; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80-0.92 (m, 6H), 1.16-1.38 (m, 12H), 1.33 (s, 12H), 1.53-1.70 (m, 4H), 3.38-3.44 (m, 4H), 7.30 (d, *J* = 3.6 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 22.5, 24.7 (2C), 26.4 (br, 2C), 27.5 (br), 28.8 (br), 31.4 (2C), 46.1 (br), 49.3 (br), 84.3, 129.1, 136.3, 144.2, 164.3; ^{11}B NMR (130 MHz, $CDCl_3$) δ 29.0; IR (neat, ν / cm^{-1}) 2956, 2929, 2862, 1625, 1525, 1463, 1419, 1372, 1350, 1287, 1270, 1210, 1143, 1063, 1021, 997, 857, 853, 820, 739, 687, 667; HRMS (ESI$^+$) Calcd for $C_{23}H_{40}BNNaO_3S$ ([M+Na]$^+$) 444.2720, Found 444.2731.

***N*,*N*-Dihexyl-2-(3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene)carboxamide (7v).** 

14% yield; pale brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75-0.96 (m, 6H), 1.03-1.53 (m, 40H), 3.05-3.22 (m, 2H), 3.35-3.55 (m, 2H), 7.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.97, 14.03, 22.4, 22.6, 24.7, 24.8, 26.2, 26.9, 27.0, 28.3, 31.3, 31.7, 45.2, 49.0, 83.6, 84.2, 143.1, 153.2, 165.5; ^{11}B NMR (130 MHz, $CDCl_3$) δ 28.6; IR (neat, ν / cm^{-1}) 3424, 2929, 2859, 1633, 1536, 1455, 1371, 1321, 1268, 1213, 1139, 1111, 1028, 1002, 967, 911, 882, 851, 829, 727, 688, 666; HRMS (ESI$^+$) Calcd for $C_{29}H_{51}B_2NNaO_5S$ ([M+Na]$^+$) 570.3572, Found 570.3551.

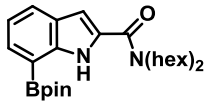
***N*,*N*-Dihexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrol-2-carboxamide (6w).** 

79% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81-0.93 (m, 6H), 1.23-1.36 (m, 24H), 1.53-1.78 (m, 4H), 3.25-3.70 (m, 4H), 6.43-6.70 (m, 1H), 6.74-6.78 (m, 1H), 9.85 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 22.5, 24.7 (2C), 26.6 (2C), 27.6 (br), 28.8 (br), 31.5 (2C), 47.2 (br), 48.5 (br), 83.8, 111.6, 120.2, 129.2, 161.5; ^{11}B NMR (130 MHz, $CDCl_3$) δ 28.3; IR (neat, ν / cm^{-1}) 3441, 3256, 2929, 2858, 1610, 1553, 1467, 1424, 1345, 1300, 1265, 1219, 1144, 973, 855, 790, 759, 704; HRMS (ESI$^+$) Calcd for $C_{23}H_{41}BN_2NaO_3$ ([M+Na]$^+$) 427.3108, Found 427.3114.

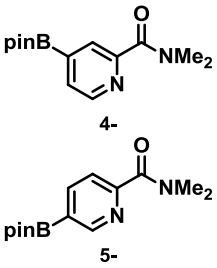
***N*,*N*-Dihexyl-(1-methyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)1*H*-pyrrol)-2-carboxamide (6x).** 

74% yield; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (5-position isomer) 0.78-0.94 (m, 6H), 1.10-1.40 (m, 24H), 1.42-1.75 (m, 4H), 3.26-3.54 (m, 4H), 3.82 (s, 3H), 6.20 (d, *J* = 4.0 Hz, 1H), 6.70 (d, *J* = 4.0 Hz, 1H), (4-position isomer) 0.78-0.94 (m, 6H), 1.10-1.40 (m,

24H), 1.42-1.75 (m, 4H), 3.26-3.54 (m, 4H), 3.71 (s, 3H), 6.56-6.60 (m, 1H), 7.04-7.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (5-position isomer) 13.9 (2C), 22.5 (2C), 24.7, 26.4 (br, 2C), 27.5 (br), 28.6 (br), 31.4 (2C), 34.6, 44.6 (br), 48.9 (br), 83.2, 109.7, 120.2, 132.5, 164.5, (4-position isomer) 13.9 (2C), 22.5 (2C), 24.7, 26.4 (2C), 27.5 (br), 28.6 (br), 31.4 (2C), 35.6, 44.6 (br), 48.9 (br), 82.9, 117.0, 127.6, 134.0, 164.0; ^{11}B NMR (130 MHz, $CDCl_3$) δ 28.3; IR (neat, ν / cm^{-1}) 2929, 2858, 1628, 1531, 1467, 1416, 1373, 1302, 1265, 1145, 1108, 1091, 965, 858, 754, 692; HRMS (ESI^+) Calcd for $C_{24}H_{43}BN_2NaO_3$ ($[M+Na]^+$) 441.3264, Found 441.3255.

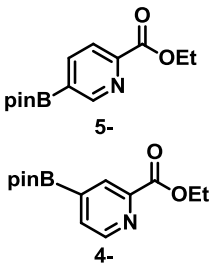


***N*,*N*-Dihexyl-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)1*H*-indole)-2-carboxamide (6y).** 71% yield; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87-0.96 (m, 6H), 1.30-1.41 (m, 12H), 1.39 (s, 12H), 1.60-1.85 (m, 4H), 3.30-3.90 (m, 4H), 6.75 (d, *J* = 2.3 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 9.94 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 22.5 (2C), 24.9, 26.6 (br, 2C), 27.6 (br), 28.8 (br), 31.5 (2C), 47.4 (br), 49.0 (br), 83.9, 103.9, 119.9, 125.3, 126.9, 129.9, 131.7, 140.0, 162.5; ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.2; IR (neat, ν / cm^{-1}) 3438, 3056, 2927, 2857, 1615, 1595, 1529, 1463, 1443, 1369, 1288, 1200, 1146, 1130, 1110, 1045, 979, 849, 813, 748, 734, 678; HRMS (ESI^+) Calcd for $C_{27}H_{43}BN_2NaO_3$ ($[M+Na]^+$) 477.3264 Found 477.3264.

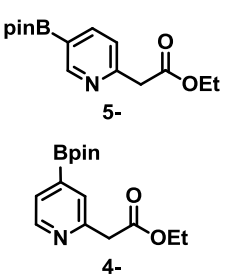


***N*,*N*-Dimethyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide (6z).** 43% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (4-position isomer) 1.34 (s, 12H), 3.04 (s, 3H), 3.13 (s, 3H), 7.65 (d, *J* = 5.8 Hz, 1H), 7.96 (s, 1H), 8.60 (d, *J* = 5.8 Hz, 1H), (5-position isomer) 1.36 (s, 12H), 3.04 (s, 3H), 3.13 (s, 3H), 7.58 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (4- and 5-position isomers) 25.0 (4- and 5-position isomers), 35.71, 35.76, 39.0, 39.1, 84.6, 84.8, 122.7, 128.5, 129.3, 143.4, 147.9, 154.07, 154.13, 156.5, 169.4 (4- and 5-position isomers); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.6; IR (neat, ν / cm^{-1}) 2979 1640, 1473, 1358, 1263, 1105, 965, 857, 752, 672; HRMS (ESI^+) Calcd for $C_{14}H_{21}BN_2NaO_3$ ($[M+Na]^+$) 299.1537, Found 299.1534.

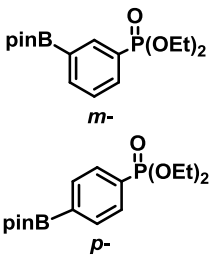
Ethyl (4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxylate (6aa). 70% yield; pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (5-position isomer) 1.32 (s, 12H), 1.41 (t, *J* = 6.9 Hz, 3H), 4.45 (q, *J* = 6.9 Hz, 2H), 8.06 (d, *J* = 8.2 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 9.01 (s, 1H), (4-position isomer) 1.22 (s, 12H), 1.42 (t, *J* = 6.9 Hz, 3H), 4.45 (q, *J* = 6.9 Hz, 2H), 7.77 (d, *J* = 4.6 Hz, 1H), 8.42 (s, 1H), 8.74 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (5-position isomer) 14.3, 24.8, 61.9, 84.5, 124.0, 143.3, 149.8, 155.3, 165.3, (4-position isomer) 14.3, 24.9, 61.8, 84.8, 130.0, 131.9, 147.5, 149.2, 149.8, 165.3; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.5; IR (KBr, ν / cm^{-1}) 2979, 2936, 1715, 1597, 1559, 1483, 1394, 1375, 1362, 1305, 1292, 1230, 1143, 1130, 1116, 1092, 1019, 963, 858, 715, 665; HRMS (ESI^+) Calcd for $C_{14}H_{20}BNNaO_4$ ($[M+Na]^+$) 300.1383, Found 300.1378.



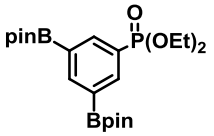
2-Ethoxycarbonylmethyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (6bb). 68% yield; pale brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (5-position isomer) 1.18-1.25 (m, 3H), 1.32 (s, 12 H), 3.83 (s, 2H), 4.10-4.20 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.86 (s, 1H), (4-position isomer) 1.18-1.25 (m, 3H), 1.32 (s, 12 H), 3.82 (s, 2H), 4.10-4.20 (m, 2H), 7.50 (d, *J* = 4.6 Hz, 1H), 7.60 (s, 1H), 8.56 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (5-position isomer) 14.1, 24.7, 44.1, 61.0, 84.1, 123.1, 142.9, 155.2, 156.8, 170.4, (4-position isomer) 14.1, 24.8, 43.8, 60.9, 84.4, 127.0, 128.9, 148.9, 153.8, 170.7; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.9; IR (neat, ν / cm^{-1}) 2980, 2934, 1739, 1600, 1557, 1480, 1403, 1371, 1258, 1166, 1145, 1099, 1028, 964, 856, 668; HRMS (ESI^+) Calcd for $C_{15}H_{22}BNNaO_4$ ($[M+Na]^+$) 314.1540, Found 314.1539.



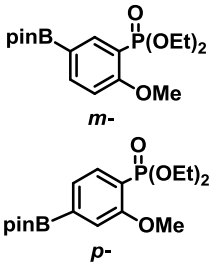
Diethyl (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylphosphonate (6cc). 41% yield; colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*meta* isomer) 1.30 (t, *J* = 7.2 Hz, 6H), 1.32 (s, 12H), 3.98-4.18 (m, 4H), 7.44 (ddd, *J* = 7.6, 7.6, 4.0 Hz, 1H), 7.88 (ddd, *J* = 13.0, 7.6, 1.3 Hz, 1H), 7.95 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.24 (d, *J* = 13.0 Hz, 1H), (*para* isomer) 1.30 (t, *J* = 7.2 Hz, 6H), 1.32 (s, 12H), 3.98-4.18 (m, 4H), 7.78 (dd, *J* = 13.0, 8.0 Hz, 2H), 7.88 (dd, *J* = 8.0, 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*meta* isomer) 16.3 (d, $J_{C\text{-}P}$ = 6.6 Hz), 24.8, 62.0 (d, $J_{C\text{-}P}$ = 5.8 Hz), 84.0, 127.6 (d, $J_{C\text{-}P}$ = 187 Hz), 127.7 (d, $J_{C\text{-}P}$ = 15.0 Hz), 134.3 (d, $J_{C\text{-}P}$ = 10.3 Hz), 138.0 (d, $J_{C\text{-}P}$ = 9.4 Hz), 138.6 (d, $J_{C\text{-}P}$ = 2.8 Hz), (*para* isomer) 16.3 (d, $J_{C\text{-}P}$ = 6.6 Hz), 24.8, 62.0 (d, $J_{C\text{-}P}$ = 5.8 Hz), 84.0, 130.9 (d, $J_{C\text{-}P}$ = 185 Hz), 130.8 (d, $J_{C\text{-}P}$ = 9.4 Hz), 134.5 (d, $J_{C\text{-}P}$ = 15.0 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.7; ^{31}P NMR (158 MHz, $CDCl_3$) δ 28.5, 28.1; IR (KBr, ν / cm^{-1}) 2980, 1599,



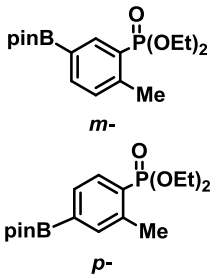
1481, 1408, 1390, 1358, 1324, 1243, 1211, 1133, 1136, 1097, 1055, 1027, 965, 869, 843, 795, 767, 704, 669; HRMS (ESI$^+$) Calcd for $C_{16}H_{26}BO_5P$ ([M+Na]$^+$) 363.1509, Found 363.1498.

Diethyl (3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (7cc). 

16% yield; colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 6H), 1.33 (s, 24H), 3.99-4.20 (m, 4H), 8.32 (dd, J = 13.0, 1.4 Hz, 1H), 8.40 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (d, $J_{C\text{-}P}$ = 6.6 Hz), 24.8, 62.0 (d, $J_{C\text{-}P}$ = 5.6 Hz), 84.0, 127.0 (d, $J_{C\text{-}P}$ = 187 Hz), 140.7 (d, $J_{C\text{-}P}$ = 10.3 Hz), 144.9 (d, $J_{C\text{-}P}$ = 1.9 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.0; ^{31}P NMR (158 MHz, $CDCl_3$) δ 30.4; IR (KBr, ν / cm^{-1}) 2977, 1597, 1389, 1331, 1318, 1272, 1248, 1214, 1168, 1141, 1048, 1019, 964, 952, 886, 848, 790, 718, 691, 662; HRMS (ESI$^+$) Calcd for $C_{22}H_{37}B_2NaO_7P$ ([M+Na]$^+$) 489.2361, Found 489.2364.

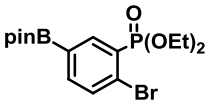
Diethyl (2-methoxy-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (6dd). 

59% yield; pale brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (*meta* isomer) 1.15-1.45 (m, 18H), 3.88 (s, 3H), 4.00-4.25 (m, 4H), 6.85-6.92 (m, 1H), 7.91 (d, J = 8.6 Hz, 1H), 8.24 (d, J = 14.9 Hz, 1H), (*para* isomer) 1.15-1.45 (m, 18H), 3.91 (s, 3H), 4.00-4.25 (m, 4H), 7.31 (d, J = 6.3 Hz, 1H), 7.41 (dd, J = 7.5, 3.4 Hz, 1H), 7.78 (dd, J = 14.3, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (*meta* isomer) 16.3, 24.8, 55.6, 62.0 (d, $J_{C\text{-}P}$ = 4.8 Hz), 83.7, 110.3 (d, $J_{C\text{-}P}$ = 8.4 Hz), 115.8 (d, $J_{C\text{-}P}$ = 186 Hz), 141.1, 142.0 (d, $J_{C\text{-}P}$ = 7.2 Hz), 163.5 (d, $J_{C\text{-}P}$ = 2.4 Hz), (*para* isomer) 16.2, 24.8, 55.8, 62.1 (d, $J_{C\text{-}P}$ = 6.0 Hz), 84.1, 116.5 (d, $J_{C\text{-}P}$ = 8.4 Hz), 119.0 (d, $J_{C\text{-}P}$ = 185 Hz), 126.5 (d, $J_{C\text{-}P}$ = 14.4 Hz), 134.2 (d, $J_{C\text{-}P}$ = 7.2 Hz), 160.5 (d, $J_{C\text{-}P}$ = 2.4 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.7; ^{31}P NMR (158 MHz, $CDCl_3$) δ 28.1, 28.5; IR (neat, ν / cm^{-1}) 2979, 2935, 2909, 1597, 1550, 1492, 1462, 1393, 1357, 1325, 1244, 1164, 1146, 1108, 1078, 1055, 1029, 965, 903, 851, 777, 760, 692, 675; HRMS (ESI$^+$) Calcd for $C_{17}H_{28}BNaO_6P$ ([M+Na]$^+$) 393.1614, Found 393.1599.

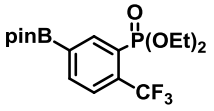
Diethyl (2-methyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (6ee). 

66% yield; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (*meta* isomer) 1.23-1.38 (m, 18H), 2.56 (s, 3H), 4.01-4.18 (m, 4H), 7.24 (dd, J = 7.5, 5.2 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 8.33 (d, J = 14.4 Hz, 1H), (*para* isomer) 1.23-1.38 (m, 18H), 2.56 (s, 3H), 4.00-4.17 (m, 4H), 7.65-7.70 (m, 2H), 7.88 (dd, J = 14.3, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*meta* isomer) 16.2 (d, $J_{C\text{-}P}$ = 6.1 Hz), 21.4 (d, $J_{C\text{-}P}$ = 3.3 Hz), 24.8, 61.7 (d, $J_{C\text{-}P}$ = 5.6 Hz), 83.8, 126.2 (d, $J_{C\text{-}P}$ = 183

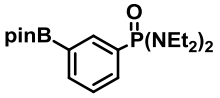
Hz), 130.5 (d, $J_{C\text{-}P}$ = 14.1 Hz), 138.6 (d, $J_{C\text{-}P}$ = 2.8 Hz), 140.4 (d, $J_{C\text{-}P}$ = 10.3 Hz), 144.8 (d, $J_{C\text{-}P}$ = 10.3 Hz), (*para* isomer) 16.2 (d, $J_{C\text{-}P}$ = 6.6 Hz), 20.9 (d, $J_{C\text{-}P}$ = 2.8 Hz), 24.8, 61.7 (d, $J_{C\text{-}P}$ = 5.6 Hz), 84.0, 129.4 (d, $J_{C\text{-}P}$ = 181 Hz), 131.5 (d, $J_{C\text{-}P}$ = 14.4 Hz), 133.0 (d, $J_{C\text{-}P}$ = 10.8 Hz), 137.2 (d, $J_{C\text{-}P}$ = 14.4 Hz), 140.7 (d, $J_{C\text{-}P}$ = 10.8 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.9; ^{31}P NMR (158 MHz, $CDCl_3$) δ 30.7, 30.2; IR (neat, ν / cm^{-1}) 2979, 2931, 2906, 1603, 1480, 1445, 1386, 1360, 1317, 1248, 1165, 1147, 1109, 1049, 1023, 963, 851, 795, 728, 674; HRMS (ESI^+) Calcd for $C_{17}H_{28}BNaO_5P$ ($[M+Na]^+$) 377.1665, Found 337.1666.

Diethyl (2-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (6ff). 

65% yield; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 12H), 1.32 (t, *J* = 7.2 Hz, 6H), 4.02-4.22 (m, 4H), 7.63 (dd, *J* = 8.1, 4.9 Hz, 1H), 7.73 (dd, *J* = 8.1, 1.3 Hz, 1H), 8.41 (d, *J* = 13.9, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2 (d, $J_{C\text{-}P}$ = 7.2 Hz), 24.8, 62.4 (d, $J_{C\text{-}P}$ = 4.8 Hz), 84.2, 128.6 (d, $J_{C\text{-}P}$ = 4.8 Hz), 128.7 (d, $J_{C\text{-}P}$ = 191 Hz), 133.6 (d, $J_{C\text{-}P}$ = 9.6 Hz), 139.5 (d, $J_{C\text{-}P}$ = 2.4 Hz), 142.6 (d, $J_{C\text{-}P}$ = 8.4 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.9; ^{31}P NMR (158 MHz, $CDCl_3$) δ 26.1; IR (neat, ν / cm^{-1}) 2979, 2932, 2906, 1585, 1552, 1476, 1444, 1373, 1356, 1319, 1262, 1251, 1214, 1166, 1145, 1098, 1054, 1024, 964, 845, 796, 766, 726, 671; HRMS (ESI^+) Calcd for $C_{16}H_{25}BBrNaO_5P$ ($[M+Na]^+$) 441.0614, Found 441.0602.

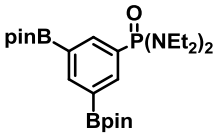
Diethyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-trifluoromethylphenyl)phosphonate (6gg). 

30% yield; pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28-1.40 (m, 18H), 4.07-4.26 (m, 4H), 7.78 (dd, *J* = 8.0, 5.7 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.64 (d, *J* = 14.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (d, $J_{C\text{-}P}$ = 6.6 Hz), 24.8, 62.6 (d, $J_{C\text{-}P}$ = 6.1 Hz), 84.5, 121.9 (qd, $J_{C\text{-}F,\ C\text{-}P}$ = 273, 4.7 Hz), 126.0 (d, $J_{C\text{-}P}$ = 184 Hz), 127.4 (dq, $J_{C\text{-}F,\ C\text{-}P}$ = 6.1 10.8 Hz), 134.3 (qd, $J_{C\text{-}F,\ C\text{-}P}$ = 32.4, 7.5 Hz), 138.6 (d, $J_{C\text{-}P}$ = 2.8 Hz), 142.1 (d, $J_{C\text{-}P}$ = 15.4 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.8; ^{19}F NMR (368 MHz, $CDCl_3$) δ -60.9 (s, 3F); ^{31}P NMR (158 MHz, $CDCl_3$) δ 26.1; IR (KBr, ν / cm^{-1}) 2993, 1377, 1362, 1325, 1308, 1280, 1244, 1148, 1135, 1104, 1059, 1029, 977, 964, 951, 849, 768, 682; HRMS (ESI^+) Calcd for $C_{17}H_{25}BF_3NaO_5P$ ($[M+Na]^+$) 431.1382, Found 431.1379.

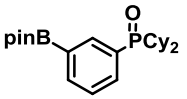
***N*,*N*,*N*',*N*'-Tetraethyl-*P*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonic diamide (6hh).** 

29% yield; pale brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.5 Hz, 12H), 1.33 (s, 12H), 3.00-3.13 (m, 8H), 7.35-7.47 (m, 1H), 7.84 (dd, *J* = 11.5, 7.5 Hz, 1H), 7.88 (d, *J* = 6.9 Hz, 1H), 8.19 (d, *J* = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6 (d, $J_{C\text{-}P}$ = 2.4 Hz), 24.9, 38.4 (d, $J_{C\text{-}P}$ = 4.8 Hz), 83.9, 127.5

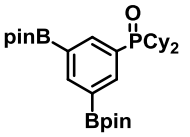
(d, $J_{C\text{-}P}$ = 12.0 Hz), 132.4 (d, $J_{C\text{-}P}$ = 158 Hz), 134.5 (d, $J_{C\text{-}P}$ = 8.4 Hz), 137.2, 138.3 (d, $J_{C\text{-}P}$ = 8.4 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.5; ^{31}P NMR (158 MHz, $CDCl_3$) δ 39.4; IR (neat, ν / cm^{-1}) 2973, 2932, 2871, 1594, 1470, 1383, 1357, 1317, 1262, 1216, 1187, 1015, 945, 866, 841, 791, 739, 711, 671, 656; HRMS (ESI^+) Calcd for $C_{20}H_{37}BN_2O_3P$ ($[M+H]^+$) 395.2635, Found 395.2639.



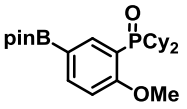
***N*,*N*,*N*',*N*'-Tetraethyl-*P*-(3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonic diamide (7hh).** 9% yield; pale brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, *J* = 6.9 Hz, 12H), 1.31 (s, 24H), 2.98-3.16 (m, 8H), 8.27 (d, *J* = 12.1 Hz, 2H), 8.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6 (d, $J_{C\text{-}P}$ = 2.4 Hz), 24.8, 38.3 (d, $J_{C\text{-}P}$ = 3.6 Hz), 83.8, 131.8 (d, $J_{C\text{-}P}$ = 154 Hz), 141.1 (d, $J_{C\text{-}P}$ = 9.6 Hz), 143.5 (d, $J_{C\text{-}P}$ = 2.4 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.3; ^{31}P NMR (158 MHz, $CDCl_3$) δ 39.5; IR (KBr, ν / cm^{-1}) 2978, 2932, 2873, 1594, 1458, 1383, 1327, 1313, 1272, 1220, 1189, 1163, 1144, 1020, 967, 945, 887, 847, 720, 659; HRMS (ESI^+) Calcd for $C_{26}H_{47}B_2N_2NaO_5P$ ($[M+Na]^+$) 543.3306, Found 543.3312.



Dicyclohexyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphine oxide (6ii). 39% yield; pale brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05-1.37 (m, 21H), 1.50-1.88 (m, 8H), 1.90-2.20 (m, 4H), 2.25-2.46 (m, 1H), 7.40-7.51 (m, 1H), 7.68-7.83 (m, 1H), 7.93 (d, *J* = 6.9 Hz, 1H), 7.98-8.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 24.9, 25.5, 25.8, 26.2-26.5 (m, 2C), 35.2 (d, $J_{C\text{-}P}$ = 66.0 Hz), 84.0, 127.4-127.6 (m), 129.1 (d, $J_{C\text{-}P}$ = 85.2 Hz), 134.1-134.4 (m), 137.2-137.5 (m), 137.6; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.9; ^{31}P NMR (158 MHz, $CDCl_3$) δ 56.7; IR (KBr, ν / cm^{-1}) 2979, 2930, 2853, 1594, 1449, 1404, 1359, 1316, 1273, 1211, 1166, 1145, 1130, 1115, 1077, 963, 891, 853, 840, 759, 731, 709, 671; HRMS (ESI^+) Calcd for $C_{24}H_{38}BNaO_3P$ ($[M+Na]^+$) 439.2549, Found 439.2567.

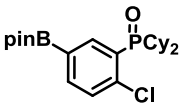


Dicyclohexyl(3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphine oxide (7ii). 35% yield; pale brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08-1.36 (m, 33H), 1.51-1.86 (m, 8H), 1.94-2.13 (m, 4H), 2.23-2.45 (m, 1H), 8.11 (d, *J* = 9.8 Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 24.8, 25.5, 25.8, 26.2-26.5 (m, 2C), 35.3 (d, $J_{C\text{-}P}$ = 67.2 Hz), 84.0, 128.5 (d, $J_{C\text{-}P}$ = 85.2 Hz), 140.2 (d, $J_{C\text{-}P}$ = 7.2 Hz), 144.0; ^{11}B NMR (130 MHz, $CDCl_3$) δ 31.2; ^{31}P NMR (158 MHz, $CDCl_3$) δ 56.4; IR (KBr, ν / cm^{-1}) 2977, 2929, 2853, 1594, 1449, 1383, 1329, 1272, 1215, 1176, 1143, 966, 888, 849, 716; HRMS (ESI^+) Calcd for $C_{30}H_{50}B_2O_5P$ ($[M+H]^+$) 543.3582, Found. 543.3588.



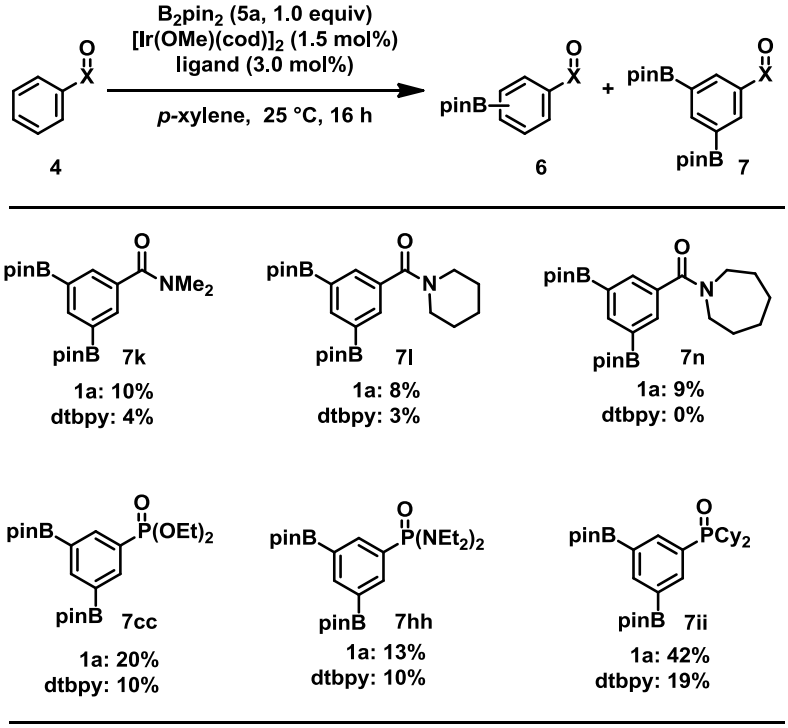
Dicyclohexyl(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphine oxide (6jj). 99% yield; pale yellow solid; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.14-1.19 (m, 4H), 1.21-1.42 (m, 16H), 1.44-1.51 (m, 4H), 1.64-1.68 (m, 4H), 1.80-1.84 (m, 2H), 2.03-2.17 (m, 4H), 3.86 (s, 3H), 6.87 (dd, *J* = 8.7, 4.7 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 8.36 (d, *J* = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.7 (d, $J_{C\text{-}P}$ = 3.8 Hz), 25.9, 26.1 (d, $J_{C\text{-}P}$ = 3.8 Hz), 26.6 (d, $J_{C\text{-}P}$ = 12.3 Hz), 26.9 (d, $J_{C\text{-}P}$ = 14.1 Hz), 36.9 (d, $J_{C\text{-}P}$ = 67.7 Hz), 55.1, 83.7, 109.3 (d, $J_{C\text{-}P}$ = 6.9 Hz), 118.3 (d, $J_{C\text{-}P}$ = 83.8 Hz), 140.1 (d, $J_{C\text{-}P}$ = 1.9 Hz), 142.8 (d, $J_{C\text{-}P}$ = 3.8 Hz), 161.5 (d, $J_{C\text{-}P}$ = 5.6 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 29.8; ^{31}P NMR (158 MHz, $CDCl_3$) δ 59.5; IR (KBr, ν / cm^{-1}) 2978, 2931, 2852, 1594, 1448, 1407, 1385, 1357, 1317, 1279, 1266, 1250, 1212, 1147, 1104, 1077, 1014, 964, 887, 851, 824, 750, 673; HRMS (ESI^+) Calcd for $C_{25}H_{40}BNaO_4P$ ($[M+Na]^+$) 469.2655, Found 469.2668.



Dicyclohexyl(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphine oxide (6kk). 99% yield; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16-1.21 (m, 4H), 1.24-1.36 (m, 18H), 1.59-1.70 (m, 6H), 1.83-1.86 (m, 2H), 2.07-2.10 (m, 2H), 2.27-2.36 (m, 2H), 7.36 (dd, *J* = 7.9, 3.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 8.49 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.7 (d, $J_{C\text{-}P}$ = 1.4 Hz), 26.2 (d, $J_{C\text{-}P}$ = 3.3 Hz), 26.3 (d, $J_{C\text{-}P}$ = 3.8 Hz), 26.5 (d, $J_{C\text{-}P}$ = 12.7 Hz), 26.7 (d, $J_{C\text{-}P}$ = 13.6 Hz), 37.4 (d, $J_{C\text{-}P}$ = 13.6 Hz), 84.2, 129.3 (d, $J_{C\text{-}P}$ = 6.1 Hz), 130.1, 137.3 (d, $J_{C\text{-}P}$ = 6.1 Hz), 138.8 (d, $J_{C\text{-}P}$ = 2.3 Hz), 143.1 (d, $J_{C\text{-}P}$ = 4.7 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.5; ^{31}P NMR (158 MHz, $CDCl_3$) δ 59.4; IR (KBr, ν / cm^{-1}) 2978, 2932, 2852, 1583, 1557, 1448, 1371, 1356, 1317, 1259, 1214, 1183, 1169, 1143, 1113, 1097, 1031, 964, 845, 755, 726, 671; HRMS (ESI^+) Calcd for $C_{24}H_{38}BClO_3P$ ($[M+H]^+$) 451.2340, Found 451.2341.

Summary of yields of di-borylated compounds



Gram-Scale Synthesis

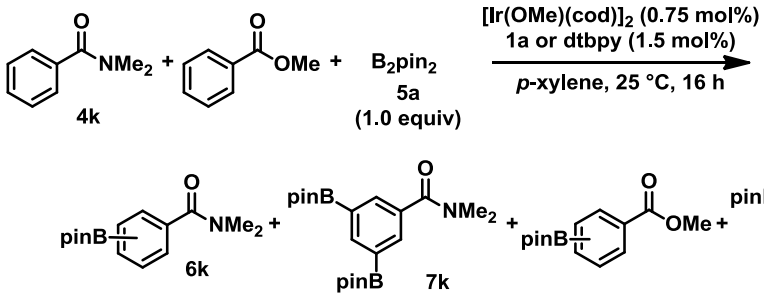
Gram-scale synthesis of 6f. In a round-bottomed flask equiped with a three way cock, a mixture of $[Ir(OMe)(cod)]_2$ (27.8 mg, 42.0 μmol, 1.5 mol%), ligand **1a** (28.8 mg, 84.0 μmol, 3.0 mol%), and **5a** (1.07 g, 4.20 mmol, 1.5 equiv) was added to a solution of **4f** (1.00 g, 2.80 mmol, 1.0 equiv) in *p*-xylene (16.8 mL). The mixture is then stirred at 25 °C for 16 h. The product was isolated by recycling preparative HPLC to give **6f** (1.23 g, 90% yield, *meta*/*para* = >30).

Mechanistic Studies

^{1}H NMR experiments for elucidation of the existence of hydrogen bonding (Figure 4a). A 1/1 mixture of ligand **1a** (0.33 mg, 1.2 μmol) and *N*,*N*-dihexylbenzamide (**4a**, 0.43 mg, 1.2 μmol) in C_6D_6, and a 1/8.7 mixture of the ligand **1a** (0.33 mg, 1.15 μmol) and amide **4a** (2.9 mg, 10 μmol) in C_6D_6 were prepared. The chemical shifts were compared with the same concentration of ligand **1a** in C_6D_6.

Competition reaction between amide 4k and methyl benzoate. In a sealed tube, a mixture of $[Ir(OMe)(cod)]_2$ (1.2 mg, 1.9 μmol, 0.75 mol%) (or dtbpy (1.0 mg, 1.9 μmol, 0.75 mol%)), **1a** (1.4 mg, 3.8 μmol, 1.5 mol%), and **5a** (47.6 mg, 0.188 mmol, 0.750 equiv) was added to a solution of **4a**

(72.4 mg, 0.250 mmol, 1.0 equiv) and methyl benzoate (34.0 mg, 0.250 mmol, 1.0 equiv) in *p*-xylene (1.5 mL). Then, the mixture was stirred at 25 °C for 16 h. The solvent was removed under reduced pressure and the crude mixture was analysed by ^{1}H NMR.



1a	44% [21]	7.7%	15% [1.0]	0%
dtbpy	28% [0.22]	0%	45% [1.0]	2.4%

第 2 章 水素結合を利用した C–H ボリル化反応の反応性の向上研究

2-1 背景

生体内では、水素結合や疎水性相互作用に代表される分子間相互作用により酵素が基質を捕捉することで、触媒活性中心付近の基質濃度を高め、かつ基質を活性化することで、反応性を向上させている。Breslow らは、基質－触媒間の可逆的な疎水性相互作用の形成により、C－H 結合変換反応の反応性が向上することを報告している（Table 2-1）。[63] 本反応では、**A** がもつ二つの水酸基の保護基に含まれる二つの 4-*tert*-ブチルフェニル基が、触媒のポルフィリン骨格の trans 位にある二つのシクロデキストリンにそれぞれ内包されることによって、特定の C－H 結合が触媒中心に接近し、高位置選択的なヒドロキシ化反応が進行している（Table 2-1、下図）。[64] 二つの 4-*tert*-ブチルフェニル基をもつ基質 **A** からは対応するトリオールが 95%の収率で得られるのに対し、*tert*-ブチルフェニル基をもたない基質 **B** を同様の反応条件に付しても酸化反応は進行しない。これより、基質 **A** とシクロデキストリン間の相互作用は、反応性の向上にも寄与していることも示唆される。

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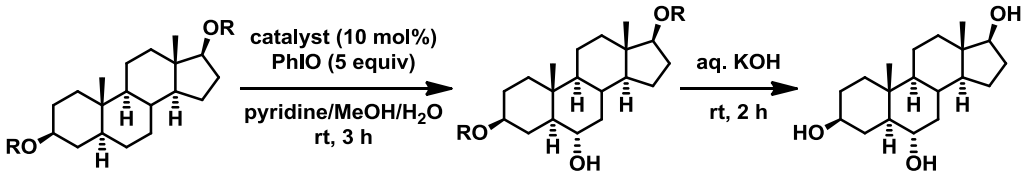
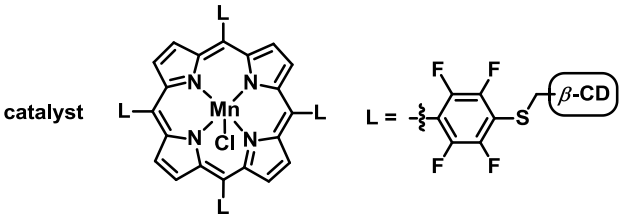
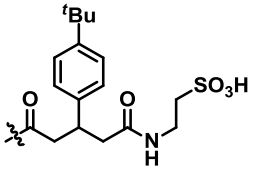
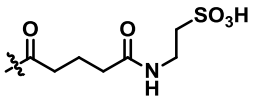
[63] Breslow, R.; Gabriele, B.; Yang, J. *Tetrahedron Lett.* **1998**, *39*, 2887.

[64] *β*－シクロデキストリンは円錐台形をもち、口径の大きい側がより親水性、小さい側が疎水性の性質をもつ。ゆえに、疎水性の *tert*-ブチルフェニル基は小径側からシクロデキストリン内部へと進入する。

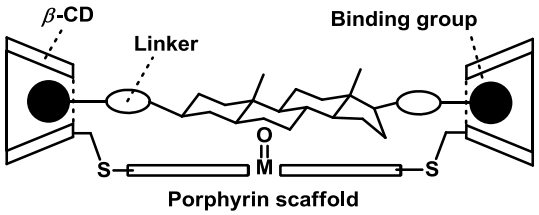
Table 2-1 | Enantio- and site-selective C-H oxidation with β-cyclodextrin (β-CD)





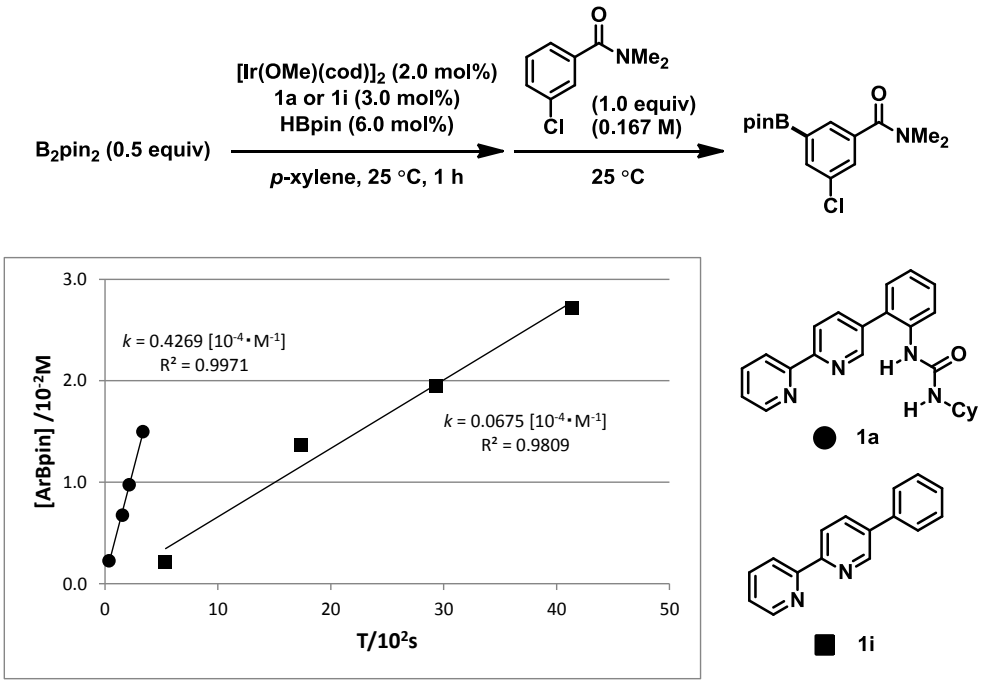
R	A	B
		
Yield (triol, %)	95	0

Proposed structure of intermediate



第 1 章で開発した **1a** もまた、尿素構造を有しないビピリジル配位子 **1i** に比べ、6 倍程度高い反応性を示した（Figure 2-1）。そこで本章では、より高い反応性の触媒を創製するために行った配位子の構造改変について記す。

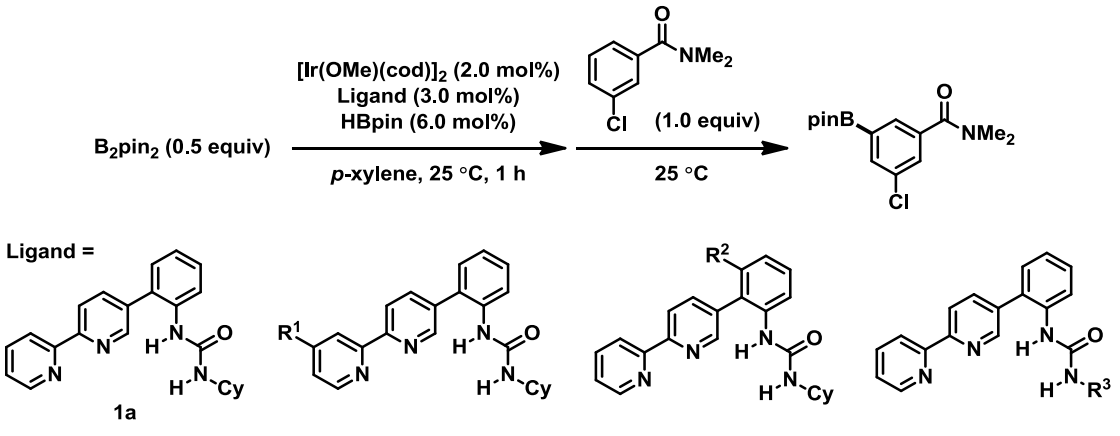
Figure 2-1 | Comparison of reactivity between 1a and 1i



2-2 反応性の向上に向けた触媒構造の改変

ビピリジル部位、リンカー部位および尿素上の置換基がそれぞれ異なる配位子を合成し、ベンズアミドの C−H ボリル化反応の初期段階における反応速度定数を比較することにより、各配位子の反応性を評価した（Scheme 2-2-1）。

Scheme 2-1 | Determination of *k* values of C-H borylation of benzamide using various ligands



ビピリジル部位の検討

イリジウムトリスボリル錯体を用いるC−H ボリル化反応では、C−H 結合の酸化的付加が反応の律速段階であることが知られている（Scheme 2-2）。[17] そこでイリジウム中心の電子密度を高めるべく、末端ピリジル基の 4 位に *tert*-ブチル基を有する **1j** を合成した。**1j** は、**1a** に比較して、2.6 倍の反応速度を示した（Figure 2-2）。

Scheme 2-2 | Mechanism of C-H borylation using Ir-dtbpy complex

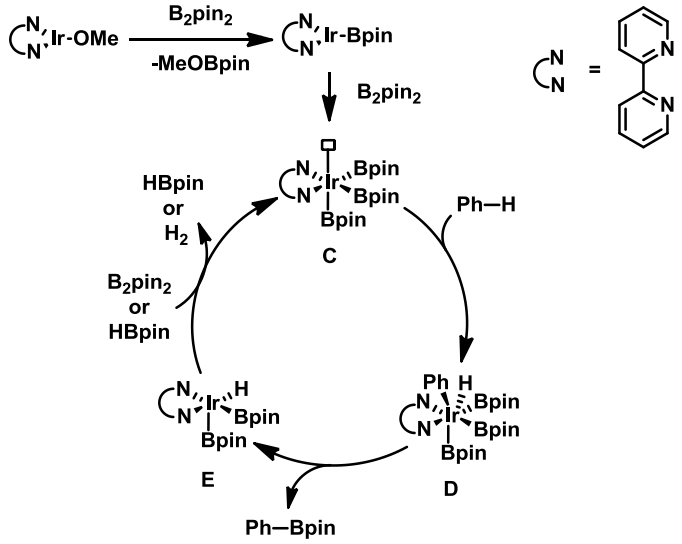
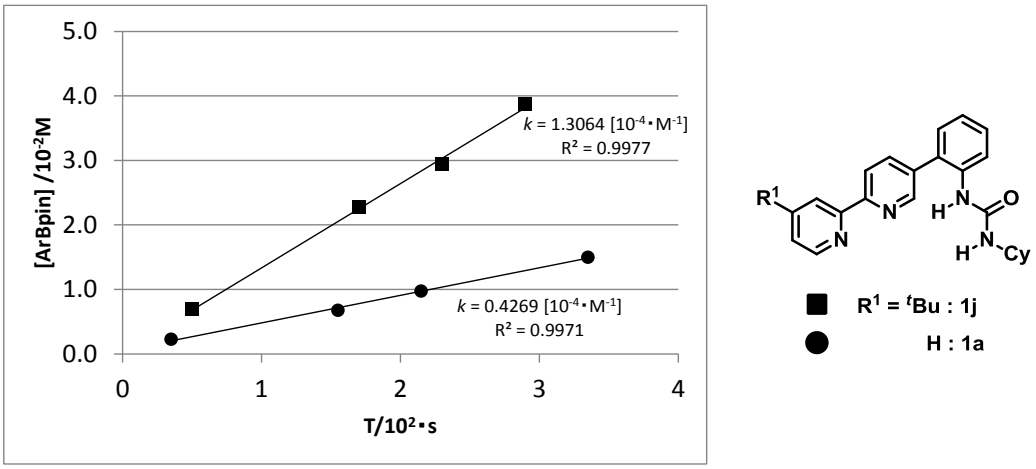


Figure 2-2 | Comparison of reactivity between 1j and 1a



リンカー部位の検討

イリジウムトリスボリル錯体（Scheme 2-2, C）は非常に嵩高いため、尿素部位が基質を捕捉したとしても、イリジウム中心が反応点であるメタ位 C－H 結合に近づきにくいことが考えられる（Figure 2-3、左図）。そこで、リンカーであるフェニレン部位に置換基を導入し、その置換基とイリジウムービピリジル部位の立体反発により、触媒活性部位と反応点の接近効率を高めることを考えた（Figure 2-3、右図）。フェニレン部位にメチル基を導入した配位子 **1k** は配位子 **1a** に比較して、5.1 倍の反応速度定数を示した（Figure 2-4）。

Figure 2-3 | Expectation for introduction of R^2 on linker

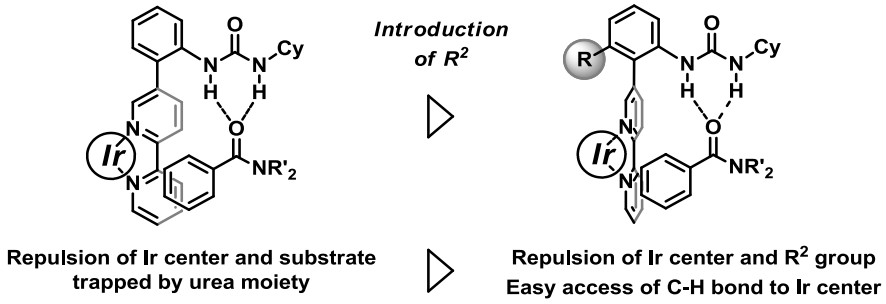
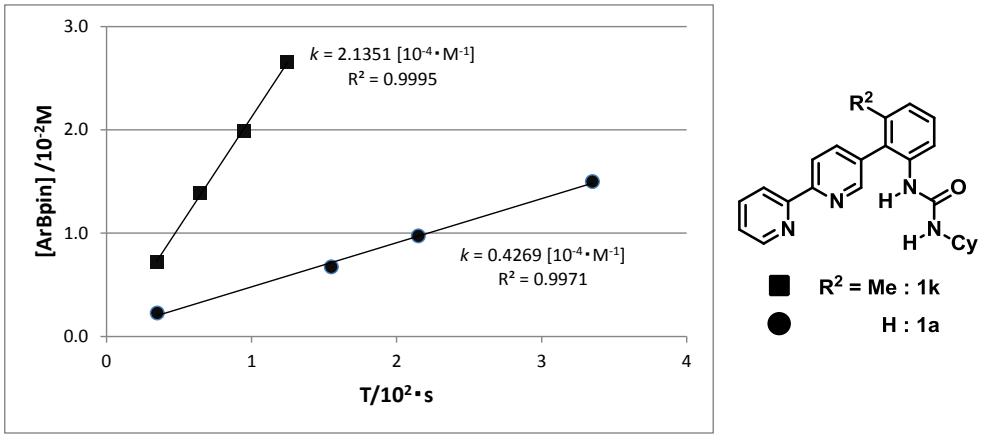


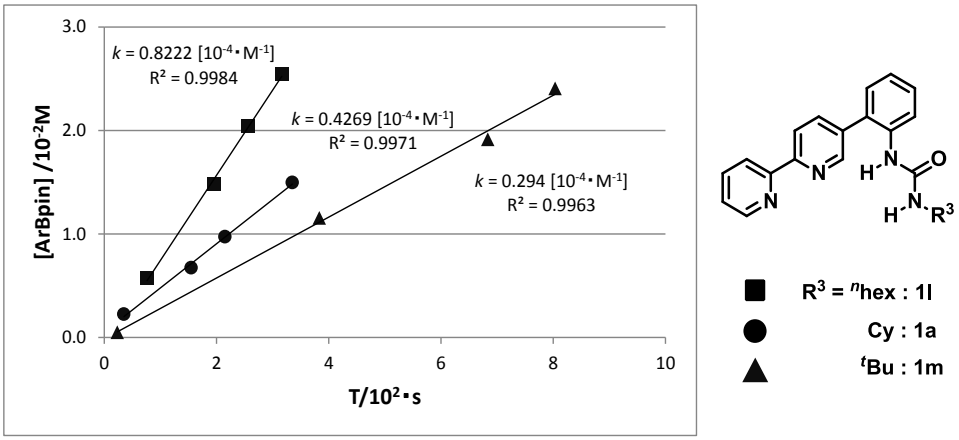
Figure 2-4 | Comparison of reactivity between 1k and 1a



尿素部位の検討

第1章の中でアルキル基がアリール基よりも高い反応性を示すことが分かったため(Table 1-1)、ここでは立体的な嵩高さの異なる一級、二級、および三級アルキル基を検討した。尿素部位の置換基の立体障害が最小の *n*-ヘキシル基をもつ配位子 **1l** の反応速度が最も大きかった（Figure 2-5)。尿素部位の立体障害が小さいと、基質分子とボリル化生成物との交換速度の低下につながり、反応速度が低下してしまう懸念があったが、その効果よりも、水素結合供与能の増大による基質と触媒活性中の接近効率の向上の影響が大きいことが示唆された。

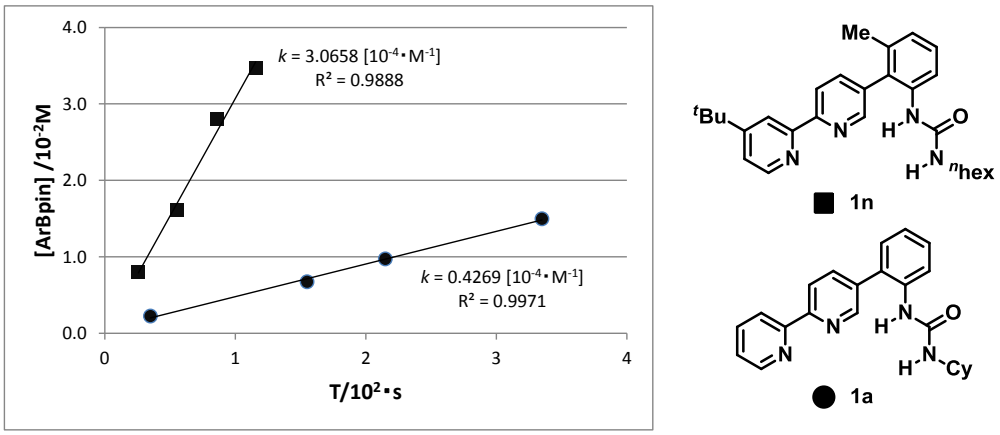
Figure 2-5 | Comparison of reactivity of 1l, 1a and 1m



ビピリジル部位、リンカー部位および尿素部位の置換基の相乗効果の検討

ビピリジル部位に *tert*-ブチル基、リンカー構造にメチル基、尿素部位に *n*-ヘキシル基を有する配位子 **1n** の反応速度を検討したところ、配位子 **1i-1m** のいずれと比べても反応速度が向上し、**1a** に対し 7.2 倍の反応速度を示した（Figure 2-6)。

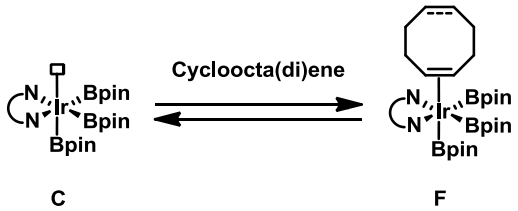
Figure 2-6 | Comparison of reactivity between 1n and 1a



2-3 小括

ビピリジル部位、リンカー部位および尿素上にそれぞれ *tert*-ブチル基、メチル基および *n*-ヘキシル基を導入した配位子 **1n** を新たに設計・合成した。その配位子を C－H ボリル化反応に利用することで、酸化的付加の加速、触媒の立体配座の改善、および分子認識部位の立体障害の軽減により、第 1 章で開発した配位子 **1a** と比較して 7.2 倍、汎用されているビピリジル配位子 dtbpy と比べて 13 倍の反応速度の向上が見られた（dtbpy: $k = 0.2337/10^{-4}$・M^{-1}, $R^2 = 0.9986$）。このことは、生体酵素が水素結合のような非共有結合性相互作用を巧みに利用することで、望みの反応の反応速度を向上させていることに対応する。特に、配位子 **1a** に比べて配位子 **1k** で見られた反応速度の変化、すなわちリンカー部位のメチル基の効果が顕著であったことが興味深い。この原因は以下二つのように考えている：（ⅰ）2-2 項で想定したように、配位子のビピリジル平面とフェニル部位のなす二面角が大きくなることで、イリジウム中心が反応点であるメタ位 C－H 結合に近接しやすくなったから（Figure 2-3）。（ⅱ）二面角の増大の結果、水素結合を介して捕捉したベンズアミド誘導体により、イリジウム周りの立体障害が増大し、その結果、シクロオクタ（ジ）エンの再配位（Scheme 2-3）[17] を抑制することで、**F** の寄与が減じているから。

Scheme 2-3 | Off-passway of 16-electron Ir catalyst

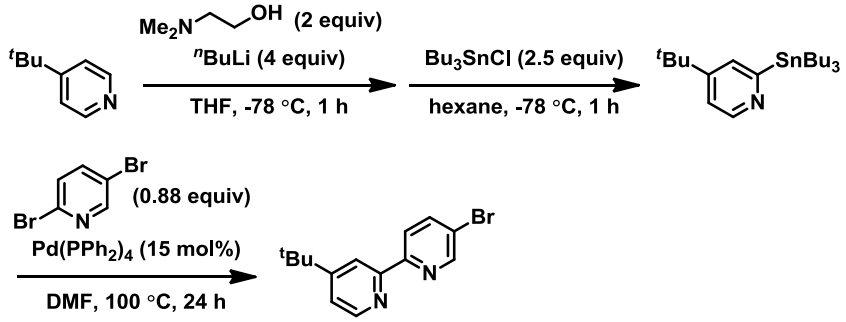


実験項

General.

All reactions were carried out in a dry solvent under an argon atmosphere. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Ligand **1g** were prepared according to the literature methods and identified by comparing the spectroscopic data with those of reported ones.[65] Column chromatography was performed with silica gel (230-400 mesh ASTM). NMR spectra were recorded on 500 MHz (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) and 400 MHz (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and 125 MHz for ^{11}B NMR) spectrometers. Proton and carbon chemical shifts are reported relative to the residual solvent used as an internal reference. Boron chemical shifts are reported relative to $BF_3{\cdot}OEt_2$ (δ 0.00 ppm) as external references. Infrared (IR) spectra were recorded on Fourier transform infrared spectrophotometer. ESI-MS spectra were measured on a spectrometer for HRMS. GC-MS was measured on Shimazu (GCMS-QP2010 Ultra).

Synthesis of 5'-bromo-4-(*tert*-butyl)-2,2'-bipyridine

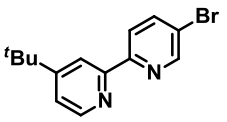


A solution of 2-(dimethylamino)ethanol (39.8 mg, 40 mmol, 2.0 equiv) in hexane (125 mL) was cooled to 0 °C and treated with ^{n}BuLi (2.6 M in hexane, 31μL, 80 mmol, 4.0 equiv) dropwise. After the mixture was kept at 0 °C for 15 min, a solution of 4-*tert*-butylpyridine (3.0 mL, 16 mmol, 1.0 equiv) in hexane (25 mL) was added dropwise. After 1 h at 0 °C, the orange solution was cooled to -78 °C and treated with a solution of tributyltin chloride (13.5 mL, 50.0 mmol, 2.5 equiv) in THF (50 mL). After 1 h at -78 °C, the mixture was warmed to room temperature. Hydrolysis was then performed at 0 °C with H_2O (75 mL). The organic layer was then extracted with diethyl ether (2×80 mL) and dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The crude product was then purified by column chromatography on silica gel (deactivated with 20% Et_3N in hexane; eluent: hexane/EtOAc = 1/3) to give 4-(*tert*-butyl)-2-(tributylstannyl)pyridine including impurities (11.3 g, impurity: ca. 30 wt%).

A mixture of one of 4-(*tert*-butyl)-2-(tributylstannyl)pyridine (5.66 g, including ca. 30 wt% impurities), 2,5-dibromopyridine (2.09 g, 8.80 mmol), and $Pd(PPh_3)_4$ (522 mg, 0.510 mmol) in DMF

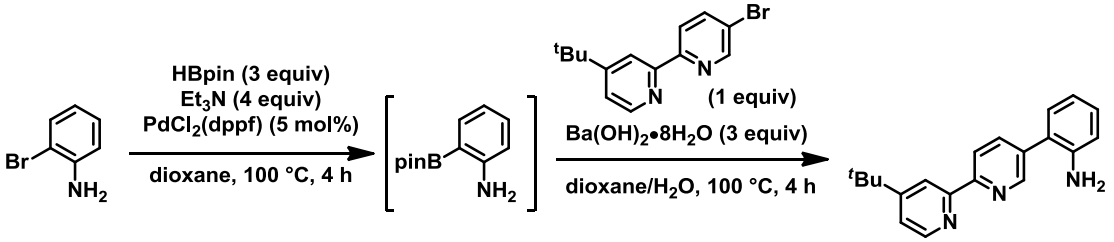
[65] Lützen, A.; Hapke, M. *Eur. J. Org. Chem.* **2002**, 2292.

(30 mL) was 100 °C for 24 h. The solvent was removed, the residue was dissolved in a mixed solvent (hexane/EtOAc = 1/20) and dried with anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The crude product was then purified by column chromatography on silica gel (deactivated with 20% Et_3N in hexane; eluent: hexane/EtOAc = 20/1) to give 5'-bromo-4-(*tert*-butyl)-2,2'-bipyridine as a white solid (1.34 g, 48% yield).

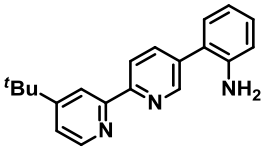


5'-Bromo-4-(*tert*-butyl)-2,2'-bipyridine. 48% yield (2 steps); white solid; R_f = 0.21 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 7.33 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.93 (dd, *J* = 8.5, 2.2 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.40 (d, *J* = 1.9 Hz, 1H), 8.57 (d, *J* = 5.3 Hz, 1H), 8.72 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.7, 35.2, 118.1, 121.0, 121.4, 122.7, 139.6, 149.3, 150.2, 155.2, 155.2, 161.4; IR (KBr, ν / cm^{-1}) 2964, 1597, 1544, 1456, 1364, 1093, 1004, 835, 793, 719; HRMS (ESI^+) Calcd for $C_{14}H_{16}BrN_2$ ($[M+H]^+$) 291.0491, Found 291.0504.

Synthesis of 2-(4'-(*tert*-butyl)-[2,2'-bipyridin]-5-yl)aniline.



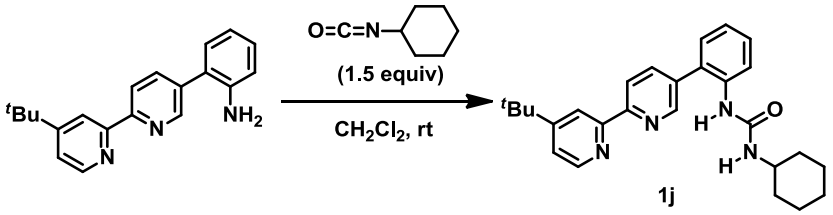
To a solution of 2-bromoaniline (705 mg, 4.1 mmol, 1.0 equiv) in dioxane (10 mL) were added Et_3N (16.2 mg, 16 mmol, 4.0 equiv), $PdCl_2$(dppf) (149 mg, 0.21 mmol), and pinacolborane (1.53 g, 12 mmol, 3.0 equiv) dropwise. The mixture was stirred at 100 °C for 4 h, then cooled to room temperature, and water (1.8 mL), $Ba(OH)_2{\cdot}8H_2O$ (3.88 g, 12.0 mmol, 3.0 equiv), and 5'-bromo-4-(*tert*-butyl)-2,2'-bipyridine (1.19 g, 4.10 mmol, 1.0 equiv) were successively added. The mixture was stirred at 100 °C for 4 h before addition of water (50 mL) at room temperature. The mixture was filtered through Celite. The eluent was extracted with ethyl acetate (3×30 mL), the organic layer was dried over Na_2SO_4, and filtered. The solvent was removed and the residue was purified by column chromatography on silica gel (deactivated with 20% Et_3N in hexane; eluent: hexane/EtOAc = 3/1) to give 2-([2,2'-bipyridin]-5-yl)aniline as a white solid (672 mg, 59% yield).



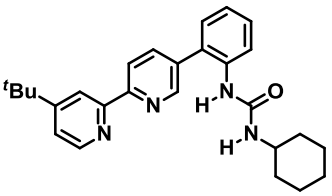
2-(4'-(*tert*-Butyl)-[2,2'-bipyridin]-5-yl)aniline. 30% yield; white solid; R_f = 0.24 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) d 1.41 (s, 9H), 1.95 (brs, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.88 (ddd, *J* = 7.8, 7.4, 1.1 Hz, 1H), 7.15-7.24 (m, 2H), 7.35 (dd, *J* = 5.4, 2.0 Hz, 1H), 7.96 (dd, *J* =

8.1, 2.0 Hz, 1H), 8.47-8.49 (m, 2H), 8.61 (d, *J* = 5.4 Hz, 1H), 8.80 (d, *J* = 2.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.7, 35.1, 116.0, 118.1, 119.0, 121.1, 121.2, 123.7, 129.5, 130.6, 135.1, 137.5, 144.0, 149.3, 149.4, 155.4, 155.8, 161.2; IR (KBr, ν / cm^{-1}) 3328, 2965, 1601, 1462, 1368, 1216, 999, 839, 751, 652; HRMS (ESI^+) Calcd for $C_{20}H_{22}N_3$ ($[M+H]^+$) 304.1808, Found 304.1813.

Synthesis 1-(2-(4'-(*tert*-butyl)-[2,2'-bipyridin]-5-yl)phenyl)-3-cyclohexylurea (1j).

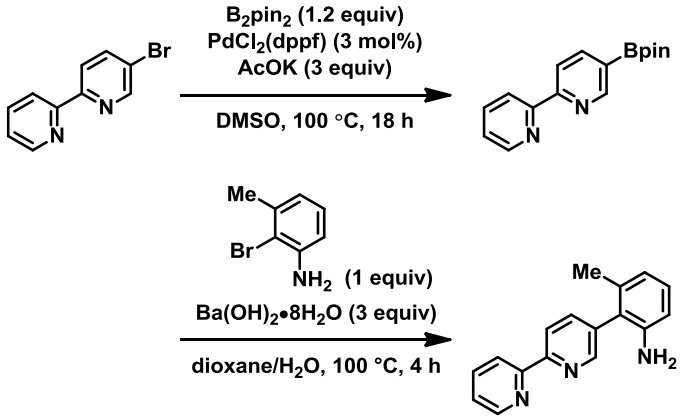


A mixture of 2-(4'-(*tert*-butyl)-[2,2'-bipyridin]-5-yl)aniline (82 mg, 0.27 mmol, 1.0 equiv) and cyclohexylisocyanate (51.3 mg, 0.41 mmol, 1.5 equiv) in dichloromethane (0.90 mL) was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was purified by recrystallization from CH_2Cl_2 and hexane to give **1j** as a white solid (87.6 mg, 76% yield).



1-(2-(4'-(*tert*-Butyl)-[2,2'-bipyridin]-5-yl)phenyl)-3-cyclohexylurea (1j). 60% yield; white solid; R_f = 0.67 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96-1.07 (m, 3H), 1.14-1.32 (m, 3H), 1.36 (s, 9H), 1.59-1.61 (m, 2H), 1.86-1.89 (m, 2H), 3.57-3.59 (m, 1H), 5.25 (brs, 1H), 6.53 (brs, 1H), 7.13 (dd, *J* = 8.6, 8.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.33 (dd, *J* = 6.1, 1.7, 1H), 7.39, (ddd, *J* = 8.6, 6.1, 1.7 Hz, 1H), 7.64 (d, *J* = 6.6 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 8.27 (s, 1H), 8.57 (d, *J* = 6.6 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 25.4, 30.4, 33.6, 34.9, 48.6, 117.9, 121.0, 121.15, 121.22, 122.4, 127.3, 129.3, 130.1, 135.0, 137.2, 137.9, 148.9, 149.0, 154.5, 154.7, 155.2, 161.4; IR (KBr, ν / cm^{-1}) 3335, 2928, 1653, 1541, 1458, 1253, 1001, 839, 753, 650; HRMS (ESI^+) Calcd for $C_{27}H_{32}N_4NaO$ ($[M+Na]^+$) 451.2468, Found 451.2451.

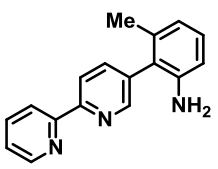
Synthesis of 2-([2,2'-bipyridin]-5-yl)-3-methylaniline



To a solution of 5'-bromo-2,2'-bipyridine (2.35 g, 10 mmol, 1.0 equiv) in DMSO (20 mL) were added AcOK (2.94 g, 30.0 mmol, 3.0 equiv), $PdCl_2$(dppf) (0.22 mg, 0.30 mmol. 3.0 mol%), and bis(pinacolato)diboron (3.05 g, 12.0 mmol, 1.2 equiv). The mixture was stirred at 100 °C for 18 h. After cooling to room temperature, the mixture was filtered through Celite, and the eluent was extracted with CH_2Cl_2. The solvent was evaporated under vacuum and then hexane and water was added to the residue. The mixture was extracted with hexane (3×30 mL) and the solvent was removed under reduced pressure. 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2'-bipyridine was obtained as a pale yellow solid including impurity (2.59 g>70%). The ^1H and ^{13}C NMR spectra corresponded to the ones in the reference.[66] The residue was utilized without further purification to the next coupling reaction.

To a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2'-bipyridine (1.13 g, 4.00 mmol, 1.0 equiv) in dioxane (8 mL) were added $PdCl_2$(dppf) (0.29 g, 0.40 mmol, 10 mol%), water (1.6 mL), $Ba(OH)_2 \cdot 8H_2O$ (3.79 g, 12 mmol, 3.0 equiv), and 2-bromo-3-methylaniline (0.50 mL, 4.0 mmol, 1.0 equiv). The mixture was stirred at 100 °C for 22 h. After cooling to room temperature, the mixture was filtered through Celite. The eluent was extracted with ethyl acetate (3×50 mL) and the organic layer was dried over Na_2SO_4. The mixture was filtered, the solvent was removed in vauo, and the residue was purified by column chromatography on silica gel (deactivated with 20% Et_3N in hexane; eluent: hexane/EtOAc = 2/1) to give 2-([2,2'-bipyridin]-5-yl)-3-methylaniline as yellow oil (483 mg, 46% yield).

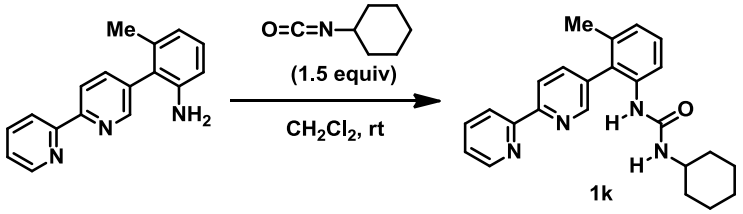
2-([2,2'-Bipyridin]-5-yl)-3-methylaniline. 46% yield; pale yellow oil; R_f = 0.32 (hexane/ethyl acetate = 1/2); ^1H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.47 (brs, 2H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 7.12 (dd, *J* =



[66] Querol, M; Bozic, B.; Salluce, N.; Belser , P. *et al. Polyhedron* **2003**, *22*, 655.

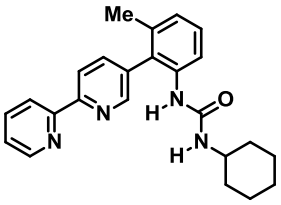
7.9, 7.6 Hz, 1H), 7.34 (ddd, *J* = 6.5, 4.6, 1.5 Hz, 1H), 7.77 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.85 (ddd, *J* = 8.0, 6.5, 2.0 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.51, (d, *J* = 8.0 Hz, 1H), 8.60 (d, *J* = 1.5 Hz, 1H), 8.71 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 112.9, 120.0, 120.9, 121.2, 123.2, 123.7, 128.7, 134.0, 136.9, 137.1, 138.7, 144.3, 149.1, 150.2, 154.9, 155.7; IR (KBr, ν / cm^{-1}) 3349, 2979, 1587, 1545, 1456, 1366, 1303, 1217, 999, 754; HRMS (ESI^+) Calcd for $C_{17}H_{16}N_3$ ($[M+H]^+$) 262.1339, Found 262.1330.

Synthesis of 1-(2-([2,2'-bipyridin]-5-yl)-3-methylphenyl)-3-cyclohexylurea (1k)



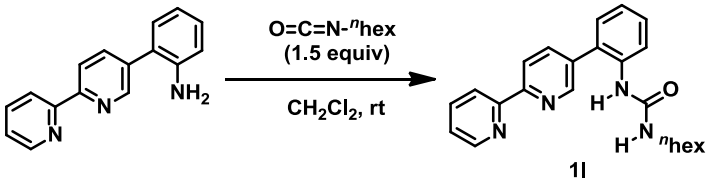
Prepared by the same method as ligand **1j** using 2-([2,2'-bipyridin]-5-yl)-3-methylaniline (583 mg, 1.80 mmol, 1.0 equiv) and cyclohexylisocyanate (350 mg, 2.80 mmol, 1.5 equiv). **1k** was isolated as a white solid (177 mg, 25% yield).

1-(2-([2,2'-Bipyridin]-5-yl)-3-methylphenyl)-3-cyclohexylurea (1k).



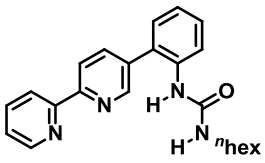
25% yield; white solid; R_f = 0.30 (hexane/ethyl acetate = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84-0.96 (m, 3H), 1.17-1.30 (m, 2H), 1.44-1.52 (m, 3H), 1.75-1.81 (m, 2H), 1.94 (s, 3H), 3.51-3.52 (m, 1H), 5.95 (brs, 1H), 6,51 (brs, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 7.29 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 5.3, 2.7 Hz, 1H), 7.83 (ddd, *J* = 8.2, 7.9, 1.8 Hz, 1H), 8.01-8.08 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.32 (d, *J* = 2.7, 1.8 Hz, 1H), 8.64 (dd, *J* = 4.9, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 24.9, 25.6, 33.6, 48.9, 118.0, 121.2, 121.5, 124.1, 124.3, 126.7, 129.2, 133.9, 136.7, 137.2, 137.8, 139.1, 149.2, 150.1, 154.7, 154.90, 154.92; IR (KBr, ν / cm^{-1}) 3339, 2929, 2853, 1654, 1548, 1465, 1366, 1220, 1065, 753; HRMS (ESI^+) Calcd for $C_{24}H_{27}N_4O$ ($[M+H]^+$) 387.2179, Found 387.2177.

Synthesis of 1-(2-([2,2'-bipyridin]-5-yl)phenyl)-3-hexylurea (1l).



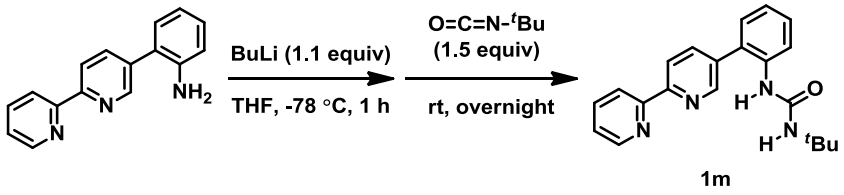
Prepared by the same method as ligand **1j** using 2-([2,2'-bipyridin]-5-yl)aniline (371 mg, 1.50 mmol, 1.0 equiv) and *n*-hexylisocyanate (434 μg, 3.00 mmol, 2.0 equiv).

1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-hexylurea was isolated as a white solid (144 mg, 25% yield).

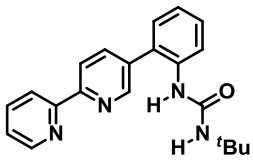


1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-hexylurea (1l). 62% yield; white solid; R_f = 0.32 (hexane/ethyl acetate = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, *J* = 6.9 Hz, 3H), 1.16-1.22 (m, 6H), 1.33-1.38 (m, 2H), 3.14 (td, *J* = 7.2, 7.2 Hz, 2H), 5.48 (brs, 1H), 6,70 (brs, 1H), 7.12-7.20 (m, 2H), 7.32 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.39 (ddd, *J* = 6.3, 4.8, 1.1 Hz, 1H), 7.69 (ddd, *J* = 8.5, 7.6, 2.2 Hz, 1H), 7.81 (ddd, *J* = 7.7, 7.6, 1.6 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.56 (d, *J* = 2.2 Hz, 1H), 8.64 (dd, *J* = 4.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 26.6, 30.0, 31.5, 40.2, 120.9, 121.1, 122.3, 123.2, 124.0, 128.4, 129.4, 130.1, 135.1, 136.8, 136.9, 137.7, 149.1, 149.4, 154.3, 155.2, 156.1; IR (KBr, ν / cm^{-1}) 3292, 2922, 2855, 1626, 1457, 1371, 1266, 1090, 856, 649; HRMS (ESI^+) Calcd for $C_{23}H_{26}N_4NaO$ ($[M+Na]^+$) 397.1999, Found 397.1997.

Synthesis of 1-(2-([2,2'-bipyridin]-5-yl)phenyl)-3-(*tert*-butyl)urea (1m).

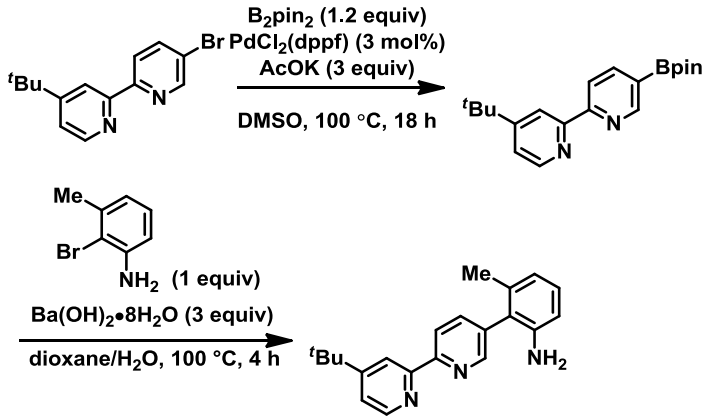


To a solution of 2-([2,2'-bipyridin]-5-yl)aniline (202 mg, 0.590 mmol, 1.0 equiv) in THF (1.2 mL), ^{n}BuLi (2.6 M solution in hexane, 0.246 mL, 1.1 equiv) was addded dropwie at -78 °C. After the mixture was stirring at -78 °C for 1 h, *tert*-butylisocyanate (87.7 mg, 0.885 mmol, 1.5 equiv) was added dropwise. After stirring at -78 °C overnight, the solvent was evaporated under vacuum. The crude product was then purified by column chromatography on silica gel (deactivated with 20% Et_3N in hexane; eluent: hexane/EtOAc = 1/3)to give **1m** as a white solid (58.9 mg, 29%).



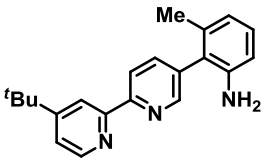
1-(2-([2,2'-Bipyridin]-5-yl)phenyl)-3-(tert-butyl)urea (1m). 77% yield; white solid; R_f = 0.38 (hexane/ethyl acetate = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 9H), 4.76 (brs, 1H), 6.14 (brs, 1H), 7.17 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.35 (dd, *J* = 7.5, 7.2 Hz, 1H), 7.39 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.08 (dd, *J* = 6.9, 6.3 Hz, 1H), 7.85 (dd, *J* = 7.2, 6.9 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 8.33-8.37 (m, 2H), 8.66 (s, 1H), 8.69 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 50.6, 121.0, 121.2, 121.7, 122.9, 124.1, 127.9, 129.4, 130.2, 135.2, 137.2, 137.2, 138.0, 149.1, 149.3, 154.3, 154.9, 155.1; IR (KBr, ν / cm^{-1}) 3371, 3306, 2968, 1644, 1565, 1439, 1278, 1210, 756, 628; HRMS (ESI^+) Calcd for $C_{21}H_{22}N_4NaO$ ($[M+Na]^+$) 369.1686, Found 369.1677.

Synthesis of 2-(4'-(*tert*-butyl)-[2,2'-bipyridin]-5-yl)-3-methylaniline.

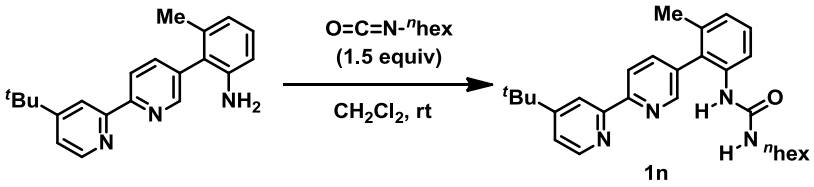


To a solution of 5'-bromo-4-(*tert*-butyl)-2,2'-bipyridine (146 mg, 0.500 mmol, 1.0 equiv) in DMSO (1 mL) were added AcOK (147 mg, 1.50 mmol, 3 equiv), $PdCl_2$(dppf) (11 mg, 0.015 mmol, 3 mol%), and bis(pinacolato)diboron (152 mg, 0.600 mmol, 1.2 equiv). The mixture was stirred at 100 °C for 22 h. After cooling to room temperature, the mixture was filtered through Celite. The eluent was extracted with CH_2Cl_2. The solvent was removed under reduced pressure and then hexane and water was added to the residue. The mixture was extracted with hexane (3×50 mL) and the solvent was evaporated under vacuum. The residue was utilized without further purification to the next coupling reaction. 4-(*tert*-Butyl)-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2'-bipyridine was obtained as white solid (140 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 12H), 1.39 (s, 9H), 7.32 (dd, *J* = 4.9, 1.4 Hz, 1H), 8.17 (dd, *J* = 7.9, 2.0 Hz, 1H), 8.35 (dd, *J* = 7.9, 0.9 Hz, 1H), 8.45 (dd, *J* = 2.0, 1.4 Hz, 1H), 8.58 (dd, *J* = 4.9, 0.9 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 30.4, 34.7, 83.9, 118.2, 120.2, 120.9, 143.0, 149.0, 154.8, 155.7, 158.2, 160.7.

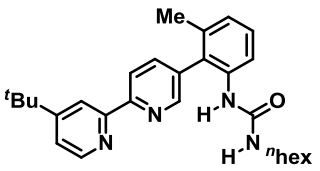
To a solution of crude 4-(*tert*-butyl)-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2'-bipyridine (140 mg, 0.410 mmol, 1.0 equiv) in dioxane (0.82 mL) were added $PdCl_2$(dppf) (30 mg, 0.041 mmol), water (0.16 mL), $Ba(OH)_2 \cdot 8H_2O$ (392 mg, 1.20 mmol, 3.0 equiv), and 2-bromo-3-methylaniline (0.11 mL, 0.83 mmol, 2 equiv) dropwise. The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was filtered through Celite. The solvent was removed and the residue was purified by column chromatography on silica gel (deactivated with 20% Et_3N in hexane; eluent: hexane/EtOAc = 5/1) to give 2-(4'-(*tert*-butyl)-[2,2'-bipyridin]-5-yl)-3-methylaniline as a white solid (93 mg, 59% yield for 2 steps).

2-(4'-(*tert*-Butyl)-[2,2'-bipyridin]-5-yl)-3-methylaniline.  59% yield (2 steps); white solid; R_f = 0.32 (hexane/ethyl acetate = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.05 (s, 3H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 7.12 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.34 (ddd, *J* = 7.6, 4.6, 1.4 Hz, 1H), 7.77 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.43 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 7.9 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 1H), 8.71 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 30.7, 35.1, 113.1, 118.1, 120.2, 121.1, 121.6, 123.6, 128.9, 133.9, 137.4, 138.9, 144.4, 149.3, 150.4, 155.7, 155.8, 161.2.

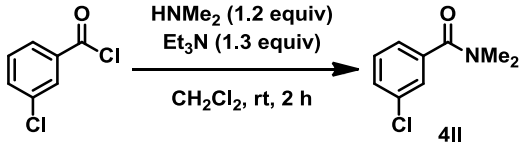
Synthesis of 1-(2-(4'-(*tert*-butyl)-[2,2'-bipyridin]-5-yl)-3-methylphenyl)-3-hexylurea (1n).



Prepared by the same method as ligand **1j** using 2-(4'-(*tert*-butyl)-[2,2'-bipyridin]-5-yl)-3-methylaniline (92.9 mg, 0.293 mmol, 1.0 equiv) and *n*-hexylisocyanate (74.5 mg, 0.59 mmol, 2.0 equiv). **1n** was isolated as a white solid (51 mg, 39% yield).

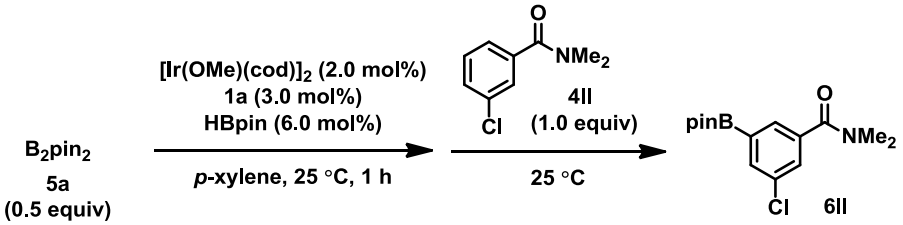
1-(2-(4'-(*tert*-Butyl)-[2,2'-bipyridin]-5-yl)-3-methylphenyl)-3-hexyl urea (1n).  39% yield; white solid; R_f = 0.42 (hexane/ethyl acetate = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (t, *J* = 6.7 Hz, 3H), 1.12-1.21 (m, 6H), 1.30-1.33 (m, 2H), 1.39 (s, 9H), 1.96 (s, 3H), 3.02-3.17 (m, 2H), 5.78 (brs, 1H), 6.40 (brs, 1H), 6.98 (d, *J* = 6.8 Hz, 1H), 7.29 (dd, *J* = 7.9, 6.8 Hz, 1H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 6.2 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 8.20 (s, 1H), 8.37 (s, 1H), 8.55 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.0, 22.5, 26.6, 29.9, 30.6, 31.4, 35.1, 40.1, 118.0, 118.1, 121.4, 121.5, 124.0, 126.4, 129.1, 133.7, 136.6, 137.8, 139.0, 149.1, 149.9, 154.7, 155.0, 155.8, 161.5; IR (KBr, ν / cm^{-1}) 3349, 2962, 1714, 1542, 1465, 1363, 1220, 1092, 1000, 755; HRMS (ESI^+) Calcd for $C_{28}H_{37}N_4O$ ($[M+H]^+$) 445.2962, Found 445.2944.

Synthesis of 3-chloro-*N*,*N*-dimethylbenzamide (4ll)

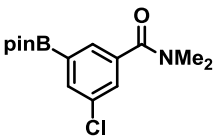


To a solution of dimethylamine (ca. 2 M in methanol, 60 mL, 120 mmol 1.2 equiv) and Et_3N (18 mL, 130 mmol, 1.3 equiv) in CH_2Cl_2 (140 mL), 3-chlorobenzoyl chloride (13 mL, 100 mmol, 1.0 equiv) was added at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The mixture was washed with aq. 1.0 M HCl (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to give **4ll** (18.4 g, 100% yield). The chemical shifts of ^1H and ^{13}C NMR corresponded to the ones in the literature.[67]

Procedure for determination of *k* value of C-H borylation.



In a round bottom flask, *p*-xylene (1.0 mL) was added to a mixture of $[Ir(OMe)(cod)]_2$ (6.6 mg, 0.010 mmol, 2.0 mol%), **1a** (5.6 mg, 0.015 mmol, 3.0 mol%), and bis(pinacolato)diboron (**5a**, 63.5 mg, 0.250 mmol, 0.50 equiv), dodecane (internal standard, 0.10 mL, 0.44 mmol, 0.88 equiv,). After the mixture was stirred at 25 °C for 1 h, a solution of 3-chloro-*N*,*N*-dimethylbenzamide (**4ll**, 91.8 mg, 0.500 mmol, 1.0 equiv)) in *p*-xylene (2.0 mL) was added. A portion of the reaction mixture (37 μL) was taken out at an appropriate interval (30 sec to 20 min). The mixture was diluted with acetone (0.70 mL) and analyzed with GCMS.



2-Chloro-*N*,*N*-dihexyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benza mide (6ll). colroless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 12H), 2.97 (s, 3H), 3.09 (s, 3H), 7.47 (s, 1H), 7.70 (s, 1H), 7.80 (s 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 39.7, 35.4, 84.5. 129.8, 131.2, 134.3, 135.6, 137.7, 170.2; ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.2; IR (neat, ν / cm^{-1}) 3398, 2977, 1640, 1390, 1348, 1212, 1143, 1096, 787, 704; HRMS (ESI^+) Calcd for $C_{15}H_{21}BClNNaO_3$ ($[M+Na]^+$) 332.1195, Found 332.1181.

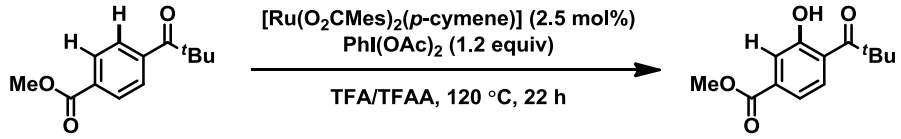
[67] Chen, W.; Li, K.; Hu, Z.; Wang, L.; Lai, G.; Li, Z. *Organometallics* **2011**, *30*, 2026.

第 3 章 官能基の水素結合能の違いに基づいた化学選択的 C–H ボリル化反応の開発研究

3-1 背景

C－H 結合官能基化反応では、基質に含まれる複数の C－H 結合のうち目的の位置でのみ反応を進行させることが求められる。配向基を用いる位置選択的 C－H 結合変換反応では、多様な官能基共存下、特定の官能基のみが配向基として働くことで、高い化学選択性の発現が実現している。例えば、ルテニウム触媒を用いたケトンのカルボニル基を配向基としたオルト位選択的な C－H ヒドロキシ化反応では、エステルの共存下でもケトンのカルボニル基のオルト位のみでヒドロキシ化反応が進行する（Scheme 3-1）。[68]

Scheme 3-1 | Competition of directing groups



ここでは、複数の種類の官能基が共存する中、アミド部位のメタ位を最も選択的にボリル化する配位子を開発することを目標とした。

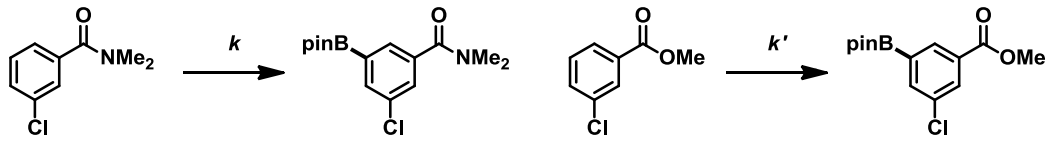
3-2 化学選択的 C－H ボリル化反応に開発に向けた配位子構造の検討

ベンズアミド **4ll** および安息香酸メチル **4mm** を基質とした際の反応速度定数をそれぞれの配位子ごとに比較することで、どの配位子が最もベンズアミドを優先的に C－H ボリル化できるかを明らかにすることにした。ベンズアミドと同様に安息香酸メチルも尿素と水素結合をすることが知られており、安息香酸メチルを共存させた系でもベンズアミド選択的に C－H ボリル化を進行させることができれば、エステル以外の官能基との間でも、アミドに対して高い化学選択性を発現することができると考えたからである。ベンズアミド **4ll** および安息香酸メチル **4mm** を基質とした際の反応速度定数およびその比を Table 3-1 に示す。尿素部位を有する配位子 **1a** および **1j**-**1n** の示す反応速度の傾向は、ベンズアミド、安息香酸メチルのいずれでもおおむね同じだった。すなわち、配位子 **1a** のビピリジル部位への *tert*-ブチル基の導入、リンカー部位へのメチル基の導入、尿素部位への *n*-ブチル基の導入による立体障害の軽減により、ベンズアミド **4ll** と同様に安息香酸メチル **4mm** の C－H ボリル化反応も加速された（entries 1- 6）。ただ、**4mm** を基質とした場合は、尿素部位を持たない配位子 **1i** および dtbpy が尿素部位を有する配位子郡よりも高い反応性を示した（entries 7 and 8）。エステルはアミドと異なり尿素との水素結合能が低いため、水素結合を介した触媒活性中心に対する近接効果が小さく、これよりも尿素部位の立体障害による反応性の低下の影響が大きく発現したためと考えている。ベンズアミド **4ll** と安息香酸メチル **4mm** の反応

[68] Thirunavukkarasu, V. S.; Ackermann, L. *Org. Lett.* **2012**, *14*, 6206.

速度定数の比 *k*/*k'*は **1a** が最大値 53 を与えたため、これを最良の化学選択性を示す配位子であると判断した。特にリンカー部位への官能基の導入および尿素部位の立体障害の軽減による反応性の増大は、ベンズアミドに対してよりも安息香酸メチルに対して大きく影響した（entries 3 and 5）。その結果、第２章で新たに合成した配位子 **1j-1n** では、ベンズアミドと安息香酸メチルのボリル化反応の反応速度の差が出にくくなり、総合的に **1a** が最も良い化学選択性を示した。

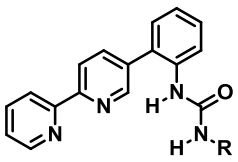
Table 3-1 | *k* values of C-H borylation using 4ll or 4mm as substrates with ligand 1i-1n and dtbpy



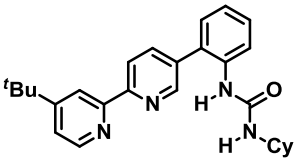
4ll　　6ll　　4mm　　6mm

Conditions: 4ll or 6mm (1.0 equiv), B_2pin_2 (0.50 equiv), $[Ir(OMe)(cod)]_2$ (2.0 mol%), ligand (3.0 mol%), HBpin (6.0 mol%), *p*-xylene, 25 °C.

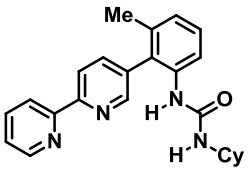
Entry	Ligand	*k* [10^{-4}•M^{-1}]	*k*' [10^{-4}•M^{-1}]	*k*/*k*'
1	1m	0.2940	0.0059	50
2	1a	0.4269	0.0080	53
3	1l	0.8222	0.0418	20
4	1j	1.3064	0.0263	50
5	1k	2.1351	0.1028	21
6	1n	3.0658	0.1067	29
7	1i	0.0675	0.1118	0.60
8	dtbpy	0.2410	0.4851	0.50



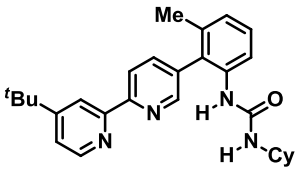
R = ^{t}Bu: 1m
Cy: 1a
^{n}hex: 1l



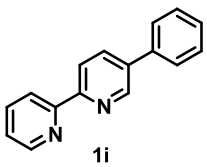
1j



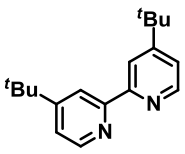
1k



1n



1i

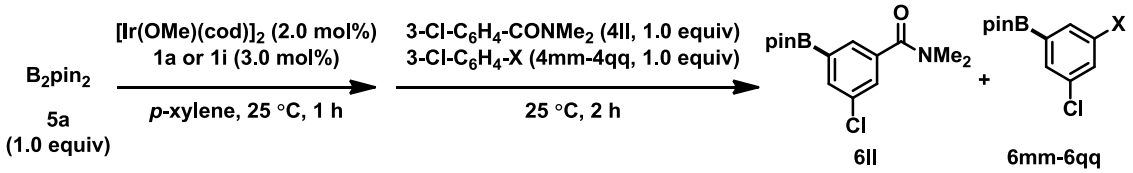


dtbpy

続いてアミドと他の官能基の間での化学選択性を評価するため、競合実験を行った（Table 3-2）。**1a** を配位子として用いたベンズアミド **4ll** と安息香酸メチル **4mm** との競合実験では、ボリル化生成物 **6ll**、**6mm** の比は 5.1 だった（entry 1）。**1i** を配位子として用いた反応系では

6ll、**6mm** の生成比が 0.70 だったことから、配位子 **1a** を用いることで選択性は 7.3 倍向上した。尿素部位との水素結合形成能は低いが、電子求引性の置換基であるクロロ基やトリフルオロメチル基をもつベンゼン誘導体 **4nn**、**4oo** と競合させた場合も、**1a** を用いた際には化学選択性が向上し、配位子 **1i** の場合と比較してそれぞれ 17 倍、18 倍の化学選択性の改善が見られた（entries 2 and 3）。アニソール誘導体 **4pp** との競合実験では配位子 **1a** を用いた場合のみ、アニソールのボリル化生成物 **6pp** の生成は見られず、ベンズアミドのボリル化生成物 **6ll** が単一の生成物として得られた（entry 4）。一方、ホスフィンオキシド **4qq** とベンズアミド **4ll** の競合実験では、配位子 **1a**、**1i** のいずれを用いてもホスフィンオキシドのボリル化体 **6qq** の生成が優先したが、配位子 **1a** を用いた場合には、ベンズアミドのボリル化体 **6ll** に比べ **6qq** の生成比が高まった（entry 5）。これらの結果をまとめると、**1a** を配位子として用いた場合の反応性はホスフィンオキシドで最も大きく、続いてベンズアミド、その次に安息香酸エステル、ベンゾトリフルオリド、クロロベンゼンの反応性が大きく、アニソールの反応性が最も小さかった（Table 3-2、下図）。

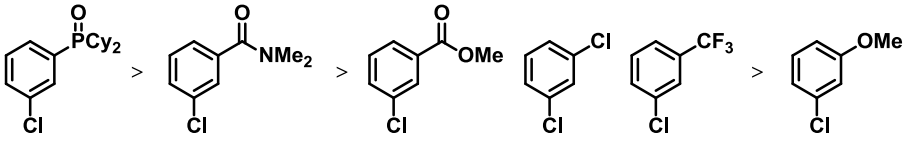
Table 3-2 | Intermolecular competition experiments



Entry	X	1a		1i	
		Yield[a]	Ratio[b]	Yield[a]	Ratio[b]
1	CO_2Me (mm)	65	5.1	53	0.70
2	Cl (nn)	65	5.8	86	0.35
3	CF_3 (oo)	76	7.0	73	0.40
4	OMe (pp)	62	>30	28	3.0
5	$POCy_2$ (qq)	85	14[c]	20	1.8[c]

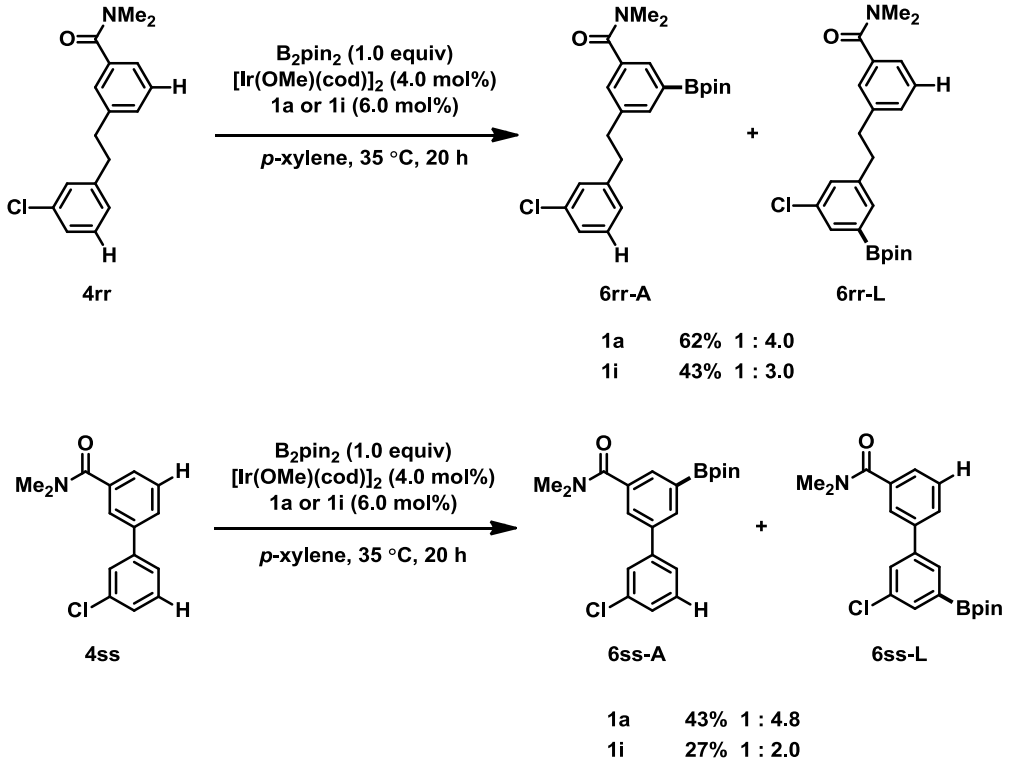
[a] Total yield of borylated benzamide 6ll and borylated competitor.
[b] Ratio of borylated benzamide 6ll and borylated competitor.
[c] Ratio of borylated phosphine oxide 6qq and borylated benzamide 6ll.

Order of the benzene derivatives based on the rate for C-H borylation reaction using 1a



次に分子内に複数の官能基を有する基質を用いて化学選択性の検討を行った（Scheme 3-2）。分子内に二つの官能基を有する基質 **4rr**、**4ss** のいずれも反応性が低く、25℃ ではボリル化反応が進行しなかった。35℃ でようやく反応は進行したが、予想に反してアミドフェニル基に対してクロロフェニル基にボリル化が優先的に進行した。[69] いずれの基質についても、反応溶液中で期待していたもの（Figure 3-1, **G** および **I**）とは異なる配座（**H** および **J**）を取りやすくなったことが、選択性の低下の原因だと考えている。すなわち、**4rr** は反応溶液中で二つのベンゼン環が重なるような配座（**H**）が優先し、**1a** と水素結合を形成した際に、クロロフェニル基のボリル化が促進された。**4ss** はアミドのカルボニル基がクロロフェニル基の側を向いた **J** の配座が優先することで、水素結合形成時、触媒活性中心とクロロフェニル基の近接効果が高まった。

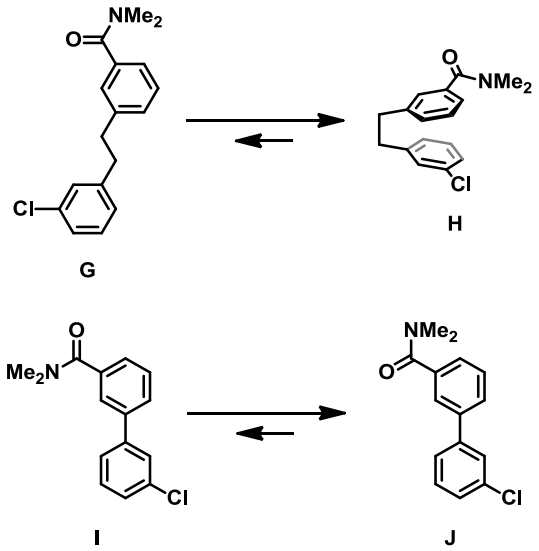
Scheme 3-2｜Intramolecular competition experiments



*Yields are shown as a mixture of borylated mono-compounds.

[69] ジボリル化体 **7rr** は、配位子 **1a** を用いた際に 22%、**1i** を用いた際に 9%の収率で得られた。**7ss** は **1a** を用いた場合にのみ生成し、収率 4%で得られた。

Figure 3-1｜ Proposed configuration of 4rr and 4ss in *p*-xylene



3-3 小括

尿素構造を有するビピリジル配位子 **1a** を用いることで、C－H ボリル化反応のアミド基やホスフィンオキシドに対する化学選択性の向上に至った。従来、イリジウム／ビピリジル錯体による C－H ボリル化反応では、ハロゲンやエステル基をもつ電子不足の芳香環が高い反応性を示すが、そのような基質に対しても、分子間における競合実験においてベンズアミドの C－H ボリル化反応が優先的に進行した。

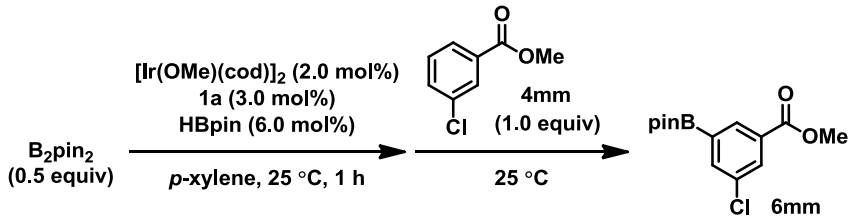
ベンズアミド誘導体 **4ll** およびベンゾトリフルオリド誘導体 **4oo** での競合実験において、ボリル化反応の選択性は、配位子 **1i** を用いた場合に比べて 18 倍改善した。分子内に複数の反応点をもつ基質 **4rr** および **4ss** では、化学選択性の発現には至らなかった。これは、前者では反応溶媒を変えることで、後者では第一級アミドを用いることで解決できると考える。

実験項

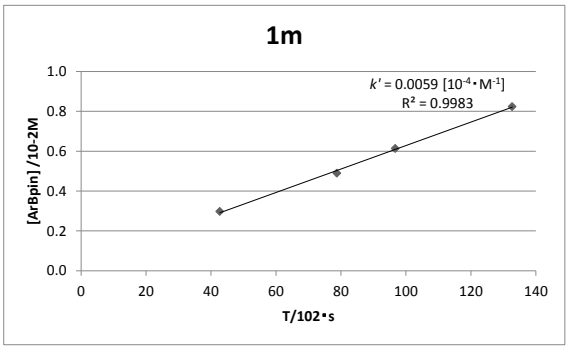
General

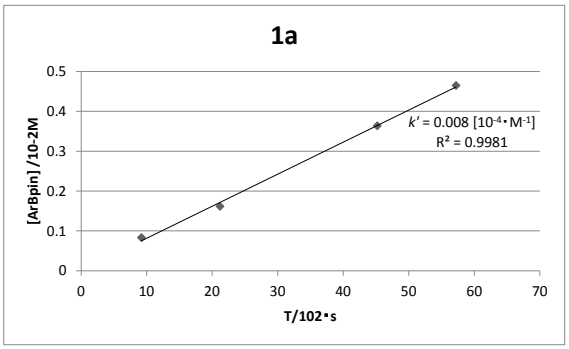
All reactions were carried out in a dry degassed solvent under an argon atmosphere. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Substrates **6mm**, **6nn**, **6oo**, and **6pp** were purchased from Tokyo Kasei Kogyo Co. Column chromatography was performed with silica gel (230-400 mesh ASTM). Recycling preparative HPLC (LC-9210NEXT; column, JAIGEL-1H and JAIGEL-2H; solvent, $CHCl_3$) was used for isolation of amide **4rr** and borylated products **6** and **7** after removing metal wastes through a short pad of silica gel. NMR spectra were recorded on 500 MHz (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) and 400 MHz (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 125 MHz for ^{11}B NMR, and 158 MHz for ^{31}P NMR) spectrometers. Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference. Fluorine, boron, and phosphorus chemical shifts are reported relative to $BF_3 \cdot OEt_2$ (δ 0.00 ppm), and triphenylphosphine (δ 5.6 ppm) as external references, respectively. Infrared (IR) spectra were recorded on Fourier transform infrared spectrophotometer. ESI-MS spectra were measured on a spectrometer for HRMS. GC-MS was measured on Shimazu (GCMS-QP2010 Ultra).

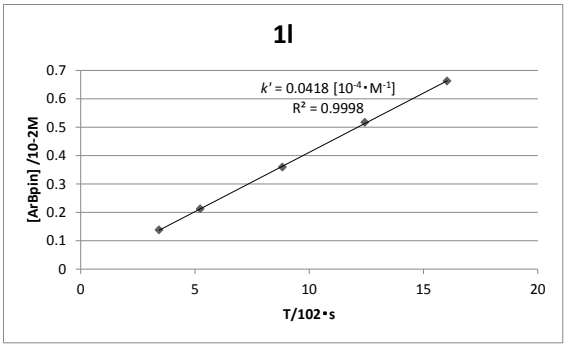
Determination of *k* values using 4mm as a substrate.

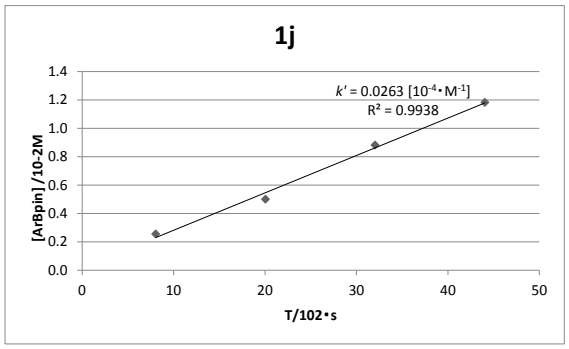


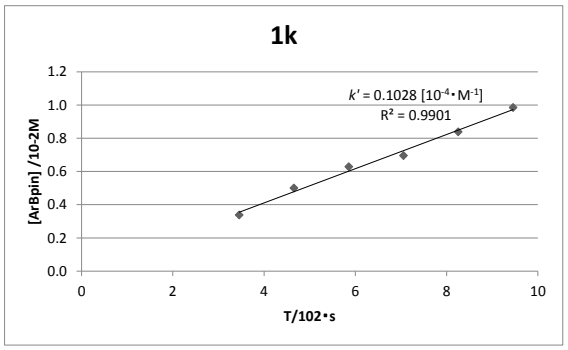
In a round bottom flask, *p*-xylene (1.0 mL) was added to a mixture of $[Ir(OMe)(cod)]_2$ (6.6 mg, 0.010 mmol, 2.0 mol%), **1a** (5.6 mg, 0.015 mmol, 3.0 mol%), and bis(pinacolato)diboron (**5a**, 63.5 mg, 0.250 mmol, 0.50 equiv), dodecane (internal standard, 0.10 mL, 0.44 mmol, 0.88 equiv,). After the mixture was stirred at 25 °C for 1 h, a solution of methyl 3-chloro-benzoate (**4mm**, 82.3 mg, 0.500 mmol, 1.0 equiv) in *p*-xylene (2.0 mL) was added. A portion of the reaction mixture (37 μL) was taken out at an appropriate interval (30 sec to 20 min). The eluent was diluted with acetone (0.70 mL) and analyzed with GCMS.

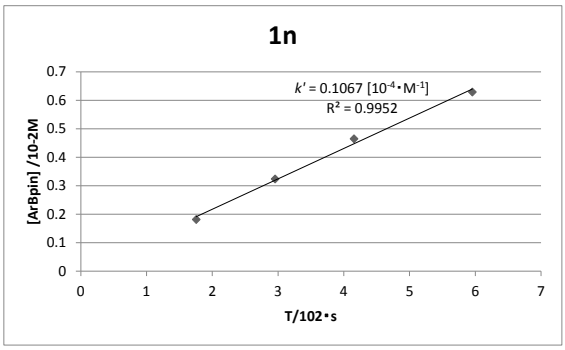


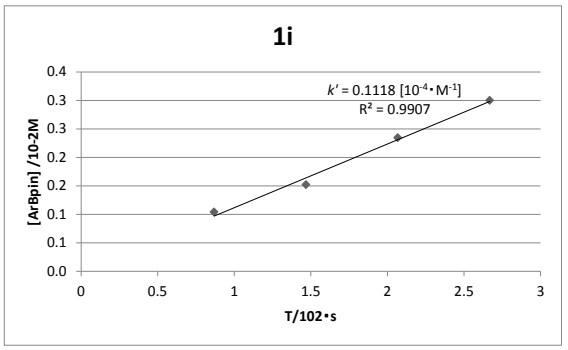


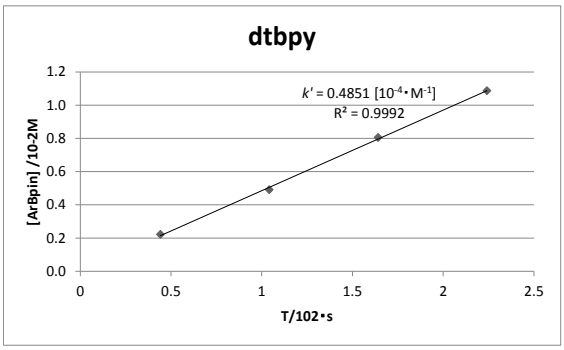




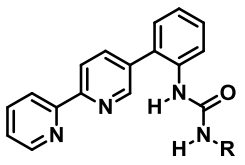


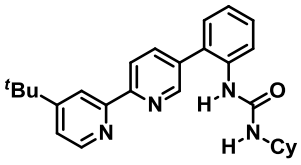


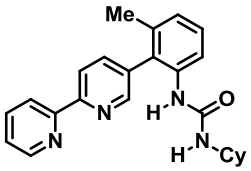


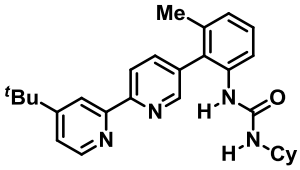


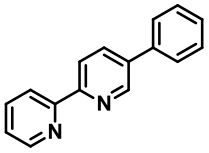
(The structures of **1m** - dtbpy are shown next.)

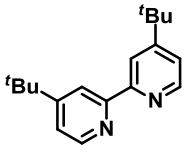




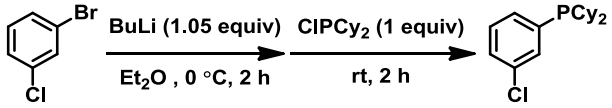




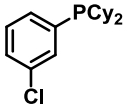




Synthesis of (3-chlorophenyl)dicyclohexylphosphine.

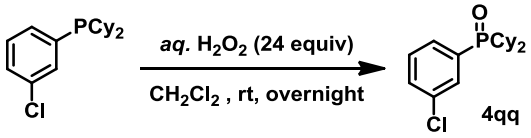


A solution of 1-bromo-2-chlorobenzene (2.4 mL, 20 mmol, 1.0 equiv) in Et_2O (46 mL) was cooled to 0 °C and treated with ^{n}BuLi (2.6 M in hexane, 8.1 mL, 21 mmol, 1.05 equiv) dropwise. After the mixture was kept at 0 °C for 2 h, chlorodicyclohexylphosphine (4.4 mL, 20 mmol, 1.0 equiv) in hexane (25 mL) was added dropwise. After 2 h at 0 °C, the mixture was warmed to room temperature. Hydrolysis was then performed at 0 °C with H_2O (75 mL). The organic layer was then extracted with diethyl ether (2×80 mL) and dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The crude product was then purified by column chromatography on silica gel (hexane/EtOAc = 20/1) to give 4-(*tert*-butyl)-2-(tributylstannyl)pyridine including impurities (11.3 g, impurity: ca. 30 wt%).

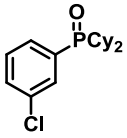


(3-Chlorophenyl)dicyclohexylphosphine. 83% yield; colorless oil; R_f = 0.67 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01-1,34 (m, 10H), 1.59-1.95 (m, 12H), 7.30 (dd, *J* = 8.1, 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.40-7.43 (m, 1H), 7.44 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9 (d, $J_{C\text{-}P}$ = 7.5 Hz), 27.2 (d, $J_{C\text{-}P}$ = 12.7 Hz), 28.8 (d, $J_{C\text{-}P}$ = 7.5 Hz), 30.0 (d, $J_{C\text{-}P}$ = 16.4 Hz), 32.5 (d, $J_{C\text{-}P}$ = 12.2 Hz), 35.2 (d, $J_{C\text{-}P}$ = 67.2 Hz), 129.0 (d, $J_{C\text{-}P}$ = 24.4 Hz), 129.0, 132.5 (d, $J_{C\text{-}P}$ = 82.2 Hz), 132.9 (d, $J_{C\text{-}P}$ = 19.7 Hz), 134.1, (d, $J_{C\text{-}P}$ = 13.2 Hz), 137.5, (d, $J_{C\text{-}P}$ = 22.1 Hz); ^{31}P NMR (158 MHz, $CDCl_3$) δ 15.2; IR (KBr, ν / cm^{-1}) 2926, 1560, 1447, 1393, 1114, 888, 851, 755, 688, 662; HRMS (ESI^+) Calcd for $C_{18}H_27ClP$ ($[M+H]^+$) 309.1533, Found 309.1531.

Synthesis of (3-chlorophenyl)dicyclohexylphosphine oxide (4qq).

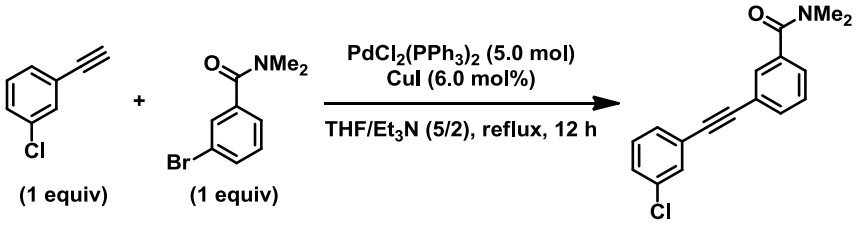


To a solution of (3-chlorophenyl)dicyclohexylphosphine (5.12 g, 16.6 mmol, 1.0 equiv) in CH_2Cl_2, aq. H_2O_2 (ca. 35%, 35 mL, 24 equiv, 0.40 mol) was added under 0 °C. The mixture was stirred at room temperature for 12 h. Under 0 °C, sat. aq. $Na_2S_2O_3$ was added. The organic layer was extracted with EtOAc (3 × 150 mL) and dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The crude product was then purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 20/1) to give (3-chlorophenyl)dicyclohexylphosphine oxide as a white solid (5.10 g, 95%).



(3-Chlorophenyl)dicyclohexylphosphine oxide (4qq). 95% yield; white solid; R_f = 0.61 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11-1.33 (m, 10H), 1.58-1.82 (m, 8H), 1.98-2.05 (m, 4H), 7.41 (ddd, *J* = 7.9, 7.7, 2.9 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.51-7.54 (m, 1H), 7.65 (d, *J* = 9.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 25.2, 25.6, 26.0 (d, $J_{C\text{-}P}$ = 12.0 Hz), 26.1 (d, $J_{C\text{-}P}$ = 12.6 Hz), 34.9 (d, $J_{C\text{-}P}$ = 67.2 Hz), 129.1, 129.4 (d, $J_{C\text{-}P}$ = 11.4 Hz), 131.2, 131.2 (d, $J_{C\text{-}P}$ = 8.4 Hz), 132,4 (d, $J_{C\text{-}P}$ = 81.5 Hz), 134.6 (d, $J_{C\text{-}P}$ = 13.2 Hz); ^{31}P NMR (158 MHz, $CDCl_3$) δ 55.7; IR (KBr, ν / cm^{-1}) 3056, 2845, 1560, 1402, 1271, 1203, 890, 824, 734, 660; HRMS (ESI^+) Calcd for $C_{18}H_{27}ClOP$ ($[M+Na]^+$) 325.1483, Found 325.1499.

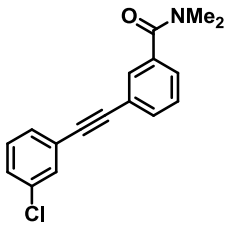
Synthesis of 3-((3-chlorophenyl)ethynyl)-*N*,*N*-dimethylbenzamide.



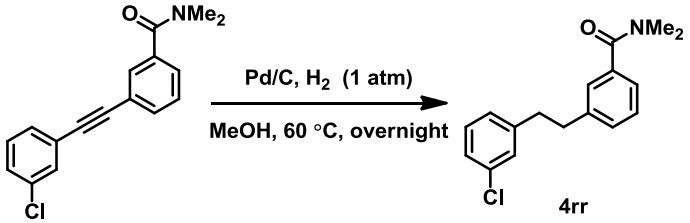
A solution of *m*-chlorophenylacetylene (1.23 mL, 10.0 mmol, 1.0 equiv), 3-bromo-*N*,*N*-dimethylbenzamide (2.28 g, 10.0 mmol, 1.0 equiv), CuI (144 mg, 0.600 mmol, 6.0 mol%), $PdCl_2(PPh_3)_2$ (351 mg, 0.500 mmol, 5.0 mol%v) in THF/Et_3N (5/2, 56 mL) was refluxed 12 h. After cooling to room temperature, the solvent was evapolated under vacuum. The residue was dissolved in ethyl acetate (30 mL) and washed with water (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/2) to give 3-((3-chlorophenyl)ethynyl)-*N*,*N*-dimethylbenzamide as pale yellow oil (2.72 g, >65%, including

3-bromo-*N*,*N*-dimethylbenzamide).

3-((3-Chlorophenyl)ethynyl)-*N*,*N*-dimethylbenzamide. <50% yield; colorless oil; R_f = 0.34 (hexane/EtOAc = 1/2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (brs, 3H), 3.12 (brs, 3H), 7.28 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.40-7.41 (m, 3H), 7.51 (s, 1H), 7.56 (d, *J* = 5.8 Hz, 1H), 7.57 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.0, 39.2, 88.4, 89.5, 122.7, 124.3, 126.9, 128.3, 128.4, 129.4, 129.5, 129.8, 131.0, 132.2, 133.8, 136.4, 170.0.

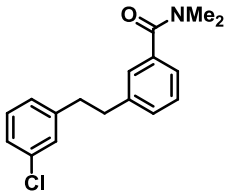


Synthesis of 3-(3-chlorophenethyl)-*N*,*N*-dimethylbenzamide.

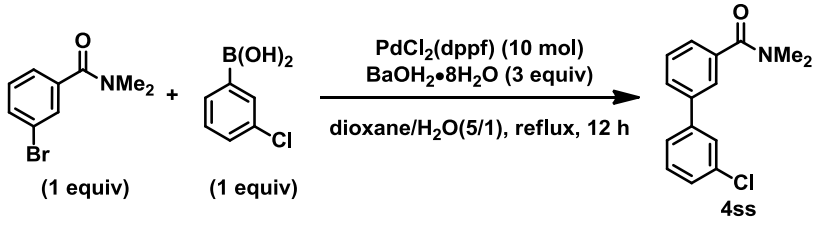


Under H_2 atmosphere, a mixture of 3-((3-chlorophenyl)ethynyl)-*N*,*N*-dimethylbenzamide (1.94 g, including ca. 35% of 3-bromo-*N*,*N*-dimethylbenzamide) and Pd/C (10 w/w%, 70 mg) in methanol (13 mL) was stirred at 60 °C. After filteration through Celite, the solvent was evapolated under reduced pressure. Purification with GPC ($CHCl_3$, 2 h) gave 3-(3-chlorophenethyl)-*N*,*N*-dimethylbenzamide as colorless oil (224 mg, 11% yield for 2steps).

3-(3-Chlorophenethyl)-*N*,*N*-dimethylbenzamide (4rr). 11% yield (2 steps); colorless oil; R_f = 0.55 (CH_2Cl_2/MeOH = 20/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96-3.01 (m, 7H), 3.16 (s, 3H), 7.01 (d, *J* = 7.3 Hz, 1H), 7.12 (s, 1H), 7.17-7.24 (m, 5H), 7.38 (dd, *J* = 7.5, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.1, 37.1, 37.2, 39.4, 124.6, 126.0, 126.6, 127.0, 128.3, 128.5, 129.46, 129.52, 133.8, 136.3, 141.1, 143.2, 171.5.

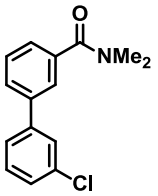


Synthesis of 3'-chloro-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (4ss).



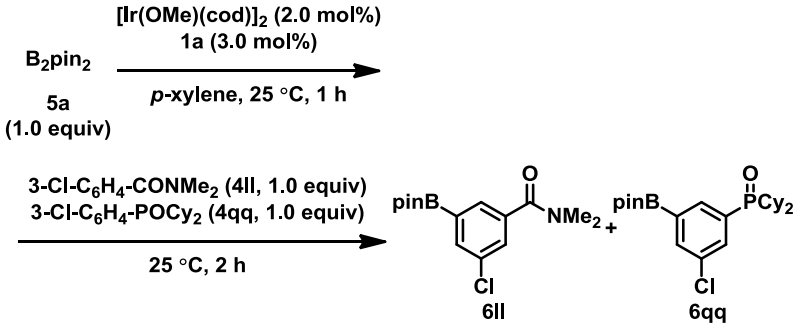
A mixture of 3'-chloro-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (1.24 g, 5.5 mmol, 1.0 equiv), (3-chlorophenyl)boronic acid (0.94 g, 6.0 mmol, 1.1 equiv), $PdCl_2$(dppf) (0.40 g, 0.55 mmol, 10

mol%), and $Ba(OH)_2 \cdot 8H_2O$ (5.16 g, 16.3 mmol, 3.0 equiv) in dioxane/water (5/1, 13.2 mL) was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was filtered through Celite. The eluent was extracted with ethyl acetate (3×70 mL) and the organic layer was dried over Na_2SO_4, and filtered. The solvent was removed and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 20/1) to give 3'-chloro-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide as yellow oil (823 mg, 58% yield).

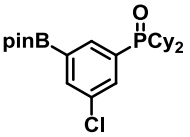


3'-Chloro-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (4ss). 58% yield; colorless oil; R_f = 0.30 (CH_2Cl_2/MeOH = 50/1); ^{1}H NMR (100 MHz, $CDCl_3$) δ 3.02 (s, 3H), 3.14 (s, 3H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.45-7.48 (m, 2H), 7.57-7.59 (m, 2H), 7.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5, 39.7, 125.4, 125.9, 126.5, 127.4, 127.8, 128.2, 129.1, 130.2, 134.8, 137.2, 140.1, 142.3, 171.2.

Typical procedure for intermolecular competition experiment.



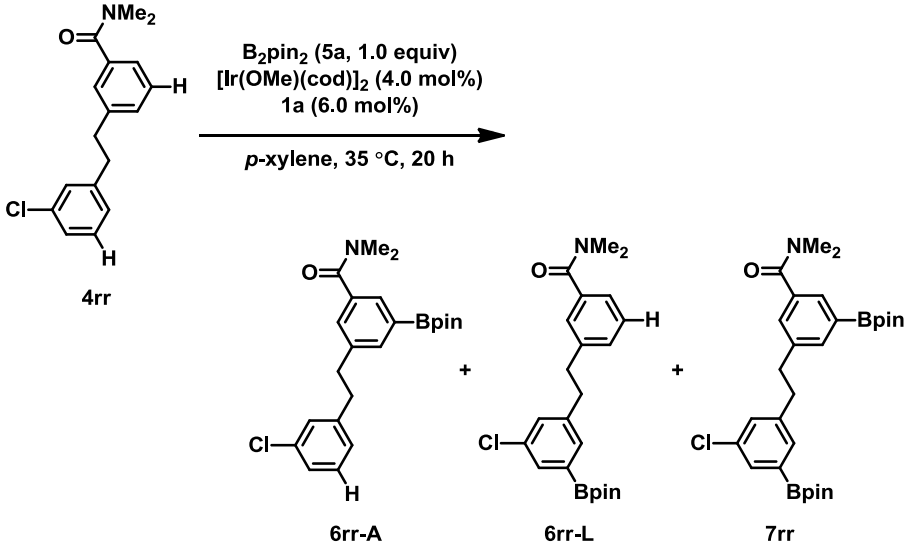
In a round bottom flask, *p*-xylene (0.5 mL) was added to a mixture of $[Ir(OMe)(cod)]_2$ (3.3 mg, 5.0 μmol, 2.0 mol%), **1a** (2.8 mg, 7.5 μmol, 3.0 mol%), and bis(pinacolato)diboron (**2a**) (63.5 mg, 0.25 mmol, 1.0 equiv). After the mixture was stirred at 25 °C for 1 h, a solution of 3-chloro-*N*,*N*-dimethylbenzamide (**4ll**, 45.9 mg 0.250 mmol, 1.0 equiv) and (3-chlorophenyl)dicyclohexylphosphine oxide (**4qq**, 81.2 mg, 0.500 mmol, 1.0 equiv) in *p*-xylene (1.0 mL) was added. After stirring at 25 °C for 2 h, MeOH (0.3 mL) was added to the mixture (bubble was generated). The yields of borylated products **6rr** and **6qq** and the ratio of **6rr**/**6qq** were determined by comparison of ^{1}H NMR spectra of the crude mixture with the authentic samples.



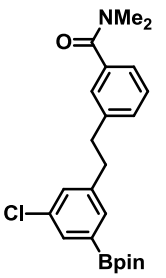
(3-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)dicyclohexyl phosphine oxide (6qq). colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10-1.33 (m, 10H), 1.31 (s, 12H), 1.55-2.01 (m, 12H), 7.70 (d, *J* = 9.8 Hz, 1H), 7.83 (d, *J* = 9.8 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7 (d, $J_{C\text{-}P}$ = 3.8 Hz), 24.9, 25.5 (d, $J_{C\text{-}P}$ = 2.4 Hz), 25.9 (d, $J_{C\text{-}P}$ = 1.3 Hz), 26.4 (d, $J_{C\text{-}P}$ = 24.0 Hz), 26.5 (d, $J_{C\text{-}P}$ = 12.1 Hz),

35.6 (d, $J_{C\text{-}P}$ = 11.9 Hz), 84.3, 131.2 (d, $J_{C\text{-}P}$ = 81.6 Hz), 134.0 (d, $J_{C\text{-}P}$ = 8.4 Hz), 134.8 (d, $J_{C\text{-}P}$ = 12.6 Hz), 135.2 (d, $J_{C\text{-}P}$ = 7.2 Hz), 137.5 (d, $J_{C\text{-}P}$ = 2.4 Hz); ^{11}B NMR (130 MHz, $CDCl_3$) δ 30.5; IR (KBr, ν / cm^{-1}) 2931, 2855, 1447, 1348, 1212, 1132, 964, 846, 753, 705; HRMS (ESI^+) Calcd for $C_{24}H_{37}BClNaO_3P$ ($[M+Na]^+$) 473.2154, Found 473.2146.

Typical procedure for intramolecular competition experiment.

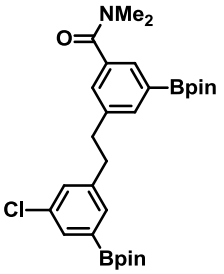


In a sealed tube, a mixture of $[Ir(OMe)(cod)]_2$ (5.5 mg, 8.0 μmol, 4.0 mol%), **1a** (4.5 mg, 12.0 μmol, 6.0 mol%), and bis(pinacolato)diboron (**5a**) (50.8 mg, 0.200 mmol, 1.0 equiv) was added to a solution of 3-(3-chlorophenethyl)-*N*,*N*-dimethylbenzamide (**4rr**, 57.6 mg, 0.200 mmol, 1.0 equiv) in *p*-xylene (1.2 mL). The mixture was then stirred at 35 °C for 16 h. The product was isolated from starting material and other byproducts by recycling preparative HPLC to give a mixture of **6rr-A** and **6rr-L** (39.3 mg, 47% yield) and **7rr** (20.4 mg, 19% yield).

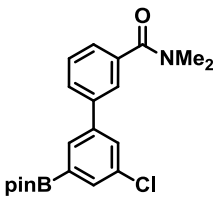


3-(3-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-*N*,*N*-dimethylbenzamide (6rr-A). 47% yield (in the reaction with **1a**, including **6rr-L**); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 12H), 2.87-2.94 (m, 7H), 3.09 (brs, 3H), 7.16 (s, 1H), 7.17 (s, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.49 (s, 1H), 7.59 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 35.4, 37.4, 37.6, 39.7, 84.3, 124.9, 127.2, 128.6, 129.7, 131.5, 132.3, 133.0, 134.0, 136.6, 141.5, 142.9, 171.8.

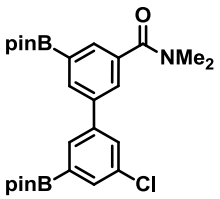
3-(3-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-*N*,*N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (7rr). 19% yield (in the reaction with **1a**); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 24H), 2.87-2.93 (m, 7H), 3.08 (brs, 3H), 7.19 (s, 1H), 7.24 (s, 1H), 7.51 (s, 1H), 7.59 (s, 1H), 7.67 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.99, 25.01, 35.3, 37.6, 37.7, 39.7, 84.1, 84.3, 129.9, 131.0, 131.5, 132.3, 133.0, 134.0, 145.9, 136.1, 140.9, 143.0, 171.9.



3'-Chloro-*N*,*N*-dimethyl-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-3-carboxamide (6ss-L). 43% yield (in the reaction with **1a**); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 12H), 3.00 (brs, 3H), 3.14 (brs, 3H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.65 (s, 1H), 7.76 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 35.5, 39.7, 84.4, 125.9, 126.3, 128.3, 129.0, 129.9, 131.6, 133.7, 134.7, 137.1, 140.1, 141.7, 171.5.



3'-Chloro-*N*,*N*-dimethyl-5,5'-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-3-carboxamide (7ss). 5% yield (in the reaction with **1a**); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 24H), 3.02 (brs, 3H), 3.14 (brs, 3H), 7.73 (s, 1H), 7.79 (s, 1H), 7.81 (s, 1H), 7.88 (s, 1H), 7.96 (s, 1H), 8.09 (s, 1H).



総括

本論文では、酵素反応に倣い、反応系中における基質と触媒配位子の間での可逆な水素結合形成を利用することで、芳香族 C－H ボリル化反応の位置選択性、反応性および化学選択性の向上に至った。

第１章では、基質認識部位として尿素構造を有するビピリジル配位子を合成し、オルトフェニレンリンカーにより尿素およびビピリジル部位を連結した誘導体が、芳香族 C－H ボリル化反応において高いメタ位選択性を示すことを見出した。[70] ^{1}H NMR 実験や尿素部位の窒素原子をメチル保護した配位子を用いた対照実験から、基質－配位子間の水素結合が位置選択性の発現に重要な役割を果たしていることが示唆された。本反応は、基質－触媒配位子間の非共有結合性相互作用を利用する位置選択的 C－H 結合変換反応としては、初めての例である。この触媒反応制御法の適用を拡大することで、C－H 結合変換の基質適用範囲の大幅な拡張および生成物の多様化が期待でき、C－H 結合変換反応の発展に大きく資するものと考えている。

第２章では、基質－配位子間の水素結合形成により、触媒反応が疑似的に分子内反応となることから期待できる、反応性の向上について検討した。第１章で見出した配位子の構造改変、すなわちビピリジル部位、リンカー部位および尿素部位の置換基を検討することにより、改変前から比較して７倍の触媒活性を示す配位子を見出すことに成功した。

第３章では、尿素部位の各種官能基に対する水素結合能の違いを利用する、芳香族 C－H ボリル化反応の化学選択性について検討した。従来、イリジウム／ビピリジル錯体による C－H ボリル化反応では、電子不足の芳香環が高い反応性を示すが、そのような基質の共存下でも、尿素部位をもつビピリジル配位子を用いることで、ベンズアミドで優先的に C－H ボリル化反応が進行することを見出した。

水素結合のような分子間相互作用を利用し、C－H 結合官能基化反応の位置選択性や化学選択性を制御する本触媒系の発展が、C－H 結合変換反応の汎用性を高め、医薬品をはじめとする複雑化合物の効率的な合成に貢献すること、さらに世界中の、一つでも多くの“生きたい”という望みを叶える一助となることに期待する。

[70] Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nature Chem.* **2015**, *7*, 712.

謝辞

本研究を行う機会を与えていただき、多大なるご指導、ご鞭撻を賜りました、東京大学 大学院薬学系研究科 金井求教授に心より御礼を申し上げます。

本研究を直接ご指導いただき、有益なご助言をくださいました、東京大学 大学院薬学研究科 ERATO 金井触媒分子生命プロジェクトグループリーダー 國信洋一郎博士に感謝いたします。

研究をはじめ、さまざまな面でお世話になりました東京大学 大学院薬学系研究科 生長幸之助講師、清水洋平助教、山次健三助教、川島茂裕特任講師、東京大学 大学院薬学研究科 ERATO 金井触媒分子生命プロジェクトグループリーダー 相馬洋平博士に感謝いたします。

折に触れ有益なご助言をくださいました、北海道大学 大学院薬学研究院 創薬化学部門 創薬化学分野 大学院生命科学院 生命分子科学講座 薬品製造化学研究室 松永茂樹教授に深く御礼申し上げます。

毎日の研究生活でお世話になりました、東京大学 大学院薬学系研究科 ERATO 金井触媒分子生命プロジェクト 西光海博士、東京大学 大学院薬学研究科 有機合成化学教室同期生の伊藤創一氏、小澤淳氏、小島正寛氏、関陽平氏、森田雄也氏をはじめ、東京大学 大学院薬学研究科 有機合成化学教室のみなさまに感謝します。

最後に研究生活を支えてくださった家族に心より感謝申し上げます。