イリジウム触媒による
sp^3 炭素–水素結合活性化を経る
不斉アルキル化反応の開発

(Iridium-Catalyzed Enantioselective Hydroalkylation *via* C(sp^3)–H Activation)

理学研究科

物質分子系専攻

令和４年度

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序文と謝辞

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山内　大輔

令和 4 年 夏

Abstract

Transition-metal-catalyzed molecular transformations involving an activation of C–H bonds have attracted attention as one of the most useful synthetic methods with high atomic efficiency. Compared to the direct transition-metal-catalyzed C(sp^2)–H functionalization reaction, C(sp^3)–H bond functionalization is more challenging, and thus it has been actively studied in recent years. In this thesis, the author describes asymmetric alkylation reactions *via* C(sp^3)–H bond activation adjacent to a nitrogen atom catalyzed by cationic iridium complexes.

Chapter 1 summarizes the background of research on transition-metal-catalyzed C(sp^3)–H functionalization reactions adjacent to a nitrogen atom.

In Chapter 2, the author describes asymmetric hydroalkylation of α-trifluoromethylstyrenes *via* C(sp^3)–H bond activation. In this study, it is described that the addition of the *N*-methyl C–H bond is accelerated by the substituent at the 3-position of the pyridyl group included in the substrates as a directing group. Additionally, the author found that a cationic iridium/ chiral diphosphine ligand gives highly enantioselective γ-branched amine derivatives with trifluoromethyl-containing tertiary carbon centers.

Chapter 3 summarizes asymmetric alkylation of cyclic amine derivatives with a benzo-fused heteroaromatic ring as a directing group. The α- C(sp^3)–H bond of cyclic amines is relatively reactive, and several functionalization methods have been developed by way of reactive intermediates such as α-amino carbanion and iminium ion. In recent years, transition-metal-catalyzed direct C(sp^3)–H functionalization has been investigated, but asymmetric alkylation of cyclic amine derivatives is underdeveloped. In this study, the author developed C(sp^3)–H asymmetric alkylation with terminal alkenes at the α-position of pyrrolidine derivatives using a benzo-fused heteroaromatic ring as the directing group. In the presence of a cationic iridium/chiral diphosphine ligand, the alkylated products were obtained highly enantioselectively.

略語表

$[\alpha]_D$	specific optical rotation
$BAr^F{}_4$	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
Boc	*tert*-butoxycarbonyl
Bpin	boronic acid pinacol ester
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMSO	dimethyl sulfoxide
EWG	electron-withdrawing group
Fmoc	9-fluorenylmethyloxycarbonyl
i-Pr	isopropyl
$LiAlH_4$	lithium aluminium hydride
n-BuLi	*n*-butyllithium
OSu	succinimide ester
s-BuLi	*sec*-butyllithium
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl

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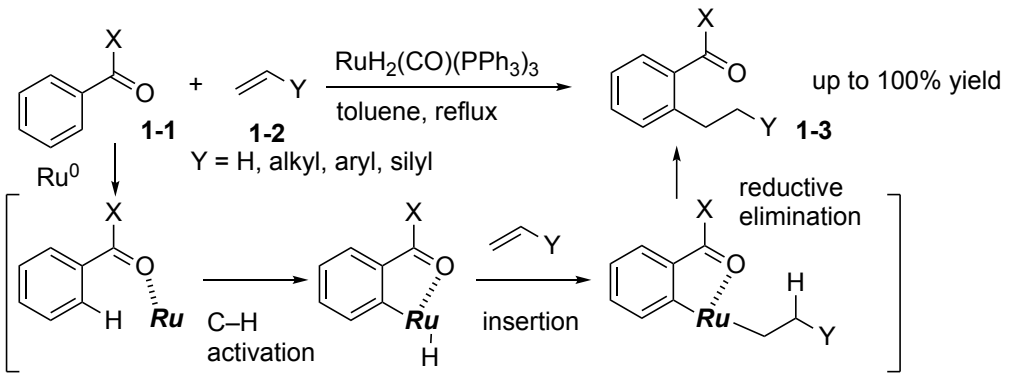
第一章　序論

1-1. 研究背景

遷移金属触媒を用いた不活性な C–H 結合の活性化を伴う直接的官能基化反応は、原子効率が高く、合成工程を短縮可能な合成手法の一つとして注目されている[1]。C–H 官能基化反応においては、金属を反応点へ近づける配向基の導入により、高い触媒活性と位置選択性を獲得できることが明らかになっている。

村井らは、1993 年に Ru 触媒を用いた芳香族ケトン **1-1** のアルケン **1-2** による一般的かつ効率的なオルトアルキル化反応を初めて報告した(Scheme 1-1)[2]。この反応では、芳香族ケトンの酸素原子が配位した Ru(0)錯体により芳香環 C–H 結合が活性化され、アリールヒドリドルテニウム(II)種を生じる。その後 Ru–H 結合への末端アルケンの挿入反応、続く還元的脱離反応により目的のアルキル化体 **1-3** を与える。このようにアルケンを用いた C–H アルキル化反応は、効率的に C–C 結合を形成できる手法として研究されている[3]。

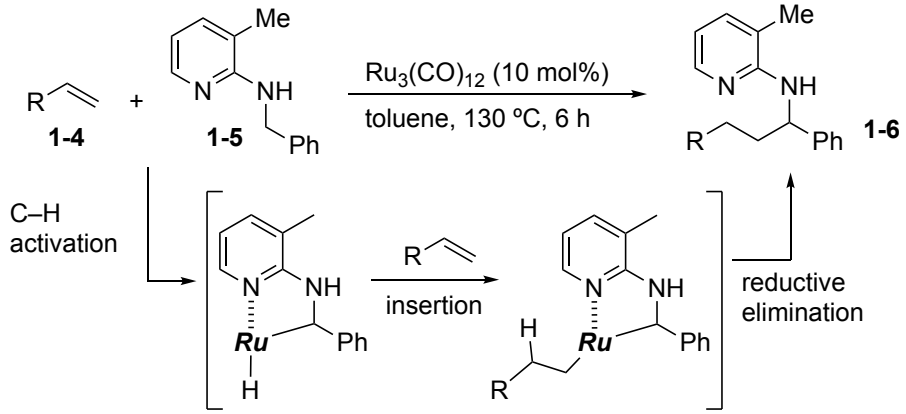
Scheme 1-1. Ru 触媒による芳香族ケトンを用いた末端アルケンのヒドロアリール化反応



遷移金属触媒による直接的な C(sp^3)–H 官能基化反応も近年活発に研究が進められている[4]。C(sp^3)–H 結合の活性化は、C(sp^2)–H 結合の活性化と比べて速度論的にも熱力学的にも好ましくないため、一般的に難しいと考えられている。Jun らは、ヘテロ原子に隣接する C(sp^3)–H が、隣接原子が炭素の場合よりも高い活性を持つことを利用して[5]、$Ru_3(CO)_{12}$ を用いたベンジルアミン誘導体 **1-5** の C(sp^3)–H 結合のアルキル化反応を 1998 年に達成した(Scheme 1-2)[6]。この反応では、ピリジル基の配位した Ru 触媒により窒素原子のα位 C(sp^3)–H 結合が活性化され、アルケンの挿入、還元的脱離

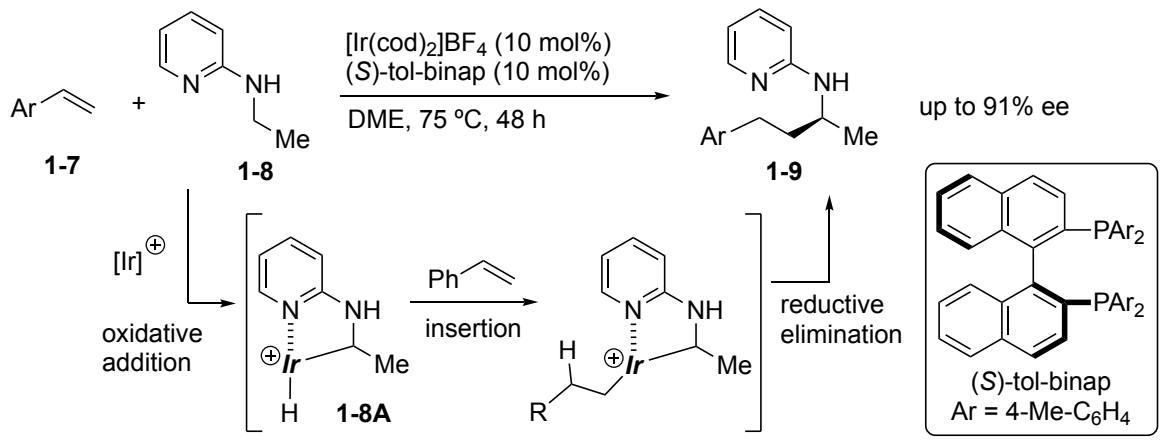
を経て目的のアルキル化体 **1-6** へと至る。この報告以来 *N*-(2-ピリジル)基は、窒素に隣接する C(sp^3)–H 結合を遷移金属触媒で活性化するために有用な配向基として研究されてきた。

Scheme 1-2. Ru 触媒による *N*-ベンジルアミンのアルキル化反応



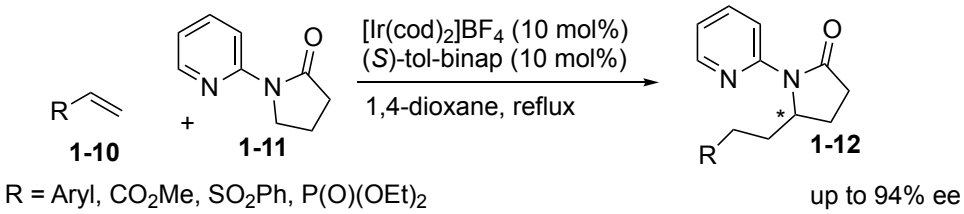
末端アルケンを用いた窒素原子 α 位 C(sp^3)–H の活性化を伴うアルキル化反応は、Ru[7]や Rh[8]のような第 5 周期遷移金属や、第 6 周期遷移金属である Ir 触媒を用いた開発が盛んに行われている。2011 年、柴田らはピリジル基を配向基とする非環状アルキルアミンの C(sp^3)–H 結合を、Ir 触媒を使ってエナンチオ選択的にアルキル化する反応を報告している(Scheme 1-3)[9]。2-(エチルアミノ)ピリジン **1-8** と 8 当量のスチレン類 **1-7** を、DME 中 75 ℃で 48 時間、[Ir(cod)$_2$]BF$_4$ (10 mol%)と(*S*)-tol-binap (10 mol%)存在下で反応させると、窒素原子 α 位 C(sp^3)–H がエナンチオ選択的にアルキル化された付加体 **1-9** が生成する。この反応系では、Ru 触媒を用いる C(sp^3)–H アルキル化反応よりも、温和な条件下で高効率的にアルキル化が進行する。反応系中で発生した活性なカチオン性イリジウム種 [Ir*]は、ピリジン窒素の配位を受けた後、エチルアミンの窒素に隣接する C(sp^3)–H 結合を切断し中間体 **1-8A** を生じる。中間体 **1-8A** の Ir–H 結合へアルケンが挿入し、続く還元的脱離を経てキラルアミン **1-9** をアルキル化体として得る。

Scheme 1-3. Ir 触媒を用いた 2-エチルアミノピリジンの α-C(sp^3)–H 不斉アルキル化反応



柴田らは 2015 年に、2-ピリジル配向基を持つγ-ブチロラクタム **1-11** の、アルケンによるエナンチオ選択的な C(sp^3)–H アルキル化反応を報告している(Scheme 1-4)[10]。[Ir(cod)$_2$]BF$_4$ と(*S*)-tol-binap 存在下、スチレン及び電子不足アルケン **1-10** を基質として用い、高エナンチオ選択的なアルキル化を達成している。

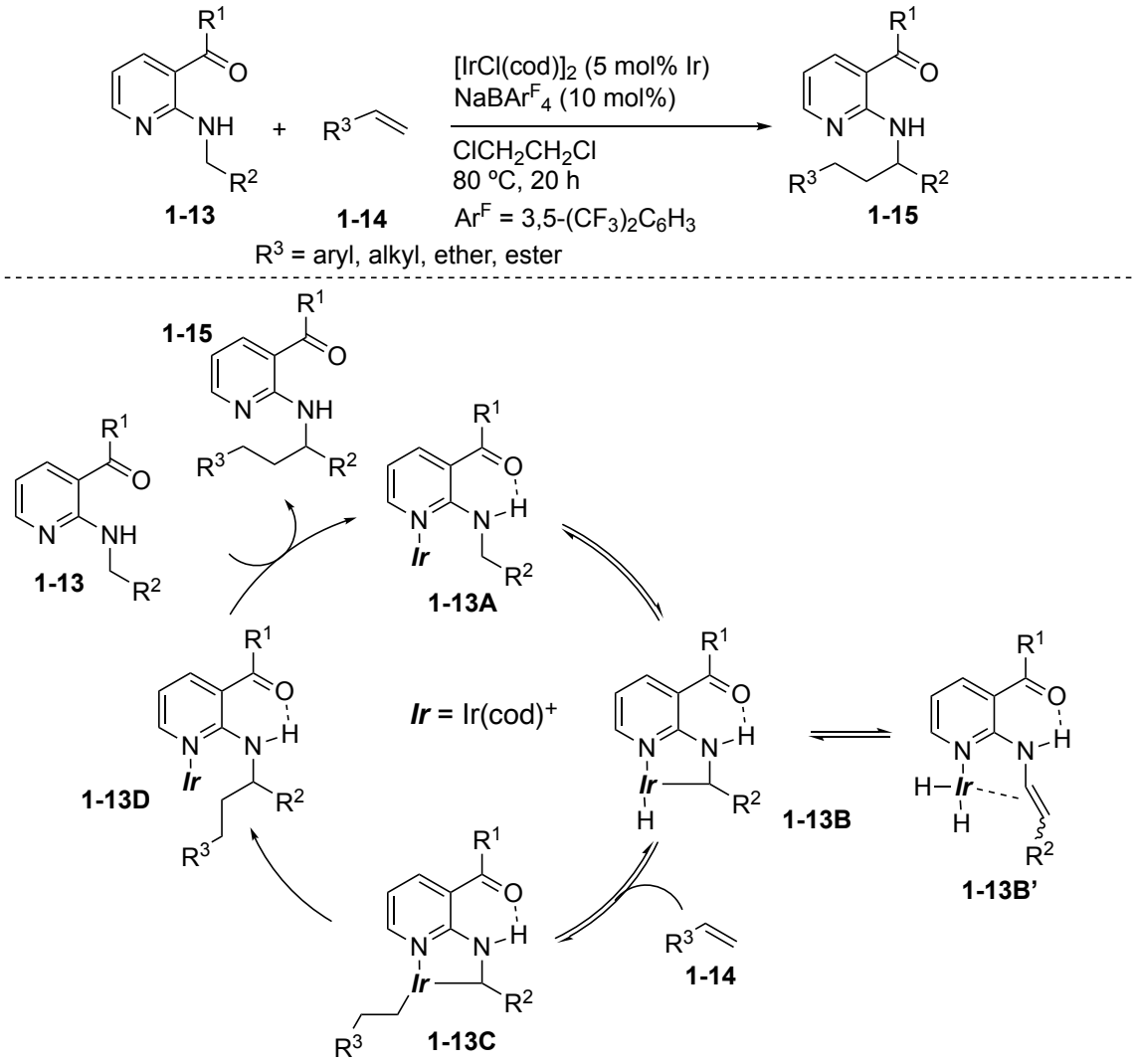
Scheme 1-4. γ-ラクタムと末端アルケンによるエナンチオ選択的アルキル化反応



西村らは、ピリジン C3 位にカルボニル基を導入した 2-(アルキルアミノ)ピリジン **1-13** と末端アルケン **1-14** による C(sp^3)–H アルキル化反応を報告している(Scheme 1-5)[11]。カチオン性イリジウム/1,5-シクロオクタジエン（cod）錯体存在下、窒素原子 α 位 C(sp^3)–H のアルキル化反応が進行する。ピリジル C3 位のカルボニル基により反応が飛躍的に促進されることを本研究で見出している。ピリジンのカルボニル部位にはアミドやケトン、エステルが適用でき、いずれの基質も高収率でアルキル化体 **1-15** を与えている。アルケンは、電子供与性および求引性基置換スチレン、単純な直鎖アルケン、アリルエステル、アリルアルコール、ビニルエーテル、アクリル酸エステルが適用可能である。重水素化したアルケン-***d*$_3$ を用いた重水素化実験を行った結果をもとに、Scheme 1-5 に示す触媒サイクルが提唱されている。ピリジン窒素からの配位を

受けたカチオン性 Ir 種 **1-13A** はアルキルアミンの αC–H 結合を活性化し、アルキル(ヒドリド)Ir 種 **1-13B** を与える。Ir–H 結合へのアルケン挿入によりアルキル Ir 種 **1-13C** を生じた後、不可逆的な還元的脱離と配位子交換を経てアルキル化体 **1-15** を与えつつ、Ir 触媒が再生する。Ir 種 **1-13B** からは、可逆的な β 水素脱離も起こっていることが、重水素標識反応の結果から明らかとなっている。

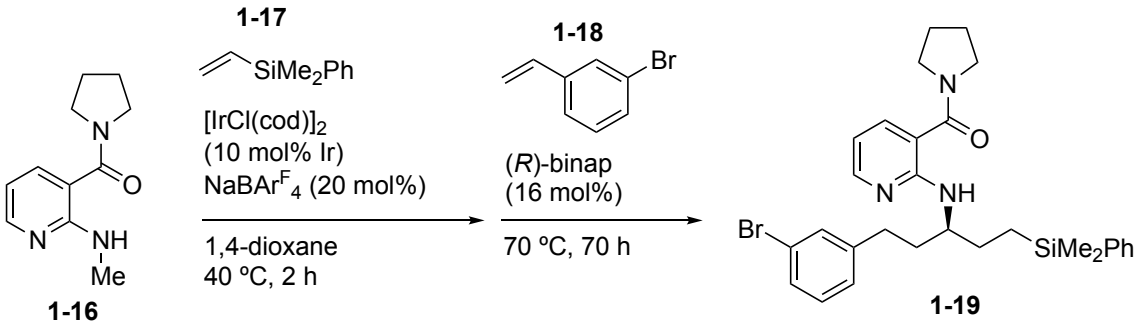
Scheme 1-5. 3-カルボニル 2-(アルキルアミノ)ピリジンとアルケンの C–H アルキル化



2018 年に西村らは、Ir 触媒を用いた 3-カルボニル-2-(メチルアミノ)ピリジン **1-16** の末端アルケンによる連続的 C(sp^3)–H 不斉アルキル化反応を報告している (Scheme 1-6)[12]。二種類の反応性の異なるアルケン **1-17**, **1-18** を、反応条件を変えながら逐次的に添加することにより、キラルな α-二置換アミン **1-19** をワンポットで合成することが可能である。より厳しい条件で反応させると、一段階目のアルケンの投入時点で

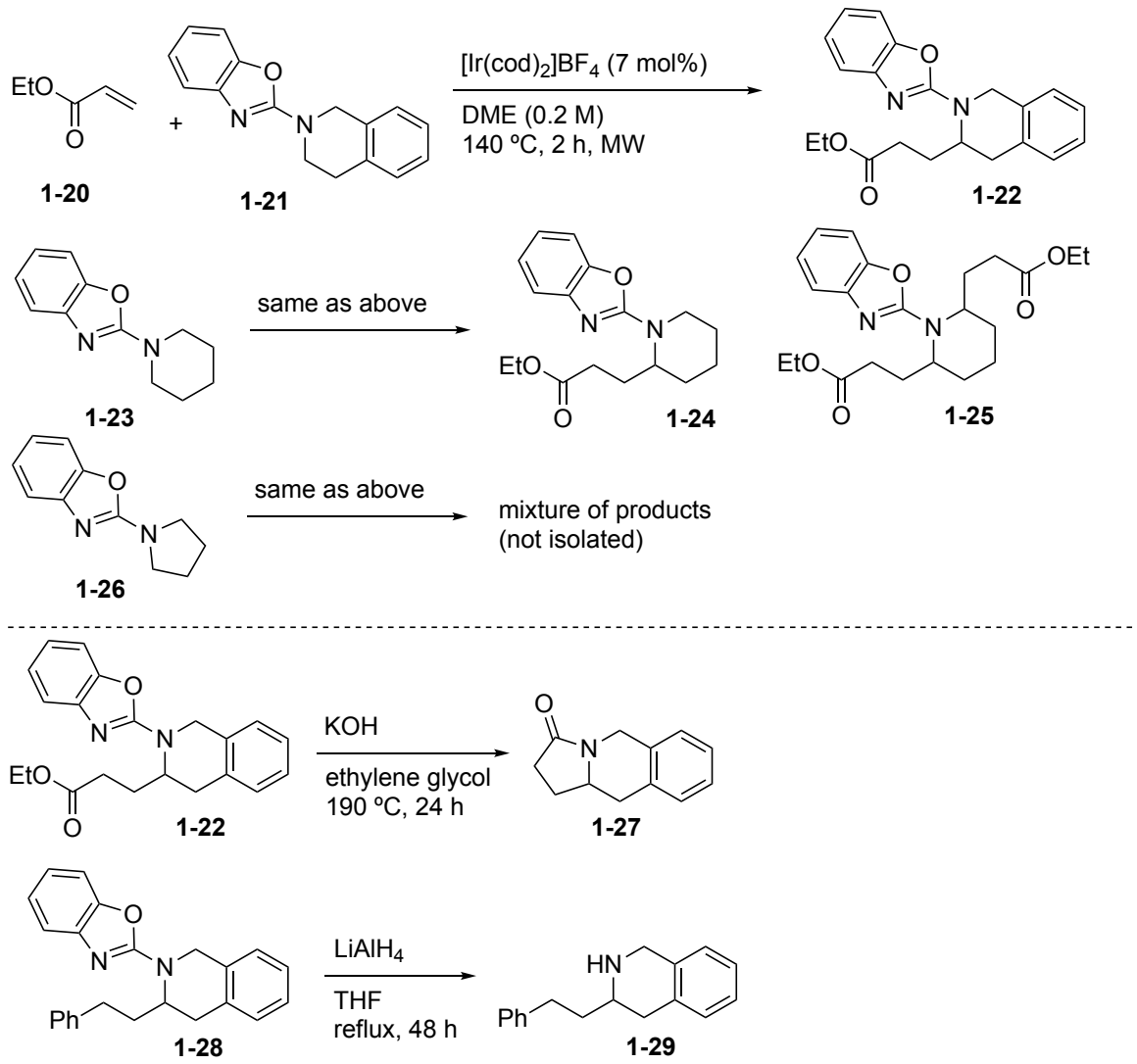
ジアルキル化体が生成するため、モノアルキル化体を得るためには温和な条件下で、ビニルシランまたはパーフルオロ-1-ヘキセンを用いることが必要である。その場合、中程度から高い収率で二種類のアルケンへ付加したジアルキル化体 **1-19** が 80～89% ee と良い選択性で得られる。

Scheme 1-6. 2-(メチルアミノ)ピリジンと二種類のアルケンとの連続的アルキル化



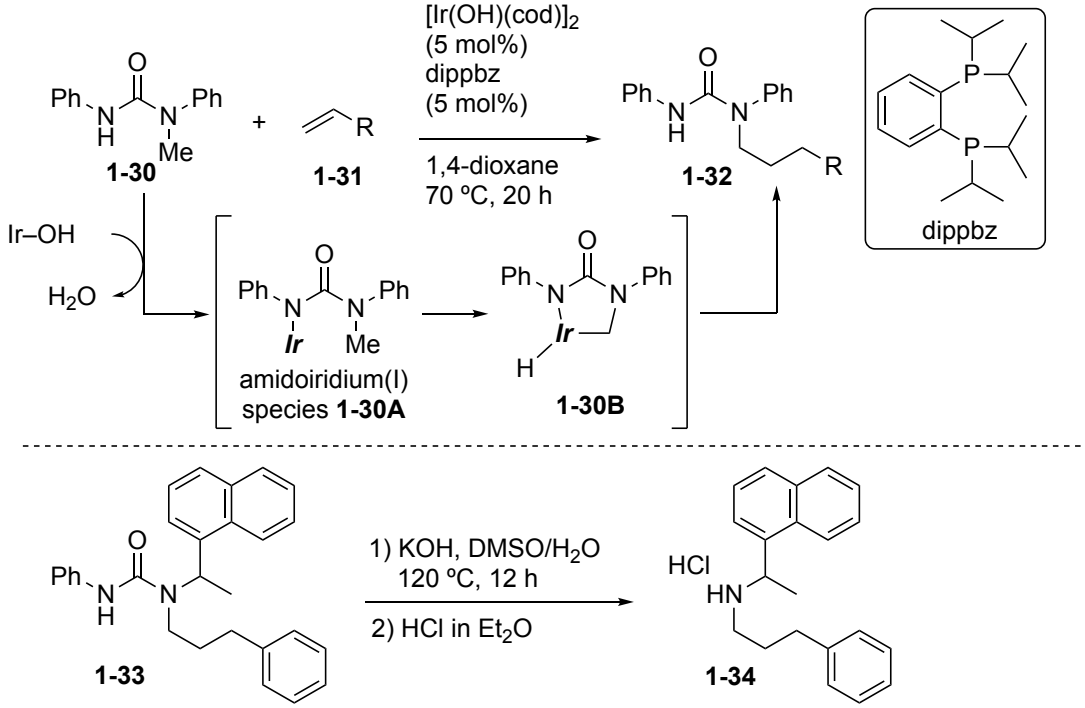
Ir 触媒による窒素原子 α 位 C(sp^3)–H アルキル化反応は、ピリジル基以外の配向基により進行することも知られている。2014 年に Opatz らは、ベンゾオキサゾールを配向基とする 1,2,3,4-テトラヒドロイソキノリン **1-21** の C3 位選択的な C–H アルキル化反応を報告している (Scheme 1-7)[13]。ベンゾオキサゾール誘導体 **1-21** は$[Ir(cod)_2]BF_4$ (7 mol%) 存在下、DME 中 140 ℃でアルケン **1-20** と反応し、1,2,3,4-テトラヒドロイソキノリンの 3 位がアルキル化された生成物 **1-22** を与える。ピリジル配向基をもつ基質で同様の反応を行うと、アルキル化生成物は低収率にとどまり、位置選択性も発現しない。本触媒系は、ピペリジン誘導体 **1-23** も適用でき、モノアルキル化体 **1-24** とジアルキル化体 **1-25** を与える。一方、ピロリジン誘導体 **1-26** の反応では複数の生成物が生じ、単離には至っていない。配向基として用いるベンゾオキサゾールは KOH、もしくは $LiAlH_4$ を用いた条件で除去することが可能である。例えば、**1-22** は KOH 存在下、190 °C という高温下で **1-27** へ変換される。また、**1-28** に $LiAlH_4$ を THF 中、80 °C で作用させるとアミン **1-29** が生成する。

Scheme 1-7. Ir 触媒によるベンゾオキサゾールを配向基とした飽和環状アミンの窒素原子 α 位 C(sp^3)–H アルキル化



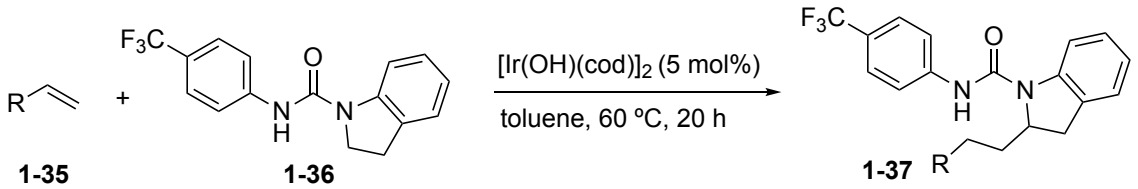
著者と西村らは 2017 年に、ヒドロキソイリジウム触媒を用いた尿素類縁体 **1-30** の C(sp^3)–H アルキル化反応を報告している (Scheme 1-8)[14]。この反応では尿素骨格の N–H 結合とヒドロキソイリジウムが脱水を伴いアミドイリジウム種 **1-30A** を生じ、NMe 基選択的に C(sp^3)–H 活性化を起こしヒドリドイリジウム種 **1-30B** を与える。その後アルケンの挿入、還元的脱離を経て目的のアルキル化体 **1-32** を得る。同報告内で、アルキル化体 **1-33** は加水分解によりアルキルアミン **1-34** へ変換可能であることが示されている。

Scheme 1-8. ヒドロキソイリジウム触媒を用いた尿素類縁体の C(sp^3)–H アルキル化



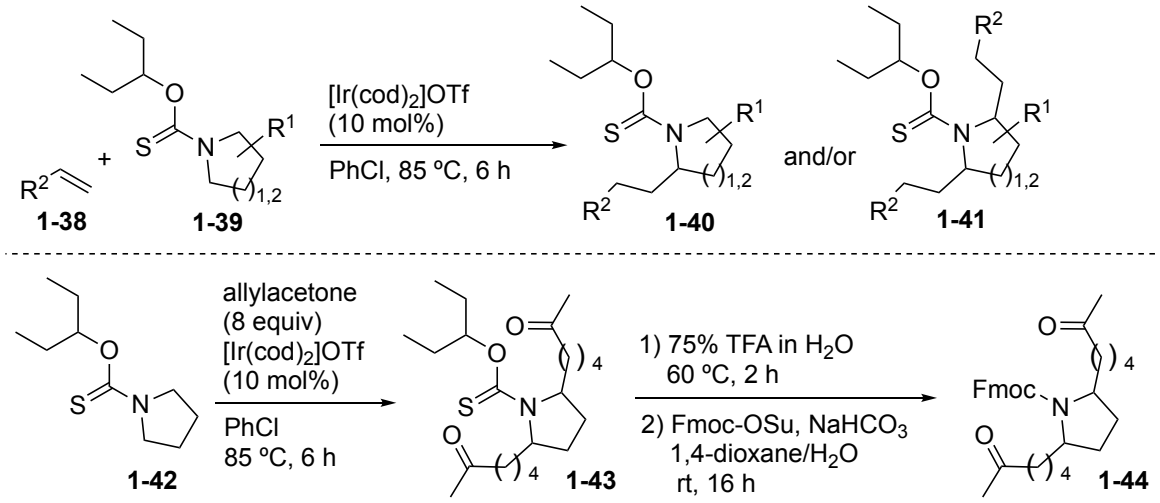
その後西村らは、ヒドロキソイリジウムと尿素 N–H 部分を配向基とした、インドリン誘導体 **1-36** の C(sp^3)–H アルキル化を報告している (Scheme 1-9)[15]。本反応ではインドリン 2 位選択的に C(sp^3)–H アルキル化が進行し、芳香環 7 位ではほとんど C(sp^2)–H アルキル化を起こさない。また、配向基部分の芳香環を電子不足にすることで収率が向上することを報告している。

Scheme 1-9. ヒドロキソイリジウムによるインドリン誘導体の C(sp^3)–H アルキル化



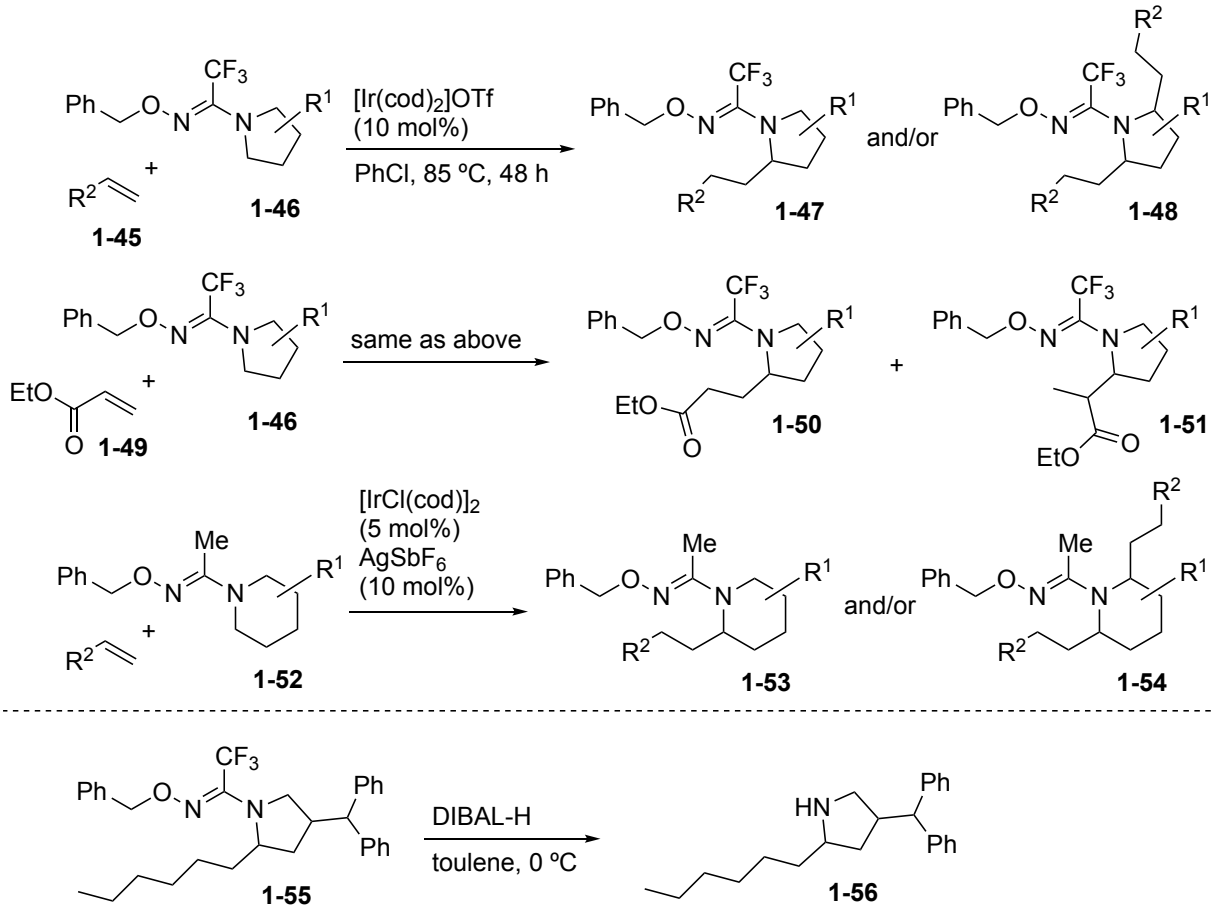
2017 年 Yu らのグループは、チオカルボニル基を有するピロリジン/ピペリジン **1-39** のアルキル化反応を報告している (Scheme 1-10)[16]。カチオン性イリジウムにより反応が進行し、モノアルキル化体 **1-40** とジアルキル化体 **1-41** を与える。チオカルボニル配向基は TFA による脱離が可能であり、**1-42** から得られたジアルキル化体 **1-43** は、Fmoc 体 **1-44** へと導くことが可能である。

Scheme 1-10. Ir 触媒によるチオカルボニル配向基を有する飽和環状アミンの窒素原子 α 位 C(sp^3)–H アルキル化



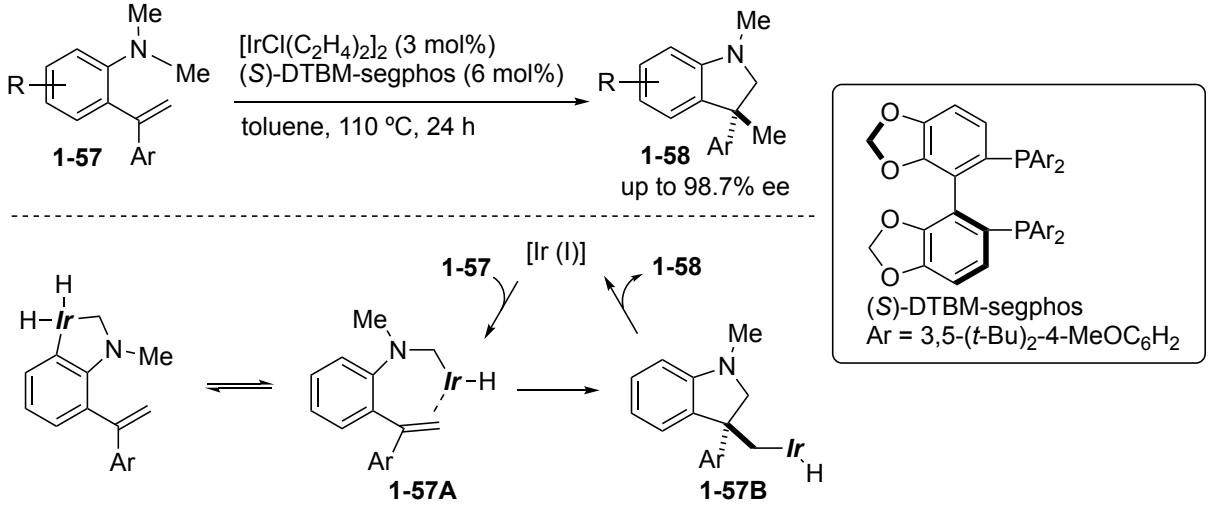
その後 Yu らは 2020 年に、アミドオキシム基が C(sp^3)–H アルキル化反応の配向基として利用可能であることを見出した(Scheme 1-11)[17]。 α-トリフルオロメチル-*O*-ベンジル-アミドオキシムを配向基として、カチオン性イリジウム触媒によるピロリジン **1-46** の窒素原子 α 位 C(sp^3)–H アルキル化が進行し、モノアルキル化体 **1-47** とジアルキル化体 **1-48** を与える。通常の末端アルケンを用いた際は直鎖選択的に反応が進行する。一方、アクリル酸エチル **1-49** を用いた場合、分岐型付加体 **1-51** も生成する。6 員環のピペリジンを基質として用いる場合、α 位をトリフルオロメチル基からメチル基へ変換することで収率が向上する。アミドオキシム部位は DIBAL-H を用いた除去が可能であり、アルキル化体 **1-55** を 1 工程でアミン **1-56** へと導いている。

Scheme 1-11. Ir 触媒によるアミドオキシム配向基を有する飽和環状アミンの窒素原子 α 位 C(sp^3)–H アルキル化



ピリジル基などのイミノ部位以外にも、分子内のアルケン部位を配向基とする C(sp^3)–H アルキル化が可能である。2017 年、大村らは$[IrCl_2(C_2H_4)_2]_2$ と segphos 系配位子存在下、トルエン中 110 ℃で分子内にアルケン部位を持つメチルアニリン **1-57** が不斉環化反応を起こすことを見出した (Scheme 1-12)[18]。基質の適用範囲が広く、高エナンチオ選択的に第四級不斉炭素中心の構築が可能である。この反応では、C=C 結合からの配位を受けたヒドリド Ir 種がメチルアニリンの C–H 結合を活性化し Ir 種 **1-57A** を生じる。続いて Ir–C 結合へのアルケン挿入により Ir 種 **1-57B** を生じた後、還元的脱離により再生した触媒と環化生成物 **1-58** を与える。この反応における律速段階は C–H 結合の活性化の過程であると考えられている。

Scheme 1-12. 2-アルケニル-*N*-メチルアニリン **44** の不斉環化反応

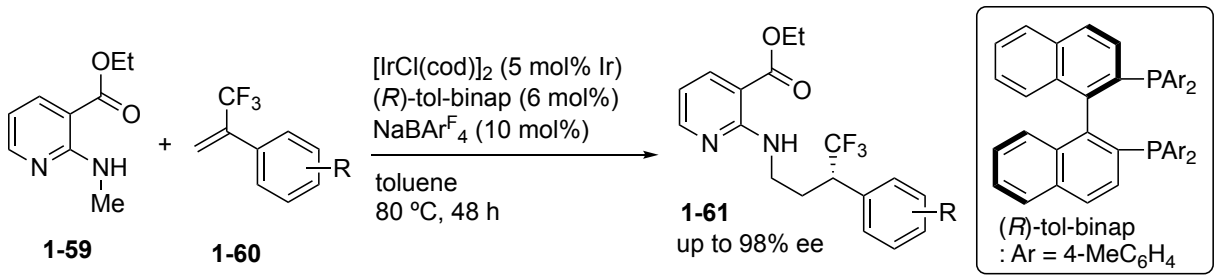


1-2. 本論文の概要

1-1 で述べた背景をもとに、筆者はカチオン性イリジウム触媒による窒素原子に隣接した C(sp^3)–H 活性化を伴うアルキル化反応の開発に着手し、２つの反応を開発した。

第二章では、3-エトキシカルボニル-2-メチルアミノピリジン **1-59** を用いたα-トリフルオロメチルスチレン **1-60** の不斉ヒドロアルキル化反応について述べる (Scheme 1-13)。この反応では、カチオン性イリジウムとキラルジホスフィン配位子を組み合わせることで目的のアルキル化反応が進行し、トリフルオロメチル含有アミン誘導体 **1-61** を高エナンチオ選択的に与えた。ピリジル基 3 位に嵩高い電子求引基を持つことが鍵である。

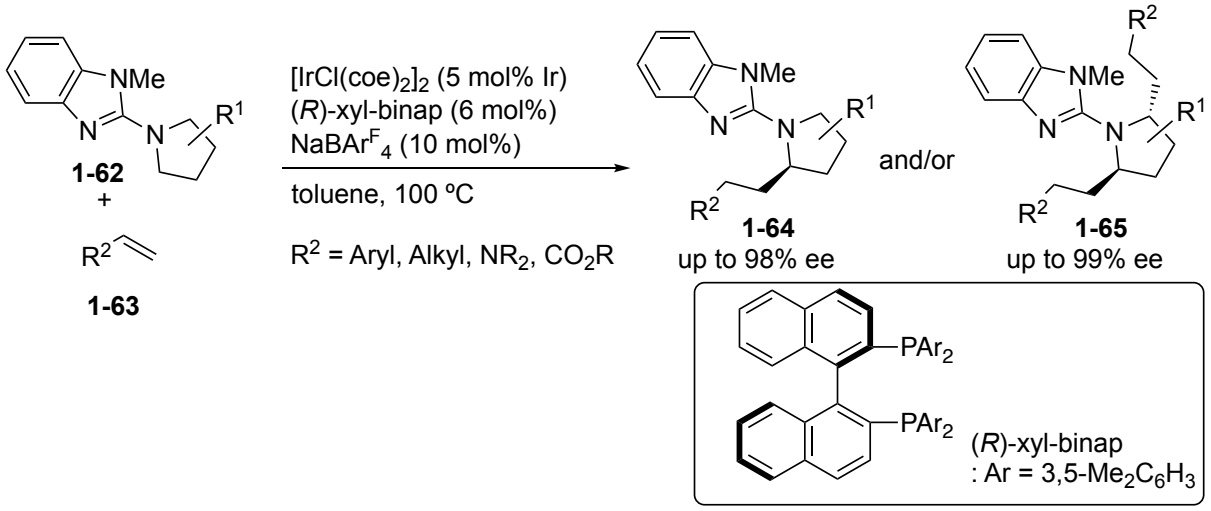
Scheme 1-13. C(sp^3)–H 活性化を伴うα-トリフルオロメチルスチレンの不斉ヒドロアルキル化反応



第三章では、*N*-メチルベンズイミダゾールを配向基とした飽和環状アミン **1-62** の窒素原子α位選択的な C(sp^3)–H 不斉アルキル化について述べる (Scheme 1-14)。カチ

オン性イリジウムとキラルジホスフィン配位子からなる触媒系により、対応するα-アルキル化体 **1-64** を高収率、高エナンチオ選択的に得た。また、キラルなα,α'-ジアルキル化体 **1-65** 合成にも、本触媒系が適用できることを見出した。

Scheme 1-14. 縮環ヘテロ芳香環を配向基とする飽和環状アミンの C(sp^3)–H 不斉アルキル化反応



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第二章

C(sp^3)–H 活性化を伴うα-トリフルオロメチルスチレンの不斉ヒドロアルキル化反応

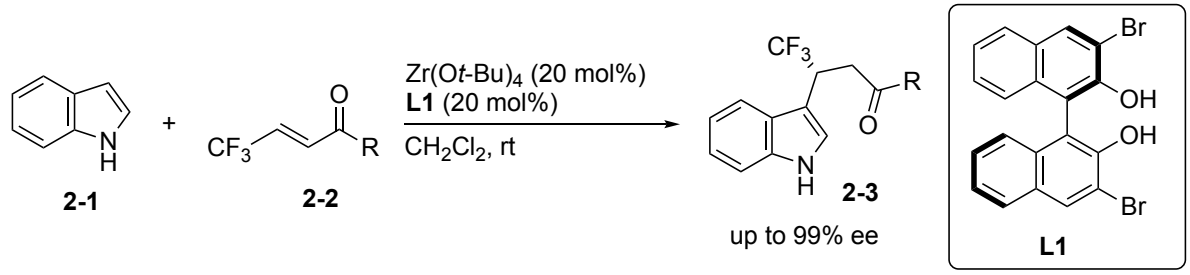
2-1. 本章の概要

本章では、3-エトキシカルボニル-2-メチルアミノピリジンを用いたα-トリフルオロメチルスチレンの不斉ヒドロアルキル化反応について述べる。本反応では、カチオン性イリジウムとキラルジホスフィン配位子を組み合わせた触媒を用いることで目的のアルキル化反応が進行し、トリフルオロメチル含有アミン誘導体を高エナンチオ選択的に与えた。また、ピリジル基 3 位に嵩高い電子求引基がある場合に、反応が効率よく進行することを見出した。

2-2. 研究の背景

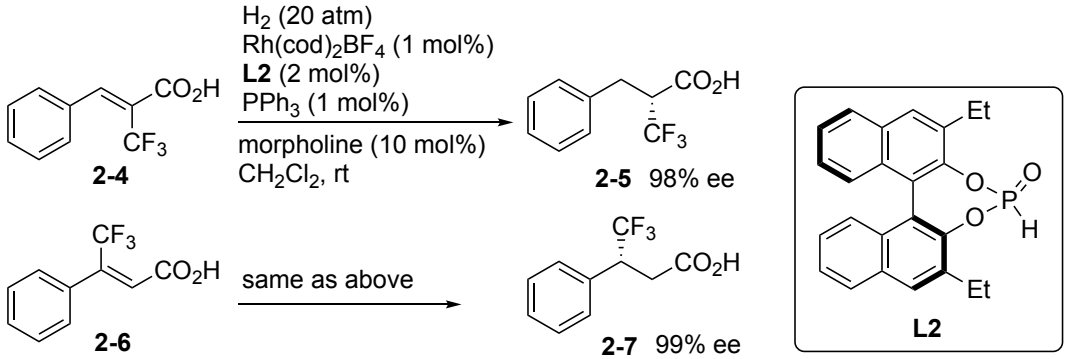
トリフルオロメチル（CF_3）基は脂溶性や膜透過性、代謝安定性など、分子特性に大きな影響を与える重要な構造の一つとして、医薬・農薬分野で活用されている[1]。C(sp^2)–CF_3 結合形成反応については数多く報告されているが、C(sp^3)–CF_3 結合形成し、かつ第三級炭素中心を構築する反応開発の例は比較的少ない[2]。トリフルオロメチル基を含む第三級炭素中心をエナンチオ選択的に合成する手法として、求核的トリフルオロメチル化反応、求電子的トリフルオロメチル化、ラジカルを経由したトリフルオロメチル化反応が報告されている[3]。さらに近年では、トリフルオロメチル基を含むプロキラルな基質を官能基化反応に適用し、不斉反応へと展開した研究がいくつか報告されている。トリフルオロメチル基を有する炭素–炭素二重結合を用いた官能基化反応[4]と遷移金属触媒によるトリフルオロメチル基を有する第二級アルキルハライドを用いたカップリング反応である[5]。例えば、2010 年に Pedro らはβ-トリフルオロメチル-α,β-不飽和ケトン **2-2** を用いたインドール **2-1** による不斉 1,4-付加反応を報告している (Scheme 2-1)[4c]。ジルコニウム触媒とキラル BINOL 配位子を組み合わせることでインドール 3 位での反応が進行し、トリフルオロメチル基を含む第三級炭素中心の構築を可能にしている。

Scheme 2-1. β-トリフルオロメチル-α,β-不飽和ケトン **2-2** への不斉 1,4-付加反応



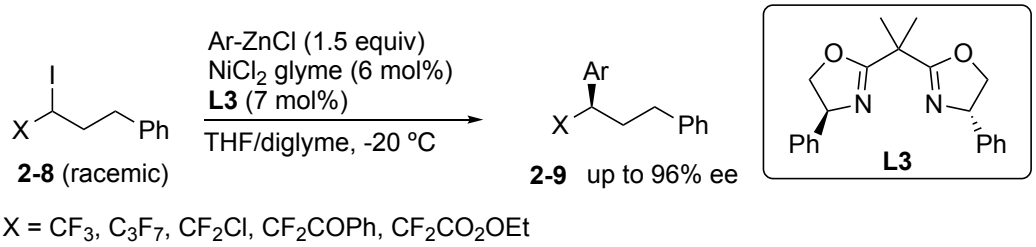
Ding らは 2013 年に、Rh 触媒を用いたβ-トリフルオロメチルアクリル酸 **2-4** の不斉水素化反応を報告している (Scheme 2-2)[4m]。カチオン性ロジウムとキラル第二級ホスフィンオキシドからなる触媒を用いると、高エナンチオ選択的に水素化反応が進行し対応する還元体 **2-5** を与える。またα-トリフルオロメチルアクリル酸 **2-6** を用いた際も同様に高エナンチオ選択的に水素化反応が進行する。

Scheme 2-2. トリフルオロメチル置換アクリル酸の不斉水素化反応



2015 年、Fu らは Ni 触媒を用いたトリフルオロメチル基含有第二級アルキルハライドを用いた不斉根岸カップリング反応を報告した (Scheme 2-3)[5a]。ラセミ体のトリフルオロメチル基含有第二級アルキルハライド **2-8** に対して、ニッケル/キラルビスオキサゾリン錯体を用いることで高エナンチオ選択的にアリール化反応が進行する。本反応では、トリフルオロメチル基以外のいくつかのフッ素含有基にも適用でき、それぞれ高立体選択的にアリール化反応が進行する。

Scheme 2-3. トリフルオロメチル置換アクリル酸の不斉水素化反応

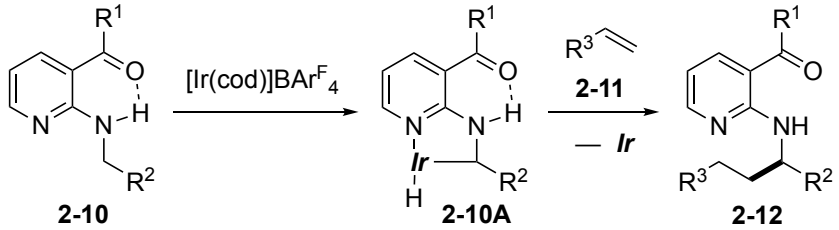


X = CF_3, C_3F_7, CF_2Cl, CF_2COPh, CF_2CO_2OEt

1-1 で示したように、遷移金属触媒を用いた窒素原子に隣接した C(sp^3)–H 活性化を伴う不斉アルキル化反応の多くでは、一置換アルケンが用いられてきた。一方、多置換アルケンは反応性の低下により、不斉アルキル化反応に用いた例は少ない[6]。

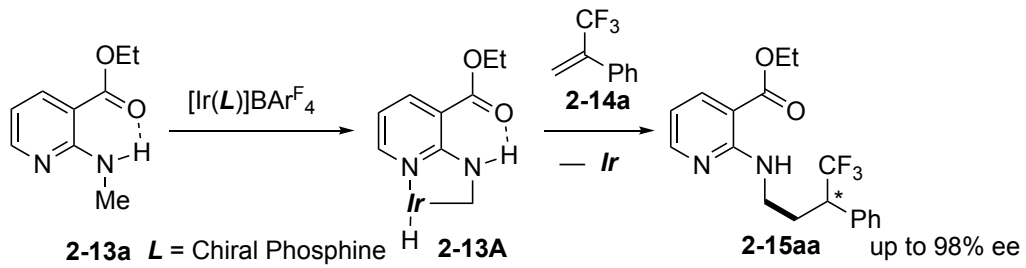
西村らは 2017 年に、カチオン性イリジウム触媒による、3-カルボニル 2-(アルキルアミノ)ピリジン **2-10** と末端アルケン **2-11** を用いた窒素原子 α 位での C(sp^3)–H アルキル化反応を報告している (Scheme 2-4)。**2-10** は N–H とピリジル基 3 位のカルボニル間で分子内水素結合を形成する[7]。コンフォーメーションが固定化されることで、窒素原子 α 位の C(sp^3)–H がイリジウムへ酸化的付加して生じる中間体 **2-10A** の形成が促進される。

Scheme 2-4. 3-カルボニル 2-(アルキルアミノ)ピリジン **2-10** の C(sp^3)–H アルキル化



筆者は、高活性な中間体 **2-10A** に着目し、多置換アルケンを用いたヒドロアルキル化反応の開発に着手した。実際に、カチオン性イリジウム/キラルビスホスフィン配位子存在下、1,1-二置換アルケン **2-13**、特に α-トリフルオロメチルスチレンを用いた際、目的のヒドロアルキル化反応が高い収率、高エナンチオ選択的に進行することを見出した (Scheme 2-5)。α-トリフルオロメチルスチレンはプロキラルな基質であり、本反応を用いることでトリフルオロメチル基を含む第三級不斉炭素中心の構築が可能となる。

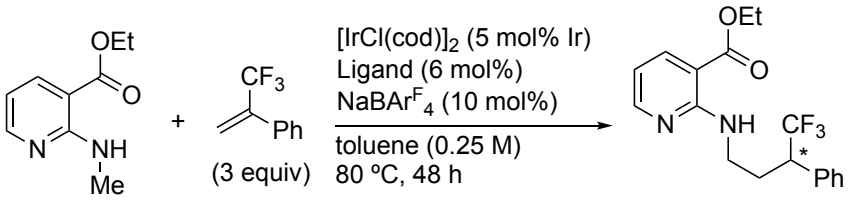
Scheme 2-5. イリジウム触媒による C(sp^3)–H 活性化を伴うα-トリフルオロメチルスチレンの不斉ヒドロアルキル化反応

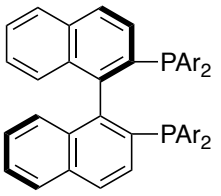


2-3. 結果と考察

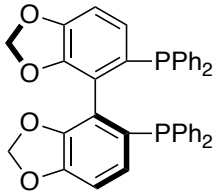
3-エトキシカルボニル-2-(メチルアミノ)ピリジン **2-13a** とα-トリフルオロメチルスチレン **2-14a** を、[IrCl(cod)]$_2$ (5 mol% Ir)、(*R*)-binap (6 mol%)、NaBAr$^F_4$ (10 mol%, Ar$^F_4$ = 3,5-(CF$_3$)$_2$C$_6$H$_3$)存在下、トルエン中 80℃で 48 時間反応させると、ヒドロアルキル化体 **2-15aa** が 92%収率、87% ee で得られた (Table 2-1, entry 1)。(*R*)-tol-binap は(*R*)-binap と同等のエナンチオ選択性を示したが (88% ee, entry 2)、(*R*)-xyl-binap はややエナンチオ選択性を低減させた (entry 3)。他のキラルジホスフィン配位子として(*S*)-segphos、(*S*,*S*)-QuinoxP*、(*S*,*S*)-chiraphos を用いたが、(*R*)-tol-binap と比べてエナンチオ選択性を下げる結果となった (entries 4-6)。本反応は、キラルジホスフィン配位子を添加せず、イリジウム/1,5-シクロオクタジエン錯体のみで進行し、**2-15aa** を 76%収率で与える (entry 7)。一方、NaBAr$^F_4$ を添加しない条件ではアルキル化反応は進行しなかった (entry 8)。触媒前駆体として[IrCl(coe)$_2$]$_2$ が本反応に適用でき、[IrCl(cod)]$_2$ と同等の結果を与えた (entry 9)。反応温度を 50 ℃に下げて反応を実施してもアルキル化反応は進行し、**2-15aa** が 85%収率、91% ee で得られた (entry 10)。本触媒系は、2.0 mmol のスケールでの反応にも適用でき、**2-15aa** を 99%収率、88% ee で得た (entry 11)。本反応はイリジウム触媒無しでは進行しない。

Table 2-1. イリジウム触媒による α-トリフルオロメチルスチレンの不斉ヒドロアルキル化反応

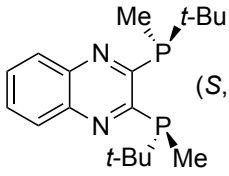




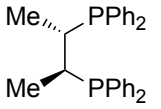
(*R*)-binap: Ar = Ph
(*R*)-tol-binap
: Ar = 4-Me-Ph
(*R*)-xyl-binap
: Ar = 3,5-Me-Ph



(*S*)-segphos



(*S*,*S*)-QuinoxP*



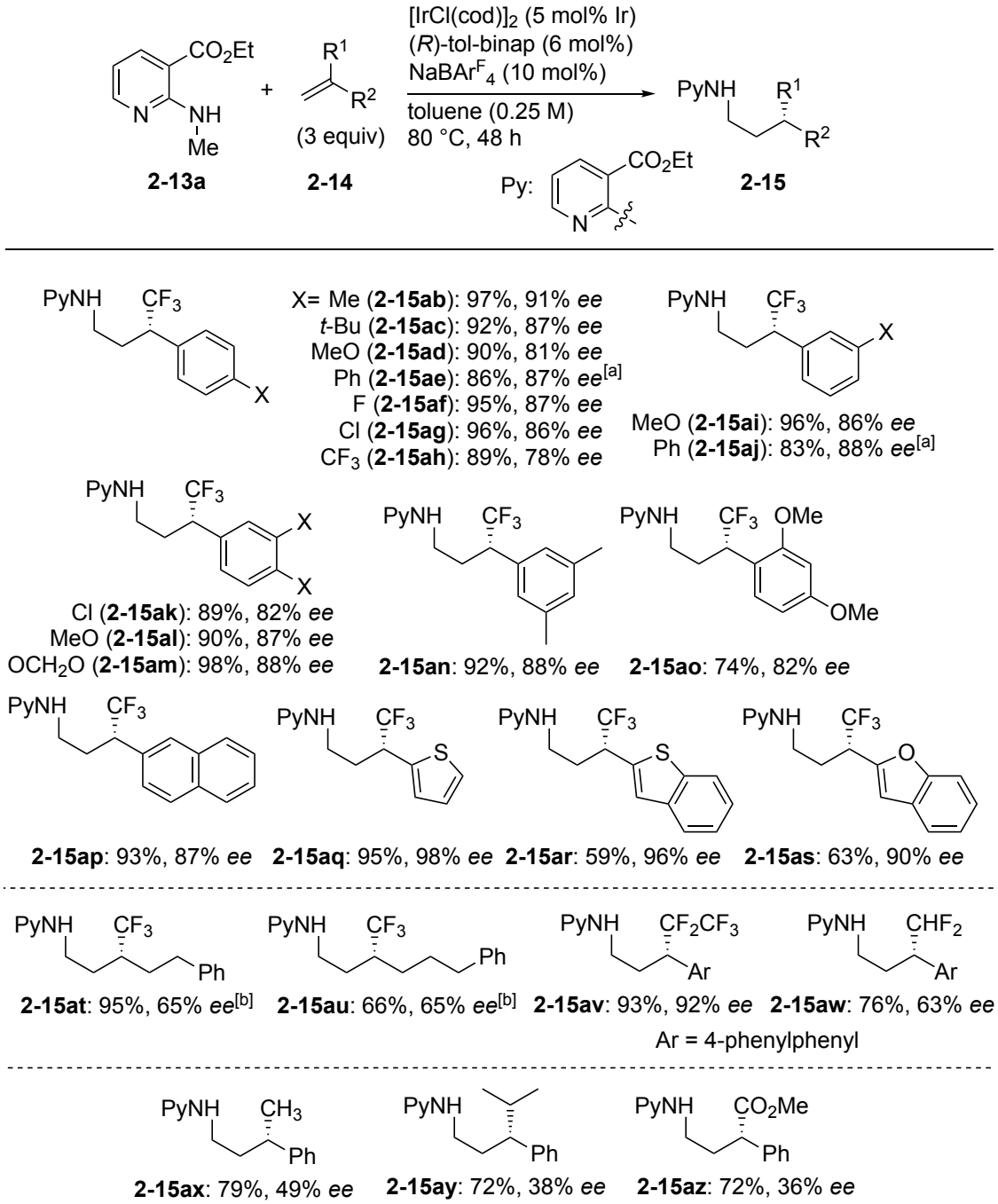
(*S*,*S*)-Chiraphos

Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	(*R*)-binap	92	87
2	(*R*)-tol-binap	94	88
3	(*R*)-xyl-binap	80	82
4	(S)-segphos	99	79
5	(*S*,*S*)-QuinoxP*	68	62
6	(*S*,*S*)-Chiraphos	24	24
7	—	76	—
8[d]	(*R*)-tol-binap	0	—
9[e]	(*R*)-tol-binap	85	88
10[f]	(*R*)-tol-binap	85	91
11[g]	(*R*)-tol-binap	99	88

[a] Reaction conditions: **2-13a** (0.10 mmol), **2-14a** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), ligand (6 mol%) and $NaBAr^F_4$ (10 mol%) in toluene (0.4 mL) at 80 °C for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Without $NaBAr^F_4$. [e] $[IrCl(coe)_2]_2$ was used instead of $[IrCl(cod)]_2$. [f] At 50 °C. [g] 20-Fold scale reaction (2.0 mmol of **2-13a**).

Scheme 2-6 に 3-エトキシカルボニル-2-(メチルアミノ)ピリジン **2-13a** を基質として、様々な 1,1-二置換アルケンに対する不斉ヒドロアルキル化を実施した結果をまとめた。パラ位置換α-トリフルオロメチルスチレンでの反応は、電子供与基（**2-14b-e**）、電子求引基（**2-14f-h**）いずれも適用でき、対応する付加体 **2-15ab-ah** を高い収率、高エナンチオ選択的に与えた（78-91% ee）。メタ位置換スチレン（**2-14i, 2-14j**）、二置換スチレン（**2-14k-o**）、ナフチル基を有する **2-14p** の反応はいずれも問題なく進行し、目的物 **2-15ai-ap** を高いエナンチオ選択性で得た。特筆すべき点として、本反応ではヘテロ芳香環を有するスチレンを用いた際にエナンチオ選択性が向上する。チオフェン（**2-14q**）、ベンゾチオフェン（**2-14r**）、ベンゾオキサゾール（**2-14s**）の中では、チオフェンを用いた場合の ee が高く、対応するアルキル化体 **2-15aq** が 98% ee で得られた。芳香環をアルキル基に置換したアルケン **2-14t** と **2-14u** を用いた際は、中程度のエナンチオ選択性でヒドロアルキル化反応が進行した（**2-15at**, **2-15au**）。α位のフルオロ基は付加体のエナンチオ選択性に影響を与える。α-ペンタフルオロエチルスチレン **2-14v** の反応は、付加体 **2-15av** を 93%収率、92% ee で与えた。一方、α-ジフルオロメチルスチレン **2-14w** の反応で得られた生成物 **2-15aw** は 63% ee であり、エナンチオ選択性の低下が見られた。トリフルオロメチル基をメチル基（**2-14x**）、イソプロピル基（**2-14y**）、メチルエステル基（**2-14z**）へ変換したが、いずれもエナンチオ選択性の大きな低下が確認された。

Scheme 2-6. 1,1-二置換アルケンの適用範囲

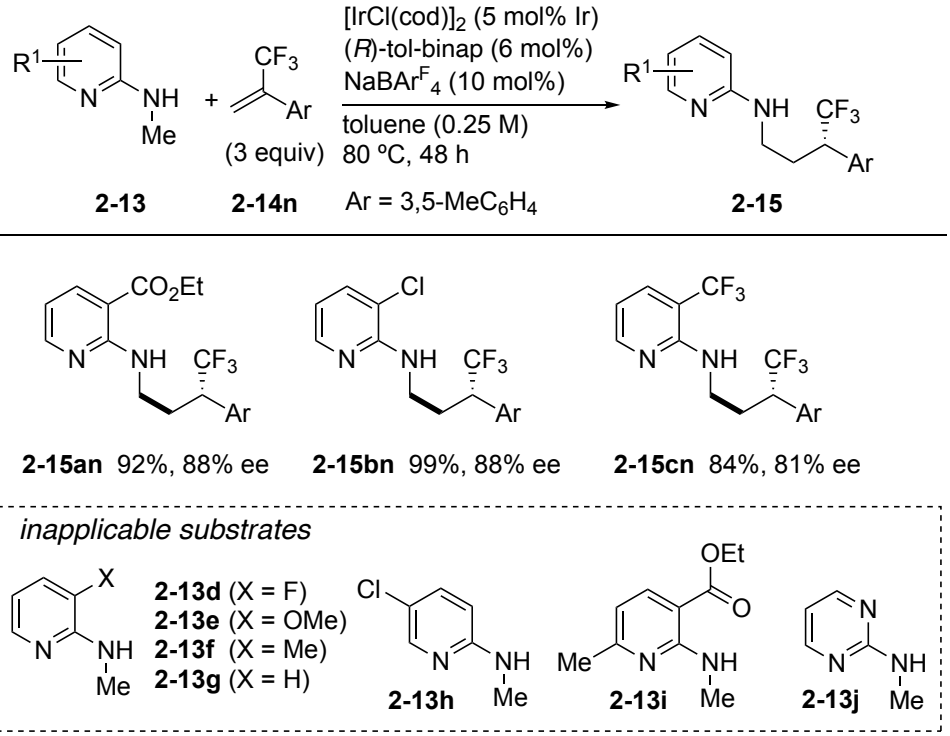


Reaction conditions: **2-13a** (0.10 mmol), **2-14** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), (*R*)-tol-binap (6 mol%) and $NaBAr^F_4$ (10 mol%) in toluene (0.4 mL) at 80 °C for 48 h. Isolated yields are shown. The *ee* was determined by chiral HPLC analysis. [a] (*R*)-Binap was used instead of (*R*)-tol-binap. [b] $[IrCl(coe)_2]_2$ was used instead of $[IrCl(cod)]_2$.

Scheme 2-7 に示すように、本反応では配向基として用いるピリジル基上の置換基は反応性に大きく影響を与える。3 位がエチルエステル基（**2-13a**）、クロロ基（**2-13b**）、トリフルオロメチル基（**2-13c**）で置換した 2-メチルアミノピリジンを使用すると、ア

ルケン **2-14n** との反応で目的のアルキル化体 **2-15an-cn** をそれぞれ高い収率、高エナンチオ選択的に与えた。一方、3 位をフルオロ基（**2-13d**）、メトキシ基（**2-13e**）、メチル基（**2-13f**）で置換した 2-メチルアミノピリジン、もしくは 2-メチルアミノピリジン **2-13g** を用いた場合アルキル化は進行しなかった。Ru 触媒による C(sp^3)–H 活性化において **2-13f** は効果的な基質であることが報告されているが[8]、本触媒系には適用できない。さらに、5-クロロ-2-メチルアミノピリジン **2-13h** では付加体を得ることはできなかった。これらの結果は、3 位に嵩高く、電子不足な特性を持つ置換基を導入することで、本反応が促進されることを示唆する。また電子求引基の導入位置が本反応に重要であることが明らかになった。6 位にメチル基を導入した **2-13i** では目的のアルキル化体は得られなかった。これはイリジウムへの配位阻害によるものと考察する。また、ピリミジル基は配向基として本触媒系に適用できなかった（**2-13j**）。

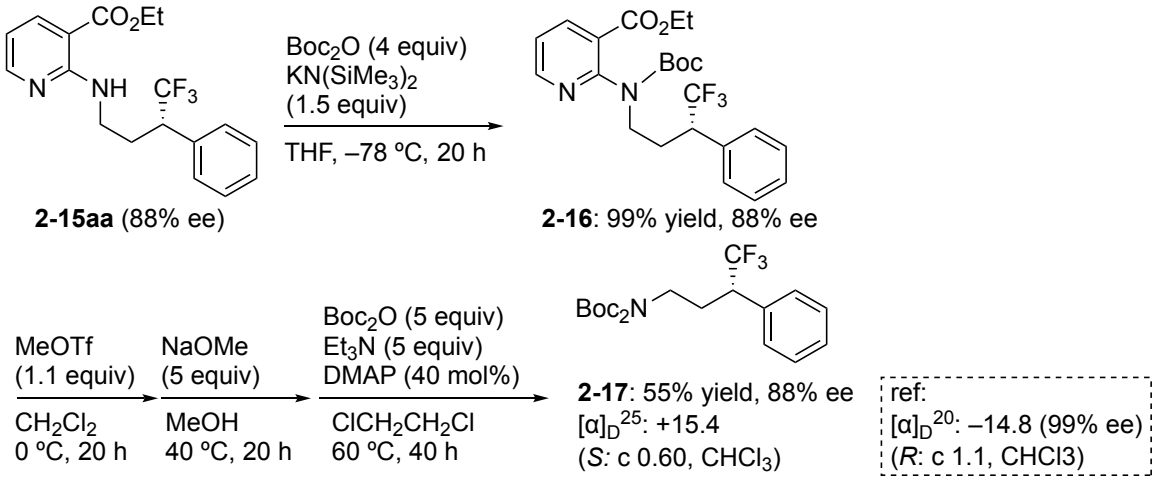
Scheme 2-7. ピリジル部位の置換基効果



Reaction conditions: **2-13** (0.10 mmol), **2-14n** (0.30 mmol), [IrCl(cod)]$_2$ (5 mol% of Ir) (*R*)-tol-binap (6 mol%), and NaBAr$^F_4$ (10 mol%) in toluene (0.4 mL) at 80 °C for 48 h. Isolated yields are shown. The *ee* was determined by chiral HPLC analysis.

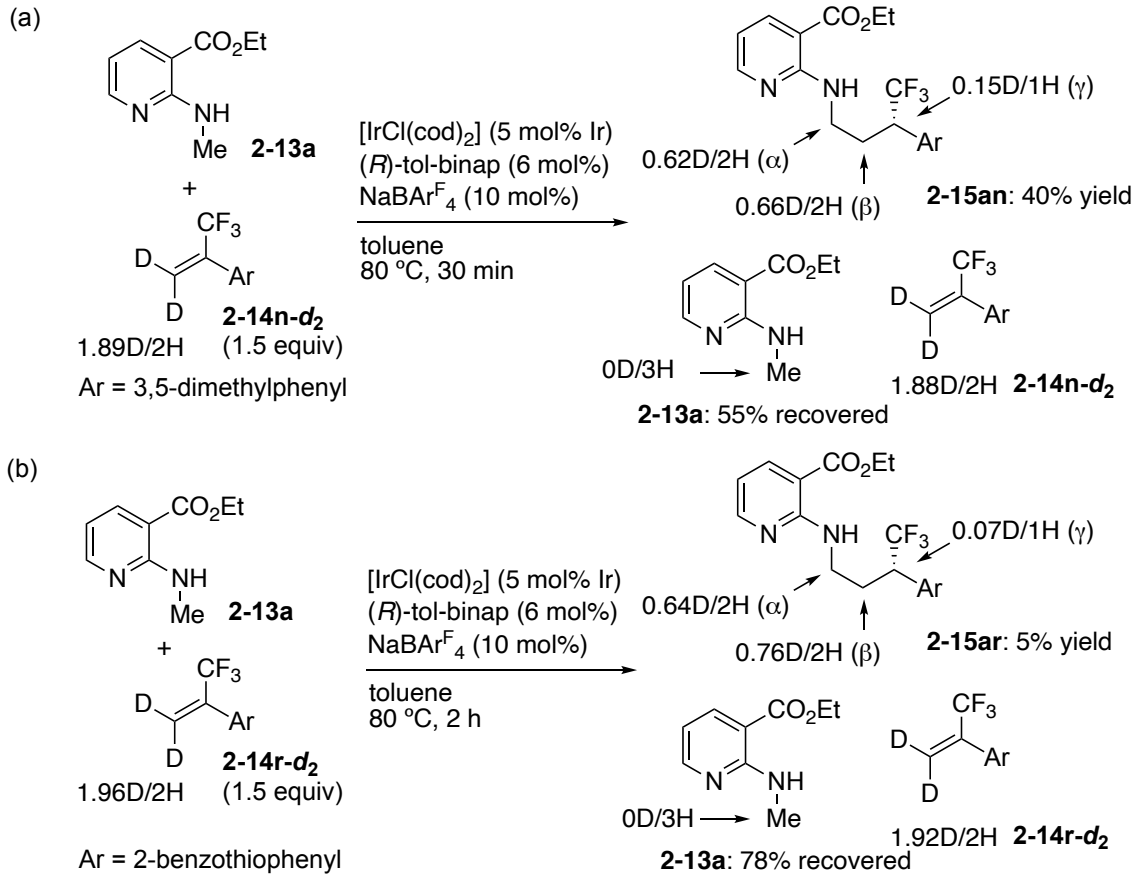
本反応の生成物が有するピリジル基は、boc 基への変換が可能であり、対応するキラルなγ分岐型アミンへ誘導できる。Scheme 2-8 に示すように、**2-15aa** から 4 工程で対応する di-boc 体 **2-17** へ変換した。この時エナンチオ選択性の低下は観測されていない。**2-17** の絶対配置は過去文献の比旋光度測定から *S* 体と決定した[4o]。

Scheme 2-8. ピリジル基の除去及び絶対配置の決定



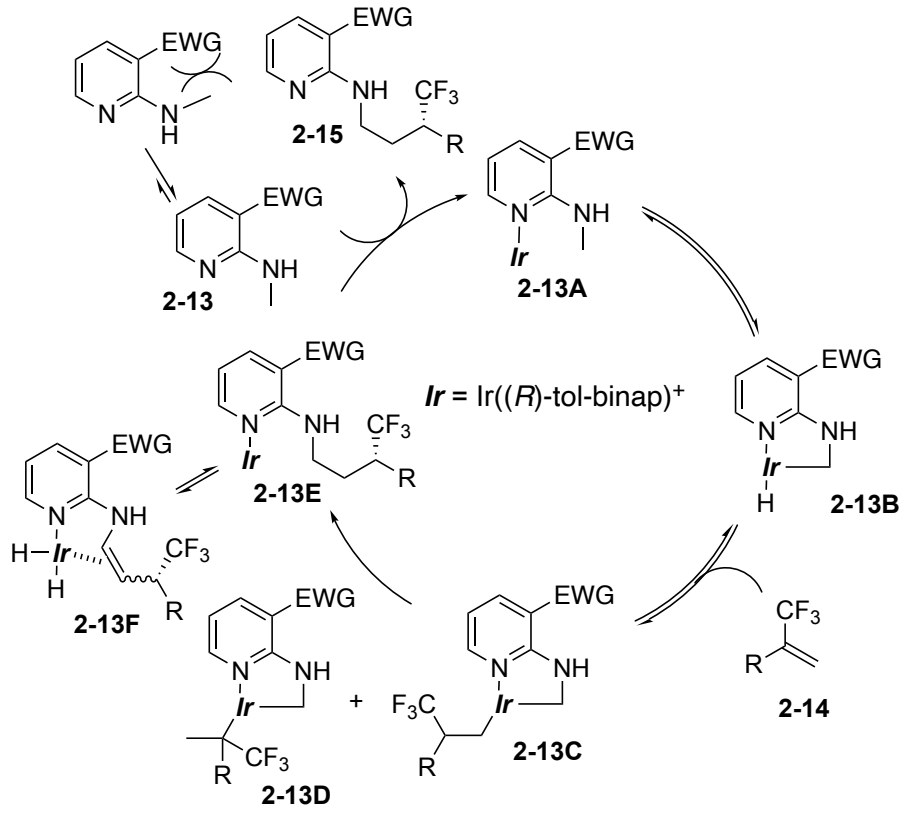
本ヒドロアルキル化反応の反応機構の情報を得るため、重水素ラベル実験を実施した（Scheme 2-9）。**2-13a** と重水素化アルケン **2-14n-*d*₂** (1.98D/2H)を 80 ℃で 30 分反応させると、アルキル化体 **2-15an** が 40%収率で得られた（Scheme 2-9a）。^{1}H NMR から **2-15an** の窒素原子α位、γ位それぞれに重水素が導入されていることが分かった。一方、原料 **2-13a** のメチル基には重水素の導入は見られなかった。異なるアルケン **2-14r-*d*₂** でも同様の傾向が見られた。アルケン **2-14r-*d*₂** (1.96D/2H)を用いて 80℃で 2 時間反応を行うと、アルキル化体 **2-15ar** が 5%収率で得られ、β位からα位、γ位への重水素の移動を観測した（Scheme 2-9b）。また、アルキル化体 **2-15an** (88% ee)を Ir/(*S*)-binap 触媒存在下加熱しても **2-15an** の ee の変化を観測できなかった。

Scheme 2-9. 重水素ラベル実験



以上の結果を踏まえて、今回の 1,1-二置換アルケンヒドロアルキル化反応の推定触媒サイクルを Scheme 2-10 に示す。ピリジル基の配位したイリジウムへ窒素原子 α 位の C(sp^3)–H が酸化的付加を起こし、ヒドリドイリジウム種 **2-13B** を与える。その後リニア選択的なアルケン **2-14** の挿入により中間体 **2-13C** を生じ、続く還元的脱離により **2-13E** を与える。**2-13** との配位子交換によりアルキル化体 **2-15** を与えるとともに、**2-13A** を再生する。重水素化ラベル実験で観測した β 位から α 位、γ 位への重水素の移動は、ブランチ選択的にアルケン **2-14** が挿入した **2-13D** により起きると考える。加えて **2-13E** の C(sp^3)–H 活性化、β 水素脱離を経て生じる **2-13F** も α 位での重水素交換に関わっていると想定する。

Scheme 2-10. 推定触媒サイクル



2-4. 本章のまとめ

本章では、筆者は 2-メチルアミノピリジン誘導体による C(sp^3)–H 活性化を経る、α-トリフルオロメチルスチレンの不斉ヒドロアルキル化反応について述べた。この反応は、カチオン性イリジウム/キラルジホスフィン触媒により促進され、トリフルオロメチル含有第三級炭素を有するγ-分岐型アミン誘導体を高エナンチオ選択的に与えた。

2-5. 実験項

2-5-1. General method

All manipulations of oxygen- and moisture-sensitive materials were carried out using standard Schlenk techniques under a nitrogen atmosphere. NMR spectra were recorded on a JEOL JNM ECZ-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) or Bruker DMX NMR spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) referenced to the residual peaks of $CDCl_3$ (δ 7.26) for ^{1}H NMR, and $CDCl_3$ (δ 77.00) for ^{13}C NMR. The following abbreviations are used; s, singlet: d, doublet: t, triplet: q, quartet: sext, sextet: m, multiplet: br, broad. High-resolution mass spectra were obtained with JEOL

AccuTOF LC-plus 4G spectrometer. Optical rotations were measured on JASCO P-2200 polarimeter. Flash column chromatography was performed with Silica Gel 70 PF_{254} (Wako). Preparative thin-layer chromatography was performed with Wakogel® B-5F (Wako).

2-5-2. Materials

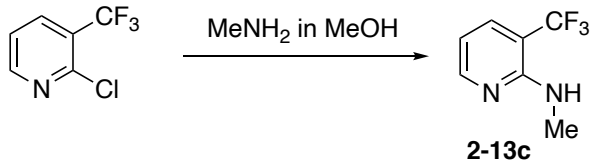
Dehydrated 1,2-dichloroethane, toluene, DMF, and 1,4-dioxane were purchased and used after deoxygenated by bubbling N_2. Iridium complexes, $[IrCl(cod)]_2$[9] and $[IrCl(coe)_2]_2$,[10] were prepared according to the reported procedures. $NaBAr^F{}_4$ was prepared according to the reported procedures.[11] Ligands, (*R*)-binap, (*R*)-tol-binap, (*R*)-DM-binap, (*S*)-segphos, (*S*,*S*)-QuinoxP*, (*S*,*S*)-chiraphos, were purchased from commercial suppliers and used as received. The corresponding racemic products were prepared by using racemic binap as a ligand. Other chemicals were purchased from commercial suppliers and used as received.

2-5-3. Preparation of methylamine derivatives 2-12 and alkenes 2-13

Compound **2-13g** (CAS: 4597-87-9) was purchased from commercial suppliers and used as received. Compounds **2-13a** (CAS: 103976-61-0),[12] **2-13b** (CAS: 468718-67-4),[13] **2-13e** (CAS: 902837-10-9),[14] and **2-13f** (CAS: 156267-13-9)[13] were prepared according to the reported procedures.

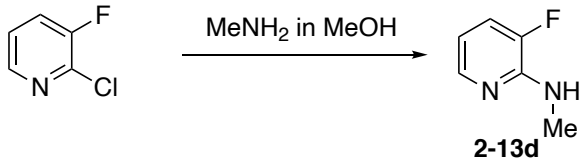
Alkenes **2-14x** was purchased from commercial suppliers and used as received. **2-14a** (CAS: 384-64-5),[15] **2-14b** (CAS: 69843-09-0),[15] **2-14c** (CAS: 185140-55-0),[15] **2-14d** (CAS: 69843-08-9),[15] **2-14e** (CAS: 1601477-35-3),[15] **2-14f** (CAS: 655-29-8),[15] **2-14g** (CAS: 69843-10-3),[15] **2-14h** (CAS: 155855-37-1),[15] **2-14i** (CAS: 946614-13-7),[15] **2-14j** (CAS: 2369617-16-1),[15] **2-14k** (CAS: 1261137-92-1),[15] **2-14l** (CAS: 1989676-91-6)[15], **2-14m** (CAS: 437552-55-1),[15] **2-14n** (CAS: 185140-57-2),[15] **2-14o** (CAS: 2358848-30-1),[16] **2-14p** (CAS: 136476-29-4),[15] **2-14q** (CAS: 1422521-62-7),[15] **2-14r** (CAS: 1541177-26-7),[15] **2-14s** (CAS: 2071669-70-8),[15] **2-14t** (CAS: 437552-58-4),[17] **2-14u** (CAS: 112298-41-6),[17] **2-14v** (CAS: 1808992-30-4),[18] **2-14w** (CAS: 1352954-05-2),[19] **2-14y** (CAS: 17498-71-4),[20] and **2-14z** (CAS: 1865-29-8)[21] were prepared according to the reported procedures.

Procedures for the preparation of compounds **2-13c** (CAS: 1036584-14-1), **2-12d** (CAS: 220714-69-2), **2-13h** (CAS: 4214-80-6),[22] **2-13i** (CAS: 1882650-38-5), **2-13n** (CAS: 185140-57-2), **2-13n-*d*$_2$**, and **2-13r-*d*$_2$** were shown below.



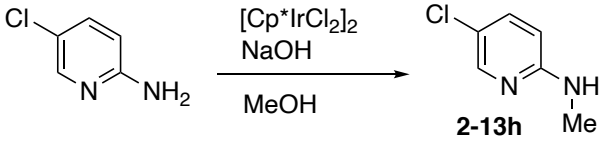
2-13c

Compound 2-13c: To a 2-chloro-3-trifluoromethylpyridine (3.63 g, 20 mmol) in a pressure bottle with a Teflon valve was added $MeNH_2$ (9.8 M in MeOH, 20 mL, 200 mmol). The mixture was heated at 80 °C for 3 days with stirring. The mixture was concentrated on a rotary evaporator, and the residue was subjected to flash column chromatography on silica gel (hexane: EtOAc = 10:1) to give **2-13c** as a colorless oil (2.46 g, 70% yield). ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J = 4.8 Hz, 1H), 7.63 (d, J = 6.8 Hz, 1H), 6.60 (dd, J = 6.8, 4.8 Hz, 1H), 4.96–4.83 (br, 1H), 3.04 (d, J = 5.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.2, 151.6 (q, $J_{F\text{-}C}$ = 29 Hz), 134.8 (d, $J_{F\text{-}C}$ = 5 Hz), 124.5 (q, $J_{F\text{-}C}$ = 271 Hz), 112.0–110.2 (m), 108.6 (q, $J_{F\text{-}C}$ = 32 Hz), 30.4–27.2 (m). HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_7H_8N_2F_3$ 177.0640; Found 177.0628.



2-13d

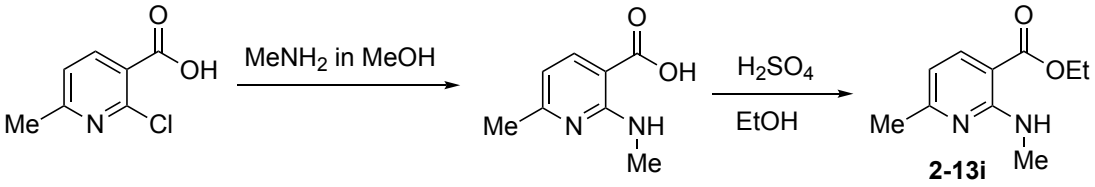
Compound 2-13d: 2-Chloro-3-fluoropyridine (575 mg, 5.0 mmol) in a pressure bottle with a Teflon valve was added $MeNH_2$ (9.8 M in MeOH, 5.1 mL, 50 mmol). The mixture was heated at 80 °C for 3 days with stirring. The mixture was concentrated on a rotary evaporator, and the residue was subjected to flash column chromatography on silica gel (hexane: EtOAc = 2:1) to give **2-13d** as a colorless oil (318 mg, 50% yield). ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 4.8 Hz, 1H), 7.11 (dd, J = 11.4, 7.8 Hz, 1H), 6.54–6.46 (m, 1H), 4.74–4.54 (br, 1H), 3.05 (d, J = 4.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.3 (d, $J_{F\text{-}C}$ = 11 Hz), 147.3 (d, $J_{F\text{-}C}$ = 252 Hz), 143.6–142.1 (m), 120.3–118.8 (m), 112.6–110.7 (m), 29.6–26.7 (m). HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_6H_8N_2F_1$ 127.0672; Found 127.0665.



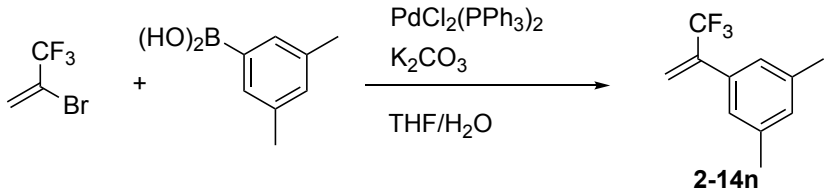
2-13h

Compound 2-13h (CAS: 4214-80-6): A mixture of 2-amino-5-chloropyridine (257 mg, 2.0 mmol), methanol (1 mL), $[Cp^*IrCl_2]_2$ (1.6 mg, 0.0020 mmol), and NaOH (80 mg, 2.0 mmol) in a pressure bottle with a Teflon valve was heated at 150 °C for 12 h. The mixture was

concentrated on a rotary evaporator and the residue was subjected to flash column chromatography on silica gel (hexane: EtOAc = 3:1) to give **2-13h** as a colorless solid (223 mg, 78% yield). ^{1}H NMR ($CDCl_3$) δ 8.03 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.33 (d, *J* = 8.8 Hz, 1H), 4.63–4.49 (br, 1H), 2.90 (d, *J* = 4.8 Hz, 3H).

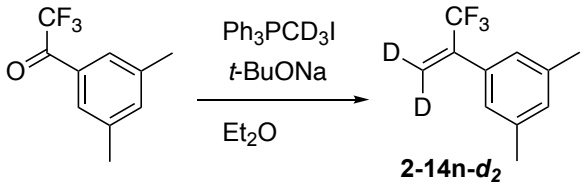


Compound 2-13i: To 2-chloro-6-methylnicotinic acid (858 mg, 5.0 mmol) in a pressure bottle with a Teflon valve was added $MeNH_2$ (9.8 M in MeOH, 5.1 mL, 50 mmol). The mixture was heated at 80 °C for 2 days with stirring, and the mixture was concentrated on a rotary evaporator. To the residue in EtOH (20 ml) was added conc. H_2SO_4 (1.4 mL) at room temperature. The mixture was stirred under reflux for 3 days. The mixture was poured into cold Na_2CO_3aq and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel (hexane: EtOAc = 4:1) to give **2-13i** as a colorless solid (490 mg, 51% yield for 2 steps). ^{1}H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.94–7.66 (br, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.05 (d, *J* = 5.2 Hz, 3H), 2.42 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.8, 163.5, 159.0, 139.9, 110.2, 103.2, 60.4, 25.1, 14.34, 14.27. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{10}H_{15}N_2O_2$ 195.1134; Found 195.1132.



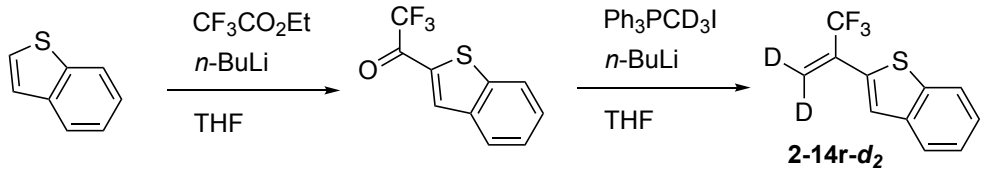
Compound 2-14n (CAS: 185140-57-2): (3,5-Dimethylphenyl)boronic acid (1.13g, 7.5 mmol) and $PdCl_2(PPh_3)_2$ (158 mg, 3 mol%) were placed in a Schlenk tube under N_2. 2-Bromo-3,3,3-trifluoroprop-1-ene (2.62 g, 15 mmol) in THF (15 mL) and K_2CO_3 (4.14 g, 30 mmol) in H_2O (10 mL) were added to the tube successively, and the mixture was stirred at 60 °C for 20 h. The reaction mixture was cooled to rt and filtered through a pad of celite with Et_2O.

The organic layer was separated and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel with hexane to give **2-14n** as a colorless oil (725 mg, 48% yield). ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 2H), 7.04 (s, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.74 (d, J = 1.2 Hz, 1H), 2.35 (s, 6H).



2-14n-*d*$_2$

Compound 2-14n-*d*$_2$: To a solution of Ph_3PCD_3I (CAS: 1560-56-1, 449 mg, 1.1 mmol)[23] in Et_2O (5 mL) was added sodium *tert*-butoxide (106 mg, 1.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. After cooling the mixture to –78 °C, 1-(3,5-dimethylphenyl)-2,2,2-trifluoroethan-1-one (202 mg, 1.0 mmol)[24] was added to the mixture. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The mixture was filtered and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel with hexane to give **2-14n-*d*$_2$** as a colorless oil (97 mg, 48% yield). Deuterium contents of **2-14n-*d*$_2$** was determined by ^{1}H NMR (1.89D/2H). ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 2H), 7.04 (s, 1H), 5.69–5.58 (m, 0.11H), 2.35 (s, 6H).



2-14r-*d*$_2$

Compound 2-14r-*d*$_2$: To a solution of benzothiophene (1.34 g, 10 mmol) in THF (20 mL) was added dropwise *n*-BuLi (1.6 M in THF, 7.5 ml, 12 mmol) at –78 °C and the mixture was stirred at the same temperature for 90 min. Then, ethyl trifluoroacetate (2.13 g, 15 mmol) was added to the mixture, and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. Saturated NH_4Cl solution was added to the mixture at 0 ºC, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel (hexane: EtOAc = 40:1) to give 2-benzothienyl trifluoromethyl ketone (1.51 g, 66% yield). To a solution of Ph_3PCD_3I (CAS: 1560-56-1, 470

mg, 1.15 mmol)[23] in THF (5 mL) was added *n*-BuLi (0.73 ml, 1.6 M in THF, 1.2 mmol) at –78 °C, and the mixture was stirred at the same temperature for 90 min. Then, 2-benzothienyl trifluoromethyl ketone (265 mg, 1.15 mmol) was added to the mixture, and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. Saturated NH_4Cl solution was added to the mixture at 0 ºC, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel with hexane to give **2-14r-*d*$_2$** as a colorless oil (1.11 g, 73% yield). Deuterium contents of **2-14r-*d*$_2$** was determined by ^{1}H NMR (1.96D / 2H). ^{1}H NMR ($CDCl_3$) δ 7.82–7.74 (m, 2H), 7.28 (d, *J* = 0.8 Hz, 1H), 7.40–7.34 (m, 2H), 5.95–5.90 (m, 0.04H).

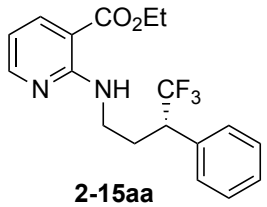
2-5-4. General procedure for Table 2-1

3-Ethoxycarbonyl-2-(methylamino)pyridine (**2-13a**: 18.0 mg, 0.10 mmol), $[IrCl(cod)]_2$ (1.7 mg, 0.0025 mmol, 5 mol% of Ir), a ligand (0.0060 mmol, 6 mol%), and $NaBAr^F{}_4$ (9.2 mg, 0.010 mmol, 10 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) and α-trifluoromethylstyrene (**2-14a**, 16.1 mg, 0.30 mmol) were added to the mixture successively, and the mixture was stirred at 80 °C for 48 h. The mixture was concentrated on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel (hexane/$CHCl_3$ = 2:3) to give **2-15aa**.

2-5-5. General procedure for Scheme 2-6 and 2-7

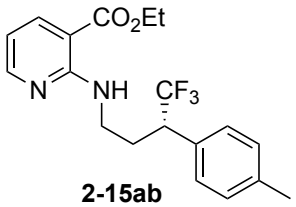
Methylamine derivatives **2-13** (0.10 mmol), $[IrCl(cod)]_2$ (1.7 mg, 0.0025 mmol, 5 mol% of Ir), (*R*)-tol-binap (0.0060 mmol, 6 mol%), and $NaBAr^F{}_4$ (9.2 mg, 0.010 mmol, 10 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) and alkene **2-14** (0.30 mmol) were added to the mixture successively, and the mixture was stirred at 80 °C for 48 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel to give **2-15**. The absolute configuration of **2-15aa** was determined to be (*S*)-(+) by correlation with compound **2-17**. The absolute configurations of other compounds were assigned by analogy with (*S*)- **2-15aa**.

2-5-6. Characterization of the products



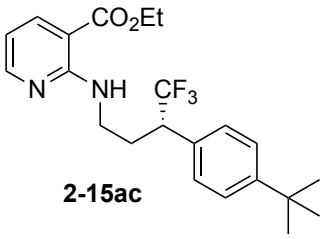
2-15aa

Compound 2-15aa (Table 2-1, entry 2; colorless oil, 33.0 mg, 94% yield, 88% ee; entry 11, 731 mg, 99% yield, 88% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 15.6 min (major), t_2 = 17.8 min (minor)); $[\alpha]^{20}_D$ +67.5 (*c* 1.08, $CHCl_3$) for 88% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.20–7.90 (br, 1H), 7.39–7.30 (m, 5H), 6.52 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.56–3.45 (m, 1H), 3.45–3.28 (m, 2H), 2.49–2.39 (m, 1H), 2.24–2.14 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 139.9, 134.2, 129.1, 128.7, 128.2, 126.9 (q, *J* = 280 Hz), 111.1, 106.2, 60.8, 47.8 (q, *J* = 27 Hz), 38.0, 28.6, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}F_3N_2O_2$ 353.1477; Found 353.1478.



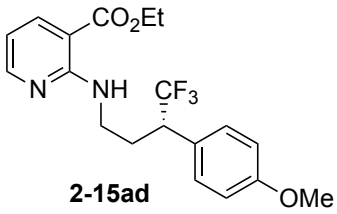
2-15ab

Compound 2-15ab (Scheme 2-6; colorless oil, 35.6 mg, 97% yield, 91% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak IC, hexane/EtOH = 500:1, flow 0.5 mL/min, 254 nm, t_1 = 19.9 min (minor), t_2 = 21.4 min (major)); $[\alpha]^{20}_D$ +79.6 (*c* 0.98, $CHCl_3$) for 91% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.98–7.92 (br, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.51 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.56–3.45 (m, 1H), 3.44–3.29 (m, 2H), 2.46–2.37 (m, 1H), 2.35 (s, 3H), 2.22–2.11 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 139.9, 138.0, 131.1, 129.4, 128.9, 127.0 (q, *J* = 279 Hz), 111.1, 106.2, 60.8, 47.8 (q, *J* = 27 Hz), 38.0, 28.6, 21.1, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}F_3N_2O_2$ 367.1633; Found 367.1640.



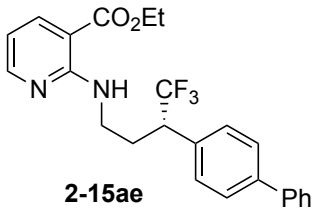
2-15ac

Compound 2-15ac (Scheme 2-6; colorless oil, 37.5 mg, 92% yield, 87% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak AD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 10.4 min (minor), t_2 = 11.1 min (major)); $[\alpha]^{20}_D$ +74.8 (*c* 0.99, $CHCl_3$) for 87% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.10 (dd, *J* = 7.4, 2.0 Hz, 1H), 8.20–7.93 (br, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.51 (dd, *J* = 7.4, 4.8 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.57–3.46 (m, 1H), 3.44–3.29 (m, 2H), 2.48–2.38 (m, 1H), 2.23–2.12 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 151.0, 139.9, 131.1, 128.7, 127.0 (q, *J* = 285 Hz), 125.6, 111.0, 106.2, 60.7, 47.3 (q, *J* = 27 Hz), 38.1, 34.5, 31.3, 28.6, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}F_3N_2O_2$ 409.2103; Found 409.2099.



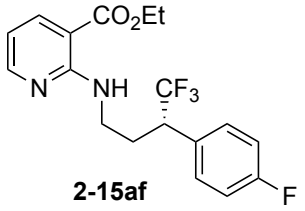
2-15ad

Compound 2-15ad (Scheme 2-6; colorless oil, 34.5 mg, 90% yield, 81% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OJ-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 14.3 min (major), t_2 = 16.5 min (minor)); $[\alpha]^{20}_D$ +77.7 (*c* 0.87, $CHCl_3$) for 81% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.11 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.03–7.90 (br, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.53 (dd, *J* = 7.4, 4.8 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.56–3.46 (m, 1H), 3.41–3.27 (m, 2H), 2.46–2.35 (m, 1H), 2.20–2.08 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 159.4, 158.4, 153.3, 139.9, 130.1, 127.2 (q, *J* = 237 Hz), 126.0, 114.1, 111.1, 106.2, 60.8, 55.2, 47.0 (q, *J* = 27 Hz), 38.0, 28.5, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}F_3N_2O_3$ 383.1583; Found 383.1579.



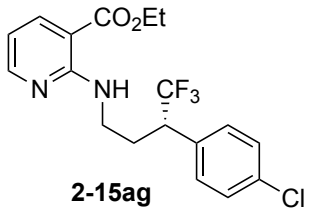
2-15ae

Compound 2-15ae (Scheme 2-6; pale yellow oil, 37.0 mg, 86% yield, 87% ee). A solution of hexane/EtOAc (4:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 18.7 min (minor), t_2 = 23.2 min (major)); $[\alpha]^{20}_D$ +84.7 (*c* 1.02, $CHCl_3$) for 87% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 4.6, 2.0 Hz, 1H), 8.10 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.03–7.94 (br, 1H), 7.61–7.55 (m, 4H), 7.47–7.33 (m, 5H), 6.53 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.62–3.51 (m, 1H), 3.50–3.36 (m, 2H), 2.51–2.42 (m, 1H), 2.30–2.19 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 141.1, 140.5, 139.9, 133.2, 129.5, 128.8, 127.4, 127.1, 126.9 (q, *J* = 280 Hz), 111.1, 106.2, 60.8, 47.6 (q, *J* = 27 Hz), 38.1, 28.6, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}F_3N_2O_2$ 429.1790; Found 429.1801.



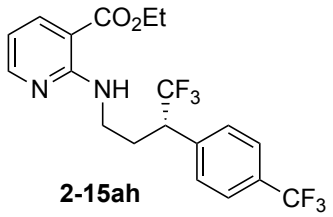
2-15af

Compound 2-15af (Scheme 2-6; colorless solid, 35.5 mg, 95% yield, 87% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 14.1 min (minor), t_2 = 16.9 min (major)); $[\alpha]^{20}_D$ +52.7 (*c* 0.98, $CHCl_3$) for 87% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 5.2, 2.0 Hz, 1H), 8.10 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.97–7.88 (br, 1H), 7.29 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.52 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.56–3.46 (m, 1H), 3.46–3.29 (m, 2H), 2.46–2.37 (m, 1H), 2.21–2.11 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 162.6 (d, *J* = 247 Hz), 158.4, 153.4, 139.9, 130.7 (d, *J* = 7.7 Hz), 130.0, 126.7 (q, *J* = 280 Hz), 115.7 (d, *J* = 22 Hz), 111.2, 106.2, 60.8, 47.2 (q, *J* = 27 Hz), 37.9, 28.6, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}F_4N_2O_2$ 371.1383; Found 371.1378.



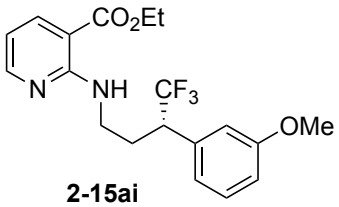
2-15ag

Compound 2-15ag (Scheme 2-6; colorless oil, 37.1 mg, 96% yield, 86% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 14.0 min (minor), t_2 = 16.2 min (major)); $[\alpha]^{20}_D$ +79.4 (*c* 1.07, $CHCl_3$) for 86% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 4.6, 2.2 Hz, 1H), 8.10 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.96–7.85 (br, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.52 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.57–3.47 (m, 1H), 3.46–3.30 (m, 2H), 2.46–2.36 (m, 1H), 2.23–2.12 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.4, 153.4, 139.9, 134.2, 132.7, 130.4, 128.9, 126.6 (q, *J* = 278 Hz), 111.2, 106.2, 60.8, 47.4 (q, *J* = 26 Hz), 37.9, 28.5, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}{}^{35}ClF_3N_2O_2$ 387.1087; Found 387.1081.



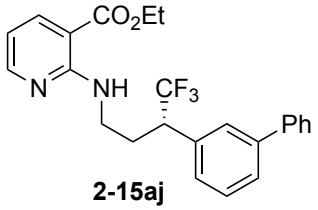
2-15ah

Compound 2-15ah (Scheme 2-6; colorless oil, 37.6 mg, 89% yield, 78% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 13.5 min (minor), t_2 = 16.7 min (major)); $[\alpha]^{20}_D$ +50.4 (*c* 1.05, $CHCl_3$) for 78% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, *J* = 4.6, 2.0 Hz, 1H), 8.09 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.99–7.90 (br, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 6.53 (dd, *J* = 7.6, 4.6 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.58–3.45 (m, 2H), 3.43–3.32 (m, 1H), 2.49–2.40 (m, 1H), 2.30–2.19 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.3, 153.3, 140.0, 138.4, 130.5 (q, *J* = 33 Hz), 129.5, 126.6 (q, *J* = 265 Hz), 125.6, 123.9 (q, *J* = 256 Hz), 111.3, 106.3,. 60.8, 47.9 (q, *J* = 28 Hz), 37.9, 28.5, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}F_6N_2O_2$ 421.1351; Found 421.1345.



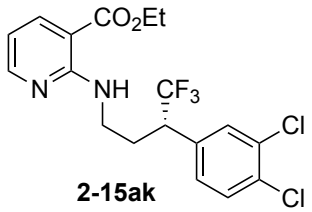
2-15ai

Compound 2-15ai (Scheme 2-6; colorless oil, 36.8 mg, 96% yield, 86% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak AD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 20.0 min (minor), t_2 = 21.7 min (major)); $[\alpha]^{20}_D$ +82.4 (*c* 0.37, $CHCl_3$) for 86% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 4.6, 2.2 Hz, 1H), 8.09 (dd, *J* = 7.6, 2.2 Hz, 1H), 8.01–7.91 (br, 1H), 7.26 (dd, *J* = 9.4, 6.0 Hz, 1H), 6.91 (d, *J* = 9.4 Hz, 1H), 6.86 (s, 1H), 6.85 (d, *J* = 6.0 Hz, 1H), 6.51 (dd, *J* = 7.6, 4.6 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.56–3.47 (m, 1H), 3.43–3.28 (m, 2H), 2.45–2.36 (m, 1H), 2.21–2.11 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 159.7, 158.5, 153.4, 139.9, 135.7, 129.7, 127.0 (q, *J* = 281 Hz), 121.4, 114.8, 113.6, 111.1, 106.2, 60.8, 55.2, 47.9 (q, *J* = 27 Hz), 38.0, 28.6, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}F_3N_2O_3$ 383.1583; Found 383.1589.



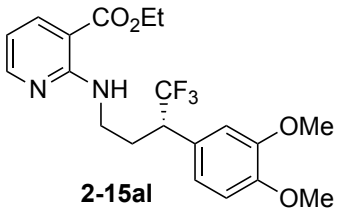
2-15aj

Compound 2-15aj (Scheme 2-6; colorless oil, 35.6 mg, 83% yield, 88% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 1.0 mL/min, 254 nm, t_1 = 9.1 min (major), t_2 = 17.9 min (minor)); $[\alpha]^{20}_D$ +79.4 (*c* 1.09, $CHCl_3$) for 88% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.06–7.98 (br, 1H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.48–7.42 (m, 3H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.51 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.64–3.54 (m, 1H), 3.54–3.46 (m, 1H), 3.45–3.34 (m, 1H), 2.53–2.42 (m, 1H), 2.34–2.22 (m, 1H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 141.7, 140.7, 139.9, 134.7, 129.1, 128.7, 128.1, 127.9, 127.4, 127.3, 127.1, 127.0 (q, *J* = 280 Hz), 111.1, 106.2, 60.8, 47.9 (q, *J* = 27 Hz), 38.0, 28.5, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}F_3N_2O_2$ 429.1790; Found 429.1787.



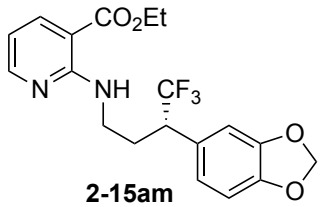
2-15ak

Compound 2-15ak (Scheme 2-6; pale yellow oil, 38.5 mg, 89% yield, 82% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-Hx2, hexane/2-propanol = 100:1, flow 0.5 mL/min, 254 nm, t_1 = 36.0 min (minor), t_2 = 45.1 min (major)); $[\alpha]^{20}_D$ +52.2 (*c* 0.98, $CHCl_3$) for 82% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.09 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.96–7.87 (br, 1H), 7.41 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.53 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.57–3.48 (m, 1H), 3.45–3.32 (m, 2H), 2.43–2.33 (m, 1H), 2.25–2.14 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.4, 153.3, 139.9, 134.5, 132.8, 132.5, 131.1, 130.5, 128.5, 126.4 (q, *J* = 279 Hz), 111.4, 106.2, 60.8, 47.3 (q, *J* = 27 Hz), 37.8, 28.4, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}F_3N_2O_2Cl_2$ 421.0697; Found 421.0697.



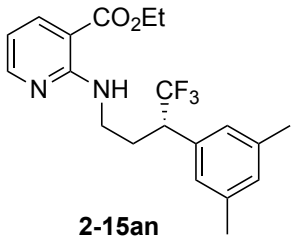
2-15al

Compound 2-15al (Scheme 2-6; colorless solid, 37.0 mg, 90% yield, 87% ee). A solution of hexane/EtOAc (4:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OJ-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 17.9 min (major), t_2 = 22.9 min (minor)); $[\alpha]^{20}_D$ +80.9 (*c* 1.24, $CHCl_3$) for 87% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.10 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.02–7.91 (br, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.82 (s, 1H), 6.52 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.61–3.50 (m, 1H), 3.41–3.27 (m, 2H), 2.45–2.34 (m, 1H), 2.20–2.09 (m, 1H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.4, 153.4, 149.0, 148.9, 139.9, 127.0 (q, *J* = 280 Hz), 126.5, 121.4, 111.9, 111.14, 111.05, 106.2, 60.7, 55.8, 47.4 (q, *J* = 27 Hz), 37.9, 28.5, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}F_3N_2O_4$ 413.1688; Found 413.1697.



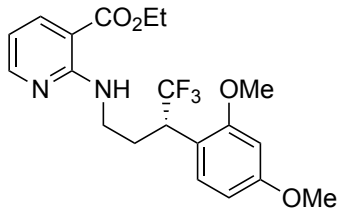
2-15am

Compound 2-15am (Scheme 2-6; pale yellow oil, 38.8 mg, 98% yield, 88% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 21.5 min (minor), t_2 = 24.2 min (major)); $[\alpha]^{20}_D$ +82.3 (*c* 1.40, $CHCl_3$) for 88% ee (*S*). ^1H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 5.0, 2.0 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.99–7.90 (m, 1H), 6.82 (s, 1H), 6.77 (s, 2H), 6.52 (dd, *J* = 7.8, 5.0 Hz, 1H), 5.96 (s, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.57–3.47 (m, 1H), 3.40-3.27 (m, 2H), 2.43–2.33 (m, 1H), 2.16–2.04 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 148.0, 147.5, 139.9, 127.7, 126.8 (q, *J* = 279 Hz), 123.0, 111.1, 108.9, 108.3, 106.2, 101.2, 60.8, 47.5 (q, *J* = 27 Hz), 37.9, 28.6, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}F_3N_2O_4$ 397.1375; Found 397.1370.



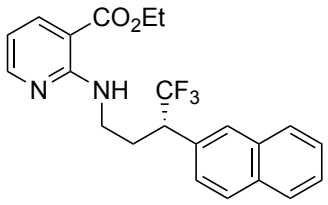
2-15an

Compound 2-15an (Scheme 2-6; colorless oil, 35.0 mg, 92% yield, 88% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 9.8 min (minor), t_2 = 11.3 min (major)); $[\alpha]^{20}_D$ +66.5 (*c* 1.02, $CHCl_3$) for 88% ee (*S*). ^1H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.10 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.99–7.92 (br, 1H), 6.95 (s, 1H), 6.92 (s, 2H), 6.51 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.53–3.43 (m, 1H), 3.42–3.26 (m, 2H), 2.47–2.34 (m, 1H), 2.31 (s, 6H), 2.22–2.12 (m, 1H),1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 139.9, 138.1, 134.0, 129.9, 127.0 (q, *J* = 279 Hz), 126.9, 111.0, 106.2, 60.7, 47.8 (q, *J* = 27 Hz), 38.1, 28.6, 21.3, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}F_3N_2O_2$ 381.1790; Found 381.1794.



2-15ao

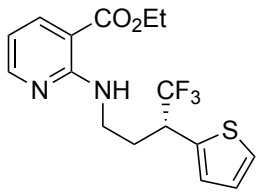
Compound 2-15ao (Scheme 2-6; colorless solid, 30.6 mg, 74% yield, 82% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 23.4 min (minor), t_2 = 32.4 min (major)); $[\alpha]^{20}_D$ +62.8 (*c* 0.95, $CHCl_3$) for 82% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.09 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.02–7.95 (br, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.51–6.46 (m, 2H), 6.45 (d, *J* = 2.8 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.13–4.01 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.63–3.51 (m, 1H), 3.30–3.19 (m, 1H), 2.41–2.31 (m, 1H), 2.09–1.99 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.3, 160.3, 158.9, 158.4, 153.3, 139.9, 128.7, 127.4 (q, *J* = 280 Hz), 115.1, 110.8, 106.1, 104.6, 98.4, 60.7, 55.5, 55.3, 37.8, 37.7 (q, *J* = 19 Hz), 28.7, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}F_3N_2O_4$ 413.1688; Found 413.1688.



2-15ap

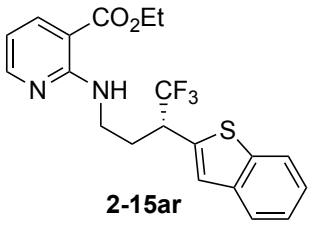
Compound 2-15ap (Scheme 2-6; pale yellow oil, 37.5 mg, 93% yield, 87% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 19.7 min (major), t_2 = 24.7 min (minor)); $[\alpha]^{20}_D$ +90.2 (*c* 0.82, $CHCl_3$) for 87% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 4.4, 2.0 Hz, 1H), 8.09 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.01–7.95 (br, 1H), 7.90–7.77 (m, 4H), 7.56–7.42 (m, 3H), 6.51 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.67–3.50 (m, 2H), 3.45–3.35 (m, 1H), 2.58–2.46 (m, 1H), 2.41–2.29 (m, 1H),1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.4, 158.4, 153.4, 139.8, 133.2, 133.1, 131.6, 128.8, 128.44, 128.38, 127.9, 127.6, 127.0 (q, *J* = 280 Hz), 126.24, 126.17, 111.1, 106.2, 60.7,148.1 (q, *J* = 27

Hz), 38.1, 28.6, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}F_3N_2O_2$ 403.1633; Found 403.1638.



2-15aq

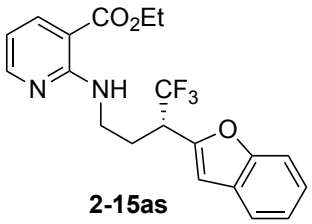
Compound 2-15aq (Scheme 2-6; colorless solid, 33.9 mg, 95% yield, 98% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OJ-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 12.3 min (major), t_2 = 13.8 min (minor)); $[\alpha]^{20}_D$ +92.5 (*c* 0.91, $CHCl_3$) for 98% ee (*R*). ^{1}H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.11 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.04–7.95 (br, 1H), 7.30 (d, *J* = 5.4 Hz, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 7.01 (dd, *J* = 5.4, 3.2 Hz, 1H), 6.53 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.81–3.69 (m, 1H), 3.64–3.55 (m, 1H), 3.44–3.35 (m, 1H), 2.52–2.43 (m, 1H), 2.16–2.05 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 139.9, 136.1, 127.8, 127.0 (q, *J* = 279 Hz), 126.9, 125.7, 111.2, 106.3, 60.8, 43.2 (q, *J* = 28 Hz), 37.9, 30.0, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}F_3N_2O_2S$ 359.1041; Found 359.1047.



2-15ar

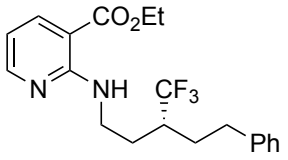
Compound 2-15ar (Scheme 2-6; pale yellow oil, 23.9 mg, 59% yield, 96% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OJ-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 15.2 min (major), t_2 = 18.5 min (minor)); $[\alpha]^{20}_D$ +123.1 (*c* 1.04, $CHCl_3$) for 96% ee (*R*). ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.06–7.98 (br, 1H), 7.81 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.75 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.38–7.31 (m, 2H), 7.30 (s, 1H), 6.53 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.88–3.77 (m, 1H), 3.70–3.61 (m, 1H), 3.52–3.42 (m, 1H), 2.56–2.47 (m, 1H), 2.25–2.15 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 139.9, 139.8, 139.2, 137.0, 126.1 (q, *J* = 280 Hz), 124.9,

124.5, 124.4, 123.6, 122.2, 111.3, 106.3, 60.8, 44.2 (q, J = 29 Hz), 37.9, 29.7, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}F_3N_2O_2S$ 409.1198; Found 409.1191.



2-15as

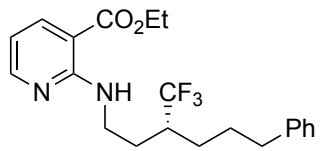
Compound 2-15as (Scheme 2-6; pale yellow oil, 24.6 mg, 63% yield, 90% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OJ-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 11.9 min (major), t_2 = 14.6 min (minor)); $[\alpha]^{20}_D$ +108.1 (*c* 0.98, $CHCl_3$) for 90% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, J = 4.8, 2.0 Hz, 1H), 8.08 (dd, J = 7.8, 2.0 Hz, 1H), 8.06–7.97 (br, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.29 (td, J = 8.4, 1.5 Hz, 1H), 7.22 (td, J = 6.8, 1.5 Hz, 1H), 6.74 (s, 1H), 6.52 (dd, J = 7.8, 4.8 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.79–3.61 (m, 2H), 3.55–3.45 (m, 1H), 2.48–2.32 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.4, 158.5, 155.0, 153.4, 150.8, 139.9, 128.0, 125.7 (q, J = 278 Hz), 124.4, 122.9, 121.0, 111.3, 111.2, 106.6, 106.3, 60.7, 42.5 (q, J = 29 Hz), 38.0, 27.1, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}F_3N_2O_3$ 393.1426; Found 393.1433.



2-15at

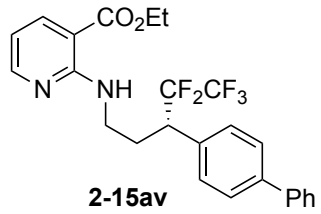
Compound 2-15at (Scheme 2-6; colorless oil, 36.2 mg, 95% yield, 65% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OJ-H, hexane/2-propanol = 19:1, flow 0.5 mL/min, 254 nm, t_1 = 11.7 min (major), t_2 = 14.0 min (minor)); $[\alpha]^{20}_D$ –5.8 (*c* 0.79, $CHCl_3$) for 65% ee (*R*). ^{1}H NMR ($CDCl_3$) δ 8.29 (dd, J = 4.4, 1.2 Hz, 1H), 8.14 (dd, J = 7.0, 1.2 Hz, 1H), 8.10–7.96 (br, 1H), 7.26 (t, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 6.56 (dd, J = 7.0, 4.4 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.74–3.64 (m, 1H), 3.64–3.52 (m, 1H), 2.79–2.65 (m, 2H), 2.30–2.16 (m, 1H), 2.04–1.86 (m, 3H), 1.86–1.76 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.4, 153.4, 141.2, 139.9, 128.5 (q, J = 270 Hz), 128.4, 128.3,

126.0, 111.1, 106.2, 60.8, 39.8 (q, J = 25 Hz), 38.3, 32.7, 29.7, 27.7, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}F_3N_2O_2$ 381.1790; Found 381.1785.



2-15au

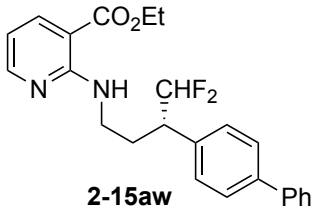
Compound 2-15au (Scheme 2-6; colorless oil, 26.0 mg, 66% yield, 65% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 1.0 mL/min, 254 nm, t_1 = 8.3 min (minor), t_2 = 10.3 min (major)); $[\alpha]^{20}_D$ –7.9 (*c* 1.31, $CHCl_3$) for 65% ee (*R*). ^{1}H NMR ($CDCl_3$) δ 8.26 (dd, J = 4.6, 2.0 Hz, 1H), 8.13 (dd, J = 7.6, 2.0 Hz, 1H), 8.09–7.99 (br, 1H), 7.27 (t, J = 7.2 Hz, 2H), 7.22–7.13 (m, 3H), 6.54 (dd, J = 7.6, 4.6 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.72–3.52 (m, 2H), 2.61 (t, J = 7.2 Hz, 2H), 2.30–2.14 (m, 1H), 2.01–1.91 (m, 1H), 1.84–1.65 (m, 4H), 1.62–1.50 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.37, 153.35, 141.8, 140.0, 128.5 (q, J = 279 Hz), 128.3, 125.8, 111.1, 106.2, 60.8, 40.4 (q, J = 25 Hz), 38.5, 35.8, 28.4, 27.9, 27.7, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}F_3N_2O_2$ 395.1946; Found 395.1946.



2-15av

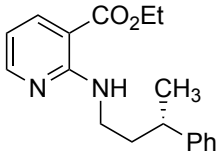
Compound 2-15av (Scheme 2-6; colorless oil, 44.5 mg, 93% yield, 92% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak IC, hexane/EtOH = 500:1, flow 0.8 mL/min, 254 nm, t_1 = 16.2 min (minor), t_2 = 21.9 min (major)); $[\alpha]^{20}_D$ +97.4 (*c* 1.11, $CHCl_3$) for 92% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, J = 4.8, 2.0 Hz, 1H), 8.10 (dd, J = 7.6, 2.0 Hz, 1H), 8.00–7.91 (br, 1H), 7.60 (d, J = 6.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.40–7.33 (m, 3H), 6.52 (dd, J = 7.6, 4.8 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.56–3.40 (m, 2H), 3.40–3.29 (m, 1H), 2.59–2.49 (m, 1H), 2.28–2.18 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 141.0, 140.4, 139.9, 132.7 (d, J = 6 Hz), 129.7, 128.8, 127.4, 127.3, 127.0, 120.7–

113.1 (m, CF_3–CF_2–), 111.1, 106.2, 60.8, 45.3 (t, J = 21 Hz), 38.1, 27.7, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{25}H_{24}F_5N_2O_2$ 479.1758; Found 479.1764.



2-15aw

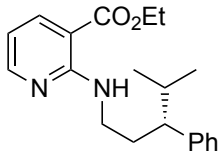
Compound 2-15aw (Scheme 2-6; colorless oil, 31.2 mg, 76% yield, 63% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 35.0 min (minor), t_2 = 40.5 min (major)); $[\alpha]^{20}_D$ +62.4 (*c* 1.00, $CHCl_3$) for 63% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 4.4, 2.0 Hz, 1H), 8.10 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.04–7.95 (br, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.38–7.32 (m, 3H), 6.51 (dd, *J* = 7.8, 4.4 Hz, 1H), 5.92 (td, *J* = 56.4, 3.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.63–3.54 (m, 1H), 3.49–3.40 (m, 1H), 3.28–3.16 (m, 1H), 2.41–2.31 (m, 1H), 2.20–2.09 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 140.7, 140.6, 139.9, 135.3, 129.3, 128.7, 127.4, 127.3, 127.1, 117.8 (t, *J* = 244 Hz), 111.0, 106.2, 60.7, 47.4 (t, *J* = 20 Hz), 38.3, 28.2, 14.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}F_2N_2O_2$ 411.1884; Found 411.1873.



2-15ax

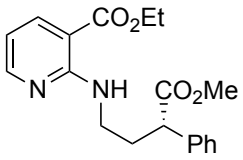
Compound 2-15ax (Scheme 2-6; pale yellow oil, 25.1 mg, 79% yield, 49% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OJ-H, hexane/2-propanol = 30:1, flow 0.5 mL/min, 254 nm, t_1 = 12.8 min (minor), t_2 = 13.9 min (major)); $[\alpha]^{20}_D$ –25.2 (*c* 0.86, $CHCl_3$) for 49% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 4.4, 2.0 Hz, 1H), 8.12 (dd, *J* = 7.4, 2.0 Hz, 1H), 8.06–7.93 (br, 1H), 7.32–7.15 (m, 5H), 6.50 (dd, *J* = 7.4, 4.4 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.52–3.34 (m, 2H), 2.88 (sext, *J* = 7.2 Hz, 1H), 2.04–1.88 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 146.8, 139.9, 128.4, 127.0, 126.0, 110.6,

105.9, 60.7, 39.3, 37.8, 37.6, 22.5, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2O_2$ 299.1760; Found 299.1755.



2-15ay

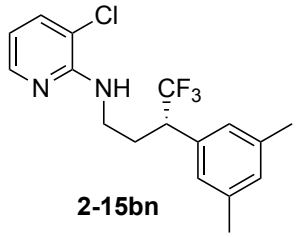
Compound 2-15ay (Scheme 2-6; pale yellow oil, 23.8 mg, 72% yield, 38% ee). A solution of hexane/$CHCl_3$ (2:3) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 13.6 min (major), t_2 = 18.5 min (minor)); $[\alpha]^{20}_D$ –17.4 (*c* 1.08, $CHCl_3$) for 38% ee (*R*). ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 5.2, 2.0 Hz, 1H), 8.10 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.02–7.82 (br, 1H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 6.48 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.39–3.20 (m, 2H), 2.47–2.37 (m, 1H), 2.23–2.13 (m, 1H), 1.96–1.78 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.73 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 158.5, 153.4, 143.6, 139.9, 128.5, 128.0, 125.9, 110.5, 105.8, 60.6, 50.6, 39.6, 33.5, 32.6, 20.9, 20.5, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}N_2O_2$ 327.2073; Found 327.2075.



2-15az

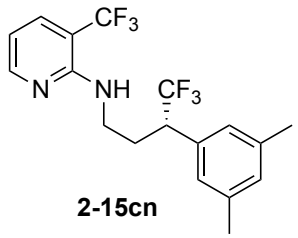
Compound 2-15az (Scheme 2-6; colorless solid, 24.7 mg, 72% yield, 36% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak AD-H, hexane/2-propanol = 30:1, flow 0.5 mL/min, 254 nm, t_1 = 9.9 min (major), t_2 = 14.6 min (minor)); $[\alpha]^{20}_D$ +27.9 (*c* 0.83, $CHCl_3$) for 36% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.24 (d, *J* = 3.6 Hz, 1H), 8.12 (d, *J* = 6.8 Hz, 1H), 8.08–7.95 (br, 1H), 7.36–7.29 (m, 4H), 7.29–7.22 (m, 1H), 6.52 (dd, *J* = 6.8, 3.6 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.79–3.66 (m, 1H), 3.64 (s, 3H), 3.60–3.49 (m, 1H), 3.49–3.38 (m, 1H), 2.53–2.41 (m, 1H), 2.18–2.07 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 167.5, 158.4, 153.3, 140.0,

138.6, 128.7, 127.9, 127.3, 110.9, 106.2, 60.7, 52.1, 49.1, 38.8, 33.0, 14.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}N_2O_4$ 343.1658; Found 343.1655.



2-15bn

Compound 2-15bn (Scheme 2-7; pale yellow oil, 30.4 mg, 99% yield, 88% ee). A solution of hexane/EtOAc (10:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 21.2 min (major), t_2 = 26.9 min (minor)); $[\alpha]^{20}_D$ +67.9 (*c* 1.05, $CHCl_3$) for 88% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 7.99 (dd, *J* = 5.2 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 6.97 (s, 1H), 6.92 (s, 2H), 6.52 (dd, *J* = 7.8, 5.2 Hz, 1H), 4.90–4.82 (br, 1H), 3.45–3.38 (m, 2H), 3.36–3.25 (m, 1H), 2.48–2.35 (m, 1H), 2.31 (s, 6H), 2.22–2.10 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.6, 145.9, 138.3, 135.9, 134.0, 130.0, 126.9 (q, *J* = 280 Hz), 126.8, 115.3, 112.9, 47.9 (q, *J* = 27 Hz), 38.9, 28.5, 21.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}{}^{35}ClF_3N_2$ 343.1189; Found 343.1187.

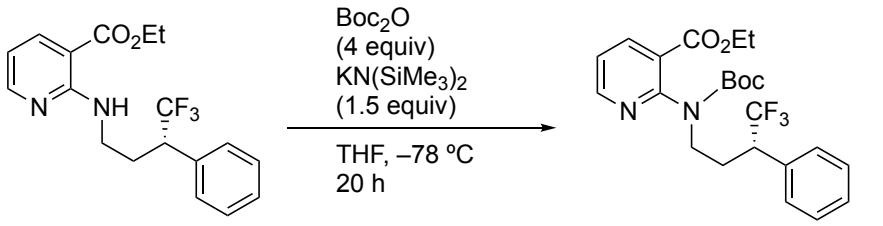


2-15cn

Compound 2-15cn (Scheme 2-7; colorless oil, 31.5 mg, 84% yield, 81% ee). A solution of hexane/EtOAc (20:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak IB x 2, hexane/2-propanol = 500:1, flow 0.5 mL/min, 254 nm, t_1 = 20.3 min (major), t_2 = 20.9 min (minor)); $[\alpha]^{20}_D$ +71.7 (*c* 0.96, $CHCl_3$) for 81% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 5.0 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 6.98 (s, 1H), 6.91 (s, 2H), 6.62 (dd, *J* = 7.0, 5.0 Hz, 1H), 4.83–4.75 (br, 1H), 3.53–3.43 (m, 1H), 3.41–3.22 (m, 2H), 2.48–2.37 (m, 1H), 2.32 (s, 6H), 2.18–2.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 154.3, 151.6, 138.3, 135.0 (q, *J* = 5 Hz), 133.9, 130.1, 126.9 (q, *J* = 279 Hz), 124.4 (q, *J* = 272 Hz), 126.8, 111.5, 108.6 (q,

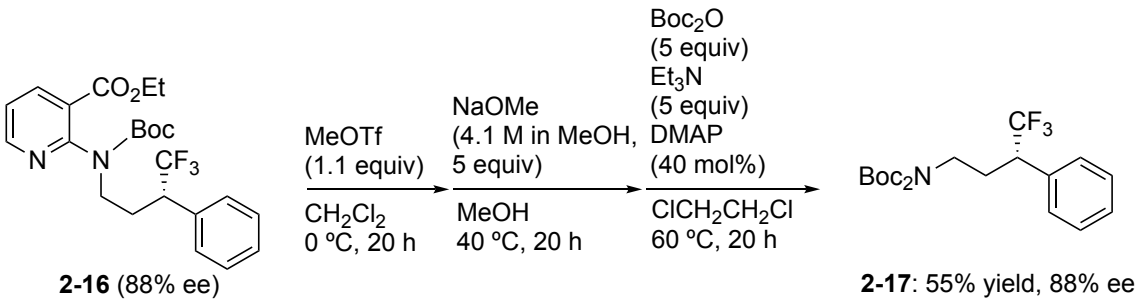
J = 31 Hz), 47.7 (q, J = 27 Hz), 38.7, 28.3, 21.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}F_6N_2$ 377.1452; Found 377.1450.

2-5-7. Removal of a pyridyl group (Scheme 2-8)



2-15aa (88% ee) **2-16**: 99% yield, 88% ee

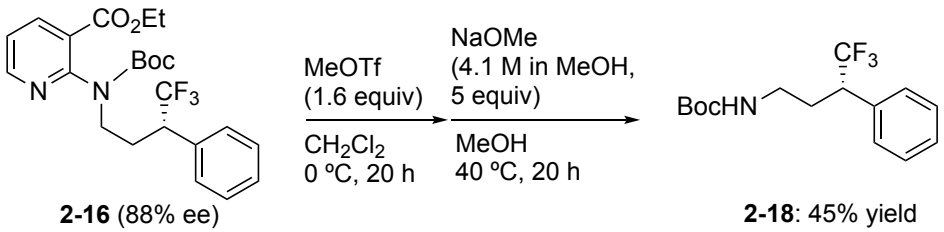
Transformation of 2-15aa into 2-16: To a solution of **2-15aa** (88% ee, 705 mg, 2.0 mmol) in THF (8.0 mL) was added potassium bis(trimethylsilyl)amide solution (8.0 mL, 0.5 M in toluene, 4.0 mmol) at –78 °C under N_2. After stirring the mixture at –78 °C for 1 h, di-*tert*-butyl dicarbonate (352 mg, 8.0 mmol) was added to the mixture, and the reaction mixture was stirred at the same temperature for 20 h. H_2O was added to the mixture at –78 °C and the resulting mixture was allowed to warm to room temperature. The resulting solution was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel with hexane to give **2-16** as a colorless oil (725 mg, 99% yield). The ee was measured by HPLC (Chiralpak AD-H, hexane/2-propanol = 19:1, flow 0.5 mL/min, 254 nm, t_1 = 10.8 min (major), t_2 = 11.7 min (minor)); $[\alpha]^{20}_D$ +5.3 (*c* 1.08, $CHCl_3$) for 88% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 8.54–8.33 (m, 1H), 8.22–8.04 (m, 1H), 7.36–7.08 (m, 6H), 4.35 (q, J = 7.4 Hz, 2H), 3.99–3.38 (m, 3H), 2.55–2.05 (m, 2H), 1.52–1.26 (m, 9H), 1.38 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.0, 150.6, 150.0, 139.5, 138.6, 134.1, 129.1, 128.5, 128.1, 126.9 (q, J = 279 Hz), 124.5, 120.7, 120.3, 81.5, 61.5, 47.9–46.7 (m), 46.1–44.9 (m), 28.1, 14.1. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}F_3N_2O_4$ 453.2001; Found 453.2012.



2-16 (88% ee)

2-17: 55% yield, 88% ee

Transformation of 2-16 into 2-17: To a solution of **2-16** (88% ee, 87.5 mg, 0.19 mmol) in CH_2Cl_2 (0.8 mL) was added methyl trifluoromethanesulfonate (23 μL, 0.21 mmol) at 0 °C, and the mixture was stirred at the same temperature for 20 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in methanol (0.8 mL). Sodium methoxide (4.1 M in methanol, 225 μL, 0.97 mmol) was added to the mixture, and the resulting mixture was stirred at 40 °C for 20 h. The mixture was passed through a short column of alumina with CH_2Cl_2 as an eluent, and the solvent was removed on a rotary evaporator. After dissolving the residue in dichloroethane (0.8 mL), di-*tert*-butyl dicarbonate (211 mg, 0.97 mmol), triethylamine (135 μL, 0.97 mmol), and 4-dimethylaminopyridine (9.4 mg, 0.080 mmol) were added to the mixture, and the reaction mixture was stirred at 60 °C for 20 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel (hexane/EtOAc = 10:1) to give **2-17** as a colorless oil (42.7 mg, 55% yield in 3 steps). The ee was measured by HPLC (Chiralpak AD-H x 3, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 26.7 min (major), t_2 = 27.7 min (minor)); $[\alpha]^{20}_D$ +15.4 (*c* 0.60, $CHCl_3$) for 88% ee (*S*). ^{1}H NMR ($CDCl_3$) δ 7.39–7.29 (m, 5H), 3.55–3.38 (m, 2H), 3.34–3.22 (m, 1H), 2.33–2.15 (m, 2H), 1.47 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 152.2, 134.0, 129.3, 128.7, 128.3, 126.6 (q, *J* = 280 Hz), 82.5, 49.0–47.2 (m), 44.2, 28.1, 27.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{29}F_3N_1O_4$ 404.2049; Found 404.2046. The absolute configuration of **2-17** was determined to be *S*-(+) by comparison of its specific rotation with the value reported previously. Mono-boc-amine **2-18** was synthesized and characterized as below, but was not corresponded to the product in the report.[8]

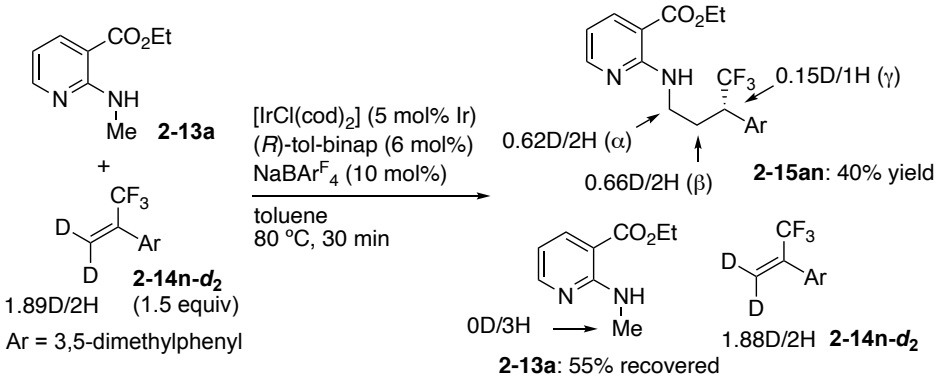


2-16 (88% ee) **2-18**: 45% yield

Transformation of 2-16 into 2-18: To a solution of **2-16** (88% ee, 49.8 mg, 0.11 mmol) in CH_2Cl_2 (0.4 mL) was added methyl trifluoromethanesulfonate (19 μL, 0.18 mmol) at 0 °C, and the mixture was stirred at the same temperature for 20 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in methanol (0.4 mL). Sodium methoxide (4.1 M in methanol, 134 μL, 0.55 mmol) was added to the mixture, and the resulting mixture was stirred at 40 °C for 20 h. The mixture was passed through a short column of alumina with CH_2Cl_2 as an eluent, and the solvent was removed on a rotary evaporator. The residue was subjected to preparative TLC on silica gel (hexane/EtOAc = 5:1) to give **2-18** as a colorless oil (15.3 mg, 45% yield in 2 steps). The ee was not measured; $[\alpha]^{20}_D$ +49.0 (*c* 0.77, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.39–7.33 (m, 3H), 7.31–7.27 (m, 2H), 4.50-4.40 (br, 1H), 3.38–3.25 (m, 1H), 3.05–2.92 (m, 2H), 2.28–2.18 (m, 1H), 2.05-1.99 (m, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.7, 134.0, 129.3, 128.9, 128.6, 126.8 (q, J = 279 Hz), 79.4, 48.6–46.5 (m), 38.1, 29.3, 28.4. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{15}H_{21}F_3N_1O_2$ 304.1524; Found 304.1532.

2-5-8. Deuterium-labeling experiments

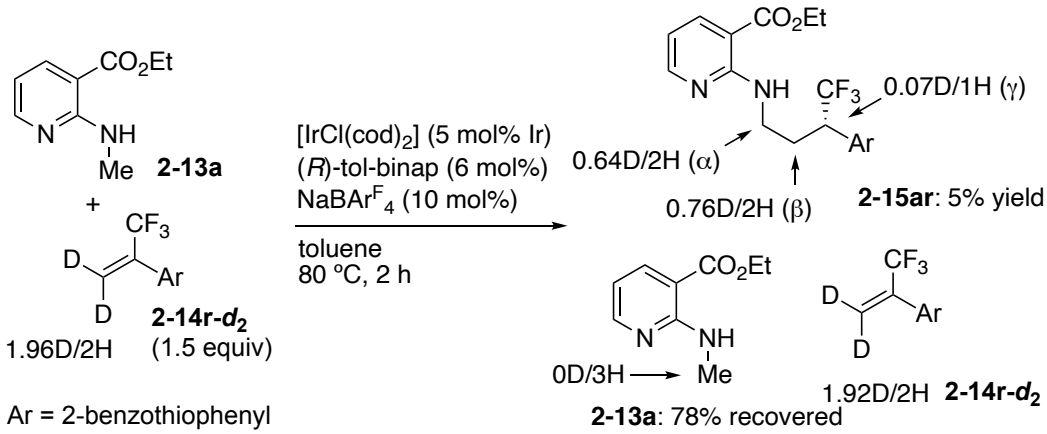
2-5-8-1. The reaction of **2-13a** with **2-14n-*d*$_2$**



A mixture of **2-13a** (18.0 mg, 0.10 mmol), **2-14n-*d*$_2$** (30.3 mg, 0.15 mmol, 1.5 equiv), $[IrCl(cod)]_2$ (1.7 mg, 0.0025 mmol, 5 mol% of Ir), (*R*)-tol-binap (4.1 mg, 0.0060 mmol, 6 mol%), and $NaBAr^F_4$ (9.2 mg, 0.010 mmol, 10 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) was added to the mixture, and the resulting mixture was stirred at 80 °C for

30 min. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel. The yields and deuterium contents of **2-13a**, **2-14n-*d*$_2$**, and **2-15an** were determined by ^{1}H NMR.

2-5-8-2. The reaction of **2-13a** with **2-14r-*d*$_2$**



A mixture of **2-13a** (18.0 mg, 0.10 mmol), **2-14r-*d*$_2$** (32.9 mg, 0.15 mmol, 1.5 equiv), [IrCl(cod)]$_2$ (1.7 mg, 0.0025 mmol, 5 mol% of Ir), (*R*)-tol-binap (4.1 mg, 0.0060 mmol, 6 mol%), and NaBAr$^F{}_4$ (9.2 mg, 0.010 mmol, 10 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) was added to the mixture, and the mixture was stirred at 80 °C for 2 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel. The yields and deuterium contents of **2-13a**, **2-14r-*d*$_2$**, and **2-15ar** were determined by ^{1}H NMR.

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第三章

縮環ヘテロ芳香環を配向基とする飽和環状アミンの不斉アルキル化反応

3-1. 本章の概要

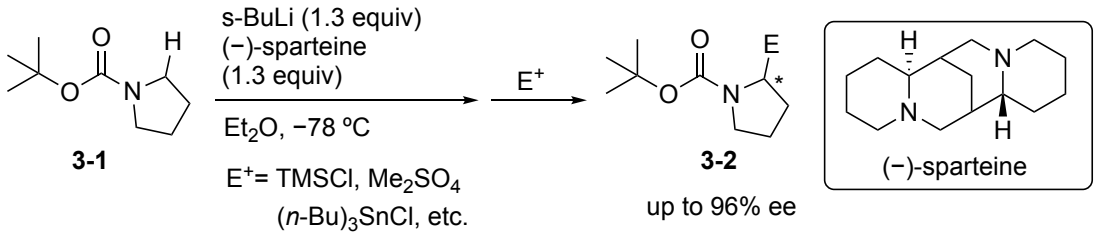
本章では、*N*-メチルベンズイミダゾールを配向基とした飽和環状アミンの窒素原子α位選択的な C(sp^3)−H 不斉アルキル化について述べる。本反応は、カチオン性イリジウムとキラルジホスフィン配位子からなる触媒によって進行し、対応するα-アルキル化体を高収率、高エナンチオ選択的に与えた。またキラルなα,α'-ジアルキル化体合成にも、本触媒系が適用できることを見出した。

3-2. 研究の背景

官能基を有する飽和環状アミンは古くから天然物や生理活性物質に多く見られる構造であるとともに[1]、医薬分野において重要な部分構造の一つとして活用されている[2]。また不斉合成において、キラルな有機触媒やキラル配位子として利用される分子の一つである[3,4]。そのため、環状アミン類の効率的な不斉合成法の開発に注目が集められてきた[5]。窒素原子α位選択的な C(sp^3)−H 官能基化反応は、キラルな飽和環状アミンの合成にも適応され研究が進められており[6]。αアミノカルボアニオン中間体を経由する手法[7]、もしくはイミニウムイオンを用いた反応例が多く報告されてきた[8,9]。

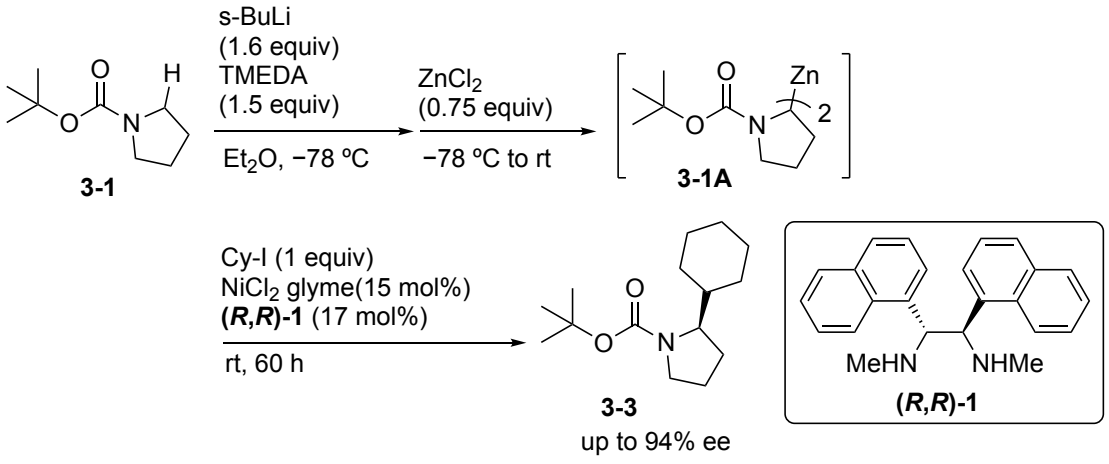
Beak らは 1994 年に、*s*-BuLi/sparteine により Boc-ピロリジン **3-1** のα位選択的、かつ立体選択的な脱プロトン化が進行することを報告している（Scheme 3-1）[7a]。立体選択的に生じたαアミノカルボアニオン中間体は様々な求電子剤と反応し、α位の C(sp^3)−H 不斉官能基化を可能にする。*s*-BuLi/sparteine により生じるαアミノカルボアニオン中間体は、この報告以降多くの C(sp^3)−H 不斉官能基化に用いられている。

Scheme 3-1. *s*-BuLi/sparteine による α 位選択的かつ立体選択的な脱プロトン化



2013 年に Fu らは、*s*-BuLi/sparteine により Boc-ピロリジン **3-1** から生じる α アミノカルボアニオン中間体を有機亜鉛中間体 **3-1A** へ変換し、第二級ハライドとの不斉カップリング反応を開発した（Scheme 3-2）[7k]。ニッケル触媒とキラルジアミン配位子を用いてカップリング反応を行うことで、目的の α 位アルキル化体を高いエナンチオ選択性で与える。本反応では、第二級ハライドとの反応は高エナンチオ選択的に進行するが、第一級ハライドとのカップリング反応はエナンチオ選択性が 60% ee 程度にとどまる。

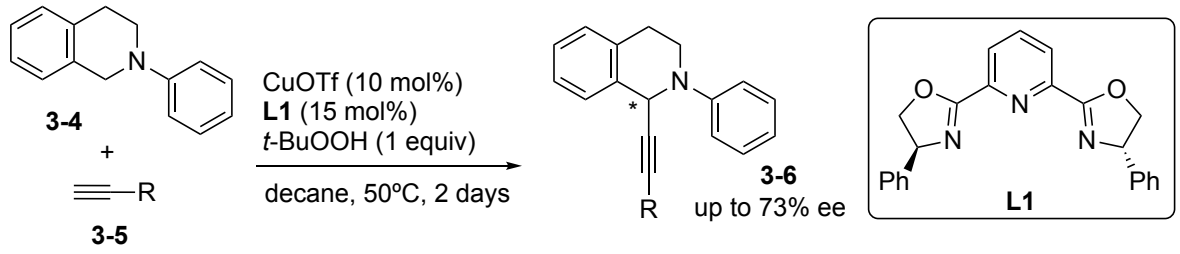
Scheme 3-2. α アミノカルボアニオンを用いた第 2 級ハライドとの不斉アルキル化



イミニウムイオンを用いた不斉合成として Li らは 2004 年に、銅触媒を用いた 1,2,3,4-テトラヒドロキノリン **3-4** の C1 位選択的な不斉 C(sp^3)−H アルキニル化反応を報告している（Scheme 3-3）[8a]。酸化剤により生じるイミニウムイオンに対して、1 価の銅触媒と 3 座配位子 **L1** を組み合わせ反応させることで、対応するアルキニル化体

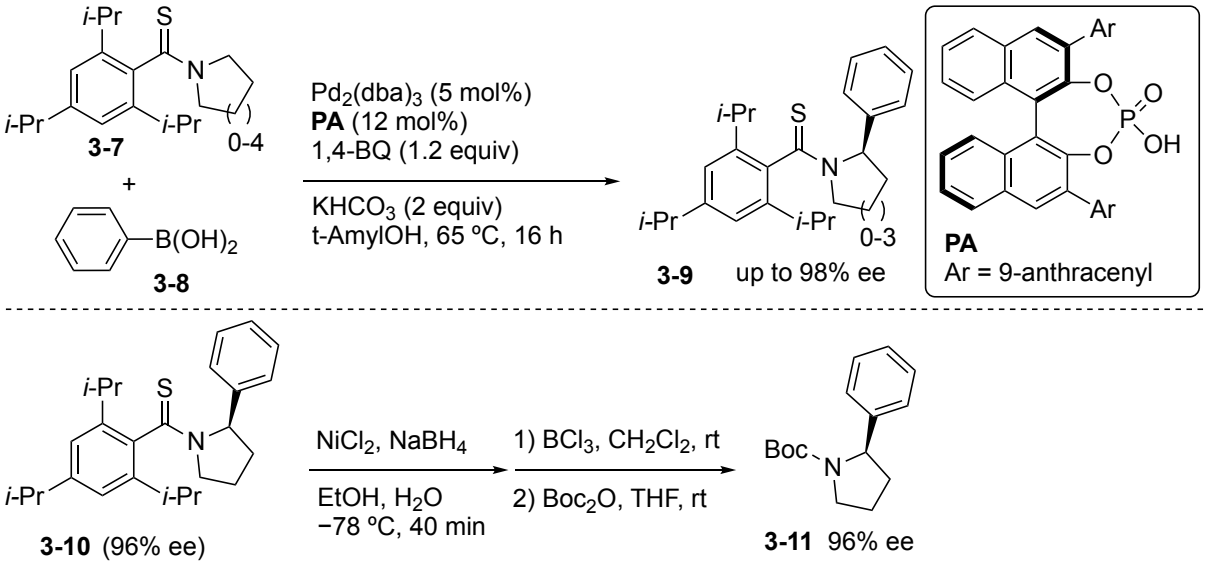
3-6 を中程度のエナンチオ選択性で得ている。この報告以降、1,2,3,4-テトラヒドロキノリンを用いた窒素原子 α 位選択的な C(sp^3)−H 官能基化反応が多く報告されている。

Scheme 3-3. α アミノカルボアニオンを用いた第 2 級ハライドとの不斉アルキル化



遷移金属触媒を用いた環状アミンの直接的な α -C(sp^3)−H 不斉官能基化も近年報告されている[10,11]。2017 年に Yu らは、嵩高いチオカルボニル基を配向基とした飽和環状アミンの α 位選択的な不斉アリール化反応を報告している（Scheme 3-4）[10a]。チオアミド **3-7** に対して Pd 触媒と嵩高いキラルリン酸配位子を用いることで、立体選択的に対応するアリール化体 **3-9** を与える。本反応には 4~8 員環の飽和環状アミンが適用でき、それぞれ高いエナンチオ選択性で付加体を与える。本反応で用いるチオカルボニル基は 3 工程で Boc 基への変換が可能である。

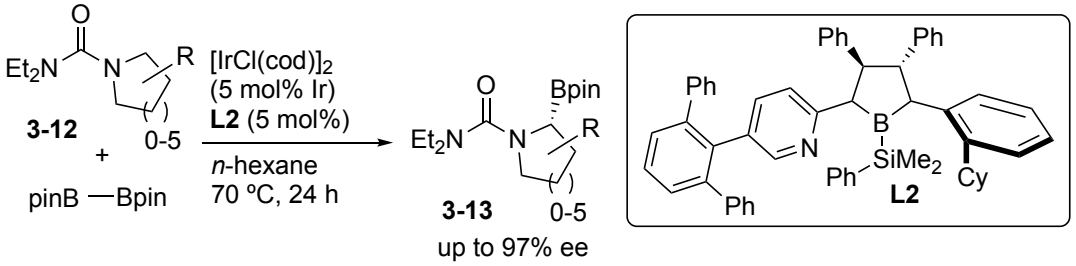
Scheme 3-4. Pd 触媒による直接的 α 位 C(sp^3)−H 不斉アリール化反応



2020 年に Xu らによって、Ir 触媒による α 位 C(sp^3)−H 不斉ボリル化が報告されている（Scheme 3-5）[11]。配向基としてジエチルカルバモイル基、キラル二座ボリル配

位子 **L2** との組み合わせで、対応するボリル化体 **3-13** を高エナンチオ選択的に得ている。本反応には、4~8 員環の飽和環状アミンが適用でき、62-94% ee のエナンチオ選択性でボリル化反応が進行する。

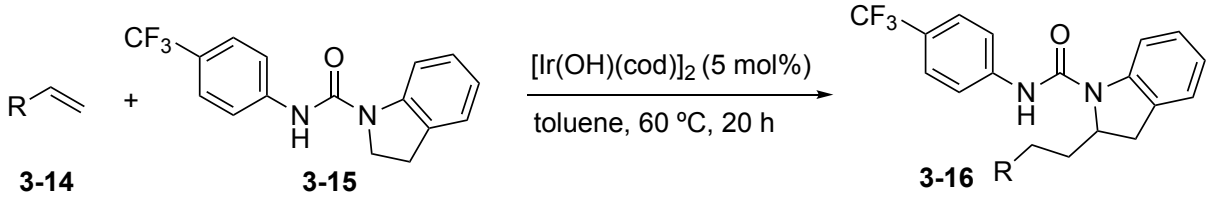
Scheme 3-5. Ir 触媒による直接的 α 位 C(sp^3)–H 不斉ボリル化反応



1-1 で示したように、飽和環状アミンの α 位選択的な C(sp^3)–H アルキル化反応は報告されているが、不斉反応は未だ達成されていない。

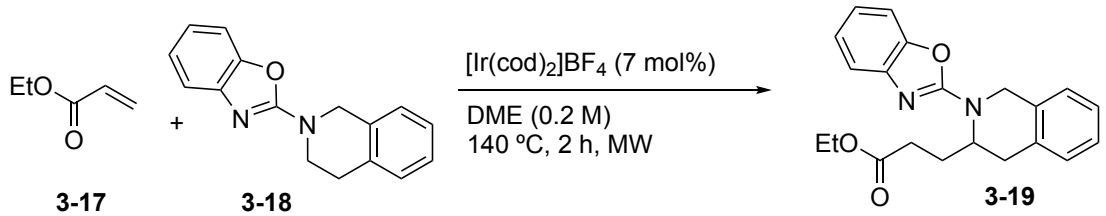
2018 年に西村らは、ヒドロキソイリジウム触媒による尿素 N–H 部分を配向基とした、インドリン誘導体 **3-15** の C(sp^3)–H アルキル化を報告している (Scheme 3-6)[12]。本反応では、1,5-シクロオクタジエン配位子存在下、良好な収率で目的のアルキル化体 **3-16** が得られたが、適切な不斉配位子を特定できず不斉反応へ展開することはできていなかった。

Scheme 3-6. ヒドロキソイリジウムによるインドリン誘導体の C(sp^3)–H アルキル化



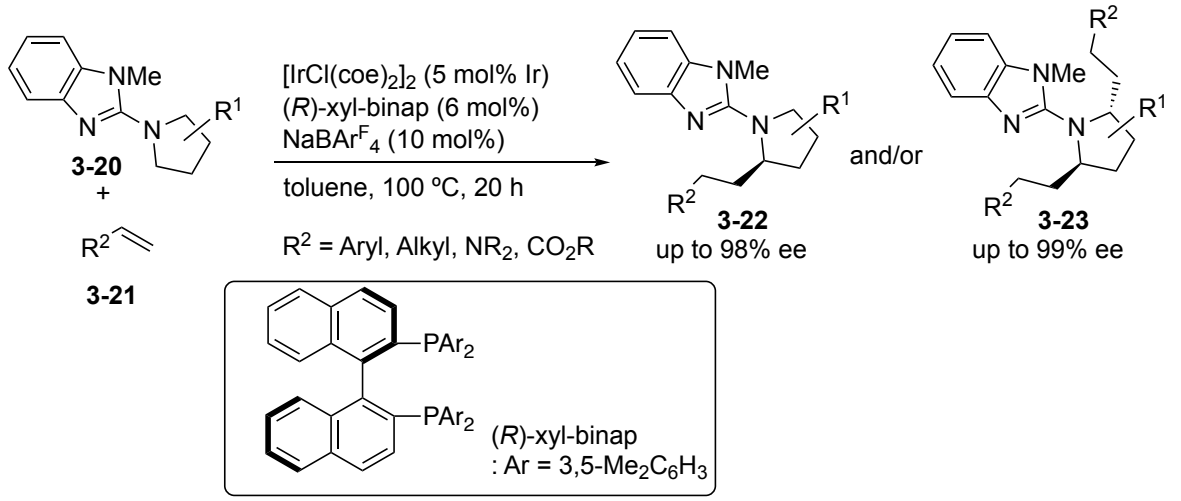
2014 年に Opatz らは、Ir 触媒によるベンゾオキサゾールを配向基とした飽和環状アミンの α 位選択的な C(sp^3)–H アルキル化反応を報告している (Scheme 3-7)[13]。本反応では、テトラヒドロキノリンやピペリジンは目的のアルキル化体を与えるが、ピロリジンでは複数の生成物が生じ、単離には至っていない。

Scheme 3-7. Ir 触媒によるベンゾオキサゾールを配向基とした飽和環状アミンの窒素原子 α 位 C(sp^3)–H アルキル化



筆者は、中性のヒドロキソイリジウムと比較して反応性の高いカチオン性イリジウム触媒を用いて、飽和環状アミン類の α 位 C(sp^3)–H 不斉アルキル化の開発に着手した。実際にキラルビスホスフィン配位子存在下、*N*-メチルベンズイミダゾールを配向基として用いると、一置換アルケンとの反応で α-アルキル化体を高収率、高エナンチオ選択性で与えることを見出した（Scheme 3-8）。また、キラルな α,α'-ジアルキル化体合成にも、本触媒系が適用できることを見出した。

Scheme 3-8. 縮環ヘテロ芳香環を配向基とする飽和環状アミンの不斉アルキル化反応

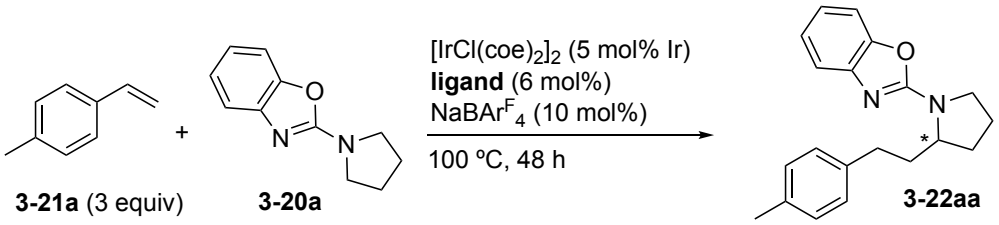


3-3. 結果と考察

2-ピロリジニルベンゾオキサゾール **3-20a** と 4-メチルスチレン **3-21a** を、$[IrCl(coe)_2]_2$ (5 mol% Ir)、(*R*)-binap (6 mol%)、$NaBAr^F_4$ (10 mol%, Ar^F_4 = 3,5-$(CF_3)_2C_6H_3$)存在下、トルエン中 100℃で 48 時間反応させると、窒素原子 α 位 C(sp^3)–H 活性化反応が進行し、モノアルキル化体 **3-22aa** を 13%収率、64% ee で得た (Table 3-1, entry 1)。本反応は、カチオン性イリジウム/ キラルジホスフィン配位子により促進され、(*R*)-binap、(*R*)-xyl-binap、(*R*)-dtbm-binap の中では、(*R*)-xyl-binap を用いた際に 90% ee と最も高いエ

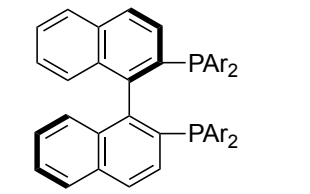
ナンチオ選択性で生成物を得た（entries 1-3）。(*S*)-segphos、(*S*)-DM-segphos、(*S*)-DM-biphep、(*R*)-H8-binap、(*S*,*S*)-QuinoxP*の中には、(*R*)-xyl-binap より高いエナンチオ選択性を示すものはなかった（entries 4-8）。P-オレフィン配位子である **L1** と **L2** を用いた際にも目的のアルキル化反応は進行するが、(*R*)-xyl-binap より高いエナンチオ選択性を示さなかった（entries 9 and 10）。

Table 3-1. C(sp^3)−H 不斉アルキル化の配位子検討

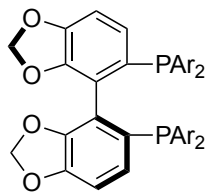


3-21a (3 equiv) **3-20a** **3-22aa**

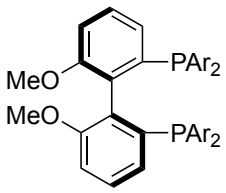
entry	**ligand**	**3aa** (%)[a]	*ee* of **3aa** (%)[b]
1	(*R*)-binap	13	64
2	(*R*)-xyl-binap	40	90
3	(*R*)-dtbm-binap	39	81
4	(*S*)-segphos	10	47
5	(*S*)-DM-segphos	15	80
6	(*S*)-DM-biphep	28	76
7	(*R*)-H8-binap	9	64
8	(*S*,*S*)-QuinoxP*	0	—
9	**L1**	3	82
10	**L2**	21	26



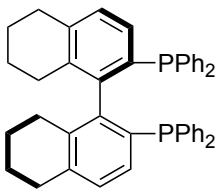
(*R*)-binap: Ar = Ph
(*R*)-xyl-binap:
Ar = 3,5-Me_2-C_6H_3
(*R*)-dtbm-binap:
Ar = 3,5-t-Bu_2-4-MeO-C_6H_2



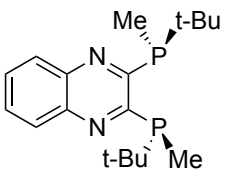
(*S*)-segphos: Ar = Ph
(*S*)-DM-segphos:
Ar = 3,5-Me_2-C_6H_3



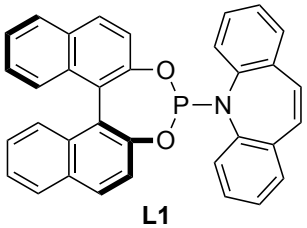
(*S*)-DM-biphep
: Ar = 3,5-Me_2-C_6H_3



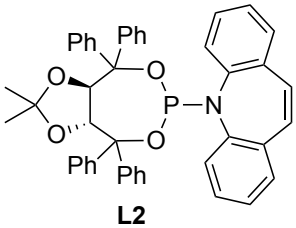
(*R*)-H8-binap



(*S*,*S*)-QuinoxP*



L1

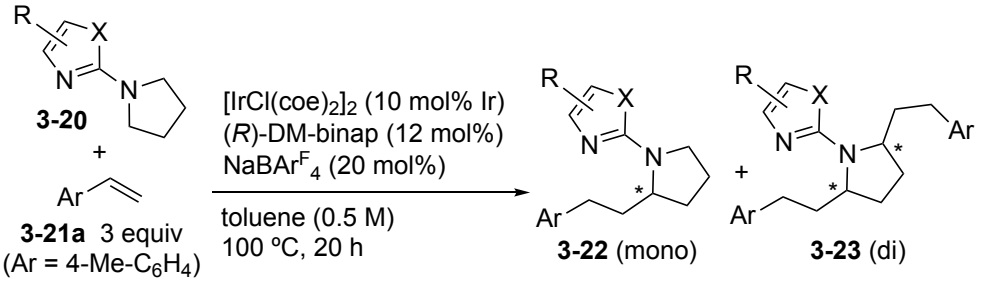


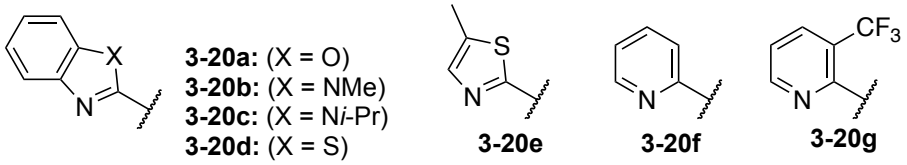
L2

Reaction conditions: **3-20a** (0.10 mmol), **3-21a** (0.30 mmol), [IrCl(coe)$_2$]$_2$ (5 mol% of Ir), **ligand** (6 mol%) and NaBAr$^F_4$ (10 mol%) in toluene (0.4 mL) at 80 °C for 48 h.[a]: Isolated yield.
[b]: Determined by HPLC analysis.

次に、Table 3-1 で見出した(*R*)-xyl-binap を用いて、配向基の検討を実施した（Table 3-2）。2-ピロリジニルベンゾオキサゾール **3-20a** と 4-メチルスチレン **3-21a** を、$[IrCl(coe)_2]_2$ (10 mol% Ir)、(*R*)-xyl-binap (12 mol%)、$NaBAr^F_4$ (20 mol%, Ar^F_4 = 3,5-$(CF_3)_2C_6H_3$)存在下、トルエン中 100 ℃で 20 時間反応させると、モノアルキル化体 **3-22aa** を 50%収率、90% ee で得るとともに、ジアルキル化体 **3-23aa** を 28%収率で得た (entry 1)。配向基を *N*-メチルベンズイミダゾールに変えると 95% ee で目的のモノアルキル化体 **3-22ba** が得られたが、*N*-イソプロピルベンズイミダゾールではややエナンチオ選択性の低下が見られた（entries 2 and 3）。ベンゾチアゾールを有する **3-20d** を用いると 97% ee とエナンチオ選択性の向上が見られたが、ベンゾオキサゾール（**3-20a**）や *N*-メチルベンズイミダゾール（**3-20b**）と比べて反応性を大きく下げる結果となった（entry 4）。5-メチルチアゾール(**3-20e**)を用いると、モノアルキル化体のエナンチオ選択性は 5% ee と大きく低下した（entry 5）。この結果から、ベンゾ縮環ヘテロ芳香環が本反応のエナンチオ選択性発現に重要であることが分かった。ピリジル配向基をもつ基質 **3-20f** と **3-20g** を用いた際は、目的のアルキル化は進行せず原料回収となった（entries 6 and 7）。本反応ではアルケンの当量でモノアルキル化体の収率を向上できる。Entry 8 に示すように、1.5 当量の **3-21a** を用いることでモノアルキル化体 **3-22ba** を 74%収率で得た。

Table 3-2. C(sp^3)–H 不斉アルキル化の配向基検討





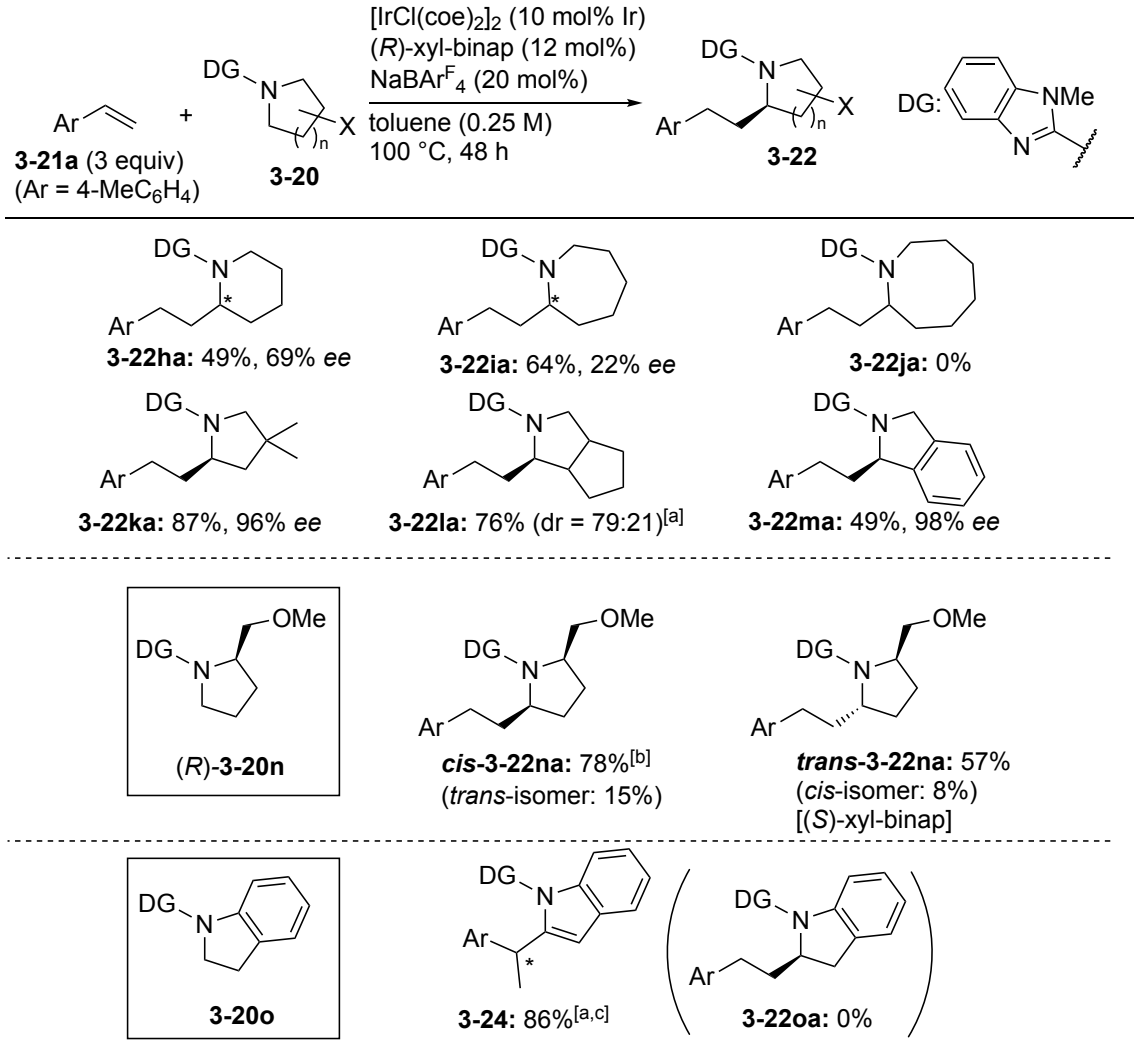
entry	3-20	3-22/3-23	Yields of 3-22/3-23[a]	ee of 3-22 [%][b]
1	**3-20a**	**3-22aa/3-23aa**	50/28	90
2	**3-20b**	**3-22ba/3-23ba**	41/43	95
3	**3-20c**	**3-22ca/3-23ca**	47/42	88
4	**3-20d**	**3-22da/3-23da**	23/15	97
5[c]	**3-20e**	**3-22ea/3-23ea**	30/43	5
6	**3-20f**	**3-22fa/3-23fa**	0/0	—
7	**3-20g**	**3-22ga/3-23ga**	0/0	—
8[c,d]	**3-20b**	**3-22ba/3-23ba**	74/21	95

Reaction conditions: **3-20** (0.10 mmol), **3-21a** (0.30 mmol), $[IrCl(coe)_2]_2$ (10 mol% of Ir), (*R*)-xyl-binap (12 mol%) and $NaBAr^F_4$ (20 mol%) in toluene (0.4 mL) at 100 °C for 20 h.
[a]: Isolated yield. [b]: Determined by HPLC analysis.[c] **3-21a** (0.15 mmol).
[d] $[IrCl(coe)_2]_2$ (5 mol% of Ir), (*R*)-xyl-binap (6 mol%) and $NaBAr^F_4$ (10 mol%).

Scheme 3-9 に示すように、飽和環状アミンの環サイズは C(sp^3)–H アルキル化の反応性やエナンチオ選択性に大きく影響を与える。6 員環ピペリジン（**3-20h**）や 7 員環アゼパン（**3-20i**）の反応は、中程度の収率でモノアルキル化体（**3-22ha**, **3-22ia**）を与えたが、5 員環ピロリジンと比べ大きくエナンチオ選択性を下げる結果となった。8 員環アゾカン（**3-20j**）では目的の C(sp^3)–H アルキル化反応は進行しなかった。3,3-ジメチルピロリジンを含む **3-20k** の反応は円滑に進行し、対応するアルキル化体 **3-22ka** を 87%収率、96% ee で与えた。二環式アミン（**3-20l**）やイソインドリン（**3-20m**）を用いてもアルキル化反応が進行し、目的の付加体 **3-22la** と **3-22ma** を得た。キラル中心を持つピロリジン(***R*)-3-20n** を用いると、シス体を優先し反応が進行する。同様の基質 (***R*)-3-20n** に対して(*S*)-xyl-binap を用いた反応では、対応するトランス体 ***trans*-3-22na** を主生成物として与えた。インドリンを含む **3-20o** を用いると、酸化されアルキル化

した **3-24** を 87%収率で得た。アルケンが直鎖型ではなく、分岐型で挿入していることから **3-20o** のアルキル化反応よりも脱水素化反応が先に進行していることが分かった。

Scheme 3-9. 飽和環状アミンの適用範囲

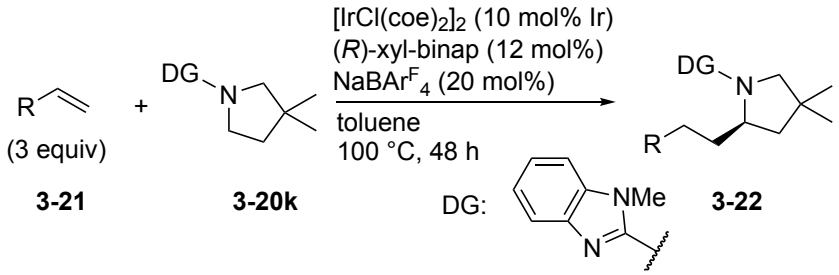


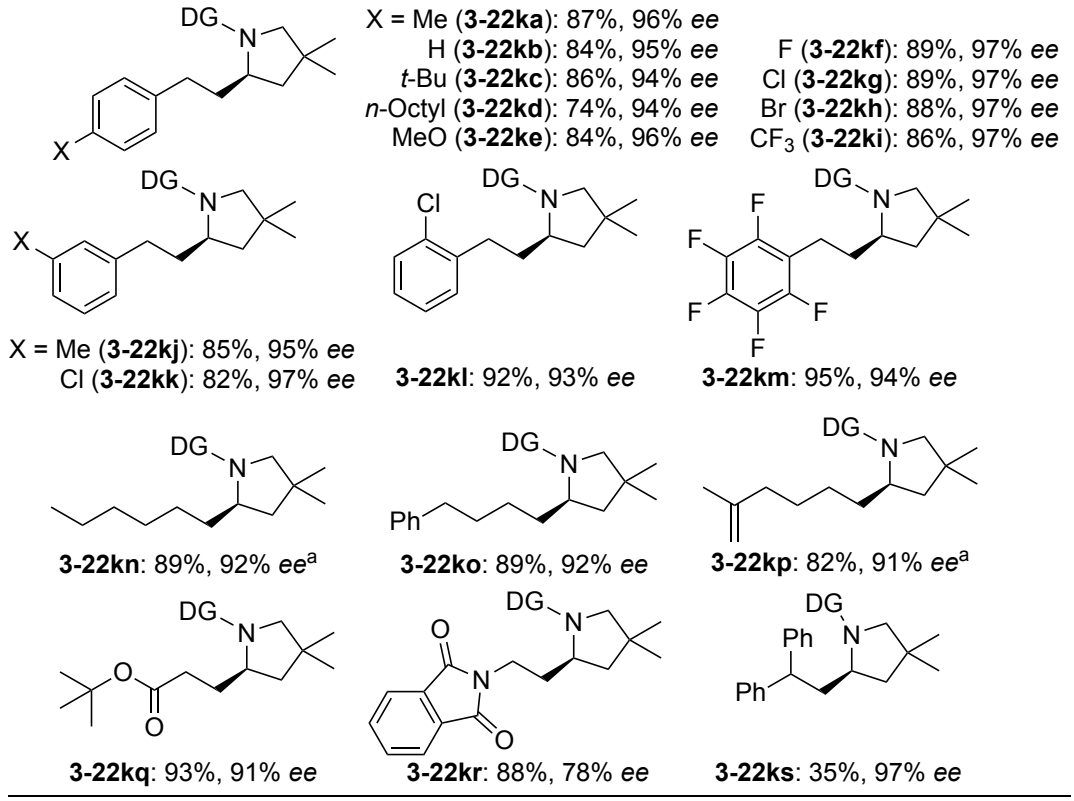
Reaction conditions: **3-20** (0.10 mmol), **3-21a** (0.30 mmol), $[IrCl(coe)_2]_2$ (10 mol% of Ir), (*R*)-xyl-binap (12 mol%) and $NaBAr^F_4$ (20 mol%) in toluene (0.4 mL) at 100 °C for 48 h. Isolated yields were shown. The *ee* was determined by HPLC analysis. [a] Ee was not determined. [b] With $[IrCl(coe)_2]_2$ (5 mol% of Ir), (*R*)-xyl-binap (6 mol%), and $NaBAr^F_4$ (10 mol%) for 20 h. [c] The isolated product contains 7% of the 7-alkylated indole derivative.

Scheme 3-10 に 3,3-ジメチルピロリジンを有する **3-20k** を基質として、様々な末端アルケンに関して不斉ヒドロアルキル化を実施した結果をまとめた。パラ位置換スチレンでの反応では、電子供与基（**3-21a-e**）、電子求引基（**3-21f-i**）のいずれも適用でき、対応する付加体 **3-22ka-ki** が高い収率、高エナンチオ選択的に得られた（94-97% ee）。メタ位置換スチレン（**3-21j**, **3-21k**）、オルト位置換スチレン（**3-21l**）、パーフルオロスチレン **3-21m** の反応はいずれも問題なく進行し、目的のモノアルキル化体 **3-22kj-km**

を高いエナンチオ選択性で与えた。1-ヘキセン **3-21n** や 4-フェニル-1-ブテン **3-21o** を用いた際も C(sp^3)–H アルキル化反応が進行し、ともに 92% ee で付加体 **3-22-kn** と **3-22-ko** を与えた。2-メチル-1,5-ヘキサジエン **3-21p** を用いるとビニル基選択的に反応が進行し、アルキル化体 **3-22kp** を 82%収率、91% ee で得た。アクリル酸 *t*-ブチル **3-21q** の不斉ヒドロアルキル化反応は 91% ee で進行したが、*N*-ビニルフタルイミド **3-21r** の反応は 78% ee とエナンチオ選択性の若干の低下が見られた。1,1-ジフェニルエチレン **3-21s** は 35%と低収率ながら C(sp^3)–H アルキル化反応が進行したが、目的物 **3-22ks** は 97% ee と高いエナンチオ選択性を示した。

Scheme 3-10. 3-20k を用いたアルケンの適応範囲

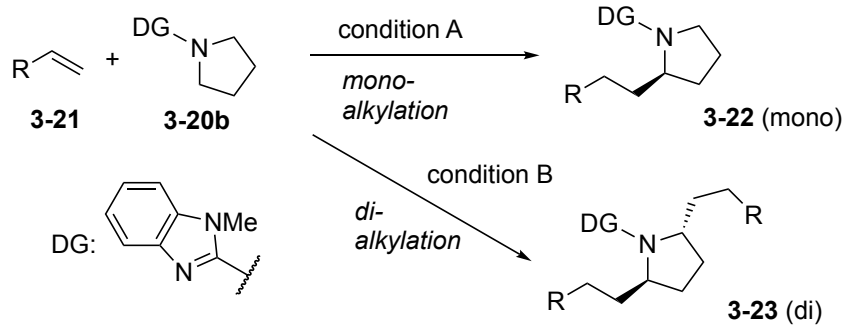


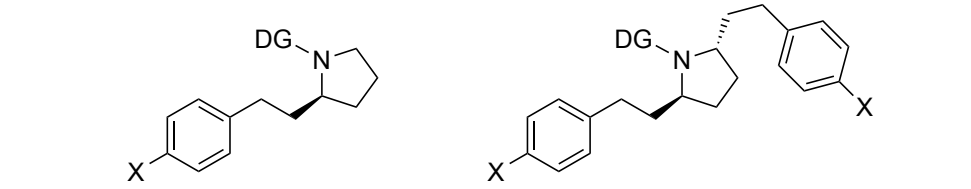


Reaction conditions: **3-20k** (0.10 mmol), **3-21** (0.30 mmol), $[IrCl(coe)_2]_2$ (10 mol% of Ir) (*R*)-xyl-binap (12 mol%) and $NaBAr^F_4$ (20 mol%) in toluene (0.4 mL) at 100 °C for 48 h. Isolated yields were shown. The *ee* was determined by HPLC analysis.
[a] 5 equiv of alkene was used.

Scheme 3-11 には、種々のアルケンを用いて、2-ピロリジル-*N*-メチルベンゾイミダゾール **3-20b** のモノアルキル化、ジアルキル化反応を実施した結果についてまとめた。5 mol%の Ir 触媒存在下、1.5 当量のアルケンと 100 ℃で 20 時間反応させることで、モノアルキル化体 **3-22** を優先して合成可能である（condition A）。スチレン類 **3-21a**、**3-21g**、**3-21i** を用いたアルキル化反応は円滑に進行し、対応する付加体 **3-22ba**、**3-22bg**、**3-22bi** を高い収率、高エナンチオ選択的に得た（95-97% ee）。イリジウム触媒の当量は 2 mol% Ir まで抑えることができる。**3-20b** (0.5 mmol)に対して 2 mol% Ir の触媒量でアルキル化反応を実施し、**3-22bb** を 83%収率、96% ee で得ている。ジアルキル化体の生成を抑えるため 1 当量の 4-フェニル-1-ブテン **3-21o** を用い、対応するモノアルキル化体 **3-22bo** を 55%収率、85% ee で得た。エナンチオ選択的なジアルキル化反応を優先的に起こすには、5 当量のアルケンと 10 mol%のイリジウム触媒が必要であった（condition B）。**3-21a**、**3-21b**、**3-21g**、**3-21i**、**3-21o** で反応を実施し、対応するジアルキル化体 **3-23ba**、**3-23bb**、**3-23bg**、**3-23bi**、**3-23bo** を良好な収率で得ている。それぞれトランス体が主生成物として得られるが、メソ体（シス体）も少量含まれる。トランス体のエナンチオ選択性はメソ体が生じるため、モノアルキル化体と比べて向上した。

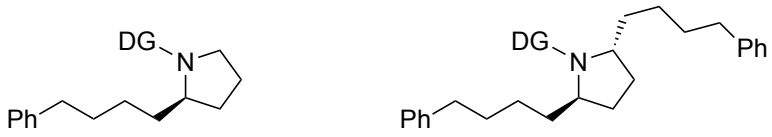
Scheme 3-11. 3-20b を用いたモノアルキル化とジアルキル化反応





X = Me (**3-22ba**, **A**): 74%, 95% *ee*
H (**3-22bb, A**): 83%, 96% *ee*[a,b]
Cl (**3-22bg, A**): 72%, 96% *ee*
CF_3 (**3-22bi, A**): 73%, 97% *ee*

X = Me (**3-23ba**, **B**): 71% (dr = 95:5), 99% ee
H (**3-23bb, B**): 72% (dr = 91:9), 98% *ee*
Cl (**3-23bg, B**): 61% (dr = 91:9), 99% *ee*
CF_3 (**3-23bi, B**): 56% (dr = 96:4), 99% *ee*



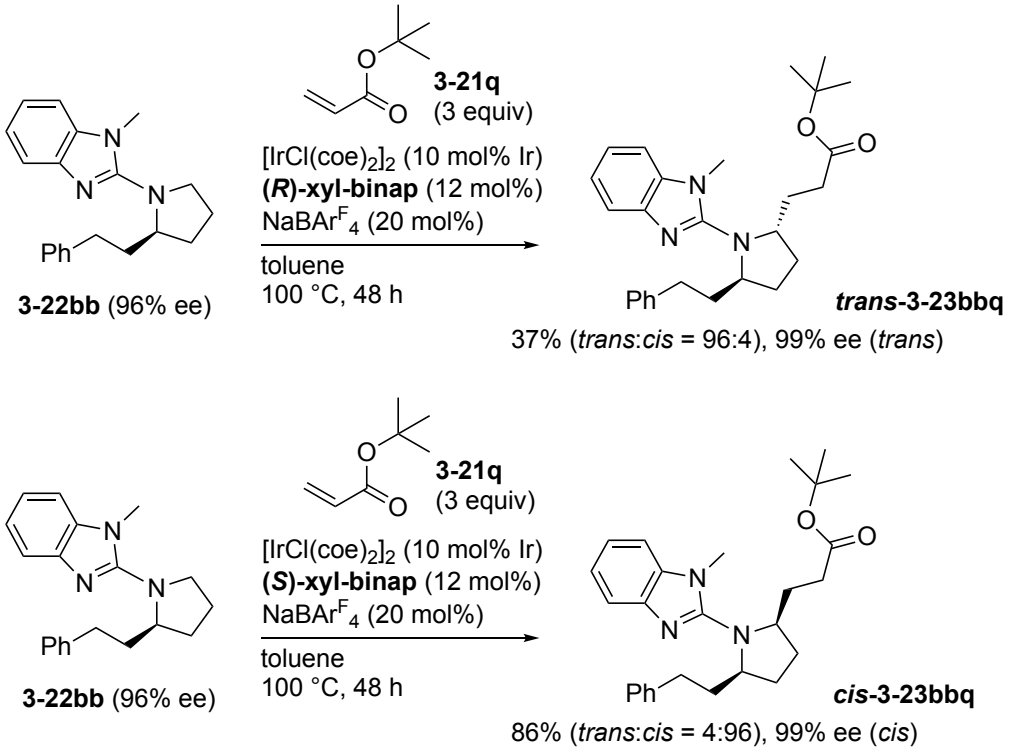
3-22bo (A): 55%, 85% *ee*[a]

3-23bo (B): 62% (dr = 90:10), 98% *ee*

Reaction conditions **A**: **3-20b** (0.10 mmol), **3-21** (0.15 mmol), $[IrCl(coe)_2]_2$ (5 mol% of Ir) (*R*)-xyl-binap (6 mol%) and $NaBAr^F_4$ (10 mol%) in toluene (0.4 mL) at 100 °C for 20 h.
Reaction conditions **B**: **3-20b** (0.10 mmol), **3-21** (0.50 mmol), $[IrCl(coe)_2]_2$ (10 mol% of Ir) (*R*)-xyl-binap (12 mol%) and $NaBAr^F_4$ (20 mol%) in toluene (0.4 mL) at 100 °C for 48 h.
Isolated yields were shown. The *ee* was determined by HPLC analysis.
[a] 0.5 mmol scale reaction (0.5 mmol of **3-20b**). [b] $[IrCl(coe)_2]_2$ (2 mol% of Ir) was used.
[c] 1 equiv of **3-21o** was used.

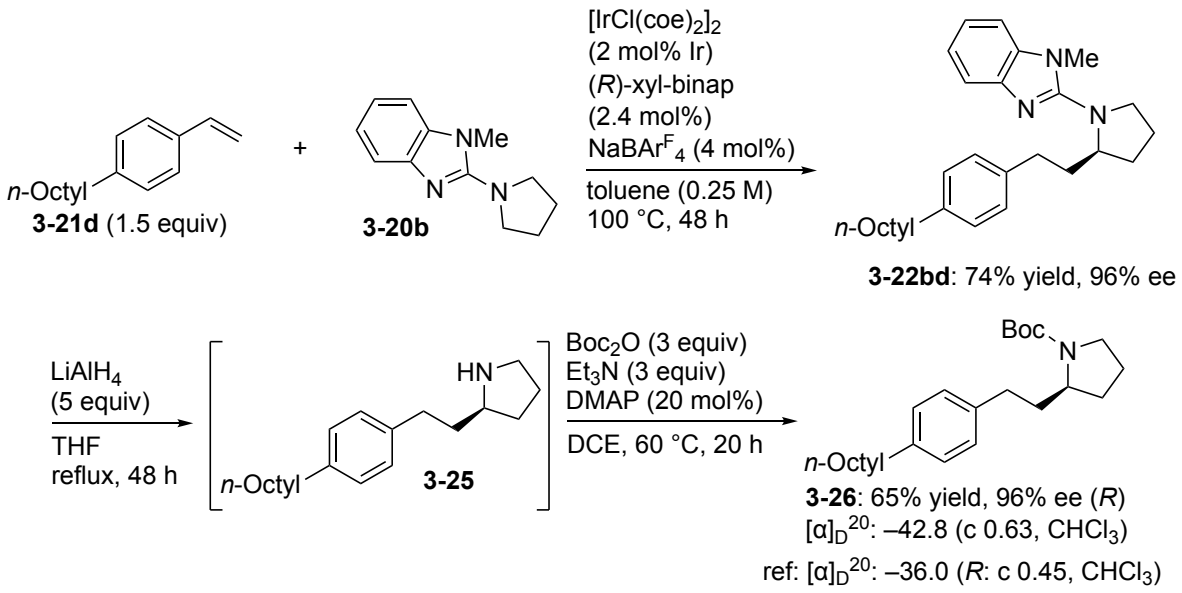
本触媒系は非対称α,α'-ジアルキル化体合成の合成にも適用可能である。Scheme 3-12 に示すように、モノアルキル化体 **3-22bb** に対して(*R*)-xyl-binap 存在下反応を行うと、**3-23 bbq** を 37%収率（*trans*:*cis*＝96:4）で、トランス体を優先的に得ることができる。一方、(*S*)-xyl-binap を用いると、86%収率（*trans*:*cis* = 4/96）で、シス体を優先的に与えることが分かった。

Scheme 3-12. 3-22bb を用いた非対称α,α'-ジアルキル化体合成



本反応の生成物が有する *N*-メチルベンズイミダゾール基は boc 基への変換が可能である。Scheme 3-13 に示すように、2 mol% Ir 量の触媒を用いて合成した **3-22bd** から、2 工程で対応する boc 体 **3-26** へ変換した。この時エナンチオ選択性の低下は観測されていない。**3-26** の絶対配置は過去文献の比旋光度測定から *R* 体と決定した[14]。Boc 基を除去した **3-25** はがん細胞の細胞毒性活性を有しており、抗がん剤候補として研究が進められている。

Scheme 3-13. *N*-ベンゾイミダゾール基の除去と絶対配置の決定



3-4. 本章のまとめ

本章では、*N*-メチルベンズイミダゾールを配向基とした飽和環状アミンの窒素原子α位選択的な C(sp^3)–H 不斉アルキル化について述べた。この反応は、カチオン性イリジウム/キラルジホスフィン触媒により促進され、対応するα-モノアルキル化体を高収率、高エナンチオ選択的に与えた。また本触媒系を用いてピロリジン誘導体のエナンチオ選択的なα,α'-ジアルキル化反応を達成した。

3-5. 実験項

3-5-1. General method

All manipulations of oxygen- and moisture-sensitive materials were carried out using standard Schlenk techniques under a nitrogen atmosphere. NMR spectra were recorded on a JEOL JNM ECZ-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) referenced to the residual peaks of $CDCl_3$ (δ 7.26) for ^{1}H NMR, and $CDCl_3$ (δ 77.00) for ^{13}C NMR. The following abbreviations are used; s, singlet: d, doublet: t, triplet: sept, septet: m, multiplet: br, broad. High-resolution mass spectra were obtained with JEOL AccuTOF LC-plus 4G spectrometer. Optical rotations were measured on JASCO P-2200 polarimeter. Flash column chromatography was performed with Silica Gel 70 PF_{254} (Wako). Preparative thin-layer chromatography was performed with Wakogel® B-5F (Wako).

3-5-2. Materials

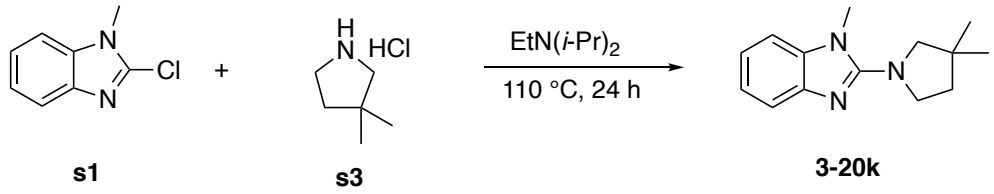
Dehydrated solvents were purchased and used after deoxygenated by bubbling N_2. Dehydrated toluene was purchased and used after deoxygenated by bubbling N_2. $[IrCl(coe)_2]_2$[15] and $NaBAr^F{}_4$ [Ar^F = 3,5-$(CF_3)_2C_6H_3$][16] were prepared according to the reported procedures. Ligands **L1** and **L2** were prepared according to the reported procedure[17].

3-5-3. Preparation of substrates 3-20 and alkenes 3-21

Compounds **3-20a** (CAS: 111888-35-8), [18] **3-20b** (CAS: 444995-65-7),[18] **3-20c** (CAS: 145326-39-2),[18] **3-20d** (CAS: 19983-29-0),[18] **3-20e** (1566532-13-5),[18] **3-20f** (CAS: 54660-06-9),[19] **3-20g** (CAS: 1355247-70-9),[20] **3-20h** (CAS: 15284-84-1),[18] **3-20i** (CAS: 1903414-38-9),[18] **3-20l** (CAS: 2327350-12-7),[18] and **3-20o** (CAS: 1903029-64-0)[21] were prepared according to the reported procedures. Compounds **3-20j**, **3-20k**, **3-20m** (CAS: 2330002-39-4), **3-20n**, and **3-21d** (CAS: 46745-66-8) were prepared as shown below. Other chemicals were purchased from commercial suppliers and used as received.

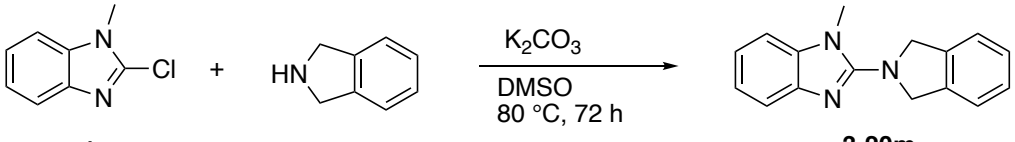
s1 **s2** **3-20j**

Compound 3-20j: A mixture of 2-chloro-1-methyl-1*H*-benzo[*d*]imidazole (**s1**, 167 mg, 1.0 mmol) and azocane (**s2**, 0.38 mL, 3.0 mmol) in a Schlenk tube was stirred at 110 °C for 24 h. After cooling the tube to room temperature, dichloromethane was added to the mixture. The mixture was filtered through a short column of silica gel eluting with ethyl acetate, and the filtrate was concentrated on a rotary evaporator. The residue was subjected to column chromatography on silica gel eluted with EtOAc to give **3-20j** as a colorless solid (185 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.16–7.07 (m, 3H), 3.63 (s, 3H), 3.58–3.53 (m, 4H), 1.84–1.67 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 141.7, 136.2, 121.4, 120.0, 116.9, 107.8, 52.2, 31.5, 27.6, 27.1, 25.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{15}H_{22}N_3$ 244.1814; Found 244.1809.



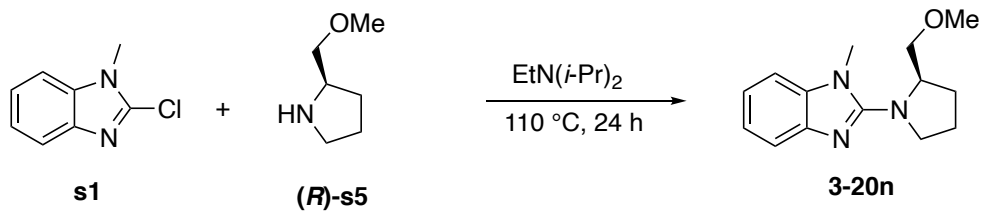
s1 **s3** **3-20k**

Compound 3-20k: A mixture of 2-chloro-1-methyl-1*H*-benzo[*d*]imidazole (**s1**, 333 mg, 2.0 mmol), 3,3-dimethylpyrrolidine hydrochloride (**s3**, 298 mg, 2.2 mmol), and *N*,*N*-diisopropylethylamine (0.87 mL, 5.0 mmol) in a Schlenk tube was stirred at 110 °C for 24 h. After cooling the tube to room temperature, dichloromethane was added to the mixture. The mixture was filtered through a short column of silica gel eluting with ethyl acetate, and the filtrate was concentrated on a rotary evaporator. The residue was subjected to column chromatography on silica gel (hexane: EtOAc = 1:1) to give **3-20k** as a colorless solid (451 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.2 Hz, 1H), 7.18–7.04 (m, 3H), 3.76 (t, J = 7.0 Hz, 2H), 3.64 (s, 3H), 3.40 (s, 2H), 2.05 (t, J = 7.0 Hz, 2H), 1.16 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.2, 142.2, 136.2, 121.3, 119.5, 116.4, 107.3, 63.1, 49.4, 39.3, 38.4, 31.1, 26.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}N_3$ 230.1657; Found 230.1653.



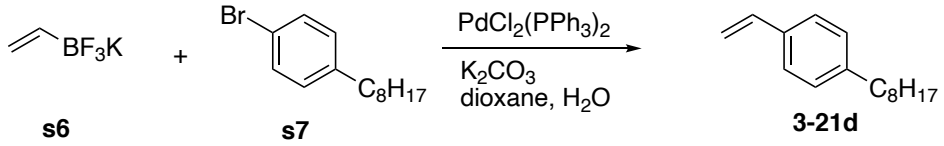
s1 **s4** **3-20m**

Compound 3-20m: A mixture of 2-chloro-1-methyl-1*H*-benzo[*d*]imidazole (**s1**, 333 mg, 2.0 mmol), isoindoline (**s4**, 293 mg, 2.45 mmol), and K_2CO_3 (276 mg, 2.0 mmol) in a Schlenk tube was stirred at 80 °C for 72 h. After cooling the tube to room temperature, dichloromethane and water were added to the mixture. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was subjected to column chromatography on silica gel (hexane: EtOAc = 3:1–2:1) to give **3-20m** as a pale brown solid (281 mg, 56% yield).



s1 (***R***)**-s5** **3-20n**

Compound 3-20n: A mixture of 2-chloro-1-methyl-1*H*-benzo[*d*]imidazole (**s1**, 333 mg, 2.0 mmol), (*R*)-2-(methoxymethyl)pyrrolidine (**(*R*)-s5**, 298 mg, 2.2 mmol), and *N*,*N*-diisopropylethylamine (0.87 mL, 5.0 mmol) in a Schlenk tube was stirred at 110 °C for 24 h. After cooling the tube to room temperature, dichloromethane was added to the mixture. The mixture was filtered through a short column of silica gel eluting with ethyl acetate, and the filtrate was concentrated on a rotary evaporator. The residue was subjected to column chromatography on silica gel (hexane: EtOAc = 1:1) to give **3-20n** as a colorless oil (451 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (m, 1H), 7.16–7.05 (m, 3H), 4.56–4.47 (m, 1H), 3.79–3.71 (m, 1H), 3.60 (s, 3H), 3.53 (dd, *J* = 9.6, 3.8 Hz, 1H), 3.43 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.42–3.35 (m, 1H), 3.30 (s, 3H), 2.20–2.10 (m, 1H), 2.07–1.87 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.1, 141.8, 135.8, 121.3, 119.9, 116.8, 107.6, 73.9, 56.6, 59.1, 52.2, 30.8, 28.3, 25.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}N_3O$ 246.1606; Found 246.1616.



s6 **s7** **3-21d**

Compound 3-21d: A mixture of potassium vinyltrifluoroborate (**s6**, 695 mg, 5.0 mmol), 1-bromo-4-octylbenzene (**s7**, 1.21 g, 4.5 mmol), $PdCl_2(PPh_3)_2$ (158 mg, 0.225 mmol), and K_2CO_3 (691 mg, 5.0 mmol) in dioxane (10 mL) and H_2O (2 mL) was stirred at 80 °C for 24 h under N_2. After cooling the tube to room temperature, the mixture was filtered through a short column of silica gel eluting with ethyl acetate, and the filtrate was concentrated on a rotary evaporator. The residue was subjected to column chromatography on silica gel with hexane to give **3-21d** as a colorless oil (555 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.70 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.70 (dd, *J* = 17.4, 1.0 Hz, 1H), 5.19 (d, *J* = 11.0, 1.0 Hz, 1H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.64–1.55 (m, 2H), 1.39–1.20 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H).

3-5-4. Ligand evaluation for α-C(sp^3)–H alkylation of 3-20a (Table 3-1)

Compound **3-20a** (0.10 mmol), $[IrCl(coe)_2]_2$ (2.2 mg, 0.0025 mmol, 5 mol% of Ir), ligand (0.0060 mmol, 6 mol%), and $NaBAr^F{}_4$ (9.2 mg, 0.010 mmol, 10 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) and 4-methylstyrene (**3-21a**, 35.5 mg, 0.30 mmol) were added to the mixture successively, and the mixture was stirred at 100 °C for 48 h. The mixture was concentrated under vacuum, and the residue was subjected to preparative TLC on silica gel (Hexane/EtOAc = 3:1) to give **3-22aa**. The corresponding racemic product was prepared by using $[IrCl(cod)]_2$[22] as a catalyst.

3-5-5. General procedure for Table 3-2 and Scheme 3-9

Compound **3-20** (0.10 mmol), $[IrCl(coe)_2]_2$ (4.5 mg, 0.0050 mmol, 10 mol% of Ir), (*R*)-xyl-binap (8.8 mg, 0.012 mmol, 12 mol%), and $NaBAr^F{}_4$ (18.4 mg, 0.020 mmol, 20 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) and 4-methylstyrene (**3-21a**, 35.5 mg, 0.30 mmol) were added to the mixture successively, and the mixture was stirred at 100 °C for 20 h or 48 h. The mixture was concentrated on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel to give **3-22**.

3-5-6. General procedure for Scheme 3-10

2-(3,3-Dimethylpyrrolidin-1-yl)-1-methyl-1*H*-benzo[d]imidazole **3-20k** (22.9 mg, 0.10 mmol), $[IrCl(coe)_2]_2$ (4.5 mg, 0.005 mmol, 10 mol% of Ir), (*R*)-xyl-binap (8.8 mg, 0.012 mmol, 12 mol%), and $NaBAr^F{}_4$ (18.4 mg, 0.020 mmol, 20 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) and alkene **3-21** (0.30 mmol) were added to the mixture successively, and the mixture was stirred at 100 °C for 48 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel to give **3-22**.

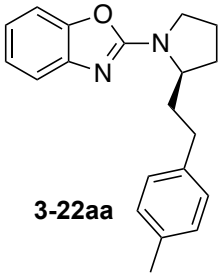
3-5-7. General procedure for Scheme 3-11 (condition A: mono-alkylation)

Compound **3-20b** (0.10 mmol), $[IrCl(coe)_2]_2$ (2.2 mg, 0.0025 mmol, 5 mol% of Ir), (*R*)-xyl-binap (4.4 mg, 0.0060 mmol, 6 mol%), and $NaBAr^F{}_4$ (9.2 mg, 0.010 mmol, 10 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) and alkene **3-21** (0.15 mmol) were added to the mixture successively, and the mixture was stirred at 100 °C for 20 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel to give **3-22**.

3-5-8. General procedure for Scheme 11 (condition B: di-alkylation)

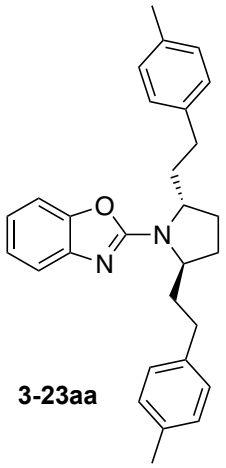
Compound **3-20b** (0.10 mmol), $[IrCl(coe)_2]_2$ (4.5 mg, 0.005 mmol, 10 mol% of Ir), (*R*)-xyl-binap (8.8 mg, 0.012 mmol, 12 mol%), and $NaBAr^F{}_4$ (18.4 mg, 0.020 mmol, 20 mol%) were placed in a Schlenk tube under N_2. Toluene (0.4 mL) and alkene **3-21** (0.50 mmol) were added to the mixture successively, and the mixture was stirred at 100 °C for 48 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel to give **3-23**.

3-5-9. Characterization of the products



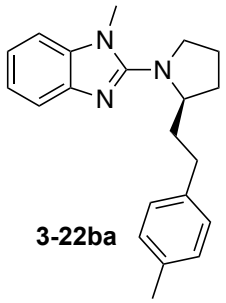
3-22aa

Compound 3-22aa (Table 3-2, entry 1; colorless oil, 15.2 mg, 50% yield, 90% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 12.0 min (major), t_2 = 21.8 min (minor)); $[\alpha]^{25}_D$ –109 (*c* 0.39, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.19–7.12 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.04–6.97 (m, 1H), 4.20–4.12 (m, 1H), 3.78–3.65 (m, 2H), 2.74–2.63 (m, 2H), 2.32 (s, 3H), 2.30–1.73 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 148.7, 138.4, 135.3, 129.0, 128.2, 123.9, 120.2, 115.9, 108.6, 59.2, 48.2, 35.7, 31.9, 30.6, 23.8, 21.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O$ 307.1810; Found 307.1809.



3-23aa

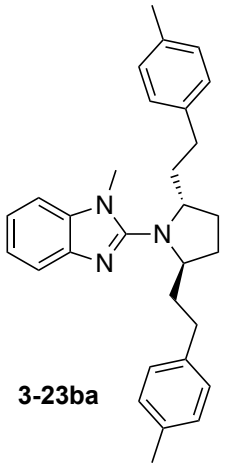
Compound 3-23aa (Table 3-2, entry 1; colorless oil, 12.0 mg, 28% yield). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The diastereoselectivity and ee were not determined. NMR data of the major isomer are shown below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.20–7.14 (m, 1H), 7.11 (d, J = 8.4 Hz, 4H), 7.08 (d, J = 8.4 Hz, 4H), 7.05–6.98 (m, 1H), 4.19 (br, 2H), 2.75–2.58 (m, 4H), 2.32 (s, 6H), 2.29–2.10 (m, 4H), 1.95–1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 148.5, 138.3, 135.3, 129.0, 128.2, 123.8, 120.2, 115.9, 108.6, 59.2, 34.2, 32.1, 27.6, 21.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{29}H_{33}N_2O$ 425.2593; Found 425.2590.



3-22ba

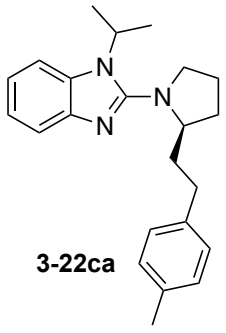
Compound 3-22ba (Table 3-2, entry 2 and Scheme 3-11; colorless oil, 23.5 mg, 74% yield, 95% ee (*R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 18.8 min (major), t_2 = 31.8 min (minor)); $[\alpha]^{25}_D$ –42 (*c* 1.07, $CHCl_3$) for 95% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.16–7.10 (m, 3H), 7.07 (d, J = 8.0 Hz, 2H), 4.46–4.35 (m, 1H), 3.80–3.70 (m, 1H), 3.53 (s, 3H), 3.40 (td, J = 13.2, 4.4 Hz, 1H), 2.70–2.58 (m, 2H), 2.30–2.20 (m, 1H), 2.28 (s, 3H), 2.14–1.88 (m, 3H), 1.80–1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 141.6, 139.0, 135.7,

135.0, 128.9, 128.1, 121.4, 120.1, 116.8, 107.6, 60.2, 52.2, 36.2, 31.8, 31.1, 30.7, 25.1, 20.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3$ 320.2127; Found 320.2129.



3-23ba

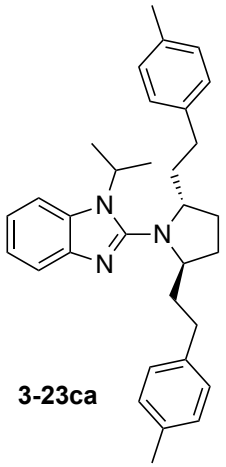
Compound 3-23ba (Scheme 3-11; colorless oil, 31.0 mg as a mixture of *trans*- and *cis*-isomers (95:5), 71% yield, 99% ee (*R,R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The corresponding racemic compound, which was isolated as a mixture of isomers [*trans* (*chiral*):*cis* (*meso*) = 61:39], was prepared by using $[IrCl(cod)]_2$ as a catalyst. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 13.9 min (minor), t_2 = 30.9 min (major)); $[\alpha]^{25}_D$ +21 (*c* 0.50, $CHCl_3$) for 99% ee (*R,R*). NMR data of the major isomer are shown below. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.20–7.09 (m, 3H), 7.02 (d, *J* = 7.8 Hz, 4H), 7.02 (d, *J* = 7.8 Hz, 4H), 4.19 (br, 2H), 3.30 (s, 3H), 2.64–2.40 (m, 4H), 2.32–2.20 (m, 2H), 2.28 (s, 6H), 1.88–1.72 (m, 4H), 1.65–1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 142.0, 138.7, 135.3, 135.1, 128.9, 128.1, 121.2, 120.2, 117.3, 107.8, 60.2, 35.5, 31.7, 30.3, 29.5, 20.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{30}H_{36}N_3$ 438.2909; Found 438.2910.



3-22ca

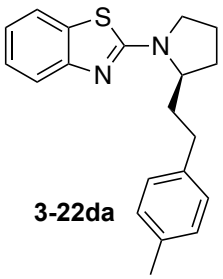
Compound 3-22ca (Table 3-2, entry 3; colorless oil, 16.2 mg, 47% yield, 88% ee (*R*)).

A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 11.0 min (major), t_2 = 11.9 min (minor)); $[\alpha]^{25}_D$ –19 (*c* 0.33, $CHCl_3$) for 88% ee (*R*). ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.18–7.07 (m, 2H), 7.07–7.00 (m, 4H), 4.72 (sept, *J* = 7.2 Hz, 1H), 4.43–4.33 (m, 1H), 3.66 (q, *J* = 8.4 Hz, 1H), 3.26 (td, *J* = 8.4, 4.0 Hz, 1H), 2.67–2.52 (m, 2H), 2.32–2.21 (m, 1H), 2.28 (s, 3H), 2.05–1.92 (m, 3H), 1.76–1.63 (m, 2H), 1.68 (d, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 139.2, 135.1, 132.4, 128.9, 128.2, 121.4, 120.4, 117.7, 111.1, 61.1, 53.7, 47.5, 36.9, 32.0, 31.1, 25.2, 21.2, 20.9, 20.8. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_3$ 348.2440; Found 348.2442.



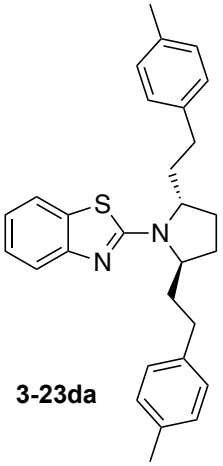
3-23ca

Compound 3-23ca (Table 3-2, entry 3; colorless oil, 19.4 mg, 42% yield). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The diastereoselectivity and ee were not determined. NMR data of the major isomer are shown below. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.21–6.84 (m, 10H), 4.63 (sept, *J* = 6.8 Hz, 1H), 4.50–4.36 (br, 2H), 2.70–2.40 (m, 4H), 2.33–2.20 (m, 8H), 1.90–1.54 (m, 6H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.40 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 138.8, 135.2, 132.2, 129.1, 128.2, 121.2, 120.5, 118.1, 111.1, 60.5 (br), 47.3, 31.9, 29.8, 21.0, 20.9, 20.7. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{32}H_{40}N_3$ 466.3222; Found 466.3217.



3-22da

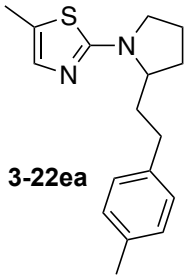
Compound 3-22da (Table 3-2, entry 4; colorless oil, 9.8 mg, 23% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak AS-H, hexane/2-propanol = 30:1, flow 0.5 mL/min, 254 nm, t_1 = 12.1 min (major), t_2 = 15.3 min (minor)); $[\alpha]^{25}_D$ –95 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.29 (t, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.05 (t, *J* = 8.4 Hz, 1H), 4.03–3.94 (m, 1H), 3.72–3.56 (m, 2H), 2.72–2.64 (m, 2H), 2.32 (s, 3H), 2.31–2.22 (m, 1H), 2.19–1.90 (m, 4H), 1.84–1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 138.3, 135.4, 129.1, 128.2, 125.8, 120.7, 120.6, 118.7, 61.4, 50.2, 34.6, 32.1, 30.5, 23.7, 21.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2S$ 323.1582; Found 323.1585.



3-23da

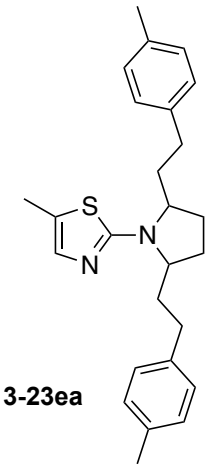
Compound 3-23da (Table 3-2, entry 4; colorless oil, 10.3 mg, 15% yield). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The diastereoselectivity and ee were not determined. NMR data of the major isomer are shown below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.14–7.00 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 4H), 7.08 (d, *J* = 8.4 Hz, 4H), 4.00 (br, 2H), 2.32–2.58 (m, 4H), 2.40–2.29 (m, 3H), 2.31 (s, 6H), 2.24–2.17 (m, 2H), 1.96–1.86 (m, 2H), 1.71–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 138.2, 135.3, 129.0, 128.2, 125.7, 120.5, 118.7, 60.9, 33.4, 32.4, 27.8, 21.0.

HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{29}H_{33}N_2S$ 441.2364; Found 441.2371.



3-22ea

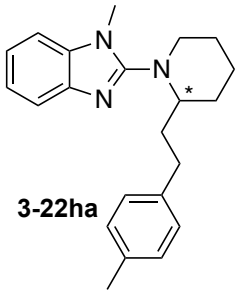
Compound 3-22ea (Table 3-2, entry 5; colorless oil, 8.6 mg, 30% yield, 4% ee). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 10.7 min (major), t_2 = 13.8 min (minor)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.81 (q, J = 1.6 Hz, 1H), 3.87–3.76 (m, 1H), 3.58–3.34 (m, 2H), 2.68–2.57 (m, 2H), 2.31 (s, 3H), 2.29 (d, J = 1.6 Hz, 3H), 2.22–1.80 (m, 5H), 1.76–1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 138.7, 136.3, 135.2, 129.0, 128.2, 120.0, 61.3, 50.2, 34.9, 32.1, 30.6, 23.8, 21.0, 12.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{17}H_{23}N_2S$ 287.1582; Found 287.1583.



3-23ea

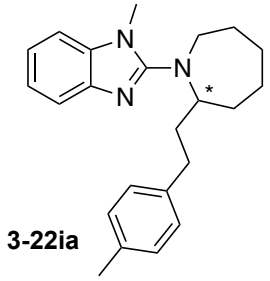
Compound 3-23ea (Table 3-2, entry 5; colorless oil, 17.6 mg, 43% yield). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The diastereoselectivity and ee were not determined. NMR data of the major isomer are shown below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.06 (m, 8H), 6.83–6.79 (m, 1H), 3.92–3.80 (m, 2H), 2.70–2.53 (m, 2H), 2.36–2.03 (m, 14H), 1.90–1.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 138.8, 135.2, 129.0, 128.2, 119.8, 63.3, 36.9, 32.2, 30.1, 21.0, 11.9. HRMS (DART) m/z: $[M + H]^+$ Calcd

for $C_{26}H_{33}N_2S$ 405.2364; Found 405.2360.



3-22ha

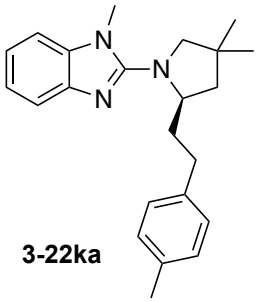
Compound 3-22ha (Scheme 3-9; colorless oil, 16.2 mg, 49% yield, 69% ee). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 17.2 min (minor), t_2 = 22.1 min (major)); $[\alpha]^{25}_D$ +15 (*c* 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 6.4 Hz, 1H), 7.21–7.10 (m, 3H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 3.59–3.50 (m, 1H), 3.40 (s, 3H), 3.38–3.24 (m, 2H), 2.69–2.52 (m, 2H), 2.56–2.40 (m, 2H), 2.27 (s, 3H), 2.02–1.59 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 141.3, 138.5, 135.1, 128.9, 128.1, 121.5, 120.9, 117.7, 108.3, 56.8, 47.5, 31.9, 31.5, 30.2, 28.6, 25.5, 20.9, 20.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3$ 334.2283; Found 334.2295.



3-22ia

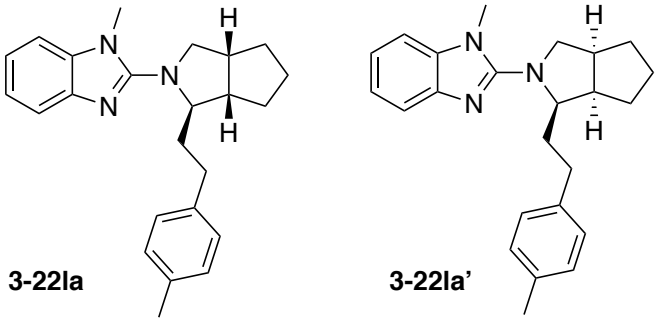
Compound 3-22ia (Scheme 3-9; colorless oil, 22.1 mg, 64% yield, 22% ee). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 19.9 min (major), t_2 = 21.3 min (minor)); $[\alpha]^{25}_D$ +6 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 1H), 7.20–7.10 (m, 3H), 6.99 (d, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 7.6 Hz, 2H), 4.23–4.15 (m, 1H), 3.87–3.79 (m, 1H), 3.50 (s, 3H), 3.24 (ddd, *J* = 15.2, 11.0, 1.6 Hz, 1H), 2.60–2.47 (m, 2H), 2.28 (s, 3H), 2.26–2.19 (m, 1H), 1.88–1.25 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 141.4, 138.9, 136.0, 135.1, 128.9, 128.1, 121.5, 120.2, 116.9, 107.9, 59.1, 46.2, 37.0, 34.8, 31.7, 29.6, 29.1, 25.0, 20.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for

$C_{23}H_{30}N_3$ 348.2440; Found 348.2449.



3-22ka

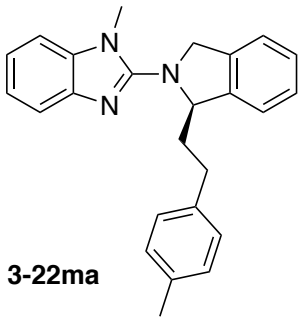
Compound 3-22ka (Scheme 3-9; colorless oil, 30.3 mg, 87% yield, 96% ee, (*R*)). A solution of hexane/AcOEt (1:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 15.6 min (minor), t_2 = 21.2 min (major)); $[\alpha]^{25}_D$ –11 (*c* 0.94, $CHCl_3$) for 96% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 1H), 7.18–7.00 (m, 7H), 4.61–4.50 (m, 1H), 3.507 (s, 3H), 3.509 (d, *J* = 9.0 Hz, 1H), 3.09 (d, *J* = 9.0 Hz, 1H), 2.69–2.52 (m, 2H), 2.28 (s, 3H), 2.18–2.07 (m, 1H), 2.01 (dd, *J* = 12.2, 6.6 Hz, 1H), 1.78–1.67 (m, 1H), 1.60 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.18 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 142.3, 139.1, 135.8, 135.0, 128.9, 128.1, 121.3, 119.7, 116.9, 107.6, 65.2, 59.5, 45.6, 38.9, 36.6, 31.6, 30.7, 26.7, 26.5, 20.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_3$ 348.2440; Found 348.2437.



3-22la **3-22la'**

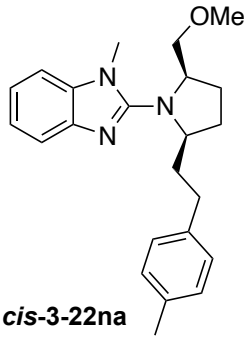
Compound 3-22la (Scheme 3-9; colorless oil, 27.2 mg, 76% yield, dr = 79:21). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. $[\alpha]^{25}_D$ –45 (*c* 1.41, $CHCl_3$). The ee of the products has not been determined. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.60 (m, 1H, major), 7.59–7.55 (m, 1H, minor), 7.20–7.10 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H, major), 7.05 (d, *J* = 8.0 Hz, 2H, major), 7.04 (d, *J* = 8.0 Hz, 2H, minor), 6.99 (d, *J* = 8.0 Hz, 2H, minor), 3.99 (ddd, J = 10.4, 6.0, 4.4 Hz, 1H, major), 3.89 (dd, 9.6, 8.0 Hz, 1H, minor), 3.84–3.79 (m, 1H, minor), 3.58 (s, 3H, major), 3.43 (s, 3H, minor), 3.27–3.19 (m, 2H, major),

3.07 (dd, J = 10.0, 4.0 Hz, 1H, minor), 2.81–2.54 (m, 5H), 2.29 (s, 3H, minor), 2.29 (s, 3H, major), 2.28–2.16 (m, 1H), 2.10–1.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) (major) δ 156.9, 141.7, 139.3, 135.0, 128.9, 128.1, 121.4, 120.8, 117.9, 108.2, 64.2, 60.2, 46.1, 41.5, 33.1, 32.4, 31.5, 29.7, 26.82, 26.78, 20.9; (minor) δ 156.2, 141.8, 138.7, 135.0, 128.9, 128.1, 121.3, 120.2, 117.3, 107.8, 67.0, 57.4, 48.7, 41.9, 34.6, 33.2, 33.0, 31.5, 30.4, 26.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{24}H_{30}N_3$ 360.2440; Found 360.2444.



3-22ma

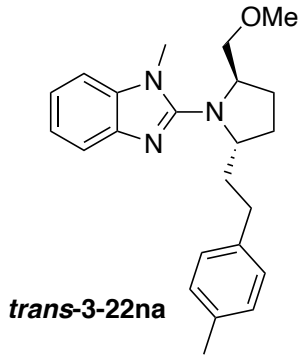
Compound 3-22ma (Scheme 3-9; colorless oil, 18.0 mg, 49% yield, 98% ee (*R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. $[\alpha]^{25}_D$ –115 (*c* 0.44, $CHCl_3$) for 98% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.56 (m, 1H), 7.39–7.28 (m, 4H), 7.22–7.12 (m, 3H), 6.98 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 5.93 (dd, J = 6.0, 3.8 Hz, 1H), 5.16 (dd, J = 12.8, 2.8 Hz, 1H), 4.64 (d, J = 12.8 Hz, 1H), 3.63 (s, 3H), 2.65–2.55 (m, 1H), 2.47–2.33 (m, 2H), 2.27 (s, 3H), 2.21–2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 142.0, 140.7, 139.0, 137.0, 136.0, 135.0, 128.8, 128.0, 127.6, 127.5, 122.5, 122.2, 121.6, 120.2, 117.0, 107.8, 65.5, 56.9, 35.9, 31.0, 29.9, 20.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{25}H_{26}N_3$ 368.2127; Found 368.2125.



***cis*-3-22na**

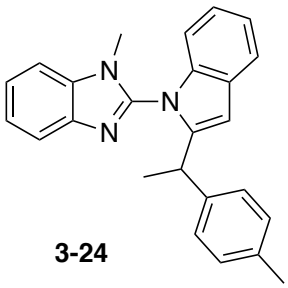
Compound *cis*-3-22na (Scheme 3-9; colorless oil, 23.5 mg, 78% yield). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. $[\alpha]^{25}_D$ –43 (*c* 1.16, $CHCl_3$) for (2*R*,5*R*)-**3-22na**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.61 (m, 1H), 7.24–7.17 (m, 3H),

7.05 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 4.11–3.94 (m, 2H), 3.60 (s, 3H), 3.46 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.36 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.28 (s, 3H), 2.65–2.44 (m, 2H), 2.29 (s, 3H), 2.22–2.08 (m, 2H), 1.97–1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 138.8, 135.2, 135.0, 129.0, 128.1, 121.7, 121.1, 118.0, 108.7, 75.6, 65.0, 63.8, 58.9, 38.0, 32.5, 29.9, 27.4, 20.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_3O$ 364.2389; Found 364.2393.



***trans*-3-22na**

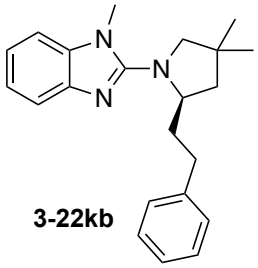
Compound *trans*-3-22na (Scheme 2; colorless oil, 20.5 mg, 57% yield). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. $[\alpha]^{25}_D$ –16 (*c* 0.63, $CHCl_3$) for (2*R*,5*S*)-**3oa**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.55 (m, 1H), 7.20–7.10 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 4.47–4.35 (m, 1H), 4.23–4.10 (m, 1H), 3.43 (s, 3H), 3.32 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.26 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.20 (s, 3H), 2.58 (ddd, *J* = 14.3, 9.3, 5.1 Hz, 1H), 2.47 (ddd, *J* = 14.3, 9.3, 7.3 Hz, 1H), 2.28 (s, 3H), 2.27–2.16 (m, 2H), 2.00–1.68 (m, 3H), 1.66–1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 141.9, 138.5, 135.4, 135.2, 128.9, 128.2, 121.3, 120.3, 117.3, 107.8, 74.0, 60.4, 59.6, 59.1, 35.1, 31.8, 30.2, 29.1, 26.8, 20.9. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_3O$ 364.2389; Found 364.2390.



3-24

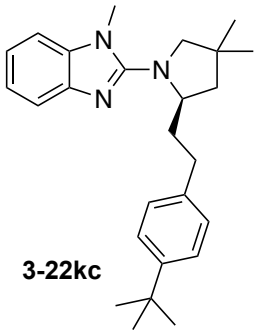
Compound 3-24 (Scheme 3-9; colorless solid, 31.3 mg isolated as a mixture of isomers (93:7), 86% yield). A solution of hexane/AcOEt (3:1) was used as an eluent for

preparative TLC. NMR data of the major isomer are shown below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.86 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.42–7.34 (m, 2H), 7.21–7.08 (m, 3H), 6.83 (d, 8.4 Hz, 1H), 6.76 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 1H), 2.61 (s, 3H), 2.16 (s, 3H), 1.68 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 144.2, 141.3, 141.1, 138.4, 135.7, 134.6, 128.6, 128.2, 127.0, 123.2, 122.6, 122.5, 121.1, 120.6, 120.1, 109.5, 101.3, 37.1, 28.9, 20.8. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{25}H_{24}N_3$ 366.1970; Found 366.1963.



3-22kb

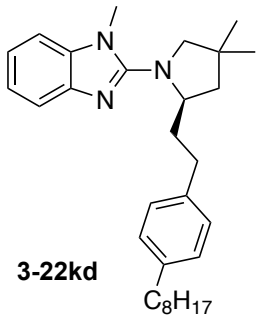
Compound 3-22kb (Scheme 3-10; colorless oil, 28.2 mg, 84% yield, 95% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 16.1 min (minor), t_2 = 22.8 min (major)); $[\alpha]^{20}_D$ –11 (*c* 0.50, $CHCl_3$) for 95% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.26–7.07 (m, 8H), 4.62–4.52 (m, 1H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.50 (s, 3H), 3.09 (dd, *J* = 9.0, 1.6 Hz, 1H), 2.74–2.57 (m, 2H), 2.20–2.10 (m, 1H), 2.01 (ddd, *J* = 12.0, 6.8, 1.2 Hz, 1H), 1.81–1.70 (m, 1H), 1.60 (dd, *J* = 12.0, 10.0 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 142.3, 135.8, 128.2, 125.6, 121.3, 119.8, 116.9, 107.6, 65.3, 59.5, 45.6, 38.9, 36.5, 32.1, 30.7, 26.7, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3$ 334.2283; Found 334.2280.



3-22kc

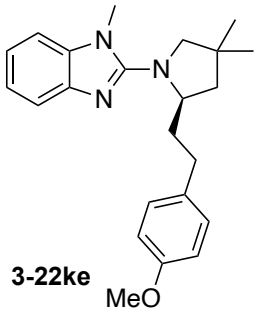
Compound 3-22kc (Scheme 3-10; colorless oil, 33.9 mg, 86% yield, 94% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was

measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 12.5 min (minor), t_2 = 16.3 min (major)); $[\alpha]^{25}_D$ –15 (*c* 0.77, $CHCl_3$) for 94% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.18–7.09 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.63–4.53 (m, 1H), 3.507 (s, 3H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.10 (dd, *J* = 9.2, 0.8 Hz, 1H), 2.71–2.55 (m, 2H), 2.19–2.09 (m, 1H), 2.02 (dd, *J* = 11.4, 6.6 Hz, 1H), 1.81–1.70 (m, 1H), 1.61 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.28 (s, 9H), 1.19 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 148.4, 142.3, 139.2, 135.8, 127.8, 125.1, 121.3, 119.8, 116.9, 107.5, 65.2, 59.5, 45.6, 38.9, 36.4, 34.3, 31.41, 31.35, 30.7, 26.7, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{26}H_{36}N_3$ 390.2909; Found 390.2904.



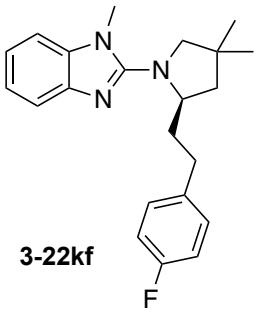
3-22kd

Compound 3-22kd (Scheme 3-10; colorless oil, 32.9 mg, 74% yield, 93% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 11.6 min (minor), t_2 = 14.6 min (major)); $[\alpha]^{25}_D$ –11 (*c* 0.74, $CHCl_3$) for 93% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.17–7.08 (m, 3H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.62–4.49 (m, 1H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.50 (s, 3H), 3.09 (dd, *J* = 9.2, 1.2 Hz, 1H), 2.70–2.49 (m, 3H), 2.19–2.07 (m, 1H), 2.01 (ddd, *J* = 12.0, 6.8, 1.2 Hz, 1H), 1.80–1.67 (m, 1H), 1.64–1.50 (m, 4H), 1.35–1.20 (m, 10H), 1.18 (s, 3H), 1.06 (s, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 140.2, 139.3, 135.7, 128.2, 128.0, 121.4, 119.9, 116.8, 107.6, 65.2, 59.6, 45.6, 38.9, 36.5, 35.5, 31.9, 31.6, 30.7, 29.5, 29.3, 29.2, 26.7, 26.5, 22.6, 14.1. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{30}H_{44}N_3$ 446.3535; Found 446.3532.



3-22ke

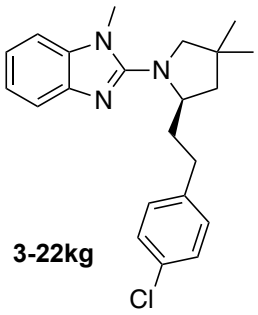
Compound 3-22ke (Scheme 3-10; colorless oil, 30.7 mg, 84% yield, 96% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 25.1 min (minor), t_2 = 38.9 min (major)); $[\alpha]^{20}_D$ –8 (*c* 0.54, $CHCl_3$) for 96% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.18–7.08 (m, 3H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.60–4.50 (m, 1H), 3.75 (s, 3H), 3.51 (s, 3H), 3.50 (d, *J* = 9.0 Hz, 1H), 3.09 (dd, *J* = 9.0, 1.2 Hz, 1H), 2.68–2.50 (m, 2H), 2.16–2.06 (m, 1H), 1.99 (ddd, *J* = 12.0, 6.0, 1.1 Hz, 1H), 1.77–1.66 (m, 1H), 1.59 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.18 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 157.5, 142.2, 135.8, 134.3, 129.1, 121.3, 119.8, 116.8, 113.6, 107.6, 65.2, 59.4, 55.2, 45.6, 38.9, 36.7, 31.1, 30.7, 26.7, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_3O$ 364.2389; Found 364.2385.



3-22kf

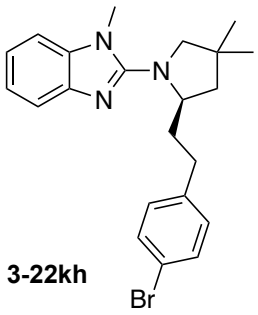
Compound 3-22kf (Scheme 3-10; colorless oil, 31.4 mg, 89% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 15.5 min (minor), t_2 = 22.5 min (major)); $[\alpha]^{25}_D$ –9 (*c* 0.53, $CHCl_3$) for 97% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.18–7.06 (m, 5H), 6.89 (t, *J* = 8.6 Hz, 2H), 4.61–4.50 (m, 1H), 3.52 (s, 3H), 3.50 (d, *J* = 9.0 Hz, 1H), 3.09 (dd, *J* = 9.0, 1.4 Hz, 1H), 2.70–2.53 (m, 2H), 2.18–2.07 (m, 1H), 1.99 (ddd, *J* = 12.4, 6.8, 1.2 Hz, 1H), 1.77–1.66 (m, 1H), 1.58 (dd, *J* = 12.0, 10.4 Hz, 1H), 1.18 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (d,

$J_{F\text{-}C}$ = 241 Hz), 157.5, 142.2, 137.9, 135.8, 129.5 (d, $J_{F\text{-}C}$ = 8 Hz), 121.3, 119.8, 116.9, 114.9 (d, $J_{F\text{-}C}$ = 21 Hz), 107.6, 65.3, 59.4, 45.6, 38.9, 36.7, 31.3, 30.7, 26.6, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}FN_3$ 352.2189; Found 352.2191.



3-22kg

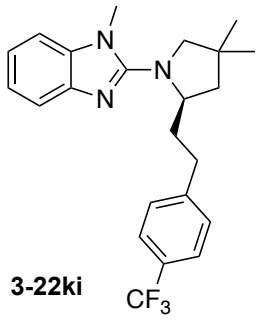
Compound 3-22kg (Scheme 3-10; colorless oil, 33.1 mg, 89% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 16.0 min (minor), t_2 = 23.1 min (major)); $[\alpha]^{25}_D$ –20 (*c* 0.80, $CHCl_3$) for 97% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.20–7.08 (m, 3H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.66–4.53 (m, 1H), 3.51 (s, 3H), 3.50 (d, *J* = 9.2 Hz, 1H), 3.09 (d, *J* = 9.2 Hz, 1H), 2.72–2.53 (m, 2H), 2.18–2.07 (m, 1H), 1.99 (dd, *J* = 11.6, 6.0 Hz, 1H), 1.79–1.68 (m, 1H), 1.58 (dd, *J* = 12.0, 10.4 Hz, 1H), 1.18 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 142.2, 140.7, 135.8, 131.2, 129.6, 128.2, 121.3, 119.9, 116.9, 107.6, 65.4, 59.4, 45.5, 39.0, 36.4, 31.5, 30.7, 26.6, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}{}^{35}ClN_3$ 368.1894; Found 368.1893.



3-22kh

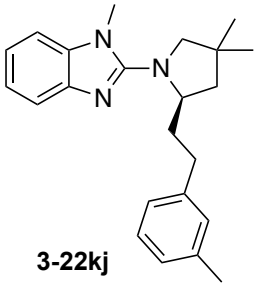
Compound 3-22kh (Scheme 3-10; colorless oil, 36.2 mg, 88% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 15.8 min (minor), t_2 = 22.7 min (major)); $[\alpha]^{25}_D$ –21 (*c* 0.81, $CHCl_3$) for 97% ee (*R*). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.18–7.07 (m, 3H), 7.01 (d, J = 8.8 Hz, 2H), 4.61–4.52 (m, 1H), 3.50 (s, 3H), 3.49 (d, J = 9.2 Hz, 1H), 3.08 (dd, J = 9.2, 1.2 Hz, 1H), 2.69–2.53 (m, 2H), 2.17–2.07 (m, 1H), 1.98 (ddd, J = 12.0, 6.8, 1.6 Hz, 1H), 1.79–1.68 (m, 1H), 1.57 (dd, J = 12.0, 10.0 Hz, 1H), 1.18 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 142.2, 141.2, 135.8, 131.2, 130.0, 121.3, 119.9, 119.3, 116.9, 107.6, 65.4, 59.4, 45.5, 39.0, 36.3, 31.6, 30.7, 26.6, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}{}^{79}BrN_3$ 412.1388; Found 412.1383.



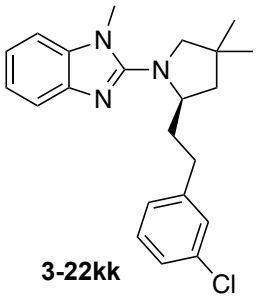
3-22ki

Compound 3-22ki (Scheme 3-10; colorless oil, 34.4 mg, 86% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 11.8 min (minor), t_2 = 16.3 min (major)); $[\alpha]^{25}_D$ –18 (*c* 0.73, $CHCl_3$) for 97% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.18–7.08 (m, 3H), 4.67–4.57 (m, 1H), 3.50 (s, 3H), 3.49 (d, J = 9.1 Hz, 1H), 3.08 (dd, J = 9.0, 1.4 Hz, 1H), 2.80–2.62 (m, 2H), 2.21–2.11 (m, 1H), 2.00 (ddd, J = 12.4, 6.8, 1.6 Hz, 1H), 1.85–1.74 (m, 1H), 1.60 (dd, J = 12.0, 10.4 Hz, 1H), 1.18 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 146.4, 142.1, 135.8, 128.5, 127.9 (q, $J_{F\text{-}C}$ = 32 Hz), 125.1 (q, $J_{F\text{-}C}$ = 4 Hz), 124.3 (q, $J_{F\text{-}C}$ = 271 Hz), 121.4, 119.9, 116.9, 107.6, 65.5, 59.4, 45.5, 39.0, 36.2, 32.0, 30.7, 26.6, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}F_3N_3$ 402.2157; Found 402.2162.



3-22kj

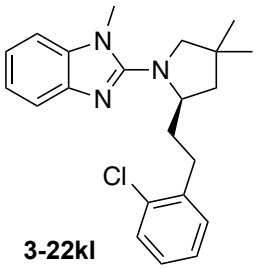
Compound 3-22kj (Scheme 3-10; colorless oil, 29.4 mg, 85% yield, 95% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 14.8 min (minor), t_2 = 20.7 min (major)); $[\alpha]^{25}_D$ –14 (*c* 0.54, $CHCl_3$) for 95% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.17–7.06 (m, 4H), 6.97–6.92 (m, 3H), 4.62–4.53 (m, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.50 (s, 3H), 3.09 (dd, *J* = 9.0, 1.4 Hz, 1H), 2.70–2.53 (m, 2H), 2.25 (s, 3H), 2.17–2.07 (m, 1H), 2.01 (ddd, *J* = 12.4, 6.8, 1.6 Hz, 1H), 1.81–1.70 (m, 1H), 1.61 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 142.26, 142.18, 137.7, 135.8, 129.0, 128.1, 126.3, 125.2, 121.3, 119.8, 116.9, 107.6, 65.3, 59.5, 45.6, 38.9, 36.5, 31.9, 30.7, 26.7, 26.5, 21.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_3$ 348.2440; Found 348.2437.



3-22kk

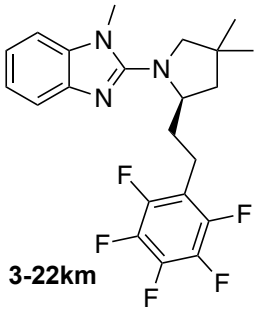
Compound 3-22kk (Scheme 3-10; colorless oil, 30.3 mg, 82% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 14.6 min (minor), t_2 = 21.2 min (major)); $[\alpha]^{25}_D$ –23 (*c* 0.69, $CHCl_3$) for 97% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.18–7.07 (m, 6H), 7.05–6.99 (m, 1H), 4.63–4.55 (m, 1H), 3.52 (s, 3H), 3.50 (d, *J* = 9.2 Hz, 1H), 3.09 (dd, *J* = 9.2, 1.6 Hz, 1H), 2.73–2.55 (m, 2H), 2.19–2.09 (m, 1H), 1.99 (ddd, *J* = 12.0, 6.8, 1.6 Hz, 1H), 1.80–1.69 (m, 1H), 1.58 (dd, *J* = 12.0, 10.0 Hz, 1H), 1.18 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 144.3,

142.2, 135.8, 133.9, 129.4, 128.3, 126.4, 125.8, 121.3, 119.9, 116.9, 107.6, 65.4, 59.4, 45.5, 39.0, 36.3, 31.8, 30.7, 26.6, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}{}^{35}ClN_3$ 368.1894; Found 368.1894.



3-22kl

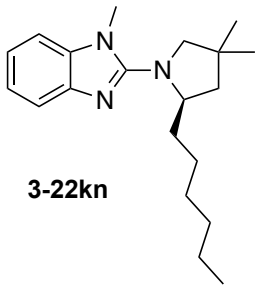
Compound 3-22kl (Scheme 3-10; colorless oil, 34.0 mg, 92% yield, 93% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 14.9 min (minor), t_2 = 19.8 min (major)); $[\alpha]^{25}_D$ –22 (*c* 0.36, $CHCl_3$) for 93% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.28–7.24 (m, 1H), 7.19–7.03 (m, 6H), 4.63–4.54 (m, 1H), 3.53 (s, 3H), 3.52 (d, *J* = 9.2 Hz, 1H), 3.09 (dd, *J* = 9.2, 1.6 Hz, 1H), 2.78–2.70 (m, 2H), 2.12–1.98 (m, 2H), 1.80–1.70 (m, 1H), 1.64 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.18 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 142.2, 139.8, 135.8, 133.7, 130.1, 129.3, 127.1, 126.7, 121.3, 119.9, 116.9, 107.6, 65.3, 59.5, 45.3, 38.9, 34.7, 30.7, 29.8, 26.7, 26.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}{}^{35}ClN_3$ 368.1894; Found 368.1896.



3-22km

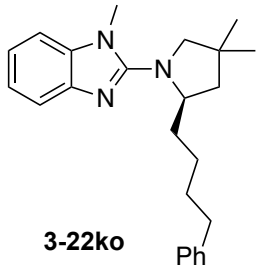
Compound 3-22km (Scheme 3-10; colorless oil, 37.7 mg, 95% yield, 94% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 10.8 min (minor), t_2 = 14.0 min (major)); $[\alpha]^{25}_D$ –9 (*c* 0.90, $CHCl_3$) for 94% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.2 Hz, 1H), 7.17–7.07 (m, 3H), 4.66–4.57 (m, 1H), 3.57 (s, 3H), 3.52 (d, *J* = 9.2 Hz, 1H), 3.09 (dd, *J* = 9.2, 1.2 Hz, 1H), 2.75–2.68 (m, 2H), 2.12–1.98 (m,

2H), 1.78–1.67 (m, 1H), 1.59 (dd, J = 12.0, 10.0 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 146.0 (m), 143.6 (m), 142.0, 138.2 (m), 136.2 (m), 121.4, 120.0, 117.0, 115.2 (m), 107.7, 65.5, 59.1, 45.2, 39.1, 34.4, 30.6, 26.6, 26.4, 19.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}F_5N_3$ 424.1812; Found 424.1819.



3-22kn

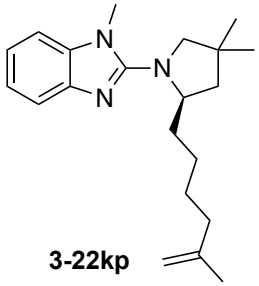
Compound 3-22kn (Scheme 3-10; colorless oil, 27.8 mg, 89% yield, 92% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 12.3 min (minor), t_2 = 15.7 min (major)); $[\alpha]^{25}_D$ +30 (*c* 0.31, $CHCl_3$) for 92% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.2 Hz, 1H), 7.17–7.06 (m, 3H), 4.49–4.38 (m, 1H), 3.58 (s, 3H), 3.51 (d, J = 9.2 Hz, 1H), 3.09 (dd, J = 9.2, 1.6 Hz, 1H), 1.95 (ddd, J = 12.0, 6.8, 1.6 Hz, 1H), 1.88–1.76 (m, 1H), 1.52 (dd, J = 12.0, 10.4 Hz, 1H), 1.40–1.20 (m, 9H), 1.17 (s, 3H), 1.05 (s, 3H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 142.4, 135.9, 121.2, 119.7, 116.8, 107.5, 65.2, 59.7, 45.7, 38.7, 34.8, 31.8, 30.8, 29.5, 26.7, 26.5, 25.6, 22.6, 14.1. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{32}N_3$ 314.2596; Found 314.2599.



3-22ko

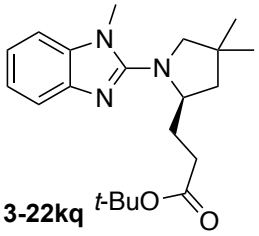
Compound 3-22ko (Scheme 3-10; colorless oil, 32.0 mg, 89% yield, 92% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 17.0 min (minor), t_2 = 22.0 min (major)); $[\alpha]^{25}_D$ +18 (*c* 0.67, $CHCl_3$) for 92% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.27–7.20 (m, 2H), 7.19–7.07 (m, 6H), 4.53–

4.40 (m, 1H), 3.55 (s, 3H), 3.49 (d, J = 9.2 Hz, 1H), 3.08 (dd, J = 9.2, 1.2 Hz, 1H), 2.65–2.51 (m, 2H), 1.93 (ddd, J = 12.4, 6.8, 1.6 Hz, 1H), 1.90–1.80 (m, 1H), 1.69–1.55 (m, 2H), 1.51 (dd, J = 12.4, 10.4 Hz, 1H), 1.49–1.25 (m, 3H), 1.16 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 142.6, 142.3, 135.9, 128.4, 128.2, 125.5, 121.2, 119.7, 116.8, 107.5, 65.3, 59.6, 45.6, 38.8, 35.8, 34.6, 31.6, 30.8, 26.6, 26.5, 25.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{24}H_{32}N_3$ 362.2596; Found 362.2598.



3-22kp

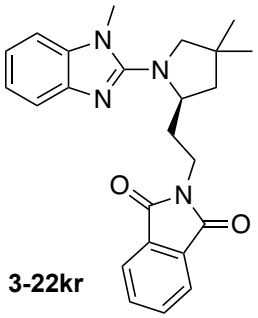
Compound 3-22kp (Scheme 3-10; colorless oil, 26.6 mg, 82% yield, 91% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 13.2 min (minor), t_2 = 17.2 min (major)); $[\alpha]^{25}_D$ +23 (*c* 0.50, $CHCl_3$) for 92% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.2 Hz, 1H), 7.15–7.05 (m, 3H), 4.65 (s, 1H), 4.62 (s, 1H), 4.50–4.40 (m, 1H), 3.57 (s, 3H), 3.50 (d, J = 9.2 Hz, 1H), 3.08 (dd, J = 9.2, 1.2 Hz, 1H), 2.00–1.90 (m, 3H), 1.88–1.79 (m, 1H), 1.67 (s, 3H), 1.51 (dd, J = 12.0, 10.0 Hz, 1H), 1.46–1.20 (m, 5H), 1.16 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 146.0, 142.4, 135.9, 121.2, 119.7, 116.8, 109.6, 107.5, 65.2, 59.7, 45.6, 38.7, 37.7, 34.7, 30.8, 27.8, 26.7, 26.5, 25.3, 22.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{21}H_{32}N_3$ 326.2596; Found 326.2605.



3-22kq

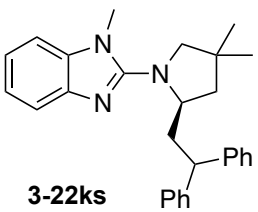
Compound 3-22kq (Scheme 3-10; colorless oil, 33.1 mg, 93% yield, 91% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 =

21.8 min (minor), t_2 = 27.7 min (major)); $[\alpha]^{25}_D$ +18 (*c* 0.66, $CHCl_3$) for 91% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 7.6 Hz, 1H), 7.12–7.06 (m, 3H), 4.59–4.48 (m, 1H), 3.57 (s, 3H), 3.49 (d, *J* = 9.2 Hz, 1H), 3.07 (dd, *J* = 9.2, 1.2 Hz, 1H), 2.32–2.16 (m, 1H), 2.10–2.00 (m, 1H), 1.91 (ddd, *J* = 12.4, 6.8, 1.2 Hz, 1H), 1.82–1.71 (m, 1H), 1.52 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.40 (s, 9H), 1.15 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 157.6, 142.2, 135.8, 121.3, 119.8, 116.9, 107.6, 80.1, 65.5, 58.9, 45.1, 39.0, 32.0, 30.8, 29.8, 28.0, 26.6, 26.4. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{21}H_{32}N_3O_2$ 358.2495; Found 358.2491.



3-22kr

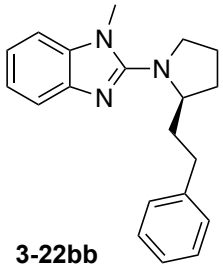
Compound 3-22kr (Scheme 3-10; colorless oil, 35.6 mg, 88% yield, 78% ee (*R*)). A solution of hexane/AcOEt (1:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 32.9 min (minor), t_2 = 35.7 min (major)); $[\alpha]^{25}_D$ +6 (*c* 1.19, $CHCl_3$) for 78% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.74 (m, 2H), 7.68–7.63 (m, 2H), 7.40 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.12–7.02 (m, 3H), 4.66–4.55 (m, 1H), 3.80–3.64 (m, 2H), 3.55 (s, 3H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.07 (dd, *J* = 9.2, 1.2 Hz, 1H), 2.20–2.08 (m, 1H), 2.07–2.00 (m, 1H), 1.98–1.87 (m, 1H), 1.64 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.17 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 157.4, 142.0, 135.8, 133.7, 132.0, 123.0, 121.3, 119.8, 116.9, 107.6, 65.4, 57.6, 45.2, 39.0, 35.1, 33.4, 30.7, 26.6, 26.4. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}N_4O_2$ 403.2134; Found 403.2130.



3-22ks

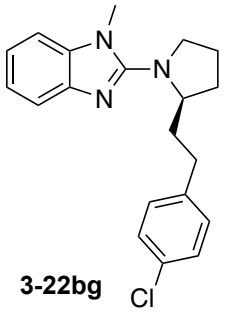
Compound 3-22ks (Scheme 3-10; colorless solid, 14.3 mg, 35% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was

measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 14.2 min (minor), t_2 = 19.4 min (major)); $[\alpha]^{25}_D$ +48 (*c* 0.51, $CHCl_3$) for 97% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.31–7.06 (m, 13H), 4.53–4.43 (m, 1H), 4.03 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.42 (d, *J* = 9.0 Hz, 1H), 3.27 (s, 3H), 3.02 (dd, *J* = 9.0, 0.8 Hz, 1H), 2.57 (ddd, *J* = 13.4, 8.8, 4.0 Hz, 1H), 2.21 (ddd, *J* = 13.4, 8.4, 6.4 Hz, 1H), 1.86 (dd, *J* = 12.4, 6.8 Hz, 1H), 1.58 (dd, *J* = 12.4, 9.6 Hz, 1H), 1.14 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 145.6, 144.4, 142.3, 135.9, 128.3, 128.2, 127.9, 127.5, 126.1, 125.9, 121.2, 119.7, 116.9, 107.5, 64.7, 58.7, 48.5, 45.7, 40.6, 38.8, 30.5, 26.8, 26.6. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{28}H_{32}N_3$ 410.2596; Found 410.2596.



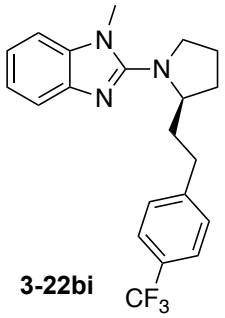
3-22bb

Compound 3-22bb (Scheme 3-11; colorless oil, 127.2 mg obtained in the reaction of 0.50 mmol of **1b** with **2b** (1.5 equiv) in the presence of 2 mol% of the Ir catalyst, 83% yield, 96% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 26.7 min (minor), t_2 = 32.3 min (major)); $[\alpha]^{25}_D$ –41 (*c* 1.00, $CHCl_3$) for 96% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 1H), 7.25–7.19 (m, 2H), 7.18–7.08 (m, 6H), 4.39 (ddd, *J* = 14.8, 7.6, 4.4 Hz, 1H), 3.73 (td, *J* = 8.9, 6.9 Hz, 1H), 3.52 (s, 3H), 3.38 (td, *J* = 8.9, 4.0 Hz, 1H), 2.74–2.60 (m, 2H), 2.30–2.20 (m, 1H), 2.15–1.88 (m, 3H), 1.80–1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 142.0, 141.6, 135.6, 128.13, 128.08, 125.5, 121.3, 119.9, 116.7, 107.6, 60.1, 52.0, 36.0, 32.1, 30.9, 30.5, 25.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}N_3$ 306.1970; Found 306.1968.



3-22bg

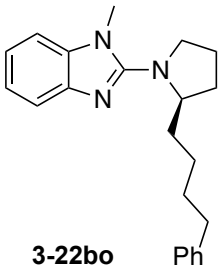
Compound 3-22bg (Scheme 3-11; colorless oil, 24.4 mg, 72% yield, 96% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 27.0 min (minor), t_2 = 33.6 min (major)); $[\alpha]^{25}_D$ –43 (*c* 0.61, $CHCl_3$) for 96% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.16–7.10 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.44–4.35 (m, 1H), 3.73 (td, *J* = 8.8, 6.8 Hz, 1H), 3.54 (s, 3H), 3.36 (td, *J* = 8.8, 3.7 Hz, 1H), 2.71–2.58 (m, 2H), 2.28–2.18 (m, 1H), 2.14–1.88 (m, 3H), 1.78–1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 140.6, 135.7, 131.3, 129.6, 128.2, 121.5, 120.2, 116.9, 107.7, 60.2, 52.4, 36.0, 31.6, 31.1, 30.7, 25.2. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}{}^{35}ClN_3$ 340.1581; Found 340.1586.



3-22bi

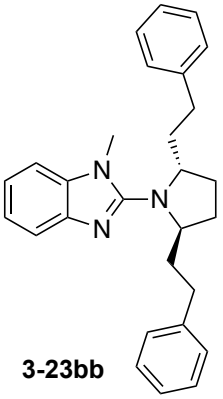
Compound 3-22bi (Scheme 3-11; colorless oil, 24.3 mg, 73% yield, 97% ee (*R*)). A solution of hexane/AcOEt (2:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 19.1 min (minor), t_2 = 22.9 min (major)); $[\alpha]^{25}_D$ –43 (*c* 0.50, $CHCl_3$) for 97% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.19–7.09 (m, 3H), 4.44 (ddd, *J* = 14.8, 7.7, 4.9 Hz, 1H), 4.44 (td, *J* = 8.8, 6.8 Hz, 1H), 3.53 (s, 3H), 3.36 (td, *J* = 8.8, 4.0 Hz, 1H), 2.82–2.66 (m, 2H), 2.30–1.88 (m, 4H), 1.84–1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 146.4, 135.7, 128.5, 128.6 (q, $J_{F\text{-}C}$ = 33 Hz), 125.1 (q, $J_{F\text{-}C}$ = 4 Hz), 124.3 (q, $J_{F\text{-}C}$ = 272 Hz), 121.5, 120.2, 116.9, 107.7, 60.2, 52.5, 35.8, 32.2, 31.1, 30.7,

25.3. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{21}H_{23}F_3N_3$ 374.1844; Found 374.1844.



3-22bo

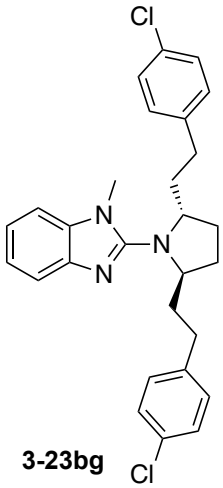
Compound 3-22bo (Scheme 3-11; colorless oil, 18.2 mg obtained in the reaction of 1 equivalent of **2o**, 55% yield, 85% ee (*R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 27.2 min (minor), t_2 = 31.6 min (major)); $[\alpha]^{25}_D$ –9 (*c* 0.57, $CHCl_3$) for 85% ee (*R*)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.18–7.08 (m, 6H), 4.34–4.25 (m, 1H), 3.73 (td, *J* = 8.8, 7.1 Hz, 1H), 3.59 (s, 3H), 3.37 (td, *J* = 8.8, 7.1 Hz, 1H), 2.64–2.52 (m, 2H), 2.12–2.14 (m, 1H), 2.04–1.57 (m, 6H), 1.48–1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 142.6, 128.4, 128.2, 125.5, 121.5, 120.1, 116.8, 107.7, 60.5, 52.3, 35.8, 34.2, 31.5, 31.1, 30.8, 25.4, 25.1. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3$ 334.2283; Found 334.2283.



3-23bb

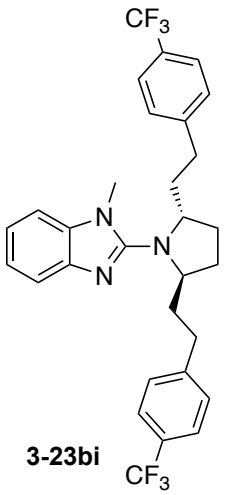
Compound 3-23bb (Scheme 3-11; colorless oil, 29.5 mg as a mixture of *trans*- and *cis*-isomers (93:7), 72% yield, 98% ee (*R,R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The corresponding racemic compound, which was isolated as a mixture of isomers [*trans* (*chiral*):*cis* (*meso*) = 62:38], was prepared by using $[IrCl(cod)]_2$ as a catalyst. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 16.0 min (minor), t_2 = 42.7 min (major)); $[\alpha]^{25}_D$ +13 (*c* 0.50, $CHCl_3$) for 98% ee (*R,R*). NMR data of the major isomer are shown below. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.57 (d, *J* = 6.8 Hz, 1H), 7.26–7.10 (m, 9H), 7.07 (d, *J* = 7.2 Hz, 4H), 4.19 (br, 2H), 3.28 (s, 3H), 2.68–2.47 (m, 4H), 2.34–2.20 (m, 2H), 1.90–1.72 (m, 4H), 1.68–1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 142.0, 141.8, 135.3, 128.3, 128.3, 125.8, 121.3, 120.3, 117.3, 107.8, 60.1, 35.4, 32.2, 30.0, 29.4. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{28}H_{32}N_3$ 410.2596; Found 410.2601.



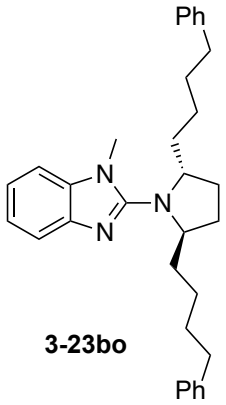
3-23bg

Compound 3-23bg (Scheme 3-11; colorless oil, 26.9 mg as a mixture of *trans*- and *cis*-isomers (91:9), 61% yield, 99% ee (*R,R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The corresponding racemic compound, which was isolated as a mixture of isomers [*trans* (*chiral*):*cis* (*meso*) = 59:41], was prepared by using $[IrCl(cod)]_2$ as a catalyst. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 17.0 min (minor), t_2 = 42.5 min (major)); $[\alpha]^{25}_D$ +22 (*c* 1.27, $CHCl_3$) for 99% ee (*R,R*). NMR data of the major isomer are shown below. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.8 Hz, 1H), 7.22–7.13 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 4H), 6.98 (d, *J* = 8.4 Hz, 4H), 4.15 (br, 2H), 3.32 (s, 3H), 2.62–2.42 (m, 4H), 2.34–2.18 (m, 2H), 1.90–1.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 141.9, 140.1, 135.2, 131.4, 129.6, 128.3, 121.4, 120.5, 117.4, 107.9, 60.0, 35.3, 31.5, 30.0, 29.4. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}{}^{35}Cl_2N_3$ 478.1817; Found 478.1827.



3-23bi

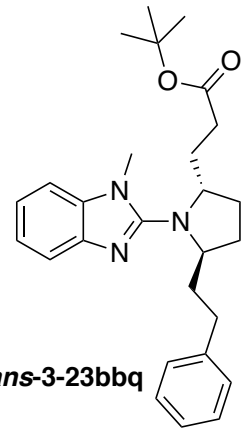
Compound 3-23bi (Scheme 3-11; colorless oil, 30.4 mg as a mixture of *trans*- and *cis*-isomers (96:4), 56% yield, 99% ee (*R*,*R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The corresponding racemic compound, which was isolated as a mixture of isomers [*trans* (*chiral*):*cis* (*meso*) = 61:39], was prepared by using $[IrCl(cod)]_2$ as a catalyst. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 10.8 min (minor), t_2 = 17.0 min (major)); $[\alpha]^{25}_D$ +5 (*c* 1.00, $CHCl_3$) for 99% ee (*R,R*). NMR data of the major isomer are shown below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 4H), 7.22–7.12 (m, 3H), 7.44 (d, *J* = 7.6 Hz, 4H), 4.18 (br, 2H), 3.32 (s, 3H), 2.72–2.50 (m, 4H), 2.35–2.20 (m, 2H), 1.98–1.58 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 145.8, 141.8, 135.2, 128.6, 128.2 (q, $J_{F\text{-}C}$ = 33 Hz), 125.2 (q, $J_{F\text{-}C}$ = 4 Hz), 124.2 (q, $J_{F\text{-}C}$ = 272 Hz), 121.5, 120.6, 117.5, 108.0, 60.1, 35.1, 32.0, 30.0, 29.5. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{30}H_{30}F_6N_3$ 546.2344; Found 546.2344.



3-23bo

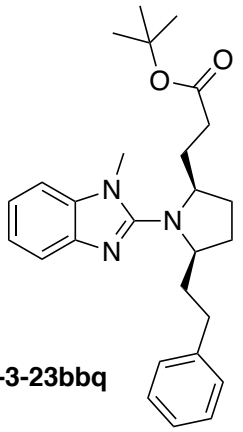
Compound 3-23bo (Scheme 3-11; colorless oil, 32.7 mg as a mixture of *trans*- and *cis*-isomers (91:9), 70% yield, 98% ee (*R,R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The corresponding racemic compound, which was isolated as

a mixture of isomers [*trans* (*chiral*):*cis* (*meso*) = 59:41], was prepared by using $[IrCl(cod)]_2$ as a catalyst. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 16.9 min (minor), t_2 = 40.0 min (major)); $[\alpha]^{25}_D$ +12 (*c* 0.50, $CHCl_3$) for 98% ee (*R,R*). NMR data of the major isomer are shown below. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.57 (m, 1H), 7.28–7.12 (m, 9H), 7.09 (d, *J* = 6.8 Hz, 4H), 4.11 (br, 2H), 3.52 (s, 3H), 2.60–2.47 (m, 4H), 2.22–2.10 (m, 2H), 1.71–1.20 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 142.4, 142.1, 135.3, 128.3, 128.2, 125.5, 121.2, 120.1, 117.3, 107.8, 60.6, 35.7, 33.6, 31.3, 30.3, 29.5, 25.4. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{32}H_{40}N_3$ 466.3222; Found 466.3220.



***trans*-3-23bbq**

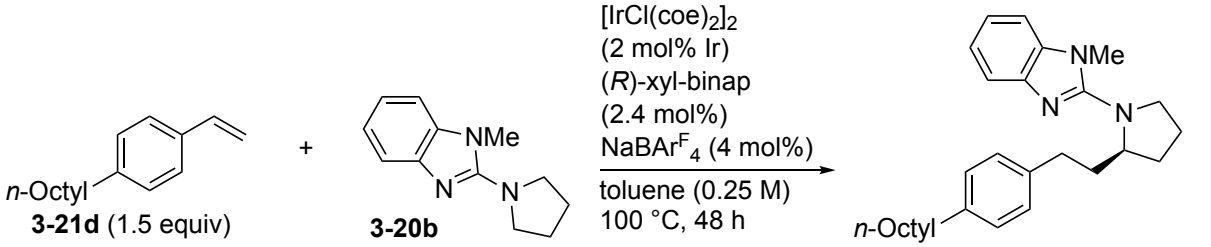
Compound *trans*-3-23bbq (Scheme 5; colorless oil, 23.5 mg obtained as a mixture of diastereomers (*trans*:*cis* = 96:4) by use of (*R*)-xyl-binap, 37% yield, 99% ee (2*S,*5*R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The corresponding racemic compound, which was isolated as a mixture of isomers [*trans*:*cis* = 51:49], was prepared by using $[IrCl(cod)]_2$ as a catalyst. The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 25.5 min (minor), t_2 = 33.5 min (major)); $[\alpha]^{25}_D$ +24 (*c* 0.80, $CHCl_3$) for 99% ee (2*S,*5*R*). NMR data of the major isomer are shown below. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.53 (m, 1H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.18–7.10 (m, 4H), 7.20 (d, *J* = 7.6 Hz, 2H), 4.32–4.05 (m, 2H), 3.41 (s, 3H), 2.61 (ddd, *J* = 14.0, 9.4, 4.8 Hz, 1H), 2.54–2.44 (m, 1H), 2.29–2.18 (m, 2H), 2.17 (t, *J* = 7.8 Hz, 2H), 1.98–1.52 (m, 6H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 154.8, 141.9, 141.6, 135.3, 128.3, 125.8, 121.3, 120.3, 117.4, 107.8, 80.2, 60.3, 59.5 (br), 32.2, 31.9, 30.1, 29.4, 29.2 (br), 29.0, 28.0, . HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{27}H_{36}N_3O_2$ 434.2808; Found 434.2801.

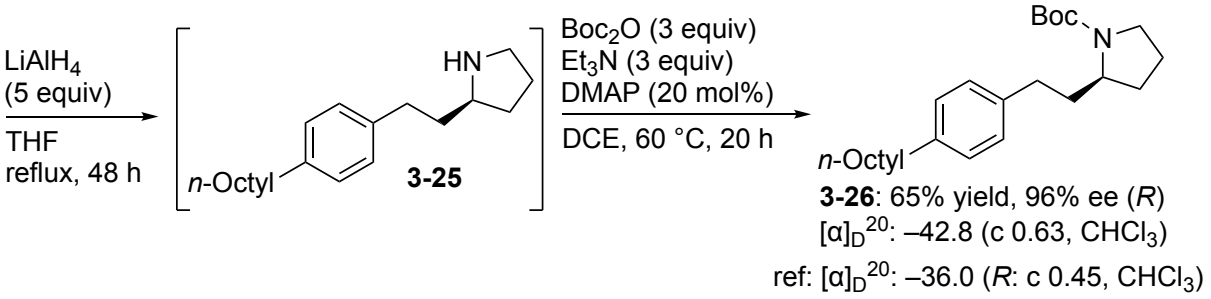


***cis*-3-23bbq**

Compound *cis*-3-23bbq (Scheme 5; colorless oil, 43.4 mg obtained as a mixture of diastereomers (*trans*:*cis* = 4:96) by use of (*S*)-xyl-binap, 86% yield, 99% ee (2*R*,5*R*)). A solution of hexane/AcOEt (3:1) was used as an eluent for preparative TLC. The corresponding racemic compound, which was isolated as a mixture of isomers [*trans*:*cis* = 51:49], was prepared by using $[IrCl(cod)]_2$ as a catalyst. The ee was measured by HPLC (Chiralpak IA3, hexane/2-propanol = 30:1, flow 0.5 mL/min, 254 nm, t_1 = 27.9 min (minor), t_2 = 31.2 min (major)); $[\alpha]^{25}_D$ –39 (*c* 0.73, $CHCl_3$). NMR data of the major isomer are shown below. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.58 (m, 1H), 7.25–7.14 (m, 6H), 7.21 (d, *J* = 7.4 Hz, 2H), 3.97–3.88 (m, 1H), 3.87–3.78 (m, 1H), 3.59 (s, 3H), 2.64 (ddd, *J* = 13.6, 10.8, 5.6 Hz, 1H), 2.52 (ddd, *J* = 13.6, 10.4, 6.4 Hz, 1H), 2.30–2.29 (m, 4H), 2.00–1.65 (m, 6H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 157.9, 141.7, 141.4, 135.1, 128.3, 125.8, 121.7, 121.1, 118.1, 108.7, 80.3, 65.1, 64.2, 37.9, 33.1, 32.6, 31.0, 29.9, 29.6, 29.3, 28.0. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{27}H_{36}N_3O_2$ 434.2808; Found 434.2802.

3-5-9. Transformation of 3-20b into 2-26





Compound **3-20b** (101 mg, 0.50 mmol), $[IrCl(coe)_2]_2$ (4.4 mg, 0.0050 mmol, 2 mol% of Ir), (*R*)-xyl-binap (8.8 mg, 0.012 mmol, 2.4 mol%), and $NaBAr^F_4$ (18.4 mg, 0.020 mmol, 4 mol%) were placed in a Schlenk tube under N_2. Toluene (1.0 mL) and alkene **3-21d** (173 mg, 0.75 mmol) were added to the mixture successively, and the mixture was stirred at 100 °C for 48 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel with hexane/AcOEt (3:1) to give **3-22bd** as a colorless oil (157 mg, 75% yield, 96% ee (*R*)). **Compound 3-22bd**: The ee was measured by HPLC (Chiralpak ID, hexane/2-propanol = 9:1, flow 0.5 mL/min, 254 nm, t_1 = 17.5 min (minor), t_2 = 18.7 min (major)); $[\alpha]^{25}_D$ –34 (*c* 1.20, $CHCl_3$) for 96% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.17–7.08 (m, 3H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.41–4.31 (m, 1H), 3.78–3.68 (m, 1H), 3.52 (s, 3H), 3.38 (td, *J* = 8.7, 3.9 Hz, 1H), 2.70–2.58 (m, 2H), 2.01 (dd, *J* = 8.2, 7.4 Hz, 2H), 2.29–2.20 (m, 1H), 2.12–1.90 (m, 3H), 1.80–1.50 (m, 4H), 1.34–1.20 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 141.8, 140.2, 139.2, 135.7, 128.2, 128.1, 121.3, 120.0, 116.9, 107.6, 60.2, 52.1, 36.1, 35.5, 31.83, 31.76, 31.5, 31.0, 30.6, 29.4, 29.3, 29.2, 25.0, 22.6, 14.1. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{28}H_{40}N_3$ 418.3222; Found 418.3228.

$LiAlH_4$ (9.5 mg, 0.25 mmol, 5 equiv) was placed in a Schlenk tube under N_2. Compound **3-22bd** (20.9 mg, 0.050 mmol) in THF (0.5 ml) was added to the tube, and the mixture was stirred at 80 °C for 48 h. The reaction mixture was cooled to 0 °C, quenched by

addition of 1N NaOH (1.5 mL), and stirred at room temperature for 1 h. The suspension was filtered by glass filter and washed with dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator. After dissolving the residue in dichloroethane (0.5 mL), di-*tert*-butyl dicarbonate (32.7 mg, 0.15 mmol, 3 equiv), triethylamine (20.9 μL, 0.15 mmol, 3 equiv), and 4-dimethylaminopyridine (1.2 mg, 0.01 mmol) were added to the mixture, and the reaction mixture was stirred at 60 °C for 20 h. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel (hexane/EtOAc = 10:1) to give **3-26** as a colorless oil (12.6 mg, 65% yield in 2 steps, 96% ee (*R*)). The ee was measured by HPLC (Chiralcel OD-H, hexane/2-propanol = 200:1, flow 0.5 mL/min, 254 nm, t_1 = 15.4 min (minor), t_2 = 16.2 min (major)); $[\alpha]^{25}_D$ –43 (*c* 0.63, $CHCl_3$) for 96% ee (*R*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 3.83–3.75 (m, 1H), 3.43–3.28 (m, 2H), 2.60–2.50 (m, 4H), 2.10–1.50 (m, 8H), 1.45 (s, 9H), 1.35–1.20 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 140.4, 139.2, 128.3, 128.1, 78.9, 57.0, 46.2, 36.3, 35.5, 32.4, 31.9, 30.3, 29.5, 29.4, 29.3, 28.6, 23.4, 22.7, 14.1. HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{25}H_{42}N_1O_2$ 388.3216; Found 388.3210.

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