博士学位論文

コバルト触媒と光酸化還元触媒の協働による
金属ヒドリド水素原子移動を用いたアルケンの分子変換

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略語表

本論文において、以下の略語を使用した

Ac	acetyl
Bn	benzyl
B(cat)	catecholboryl
B(pin)	pinacolboryl
bpy	2,2′-bipyridine
Cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory
dFppy	2-(2,4-difluorophenyl)pyridine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC·HCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et	ethyl
GC	gas chromatograph
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
*i*Pr	isopropyl
IR	infrared absorption spectrometry
LC	liquid chromatography
LRMS	low resolution mass spectrometer
MeCN	acetonitrile
MOM	methoxymethyl
HRMS	high resolution mass spectrometer
MS	mass spectrometry
nbd	2,5-norbornadiene
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
PTH	phenylphenothiazine
*t*Bu	tertiary butyl

TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TPP	5,10,15,20-tetrakisphenyl-porphyrin
Ts	p-toluenesulfonyl
TBA	tetrabutylammonium

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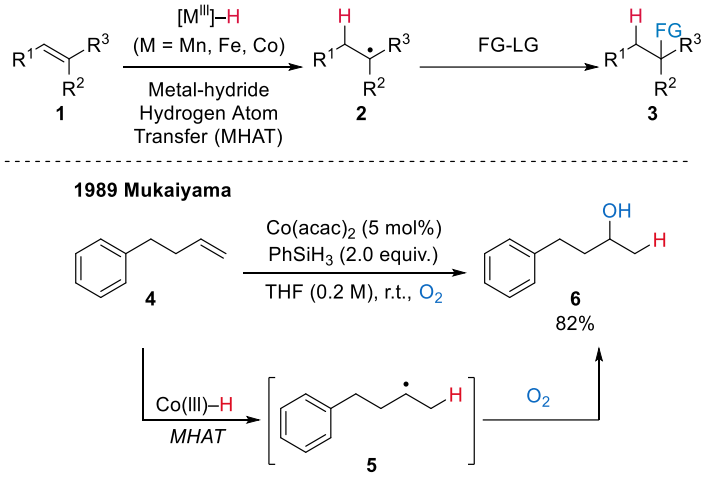
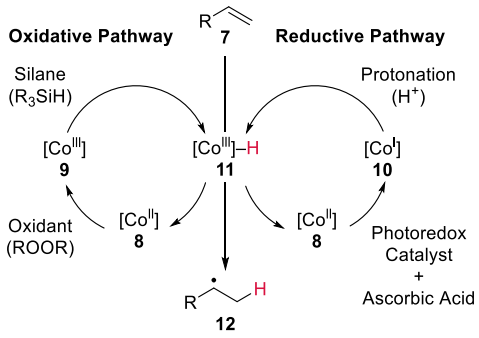
序論

金属ヒドリドからアルケンへの金属ヒドリド水素原子移動(Metal-hydride Hydrigen Atom Transfer, MHAT)によるマルコフニコフヒドロ官能基化反応は、炭素ラジカルを起点とする反応であり、高い化学選択的、かつラジカル反応特有の高い官能基許容性でアルケンに多様な官能基を導入できる優れた手法である(Scheme 1.)[1a, b]。向山らは、コバルトビスアセチルアセトナートを触媒として、酸素雰囲気下、フェニルシランを用いることで、向山水和反応として知られるヒドロアルコキシ化反応を開発した[2]。この反応を皮切りに Correira[3]、Boger[4]、重久[5]、Shenvi[6]、Herzon[7]、Baran[8]らにより、酸化剤と有機シランを用いた MHAT によるマルコフニコフヒドロ官能基化反応は大きく発展を遂げていった。

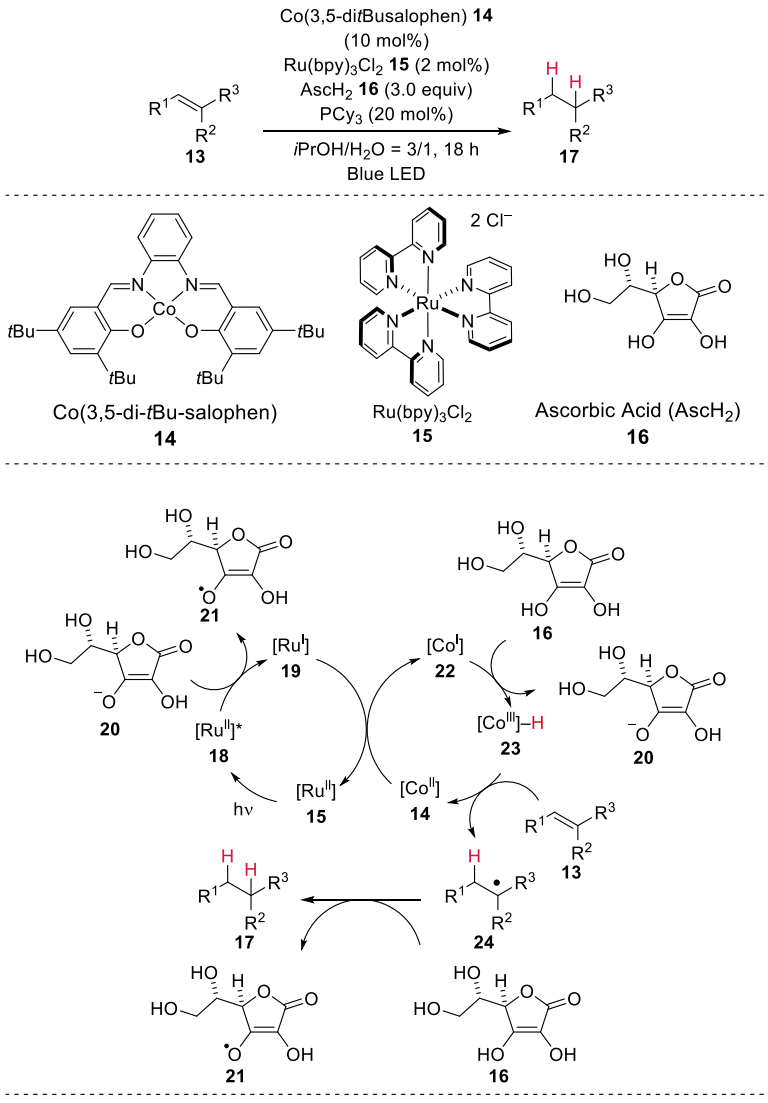


Scheme 1. Overview of Hydrofunctionalization of Alkenes and Initial Report of Mukaiyama Hydration

MHAT を用いるヒドロ官能基化反応における高原子価金属ヒドリド錯体の生成には、ペルオキシドや *N*-フルオロピリジニウム塩といった酸化剤と、ヒドリド源となる有機シランが用いられてきた。この金属ヒドリド生成では、潜在的に爆発性のある酸化剤を用いることから、安全面への懸念が存在する。また、ヒドリド源として高価な有機シランを用いることから、経済面の問題も抱えていた。当研究室では、コバルトサレン錯体、光酸化還元触媒、環境調和性の高い、安価な有機還元剤であるアスコルビン酸共存下、可視光を照射することで、還元的に生成した求核性を持つコバルト(Ⅰ)**10** のプロトン化によりコバルト(Ⅲ)ヒドリド **11** が生成することを見出し(Scheme 2)、この反応系を利用した MHAT によるアルケンの水素化反応を世界に先駆けて報告した(Scheme 3)[9a]。以下に詳細な反応機構について述べる。まず光酸化還元触媒 **15** が可視光により励起され、アスコルビン酸アニオン **20** による一電子還元を受け、ラジカルアニオン種 **19** 生成する。これがコバルト(Ⅱ) **14** を一電子還元し、光酸化還元触媒は基底状態 **15** に戻る。この時、求核性を持ったコバルト(Ⅰ)**22** が生成し、アスコルビン酸 **16** よりプロトン化を受け、触媒活性種であるコバルト(Ⅲ)ヒドリド **23** が生成する。これがアルケン **13** に MHAT を起こし、アルキルラジカル中間体 **24** が生成し、アスコルビン酸 **16** から水素原子を引き抜くことで、水素化反応が進行すると想定している。この反応では、潜在的な爆発性を持つ酸化剤や高価な有機シランの使用を回避でき、安全面や経済面の問題の解決に成功し、環境調和性の高い反応に発展させることができた。

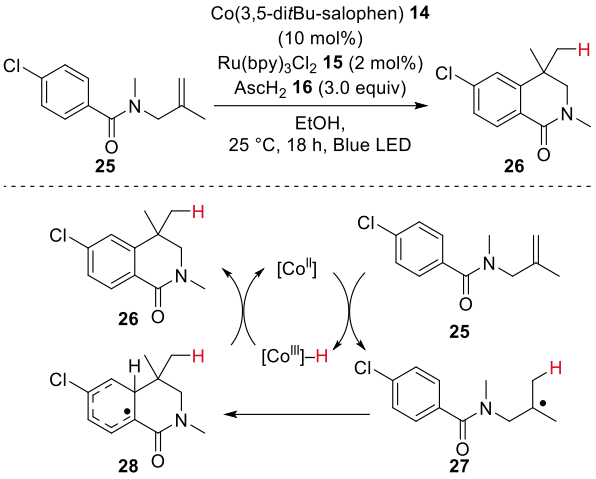


Scheme 2. Genneration of Metal Hydride

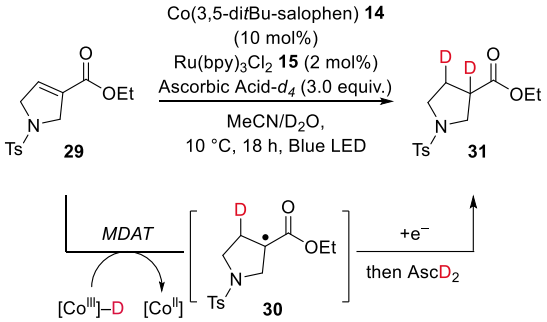


Scheme 3. Hydrogenation of Alkenes via MHAT

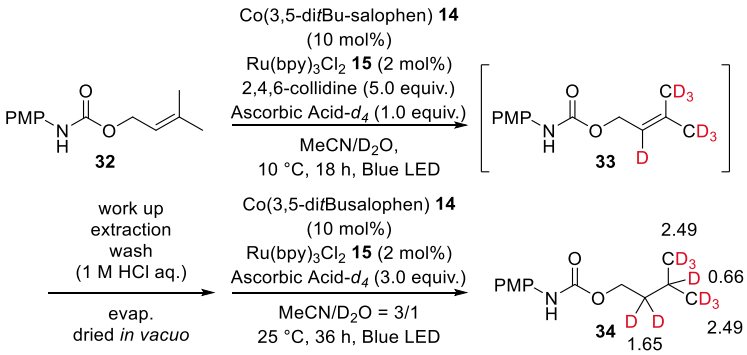
当研究室では、このアスコルビン酸をプロトン源かつ還元剤として用いた還元的サイクルによるコバルト(Ⅲ)ヒドリドの生成を用いた MHAT によるアルケンの分子内ヒドロアリール化反応[9b](Scheme 4)、電子不足アルケンの重水素化反応(Scheme 5)[9c]、及び不活性アルケンの多重水素化反応(Scheme 6)[9d]、ヒドロベンジル化反応[9e](Scheme 7)、遠隔位転移反応[9f](Scheme 8)を報告した。



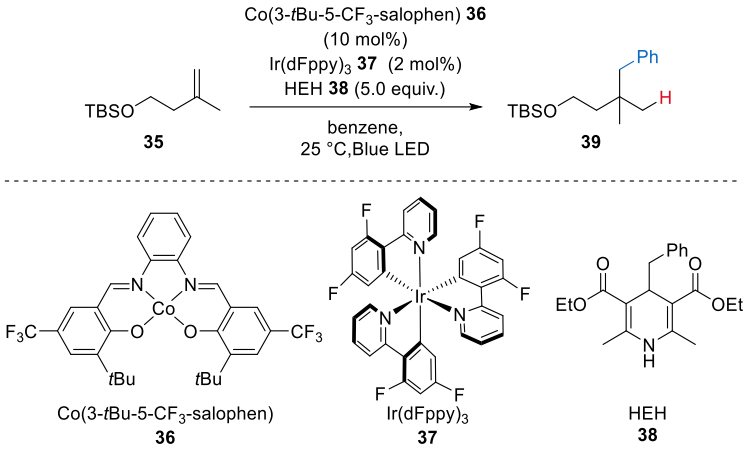
Scheme 4. Intermolecular Hydroarylation of Alkenes via MHAT



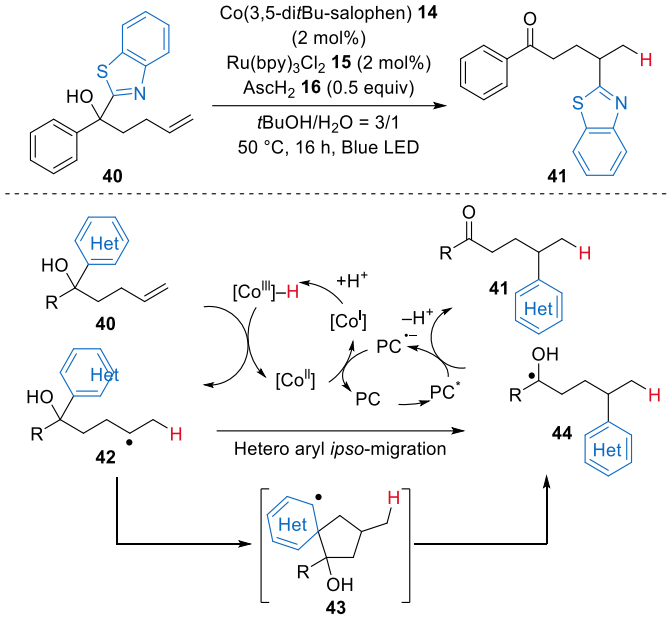
Scheme 5. Deuterium Atom Transfer Deuteration of Electron-Deficient Alkenes



Scheme 6. Multiple Deuterium Atom Transfer Perdeuteration of UnactivatedAlkenes



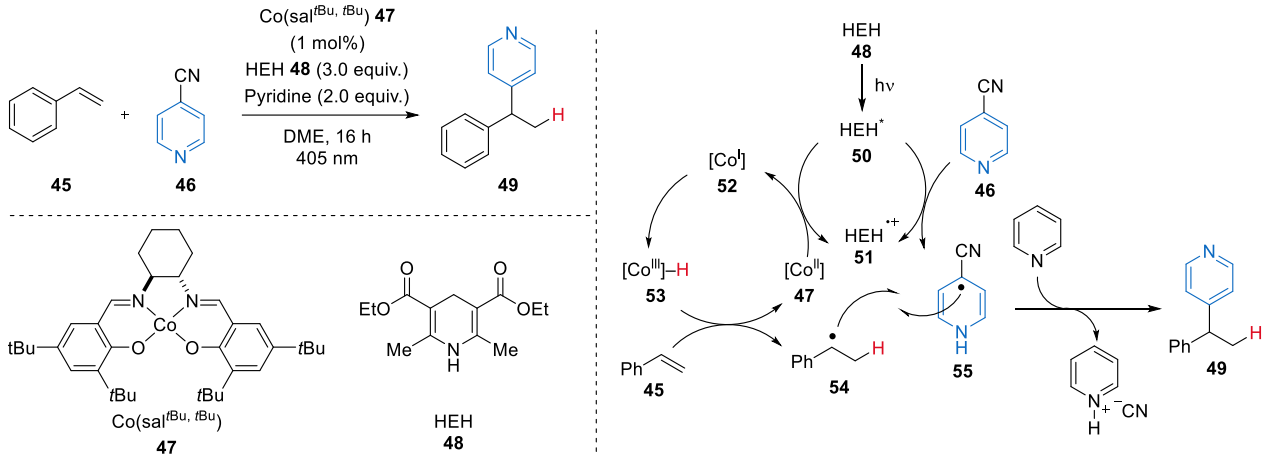
Scheme 7. Cobalt/Photoredox Dual-Catalyzed Cross-Radical Coupling of Alkenes via Hydrogen Atom Transfer



Scheme 8. Distal Heteroaryl Ipso-Migration of Unactivated Alkenes via MHAT

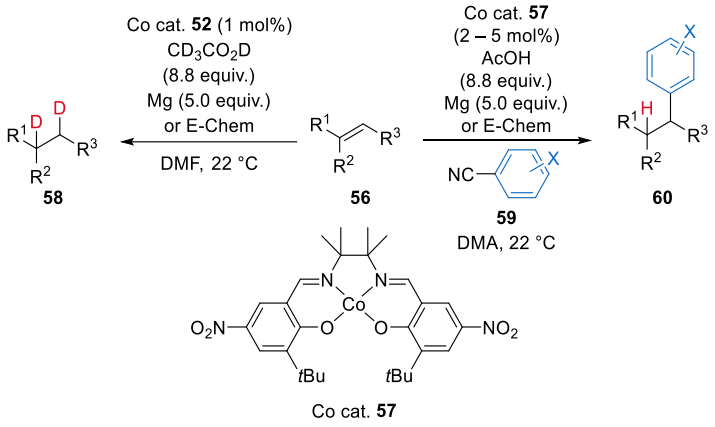
当研究室で世界に先駆けて報告されたこの還元的サイクルによる MHAT を用いたアルケンのヒドロ官能基化反応は、大きく 3 つの反応系に分かれ、発展をしてきた。まず初めに、当研究室でも研究がなされてきた、犠牲還元剤を用いた還元的サイクルによる MHAT を用いたヒドロ官能基化について述べる。Teskey はコバルトサレン錯体と有機光酸化還元触媒、犠牲有機還元剤かつプロトン源であるハンチュエステルを用いたスチレンやジエンのヒドロアリール化反応を報告した(Scheme 9)[10a]。想定反応機構について以下に示す。可視光により励起されたハンチュエステル **50** がコバルト触媒 **47** を 1 電子還元し、求核性を持ったコバルト(Ⅰ)錯体 **52** が生成する。これが 1 電子酸化されたハンチュエステル **51** から生じたプロトンを捕捉することで、触媒活性種であるコバルト(Ⅲ)ヒドリド **53** が生成する。これがスチレン **45** に対して MHAT を起こし、ベンジルラジカル **54** が生成する。生じたベンジルラジカルが励起されたハンチュエステル **50** により 1 電子還元された 4-シアノピリジン **55** とラジカル-ラジカルカップリングを起こし、ピリジンによりプロトンとシアノ基が脱離することで、ヒドロアリール化体 **49** が生成する。Teskey らは、この反応系を発展させ、還元的サイクルによる MHAT を用いたジエンのヘテロアリール化反応[10b]、スチレンやジエンとのジアリールケトンとの還元的カップリング[10c]、MHAT を起点とした 1,2-アリール転移反応[10d]、MHAT を起点としたスマイルズ転移によるアリルスルホンアミドからの β-アリールエチル

アミン合成[10e]、還元的 Radical-Polar-Crossover を用いたスチレン類のヒドロカルボキシル化反応[10f]を報告している。



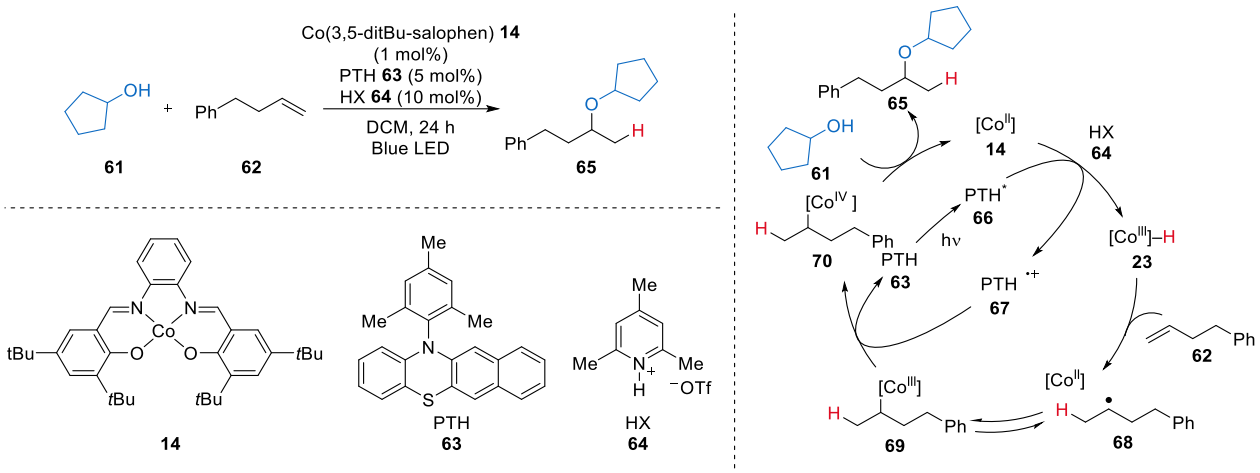
Scheme 9. Light-Driven Cobalt Hydride Catalyzed Hydroarylation of Styrenes

Lin らは、電気化学的な還元、もしくは金属還元剤とプロトン源として酢酸や重酢酸を用いた還元的なサイクルによる MHAT を用いた重水素化反応およびヒドロアリール化反応を報告した(Scheme 10)[11]。



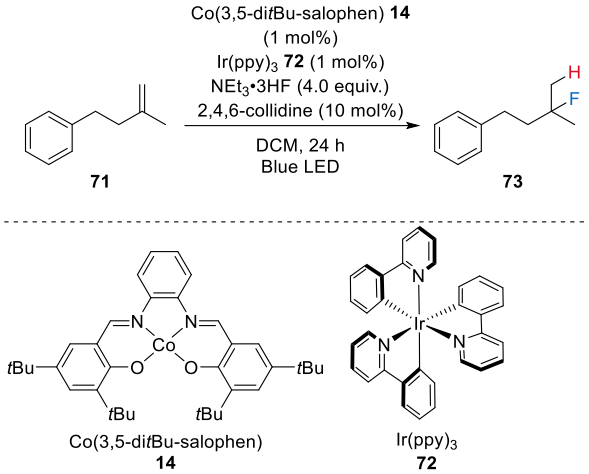
Scheme 10. Deuteration and Hydroarylation of Alkenes via MHAT

次に犠牲還元剤を用いないレドックスニュートラルな還元的サイクルによる MHAT を用いたアルケンのヒドロ官能基化反応について述べる。大宮らは、コバルト錯体と有機光酸化還元触媒の協働系による還元的サイクルによるコバルト(Ⅲ)ヒドリド錯体生成と酸化的 Radical-Polar-Crossover を用いたレドックスニュートラルなアルケンのヒドロエーテル化反応を報告した(Scheme 11)[12a]。光酸化還元触媒である PTH **63** が可視光により励起され、PTH* **66** となり、コバルト(Ⅱ) 錯体 **14** を一電子還元し、コバルト(Ⅰ)錯体 **22** が生成する。これがプロトン源である HX **64** によってプロトン化されることで、触媒活性種であるコバルト(Ⅲ)ヒドリド **23** が生成する。これがアルケン **62** へ MHAT を起こし、アルキルラジカル中間体 **68** を経て、アルキルコバルト(Ⅲ) **69** が生成する。このアルキルコバルト(Ⅲ) **69** がラジカルカチオン種 **67** によって酸化されることで、求電子的な化学種であるアルキルコバルト(Ⅳ) **70** が生じ、アルコール **61** と求核置換反応を起こすことで、エーテル **65** が得られる。このような犠牲還元剤を用いない還元的サイクルによる MHAT を用いたヒドロ官能基化反応は大宮らにより精力的に研究が行われ、レドックスニュートラルな MHAT による触媒系を用いたヒドロアシル化反応[12b]、ヒドロハロゲン化反応[12c]、遠隔位官能基化反応[12d]が報告された。



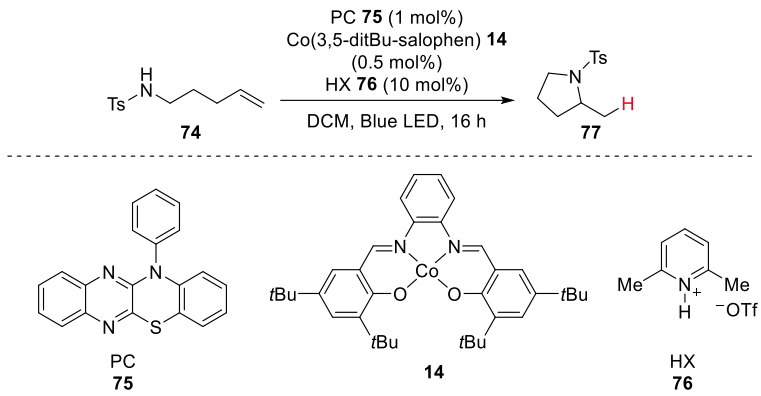
Scheme 11. Photoredox/Cobalt/Brønsted Acid Catalysis Enabling Markovnikov Hydroalkoxylation of Unactivated Alkenes

Lin らは、コバルトサレン錯体と光酸化還元触媒を用いた還元的サイクルによるコバルト(III)ヒドリド生成と酸化的 Radical-Polar-Crossover を組み合わせたレドックスニュートラルなアルケンのヒドロフッ素化反応を報告している(Scheme 12)[13]。



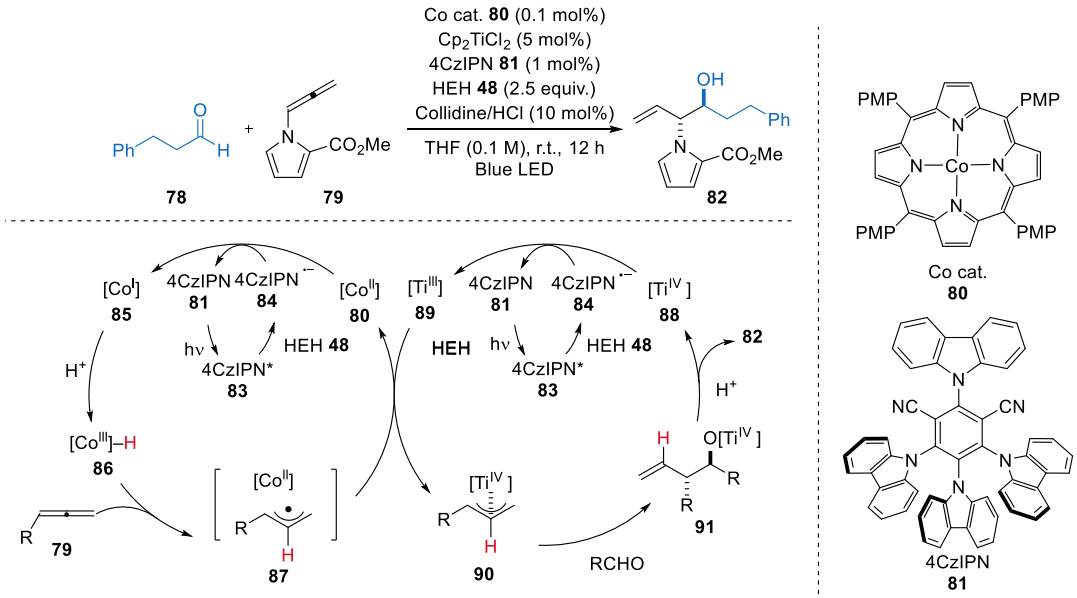
Scheme 12. Hydrofluorination of Alkenes via MHAT

Carreira らは、コバルトサレン錯体と光酸化還元触媒を用いた還元的サイクルによるコバルト(III)ヒドリド生成と酸化的 Radical-Polar-Crossover を組み合わせたレドックスニュートラルなアルケンの分子内環化異性化反応を報告した(Scheme 13)[14a]。またこの反応系を用いたアリルアルコールのセミピナコール転移反応も報告している[14b]。



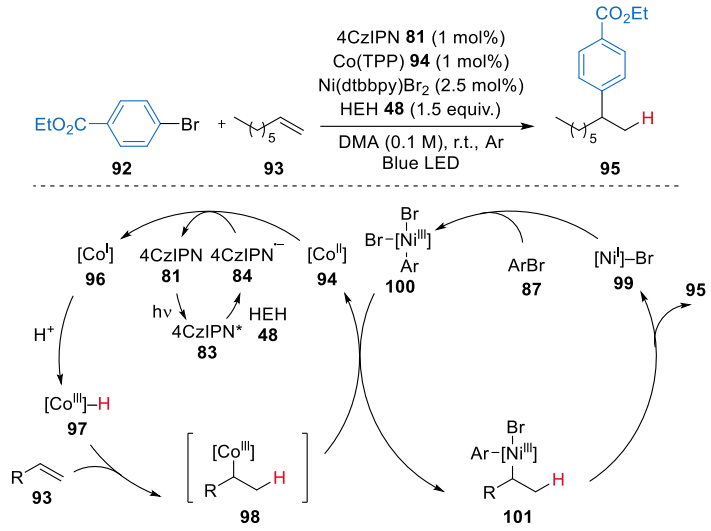
Scheme 13. Photo- and Cobalt-Catalyzed Synthesis of Heterocycles via Cycloisomerization of Unactivated Olefins

最後に、コバルト触媒による還元的サイクルによる MHAT ともう 1 つの遷移金属触媒による触媒系を組み合わせたアルケンのヒドロ官能基化反応について述べる。Shi らは、コバルトポルフィリン触媒とチタン触媒、光酸化還元触媒の協働系によるアレンとアルデヒドの還元的カップリングを報告した(Scheme 14)[15a]。MHAT により生じたアルキルラジカル **87** が、光酸化還元触媒 **81** による一電子還元により生じたチタン(Ⅲ) 錯体 **89** と反応し、アルキルチタン(Ⅳ) **90** 生じる。それがアルデヒド **78** に対して求核付加反応を起こすことで、ホモアリルアルコール **82** が得られる。Shi らは、本反応系を拡張し、コバルトポルフィリン触媒とチタン触媒、光酸化還元触媒の協働系によるジエンとアルデヒドの還元的カップリング [15b]、コバルトポルフィリン触媒とクロム触媒を用いたアレンやジエンとアルデヒドの還元的カップリング [15c, d] を報告している。



Scheme 14. Photocatalytic Metal Hydride Hydrogen Atom Transfer Mediated Allene Functionalization by Cobalt and Titanium Dual Catalysis

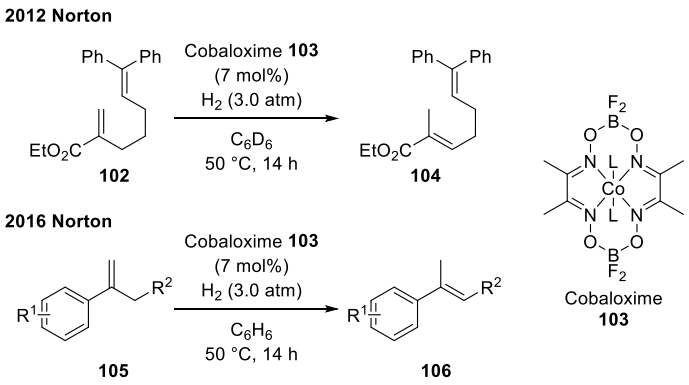
Liang らは、コバルトポルフィリン触媒とニッケル触媒、光酸化還元触媒の協働系を用いることにより、還元的サイクルによる MHAT により生じたアルキルコバルト(Ⅲ) **98** と、光酸化還元触媒 **81** によりニッケル(Ⅱ)触媒の一電子還元と、アリールブロミド **92** の酸化的付加により生じたアリールニッケル(Ⅲ) **100** とのトランスメタル化、続くアリールアルキルニッケル(Ⅲ)種 **101** からの還元的脱離による不活性アルケンのマルコフニコフヒドロアリール化反応を報告している(Scheme 15)[16]。



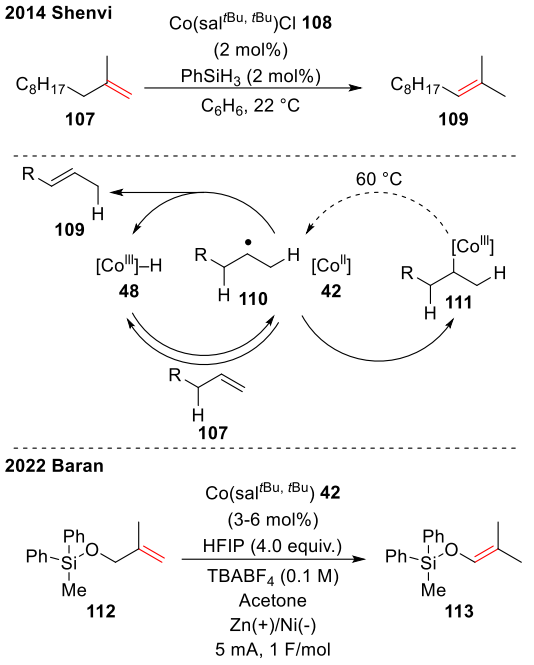
Scheme 15. Photoinduced Co/Ni-cocatalyzed Markovnikov Hydroarylation of Unactivated Olefins with Aryl Bromides

このように還元的サイクルによる MHAT を用いた炭素ラジカルを起点とするヒドロ官能基化反応は、炭素-ヘテロ原子結合形成や炭素-炭素結合形成といった多種多様なヒドロ官能基化反応に活用され、アルケンのヒドロ官能基化反応の手法として、確固たる地位を確立しつつある。

しかし、MHAT を用いた分子変換のうち、アルケンの異性化反応は、合成化学的に有用な化合物合成に繋がるポテンシャルを有するにもかかわらず、発展途上であった。2012 年に Norton らは、水素加圧条件下でコバロキシム錯体 **103** からコバルト(Ⅲ)ヒドリド錯体を生成させ、不飽和カルボニル化合物 **102** のアルケン異性化反応が進行することを報告し[17]、2016 年には、MHAT によるスチレン類 **105** の異性化反応も報告した(Scheme 16)[18]。2014 年に Shenvi らは、コバルトサレン錯体を用いた不活性アルケンの異性化反応を報告し、この異性化反応は、高い化学選択性、官能基許容性で異性化反応が進行することを示した(Scheme 17)[19]。2022 年に Baran らは、電気化学的な手法を用いた還元的サイクルによる MHAT を用いたアルケン異性化反応も報告している[20]。しかしながら、適用した基質は単純な不活性アルケンのみであり、MHAT によるアルケン異性化反応を用いた合成化学的に有用な化合物合成につながる反応開発が期待されている。



Scheme 16. Isomerization of Activated Alkenes via MHAT



Scheme 17. Isomerization of Unactivated Alkenes via MHAT

また、MHAT により多様なアルケンのマルコフニコフヒドロ官能基化反応が可能となった一方で、MHAT によるマルコフニコフヒドロホウ素化反応やマルコフニコフヒドロリン酸化反応といった未だ達成されていない合成化学的に有用な官能基化反応も存在しており、MHAT による官能基化反応は未だ発展の余地を残している[1a]。

これらの背景を踏まえ、今回筆者は、当研究室で開発されたコバルトサレン触媒と光酸化還元触媒の協働系による MHAT を用いたアルケンの分子変換の反応系の更なる拡張と、合成化学的に有用な化合物合成を目指した反応開発研究を行った。本論文では、その経緯並びに成果について、

第 1 章　コバルト触媒と光酸化還元触媒の協働系による MHAT を用いたアルケン異性化反応による多置換エナミド合成法の開発

第 2 章　コバルト触媒と光酸化還元触媒の協働による MHAT を用いた不活性アルケンのマルコフニコフヒドロホウ素化反応の開発

という順序で以下に詳述する。

序論

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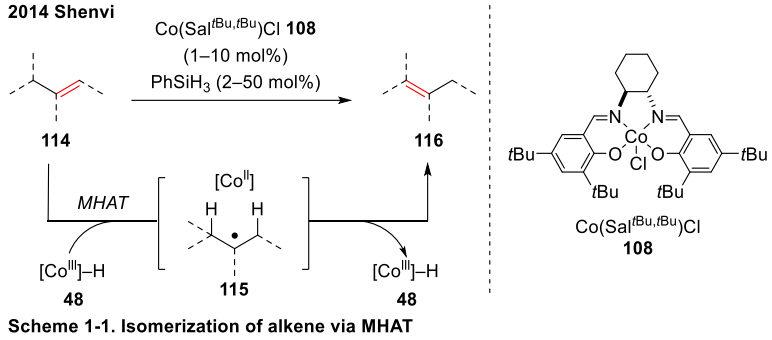
第 1 章　コバルト触媒と光酸化還元触媒の協働系による MHAT を用いたアルケン異性化反応による多置換エナミド合成法の開発

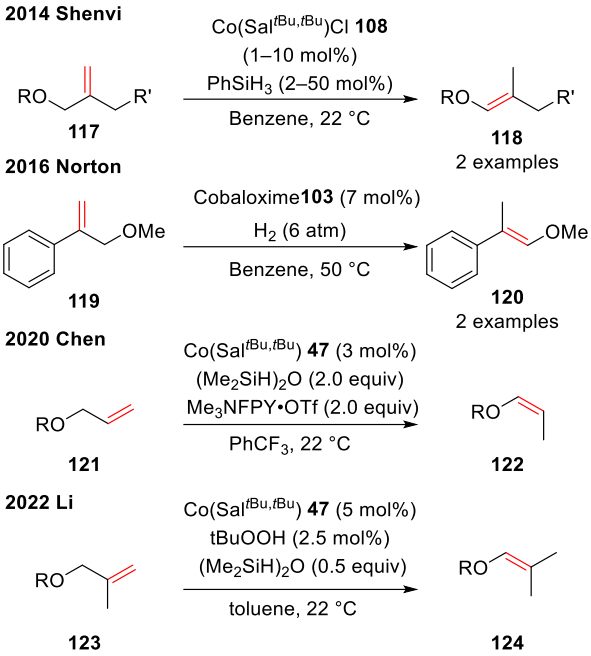
第 1 節　背景

MHAT は高い化学選択性と官能基許容性でアルケンの官能基化反応を行うことができる優れた手法である。その中でも、MHAT を用いたラジカル的なアルケンの異性化反応は、高い化学選択性と官能基許容性で多置換アルケンを得ることができる優れた手法である。2014 年に Shenvi らは、コバルトサレン錯体 **108** を用いた MHAT によるラジカル的なアルケン異性化反応を報告した(Scheme 1-1)[1]。しかしながら、この MHAT によるラジカル的なアルケン異性化反応によるヘテロ原子置換アルケンの合成は、いまだ発展途上である。



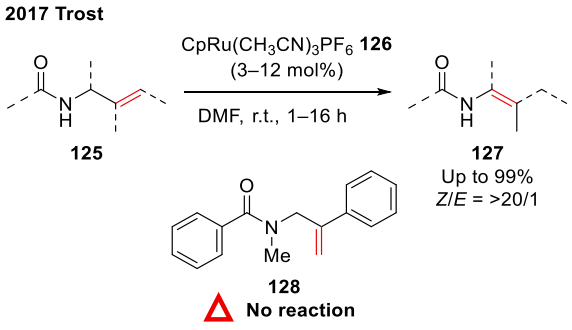
Scheme 1-1. Isomerization of alkene via MHAT

MHAT によるラジカル的なアルケン異性化反応を用いたヘテロ原子置換アルケン合成の例として、アリルエーテルからのビニルエーテル合成が報告されている(Scheme 1-2)。2014 年に Shenvi らは、コバルトサレン錯体を用いたアリルエーテルからのビニルエーテル合成を報告している [1]。2016 年に Norton らは、水素加圧条件下でのコバロキシムからコバルト(Ⅲ)ヒドリドの生成によるアルケンの異性化反応において、アリルエーテルからのビニルエーテル合成を報告している [2]。2020 年に Chen らは、MHAT と酸化的 Radical-Polar-Crossover を用いたジアリルエーテルからのジビニルエーテル合成を報告している [3]。2022 年に Li らは、Shenvi と同様な反応系で、アリルエーテルからのビニルエーテル合成を報告している [4]。しかしながら、MHAT によるラジカル的なアルケン異性化反応を用いたヘテロ原子置換アルケン合成の例は、アリルエーテルからのビニルエーテル合成に限られており、他のヘテロ原子置換アルケンの合成は報告されていなかった。

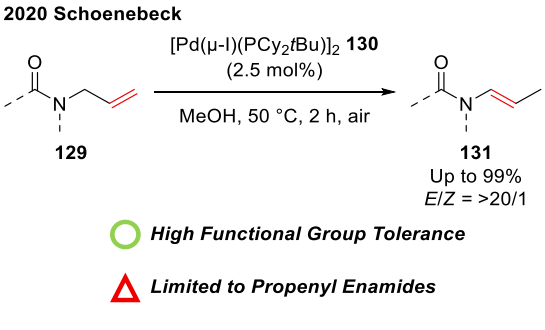


Scheme 1-2. Examples of synthesis hetero-atom substituted alkenes via MHAT

多くのヘテロ原子置換アルケンの中でも、エナミドは安定で取り扱いが容易であるにも関わらず、反応性に富んだ電子豊富な二重結合を有する化合物であり、含窒素化合物のビルディングブロックとして用いられる有用な化合物である [5]。天然物においてもエナミド構造を含む化合物が多く発見されており [6]、全合成研究においても、新たなエナミド合成法の開発が望まれている。多くのエナミド合成法の中に、*N*-アリルアミドの異性化反応によるエナミド合成がある。アトムエコノミーに優れているが、官能基許容性や多置換エナミド合成に課題を残していた [7]。そのような中、2017 年に Trost らは、ルテニウムシクロペンタジエン錯体 **126** を用いたアルケン異性化反応による *Z* 体選択的な多置換エナミド合成法を報告した(Scheme 1-3)[8]。しかし、第 3 級アミド **128** では、まったく反応が進行しないことといった、基質一般性に課題を残していた。2020 年に Schoenebeck らは、パラジウムダイマー錯体 **130** を用いたアルケン異性化反応による *E*体選択的なエナミド合成法を報告した(Scheme 1-4)[9]。高い立体選択性、官能基許容性でエナミドが得られるが、適用可能な基質が末端アルケンに限られており、多置換エナミド合成に課題を残していた。



Scheme 1-3. Synthesis of polysubstituted enamides



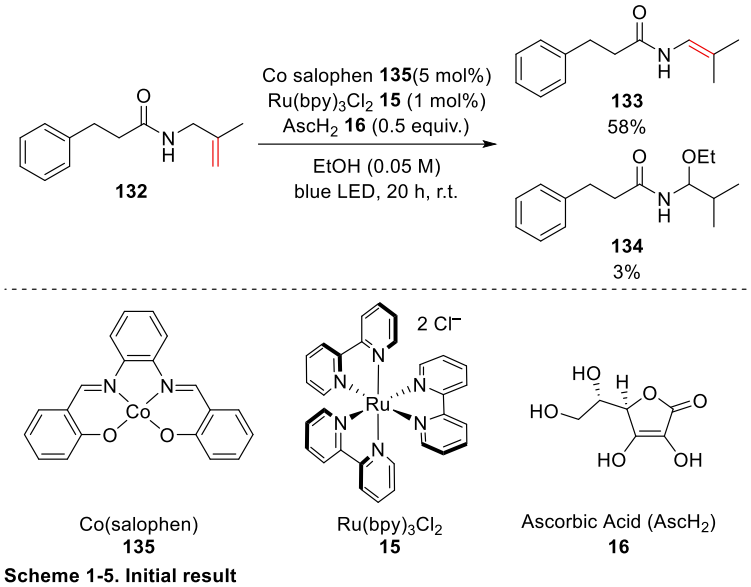
Scheme 1-4. Synthesis of propenyl enamides

著者は、MHAT によるラジカル的なアルケン異性化反応の反応系を、*N*-アリルアミドの異性化反応によるエナミド合成に応用することにより、*N*-アリルアミド異性化反応によるエナミド合成で課題となっていた官能基許容性や多置換エナミド合成の解決法となるのではないかと考え、研究を行った。

第 2 節　反応条件最適化検討

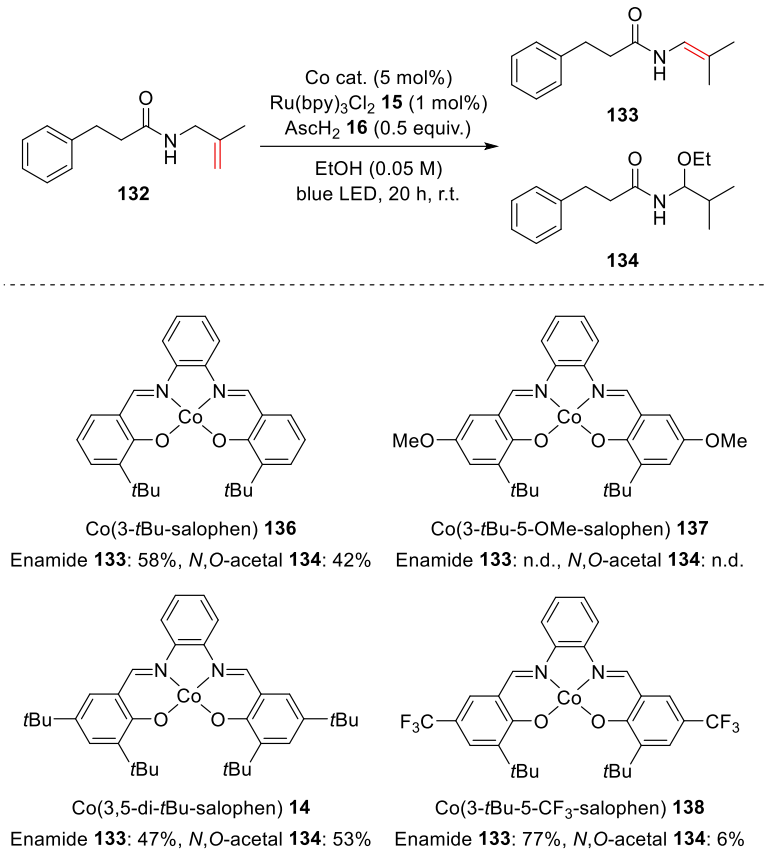
1.　コバルト触媒の置換基及び電子効果の影響について

初期検討として、アリルアミド **132**、コバルト触媒として Co(salophen) **135**、光酸化還元触媒として $Ru(bpy)_3Cl_2$ **15**、プロトン源かつ還元剤として、アスコルビン酸($AscH_2$) **16** を用い、エタノール溶媒中、可視光照射下、20 時間反応を行った。その結果、アリルアミド **132** が残存し、目的のエナミド **133** が NMR 収率 58%で得られ、副生成物として、*N,O*-アセタール **134** が NMR 収率 3%で得られた(Scheme 1-5)。



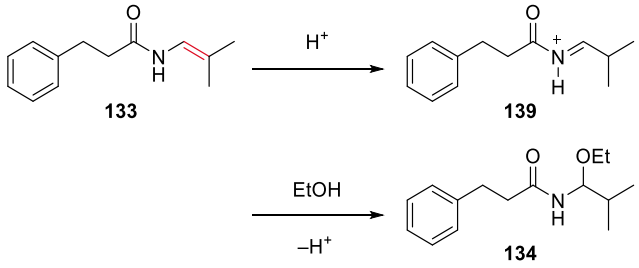
Scheme 1-5. Initial result

次に反応性の向上を期待し、コバルト触媒の置換基の検討を行った(Scheme 1-6)。3 位に *t*Bu 基を有するコバルト触媒 **136** を用いた際には、反応性が向上し、基質が完全に消費されたが、エナミド **133** の収率は向上せず NMR 収率 58%に留まり、副生成物である *N,O*-アセタール **134** が NMR 収率 42%で得られた。3 位に *t*Bu 基を有するコバルト触媒 **136** を用いた時に反応性が向上した理由について、コバルト中心近傍の立体障害が大きくなることで、不安定な化学種であるコバルト(Ⅲ)ヒドリドの速度論的安定性が向上することにより、コバルト(Ⅲ)ヒドリドの不活性化が抑制されることで、反応性が向上したと想定している。次にコバルト触媒の電子的性質のチューニングを行った。メトキシ基を有するコバルト触媒 **137** を用いた際には、全く反応が進行しなかった。反応が進行しなかった理由として、エタノール溶媒に対するコバルト触媒 **137** の溶解性が低いことや、電子供与基を導入したことで、光酸化還元触媒 **15** の還元力ではコバルト触媒 **137** を十分に一電子還元できないことが想定された。3 位と 5 位に *t*Bu 基を有するコバルト触媒 **14** を用いた際には、エナミド **133** と *N,O*-アセタール **134** がほぼ等量で得られ、副生成物の生成は抑制されなかった。電子求引基であるトリフルオロメチル基を有するコバルト触媒 **138** を用いた際には、目的のエナミド **133** が単離収率 77%で得られ、副生成物である *N,O*-アセタール **134** の生成は、NMR 収率 6%まで抑制された。



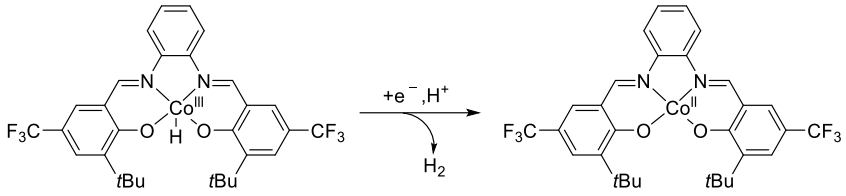
Scheme 1-6. Screening of Co cat.

副生成物である *N,O*-アセタール **134** の生成は、アスコルビン酸に由来するプロトンが生成したエナミド **133** と反応することによりイミニウム中間体 **139** が生じ、溶媒であるエタノールが付加することによって生じると考えている(Scheme 1-7)。



Scheme 1-7. Generation of *N,O*- acetal

電子不足なコバルト触媒を用いた際に副生成物である *N,O*-アセタール **134** の生成が抑制された理由について、コバルト(Ⅲ)ヒドリド **140** が反応系中のアスコルビン酸由来のプロトンと反応し、水素が生成することで、反応系中のプロトン濃度が低下したからであると想定している。コバルト(Ⅲ)ヒドリド **140** は還元されつつ、プロトンと反応することで、水素を生成することが知られている [10]。コバルト触媒に電子求引基を導入することで、この水素生成が促進され、反応系中のプロトン濃度が低下し、酸触媒的な *N,O*-アセタールが抑制されたと想定している(Scheme 1-8)。

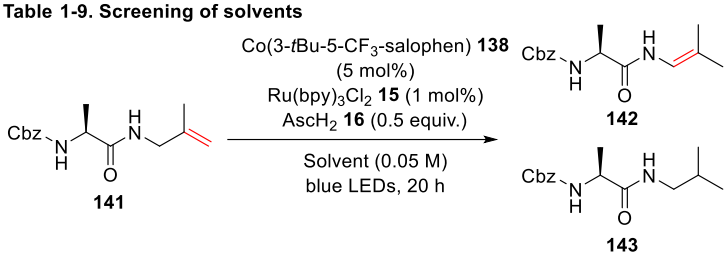


Scheme 1-8. Generation of hydrogen via protonation of cobalt(III) hydride

2. 溶媒効果について

アリルアミド **141** を用い、溶媒のスクリーニングを行った(Table 1-9)。アスコルビン酸の有機溶媒への溶解性も考慮し、水系溶媒の検討も行った。エタノールを用いると目的のエナミド **142** が NMR 収率 90%で得られた(entry 1)。エタノール/水の混合溶媒を用いた際には、エナミド **142** の収率が低下し、副生成物として水素化体 **143** が NMR 収率 30%で得られた(entry 2)。イソプロピルアルコール(IPA)を用いた際には、ほとんど反応は進行しなかった(entry 3)。イソプロピルアルコール/水混合溶媒を用いた際には、エナミド **142** が NMR 収率 55%で得られた一方で、水素化体 **143** が NMR 収率 28%で得られた(entry 4)。メタノールを用いると NMR 収率 69%で目的のエナミド **142** が得られ、水素化体 **143** は NMR 収率 7%で得られた(entry 5)。メタノール/水混合溶媒を用いると、エタノール、イソプロピルアルコール/水混合溶媒を用いた時と同様の結果を示した(entry 6)。*N,N*-ジメチルホルムアミド(DMF)を用いた際には、ほとんど反応が進行せず(entry 7)、*N,N*-ジメチルホルムアミド/水混合溶媒を用いた時にもアリルアミド **141** が多く残存し、少量のエナミド **142** と水素化体 **143** が得られた(entry 8)。アセトニトリル(MeCN)を用いた時、低収率ながら目的のエナミド **142** が得られた(entry 9)。アセトニトリル/水混合溶媒では、エナミド **142** と水素化体 **143** が低収率ながらほぼ同量得られた(entry 10)。アセトンを用いた際には、エナミド **142** が NMR 収率 35%、水素化体 **143** が NMR 収率 3%で得られ(entry 11)、アセトン/水混合溶媒を用いると、エナミドの収率が低下し、水素化体 **143** が NMR 収率 30%で得られた。ジメトキシエタン(DME)を用いた時には、反応は進行しなかった(entry 13)。水系溶媒を用いた際に、水素化体 **143** が増加した理由として、反応系中に存在するアスコルビン酸モノアニオン **20** の増加が考えられる。有機溶媒中では、アスコルビン酸 **16** は酸解離せず、分子型のアスコルビン酸 **16** が大半を占めると考えられる。その一方で、水系溶媒中では、アスコルビン酸 **16** が酸解離することで、アスコルビン酸モノアニオン **20** が増加する。このアスコルビン酸モノアニオン **20** が分子型のアスコルビン酸 **16** よりも、高い還元能を持つため、水系溶媒を用いた際に、水素化体が増加したと想定している。

Table 1-9. Screening of solvents

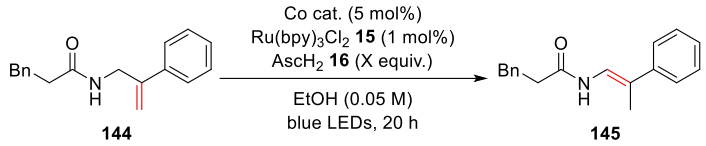


entry	Solvent	**141** (%)[a]	**142** (%)[a]	**143** (%)[a]
1	EtOH	4	90	trace
2	EtOH/H_2O=9/1	5	52	30
3	*i*PrOH	94	5	0
4	*i*PrOH/H_2O=9/1	12	55	28
5	MeOH	14	69	7
6	MeOH/H_2O=9/1	21	53	21
7	DMF	97	0	1
8	DMF/H_2O=3/1	87	12	6
9	MeCN	79	21	3
10	MeCN/H_2O=3/1	35	23	29
11	Acetone	59	35	3
12	Acetone/H_2O=3/1	54	14	30
13	DME	97	0	0

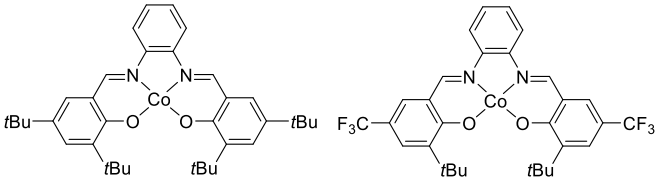
3.　スチレン誘導体への適用検討

次にスチレン誘導体 **144** に対する検討を行った(Table 1-10)。上記で得られた最適条件をスチレン誘導体 **144** に付した時、スチレン **144** が完全に消失し、目的のエナミド **145** が NMR 収率 54%、*E*/*Z* 比 5.7/1 で得られた(entry 1)。アスコルビン酸 **16** の当量を 0.75 当量に増加させた場合には、目的のエナミド **145** は NMR 収率 35% 、*E*/*Z* 比 3.5/1 で得られ、収率と *E*/*Z* 選択性は低下した(entry 2)。電子不足なコバルト触媒 **138** を用いた際に良好な結果が得られなかった理由として以下のことを想定している。スチレン誘導体 **144** に MHAT した際に生じるベンジルラジカルが電子不足なコバルト触媒 **138** と結合しアルキルコバルト種が生成するが、電子求引基を導入することによって、炭素-コバルト結合が分極しやすくなりアルキルラジカル等価体としてのアルキルコバルト種の寿命が長くなる。このことにより、スチレン誘導体 **144** とのラジカル重合を起こしやすくなり、反応が複雑化し、低い収率、*E*/*Z* 選択性になったと想定している。コバルト触媒を 3 位と 5 位に *t*Bu 基を有するコバルト触媒 **14** を用い、アスコルビン酸の当量を 0.5 当量として反応を行うと、スチレン誘導体 **144** が 35%回収され、目的のエナミド **145** が NMR 収率 56%、*E*/*Z* 比 6.6/1 で得られた(entry 3)。アスコルビン酸の当量を 0.5 当量から 0.75 当量に増加させた時、目的のエナミド **145** が NMR 収率 75%、*E*/*Z* 比 21/1 で得られた(entry 4)。

Table 1-10. Application of styrene derivative

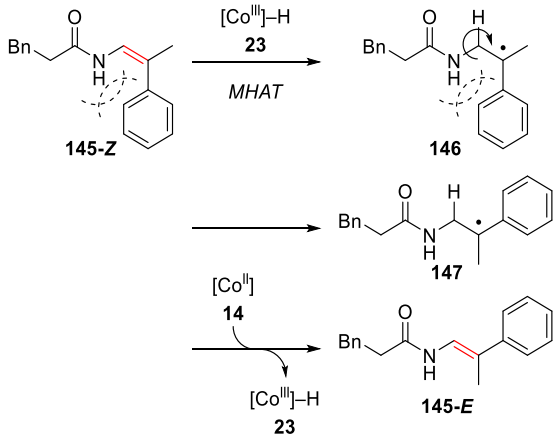


entry	Co cat.	X	**144** (%)	**145**(%)	*E*/*Z*
1	**138**	0.5	0	54	5.7/1
2	**138**	0.75	0	35	3.5/1
3	**14**	0.5	35	56	6.6/1
4	**14**	0.75	0	75	21/1



Co(3,5-di-*t*Bu-salophen) **14**　　Co(3-*t*Bu-5-CF_3-salophen) **138**

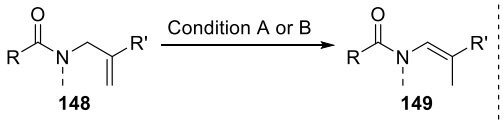
これらの反応で、*E* 体のエナミド **145-*E*** が優先して得られた理由として、MHAT を介したアルケンの *E*/*Z* 異性化反応が関与していると想定している。生じた *E* 体、*Z* 体のエナミドのうち *Z* 体のエナミド **145-*Z*** に対して MHAT が進行し、ベンジルラジカル中間体 **146** が生成する。これが熱力学的に安定な配座 **147** となったのちに、コバルト触媒による水素原子引き抜きを受けることによって、*E* 体のエナミド **145-*E*** が生成すると想定している。3 位と 5 位に *t*Bu 基を有するコバルト触媒 **14** を用いることで、*Z* 体のエナミド **145-*Z*** に対して MHAT が進行され、アスコルビン酸 **16** を増加させることで、MHAT による *E*/*Z* 異性化反応に十分な量のコバルト(Ⅲ)ヒドリドが生成させることが可能となり、ベンジルラジカル中間体 **146** を介した *E*/*Z* 異性化反応が十分に進行し、優先して *E* 体のエナミド **145-*E*** が生成したと想定している（Scheme 1-11）。

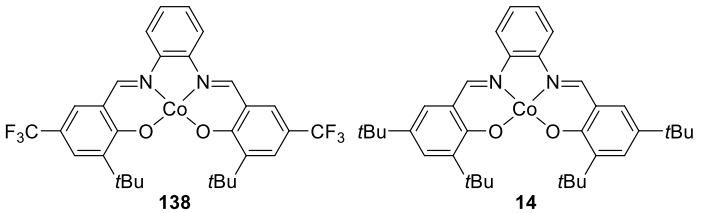


Scheme 1-11. *E*/*Z* Isomerization of enamides via MHAT

第 3 節　基質適用範囲

これらの最適条件を基に基質適用範囲の検討を行った(Scheme 1-12.)。まずアルキル置換エナミドの基質適用範囲の検討を行った(condition A)。メチル基やメトキシ基が置換した電子豊富な芳香環を有する基質、シアノ基、トリフルオロメチル基が置換した電子不足な芳香環、フルオロ基やクロロ基、還元的に脱離しやすいブロモ基を有する基質いずれにおいても良好な収率で目的のエナミドが得られた(**149a-149h**)。チオフェンやピリジンといった複素環を有する基質でも問題なく反応が進行し(**149i**, **149j**)、ベンズアミド誘導体、カルバマート誘導体、ホスファミド誘導体においても良好な収率で目的物が得られた(**149k-149m**)。アラニンやセリン、トリプトファンといったアミノ酸の誘導体でも良好な収率で目的のエナミドが得られた(**149n-149p**)。次にスチレン誘導体の基質適用範囲の検討を行った(condition B)。電子豊富、電子不足なスチレン誘導体においても、問題なく反応が進行した(**149q-149s**)。アラニンやセリンといったアミノ酸の誘導体でも、良好な *E*/*Z* 選択性で目的のエナミドが得られた(**149t**,**149u**)。エトドラクやベンダザック、オキサプロジンといった医薬品の誘導体においても良好な収率、*E*/*Z* 選択性で目的のエナミドが得られた(**149v-149x**)。光酸化還元触媒を 4CzIPN に変更することによって、第 3 級エナミドや四置換エナミドの合成も可能となり、鎖状の第 3 級エナミドは良好な収率で(**149y**)、環状の第 3 級エナミド、第 2 級四置換エナミドは中程度の収率で目的のエナミドが得られた(**149z-149ab**)。





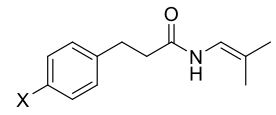
Conditions A

138 (5 mol%), $Ru(bpy)_3Cl_2•6H_2O$ **15** (1 mol%), $AscH_2$ **16** (0.50 equiv), EtOH (0.05 M), r.t., 20 h, Blue LEDs

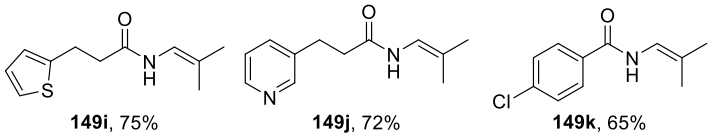
Conditions B

14 (5 mol%), $Ru(bpy)_3Cl_2•6H_2O$ **15** (1 mol%), $AscH_2$ **16** (0.50-1.5 equiv), EtOH (0.05 M), r.t., 20 h, Blue LEDs

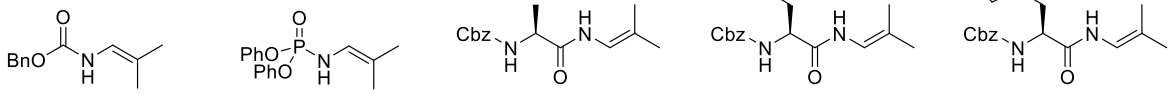
Conditions A



X = H (**149a**) : 77%
= Me (**149b**) : 77%
= OMe (**149c**) : 75%
= F (**149d**) : 79%
= Cl (**149e**) : 78%
= Br (**149f**) : 71%
= CN (**149g**) : 71%
= CF_3 (**149h**) : 79%

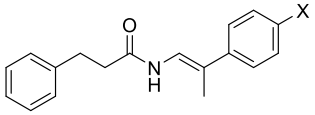


149i, 75%　**149j**, 72%　**149k**, 65%

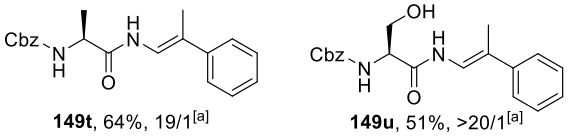


149l, 60%　**149m**, 87%　**149n**, 84%　**149o**, 81%　**149p**, 81%

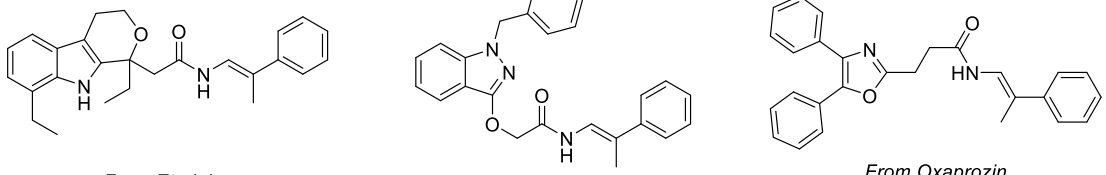
Conditions B



X = H (**149q**) : 75%, 21/1[a]
= *t*Bu (**149r**) : 59%, 11/1[a]
= Cl (**149s**) : 76%, 7/1[a]



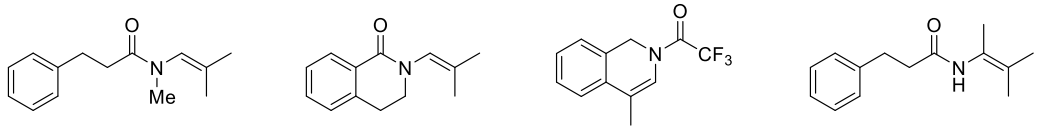
149t, 64%, 19/1[a]　**149u**, 51%, >20/1[a]



From Etodolac
149v, 63%, 6/1[a]

From Bendazac
149w, 77%, 7/1[a]

From Oxaprozin
149x, 69%, 12/1[a]

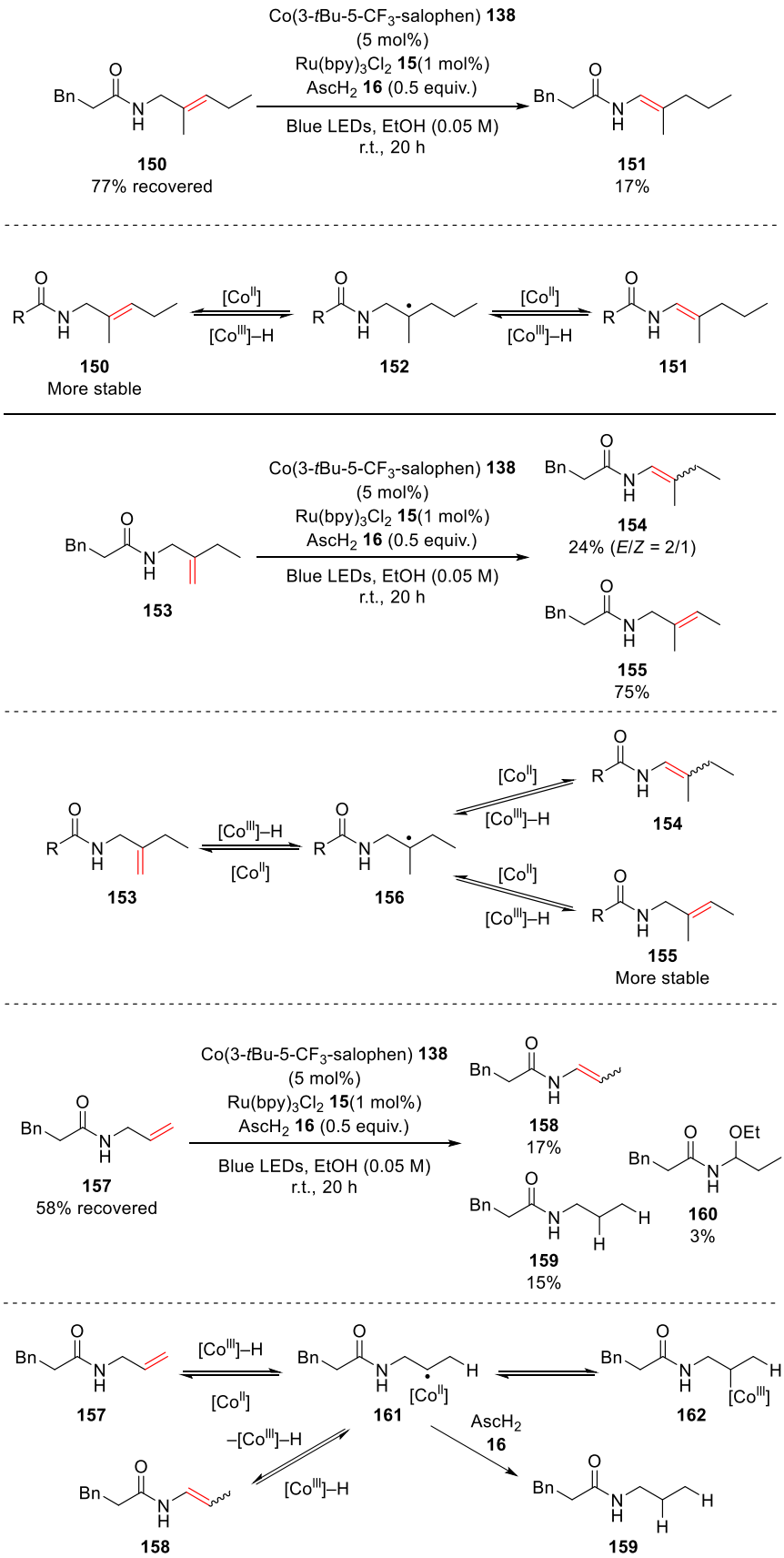


149y, 70%[b, c]　**149z**, 59%[c]　**149aa**, 58%　**149ab**, 52%[c]

[a] *E*/*Z* selectivity was determined by ^1H NMR analysis of crude mixture.
[b] The yield was determined by ^1H NMR analysis of the purified material containing **149y** and hydrogenated product.
[c] 4CzIPN was used instead of $Ru(bpy)_3Cl_2•6H_2O$.

Scheme 1-12. Substrate scope

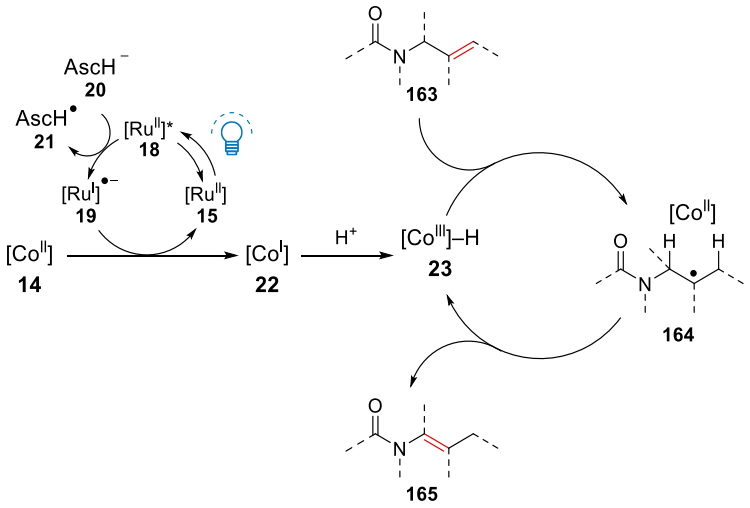
以下に良好な結果を示さなかった基質を示す(Scheme 1-13)。アリルアミド **150** を得られた最適条件に付した時、目的のエナミド **151** は、NMR 収率 17%しか得られず、基質を NMR 収率 77%で回収した。MHAT で生じたアルキルラジカル中間体 **152** がコバルト触媒による水素原子引き抜きを受け、異性化反応が進行するが、これらの反応は平衡状態になっていると想定している。基質のアリルアミド **150** がエナミド **151** よりも熱力学的に安定であるため、出発物側に平衡が偏り、最終的にアリルアミド **150** が回収されたと想定している。アリルアミド **153** の場合も同様に、エナミド **154** よりもアリルアミド **155** が熱力学的に安定となるため、アリルアミド **155** が主生成物として得られたと想定している。末端アルケンを有するアリルアミド **157** を用いた際には、アリルアミド **157** を 58%回収し、エナミド **158** は NMR 収率 17%、水素化体 **159** が NMR 収率 15%、*N*,*O*-アセタール **160** が NMR 収率 3%で得られた。反応が効率良く進行しなかった理由として、生じる第 2 級アルキルラジカル **161** は第 3 級アルキルラジカルと比べ、立体障害が小さく、休息状態としてのアルキルコバルト(Ⅲ)**162** を生じやすくなり、MHAT による異性化反応に関与するコバルト触媒 **138** が減少したことが原因であると考えている。水素化反応が進行している理由について、MHAT により生じる第 2 級ラジカル **161** が第 3 級アルキルラジカルよりも不安定であるため、よりアスコルビン酸 **16** からの水素原子引き抜きが起こりやすいからであると想定している。



Scheme 1-13. Unsuccessful substrates

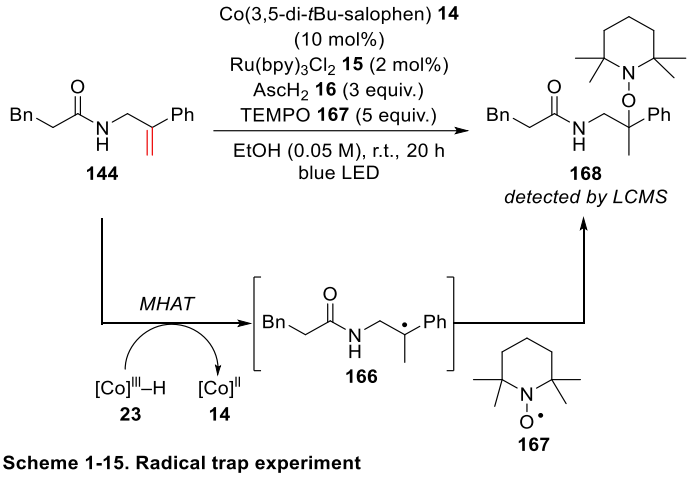
第 4 節　反応機構に関する実験、及び DFT 計算

想定反応機構について、以下に示す(Scheme 1-14)。まず可視光によって光酸化還元触媒 **15** が励起され、励起種 **18** が生じ、それがアスコルビン酸アニオン **20** により一電子還元され、ラジカルアニオン **19** が生成する。これが 2 価のコバルト **14** を一電子還元することで、求核性を持つ 1 価のコバルト触媒 **22** が生成し、反応系中のプロトンを捕捉することで、触媒活性種であるコバルト(Ⅲ)ヒドリド **23** が生成する。コバルト(Ⅲ)ヒドリド **23** が *N*-アリルアミド **163** のアルケンに MHAT を起こし、アルキルラジカル中間体 **164** を経て、エナミド **165** へ異性化し、触媒活性種であるコバルト(Ⅲ)ヒドリド **23** が再生すると想定している。



Scheme 1-14. Proposed reaction mechanism

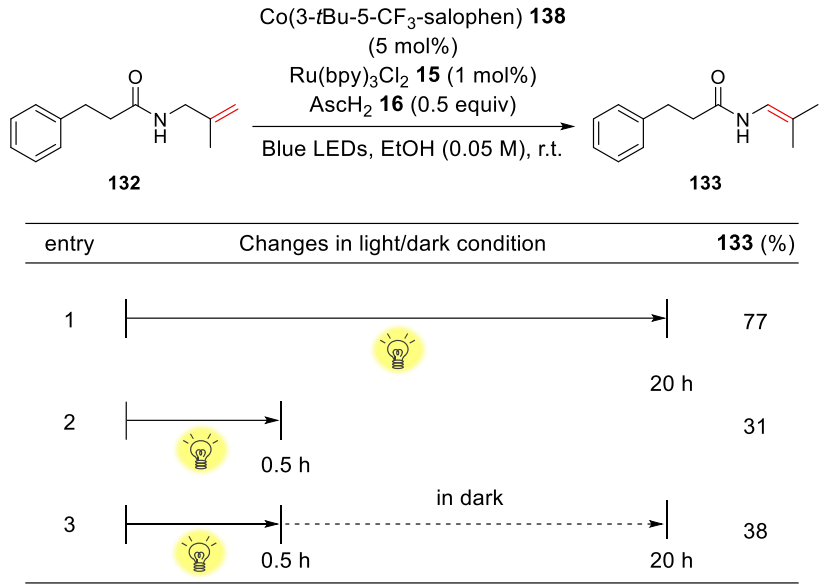
アルケンへの MHAT によるアルキルラジカル中間体 **166** を実験的に確認するため、TEMPO**167** を用いたラジカル捕捉実験を行った(Scheme 1-15)。その結果、LCMS にてアルケンへの MHAT により生じたアルキルラジカル中間体 **166** が TEMPO**167** により捕捉された TEMPO 付加体 **168** が観測された。このことからアルケンへの MHAT によるアルキルラジカル中間体 **166** の生成が示唆された。



Scheme 1-15. Radical trap experiment

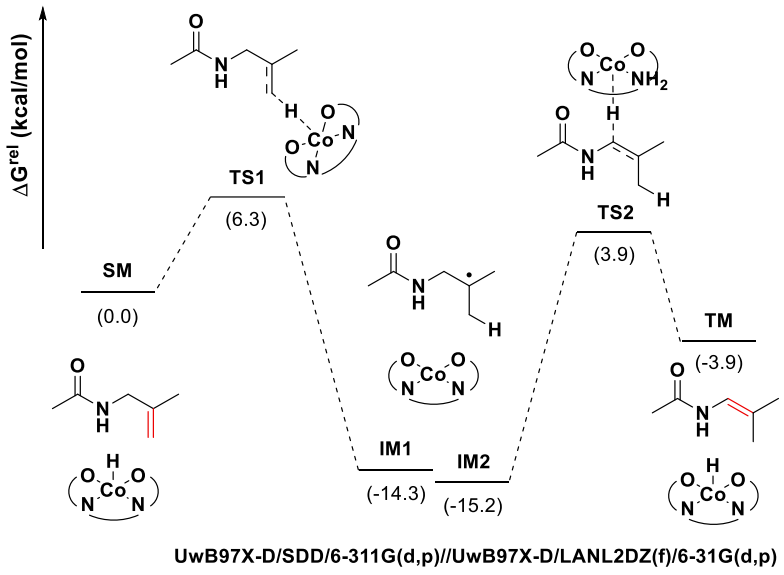
想定反応機構上、触媒量のコバルト(Ⅲ)ヒドリドが生じれば反応が進行し、持続的な可視光照射は必要がないと考えられる。そこで、Light on/Light off 実験を行った(Scheme 1-16)。持続的な可視光照射を行った際には、目的のエナミド **133** が NMR 収率 77%で得られた(entry 1)。30 分間で反応を停止させた際に

は、目的のエナミド **133** は NMR 収率 31%で得られた(entry 2)。30 分間可視光照射を行い、その後遮光下で反応を行うと、目的のエナミド **133** は NMR 収率 38%で得られた(entry 3)。これらの結果から、30 分間可視光照射を行い、その後遮光下で反応を行った場合には、多少の触媒回転が見られるものの、良好な収率で目的のエナミドを得るには、持続的な可視光照射が必要であることが分かった。この理由として、触媒活性種であるコバルト(Ⅲ)ヒドリドが不安定な化学種であり、反応途中に失活しやすいため、持続的に可視光照射を行い、十分量のコバルト(Ⅲ)ヒドリドを反応系に供給する必要があるからだと想定している。



Scheme 1-16. Light on/Light off Experiment

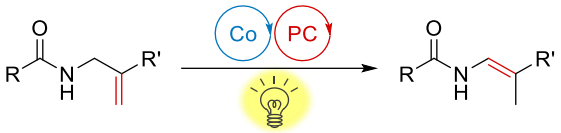
想定反応機構を基に DFT 計算によるエネルギーダイヤグラムの算出を行った(Scheme 1-17)。アルケンへの MHAT の段階(**SM➡TS1**)の活性化エネルギーは 6.3kcal/mol、異性化の段階(**IM2➡TS2**)の活性化エネルギーは 19.1kcal/mol であり、室温で反応が進行しうることが示唆され、MHAT 機構での異性化反応を支持する結果を得た。



Scheme 1-17. DFT calculation

第 5 節　小括

ここまでの内容を小括する。筆者はコバルトサレン触媒と光酸化還元触媒の協働による MHAT を用いたアルケン異性化反応による多置換エナミド合成法を開発した。この多置換エナミド合成法は、MHAT 特有の高い官能基許容性を持ち、還元的に脱離しやすいブロモ基や無保護アミノ酸の誘導体、医薬品の誘導体においても適用が可能であった。本成果は論文として、査読付き国際学術誌に投稿し、採択された [11]。



via Metal-catalyzed Hydrogen Atom Transfer
up to 87%, E/Z > 20/1

第 6 節　実験項

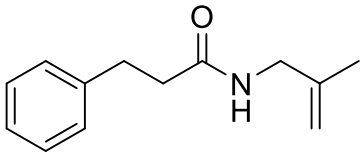
Contents

1. General Information

Reactions were carried out under argon atmosphere unless otherwise noted. NMR spectra were recorded on JEOL JNM-ECS400 spectrometers operating at 391.78 MHz for ^{1}H NMR and 98.52 MHz for ^{13}C NMR and 368.59 MHz for ^{19}F NMR, JEOL JNM-ECX400 spectrometers operating at 395.88 MHz for ^{1}H NMR and 99.55 MHz for ^{13}C NMR and 372.48 MHz for ^{19}F NMR, and JNM-ECZ400S spectrometers operating at 399.78 MHz for ^{1}H NMR and 100.53 MHz for ^{13}C NMR and 368.61 MHz for ^{19}F NMR. Chemical shifts were reported in the scale relative to TMS (0.00 ppm for ^{1}H NMR in $CDCl_3$), $CHCl_3$ (7.26 ppm for ^{1}H NMR in $CDCl_3$), CD_3OD (3.31 ppm for ^{1}H NMR in CD_3OD), C_6D_6 (7.16 ppm for ^{1}H NMR in C_6D_6), $CDCl_3$ (77.00 ppm for ^{13}C NMR in $CDCl_3$), DMSO-*d*$_6$ (39.50 ppm for ^{13}C NMR in DMSO-*d*$_6$), $PhCF_3$ (–63.72 ppm for ^{19}F NMR in $CDCl_3$) and C_6H_5F (–113.20 ppm for ^{19}F NMR in $CDCl_3$) as an internal reference, respectively. ESI mass spectra were measured on Thermo Scientific Exactive (HRMS, orbitrap) or Waters ACQUITY QDa (LRMS). Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrophotometer, and absorbance bands are reported in wavenumbers (inverse centimeters). Column chromatography was performed with silica gel Kanto Silica gel 60 N (40-50 mesh) or Yamazen YFLC AI-580 using Universal Column SiOH. All non-aqueous reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted or in an argon-filled glove box. Dichloromethane (DCM), tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene were purified by Glass Contour solvent purification system (Nikko Hansen & Co., Ltd.,) before use. All other reagents were commercially available and used as received unless otherwise noted. Irradiation was performed with ISLM-150X150-BB447 (purchased from CCS Inc.; Wavelength of peak intensity = 447 nm; intensity (PPFD) = ca. 900 μmol m^{-2} s^{-1} at 10 cm distance from the LED panel) as photon source.

2. Synthesis of substrates

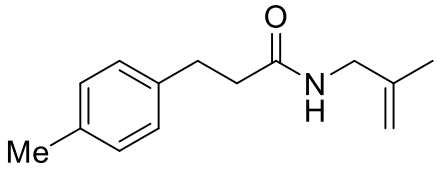
***N*-(2-methylallyl)-3-phenylpropanamide (148a)**



To a solution of 3-phenylpropanoic acid (0.30 g, 2 mmol) in $SOCl_2$ (2 mL) was added dropwise DMF (77 μL, 1 mmol) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (4 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.20 mL, 2.2 mmol) and NEt_3 (0.33 mL, 2.4 mmol). The solution was stirred for 20 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =3/2) to give **148a** as

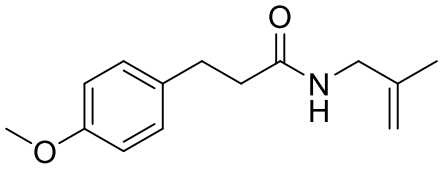
a colorless solid (0.26 g, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.24-7.17 (m, 3H), 5.40 (br s, 1H), 4.80-4.75 (m, 1H), 4.70-4.65 (m, 1H), 3.78 (d, J = 5.9 Hz, 2H), 2.99 (t, J = 7.7 Hz, 2H), 2.52 (t, J = 7.7 Hz, 2H), 1.66 (d, J = 5.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9, 141.8, 140.8, 128.4, 128.3, 126.1, 110.7, 44.9, 38.3, 31.6, 20.2. **LRMS** (ESI): $[M+Na]^+$: found: 226.11. Reported compound[12]

_N_-(2-methylprop-1-en-1-yl)-3-(p-tolyl)propanamide (148b)



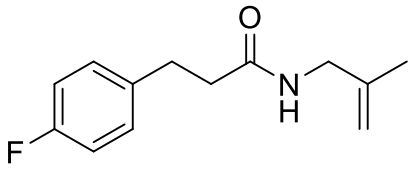
To a solution of 3-(p-tolyl)propanoic acid (0.33 g, 2 mmol) in DCM (6.7 mL) was added oxalyl chloride (0.50 mL, 6 mmol) followed by DMF (2 drops) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (4 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.20 mL, 2.2 mmol) and NEt_3 (0.33 mL, 2.4 mmol). The solution was stirred for 3 days, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 66/34 to 45/55) to give **148b** as a colorless solid (0.34 g, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15-7.06 (m, 4H), 5.37 (br s, 1H), 4.81-4.75 (m, 1H), 4.72-4.67 (m, 1H), 3.78 (d, J = 5.8 Hz, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.50 (t, J = 7.7 Hz, 2H), 2.31 (s, 3H), 1.67 (d, J = 0.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0, 141.9, 137.7, 135.6, 129.1, 128.1, 110.7, 44.9, 38.5, 31.2, 20.9, 20.2. **IR** (KBr) 3300, 3080, 2924, 1648, 1547, 1516, 1445, 1372, 1229, 892, 811 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{19}lONNa$ $[M+Na]^+$: 240.13589, found: 240.13505. **Rf** 0.38 (hexane/AcOEt = 1:1).

3-(4-methoxyphenyl)-_N_-(2-methylallyl)propanamide (148c)



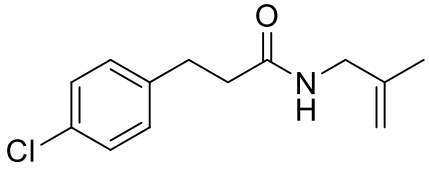
To a solution of 3-(4-methoxyphenyl)propanoic acid (0.36 g, 2 mmol) in DCM (6.7 mL) was added oxalyl chloride (0.50 mL, 6 mmol) followed by DMF (2 drops) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (4 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.20 mL, 2.2 mmol) and NEt_3 (0.33 mL, 2.4 mmol). The solution was stirred for 3 days, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =56/44 to 35/65) to give **148c** as a colorless solid (0.37 g, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16-7.09 (m, 2H), 6.86-6.80 (m, 2H), 5.38 (br s, 1H), 4.80-4.76 (m, 1H), 4.71-4.67 (m, 1H), 3.81-3.74 (m, 5H), 2.93 (t, J = 7.5 Hz, 2H), 2.48 (t, J = 7.6 Hz, 2H), 1.67 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0, 158.0, 141.9, 132.8, 129.2, 113.9, 110.8, 55.2, 44.9, 38.7, 30.8, 20.2. **IR** (KBr) 3303, 3073, 2969, 2941, 1633, 1540, 1512, 1442, 1251, 1177, 1028, 899, 819 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{19}NO_2Na$ $[M+Na]^+$: 256.13080, found: 256.12989. **Rf** 0.26 (hexane/ AcOEt = 1:1).

3-(4-fluorophenyl)-*N*-(2-methylallyl)propanamide (148d)



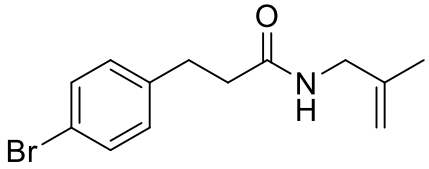
To a solution of 3-(4-fluorophenyl)propanoic acid (0.84 g, 5 mmol) in DCM (17 mL) was added oxalyl chloride (1.3 mL, 15 mmol) followed by DMF (2 drops) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (10 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.50 mL, 5.5 mmol) and NEt_3 (0.84 mL, 6 mmol). The solution was stirred for 15 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (1 x) and brine (1 x), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =54/46 to 33/67) to give **148d** as a colorless solid (1.0 g, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20-7.13 (m, 2H), 7.00-6.93 (m, 2H), 5.37 (br s, 1H), 4.82-4.76 (m, 1H), 4.72-4.66 (m, 1H), 3.78 (d, J = 6.1 Hz 2H), 2.96 (t, J = 7.5 Hz, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.67 (d, J = 0.6 Hz, 3H). **^{13}C{^{1}H, ^{19}F}NMR** (100 MHz, $CDCl_3$) δ 171.7, 161.4, 141.8, 136.4, 129.7, 115.1, 110.8, 44.9, 38.4, 30.8, 20.2. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−63.72 as an internal standard)] δ −118.10. **IR** (KBr) 3296, 3077, 2916, 1644, 1543, 1508, 1449, 1372, 1216, 895, 829 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{16}$lFNONa $[M+Na]^+$: 244.11981, found: 244.11011. **Rf** 0.33 (hexane/AcOEt = 1/1).

3-(4-chlorophenyl)-*N*-(2-methylallyl)propanamide (148e)



To a solution of 3-(4-chlorophenyl)propanoic acid (0.55 g, 3 mmol) in $SOCl_2$ (3 mL) was added dropwise DMF (0.12 mL,1.5 mmol) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (6 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.30 mL, 3.3 mmol) and NEt_3 (0.50 mL, 3.6 mmol). The solution was stirred for 21 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =1/1) to give **148e** as a colorless solid (0.50 g, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.21 (m, 2H), 7.17-7.11 (m, 2H), 5.38 (br s, 1H), 4.82-4.77 (m, 1H), 4.72-4.66 (m, 1H), 3.78 (d, J = 5.7 Hz 2H), 2.96 (t, J = 7.5 Hz, 2H), 2.49 (t, J = 7.5 Hz, 2H), 1.67 (d, J = 0.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 141.8, 139.3, 131.9, 129.7, 128.5, 110.8, 45.0, 38.1, 30.9, 20.2. **IR** (KBr) 3293, 3083, 2933, 1641, 1547, 1491, 1445, 1372, 1097, 1013, 892, 822 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{16}$ClNONa $[M+Na]^+$: 260.08126, found: 260.08053. **Rf** 0.16 (hexane/AcOEt = 2/1).

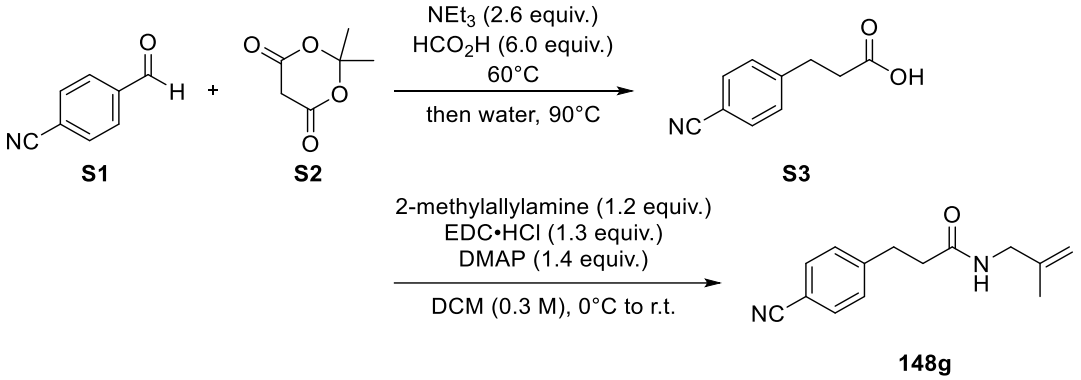
3-(4-bromophenyl)-*N*-(2-methylallyl)propanamide (148f)



To a solution of 3-(4-bromophenyl)propanoic acid (0.69 g, 3 mmol) in $SOCl_2$ (3 mL) was added dropwise DMF (0.12 mL, 1.5 mmol) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was

dissolved in Et_2O (6 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.30 mL,3.3 mmol) and NEt_3 (0.50 mL, 3.6 mmol). The solution was stirred for 21 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =5/4) to give **148f** as a colorless solid (0.61 g, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 2H), 7.12-7.04 (m, 2H), 5.38 (br s, 1H), 4.82-4.76 (m, 1H), 4.72-4.64 (m, 1H), 3.78 (d, J = 5.9 Hz 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.67 (d, J = 0.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 141.8, 139.8, 131.5, 130.1, 119.9, 110.8, 44.9, 38.1, 31.0, 20.2. **IR** (KBr) 3293, 3077, 2926, 1641, 1542, 1488, 1445, 1372, 1229, 1069, 1013, 902, 808 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{16}BrNONa$ $[M+Na]^+$: 304.03075, found: 304.02990. **Rf** 0.24 (hexane/AcOEt = 1/1).

3-(4-cyanophenyl)-*N*-(2-methylallyl)propanamide (148g)

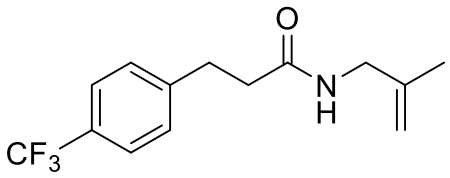


A solution of **S1** (1.05 g, 8 mmol) and **S2** (1.15 g, 8 mmol) in TEA (2.9 mL, 20.8 mmol) and HCO_2H (1.8 mL, 48 mmol) was stirred 46 h at 65 °C, after which water (2 mL) was added and the solution was stirred for 23 h at 90 °C. To this solution was added 1 M HCl aq. (50 mL) and the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with water and concentrated. The crude was diluted with AcOEt, extracted with sat. $NaHCO_3$ (x 3) and the combined aqueous layers were washed with AcOEt (x 3). To the aqueous layer was added 2 M HCl aq. to pH 1. The acidic aqueous layer was extracted with AcOEt (x 3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give the crude **S3** as a colorless solid (1.26 g, 90%), which was used for next step without further purification.

To a solution EDC•HCl (1.24 g, 6.5 mmol) and DMAP (0.86 g, 7 mmol) in dry DCM (13 mL) was added the crude **S3** (0.86 g, 5 mmol) followed by 2-methylallylamine (0.54 mL, 6 mmol) at 0 °C. The solution was stirred overnight, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =43/57 to 22/78) to give **148g** as a colorless solid (0.86 g, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2H), 7.34-7.31 (m, 2H), 5.41 (br s, 1H), 4.81-4.78 (m, 1H), 4.70-4.66 (m, 1H), 3.78 (d, J = 6.0 Hz, 2H), 3.06 (t, J = 7.4 Hz, 2H), 2.52 (t, J = 7.4 Hz, 2H), 1.67 (d, J = 0.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 146.6, 141.7, 132.2, 129.2, 118.9, 110.8, 110.0, 44.9, 37.3, 31.4, 20.2. **IR** (KBr) 3317, 3077, 2965, 2930, 2220, 1644, 1550, 1442, 1376, 1244, 1233, 899, 829 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{16}N_2ONa$ $[M+Na]^+$: 251.11548, found:

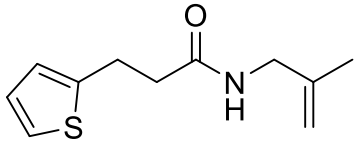
251.11486. **Rf** 0.17 (hexane/AcOEt = 1/1)

***N*-(2-methylallyl)-3-(4-(trifluoromethyl)phenyl)propanamide (148h)**



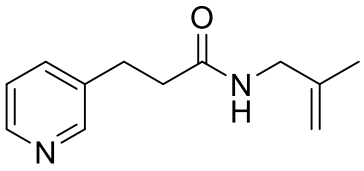
To a solution of 3-[4-(trifluoromethyl)phenyl]propanoic acid (0.84 g, 5 mmol) in DCM (17 mL) was added oxalyl chloride (1.3 mL,15 mmol) was added dropwise DMF (2 drops) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (10 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.50 mL, 5.5 mmol) and NEt_3 (0.84 mL, 6 mmol). The solution was stirred for 20 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 1) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =1/1) to give **148h** as a colorless solid (1.2 g, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 5.38 (br s, 1H), 4.81-4.76 (m, 1H), 4.69-4.64 (m, 1H), 3.78 (d, J = 6.1 Hz, 2H), 3.05 (t, J = 7.55 Hz, 2H), 2.52 (t, J = 7.5 Hz, 2H), 1.66 (s, 3H). **^{13}C{^{1}H, ^{19}F}NMR** (100 MHz, $CDCl_3$) δ 171.3, 145.0, 141.8, 128.7, 128.6, 125.4, 124.2, 110.9, 45.0, 37.9, 31.3, 20.2. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −62.53. **IR** (KBr) 3300, 3084, 2933, 1637, 1550, 1335, 1167, 1128, 1108, 1065, 1020, 909, 853, 825 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{16}F_3NONa$ $[M+Na]^+$: 294.10762, found: 294.10648. **Rf** 0.38 (Hexane/AcOEt = 1/1). **Rf** 0.26 (hexane/AcOEt 1/1).

***N*-(2-methylallyl)-3-(thiophen-2-yl)propanamide (148i)**



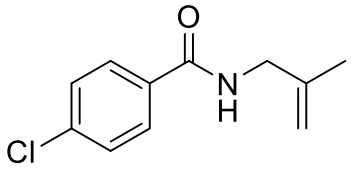
To a solution of 3-(2-thienyl)propanoic acid (0.78 g, 5 mmol) in DCM (17 mL) was added oxalyl chloride (1.3 mL, 15 mmol) was added dropwise DMF (2 drops) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (10 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.54 mL, 5.5 mmol) and NEt_3 (0.84 mL, 6 mmol). The solution was stirred for 17 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 1) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =1/1) to give **148i** as a colorless oil (0.77 g, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 5.2, 1.2 Hz, 1H), 6.91 (dd, J = 5.1, 3.5 Hz,1H), 6.86-6.80 (m, 1H), 5.47 (br s, 1H), 4.82-4.78 (m, 1H), 4.74-4.69 (m, 1H), 3.80 (d, J = 6.0 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H), 2.57 (t, J = 7.4 Hz, 2H), 1.68 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.4, 143.3, 141.8, 126.8, 124.7, 123.4, 110.8, 45.0, 38.5, 25.8, 20.2. **IR** (neat) 3293, 3080, 2920, 1658, 1547, 1435, 1372, 1268, 1233, 899, 849, 700 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{11}H_{15}NOSNa$ $[M+Na]^+$: 232.07666, found: 232.07607. **Rf** 0.32 (hexane/AcOEt = 1/1).

***N*-(2-methylallyl)-3-(pyridin-3-yl)propanamide (148j)**



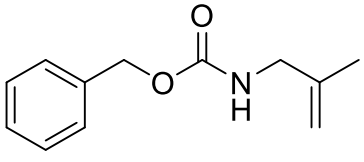
To a solution of 3-(3-pyridyl)propanoic acid (0.76 g, 5 mmol) in DCM (17 mL) was added oxalyl chloride (1.3 mL, 15 mmol) was added dropwise DMF (2 drops) at 0 °C under an atmosphere of Ar. The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (10 mL) and placed in an ice bath. To this solution were added dropwise 2-methylallylamine (0.54 mL, 5.5 mmol) and NEt_3 (0.84 mL,6 mmol). The solution was stirred for 17 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with Et_2O (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 1) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, DCM/MeOH =10/1) to give **148j** as a colorless solid (0.80 g, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, J = 1.9 Hz, 1H), 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 7.59-7.50 (m, 1H), 7.23-7.17 (m, 1H), 5.52 (br s, 1H), 4.82-4.77 (m, 1H), 4.72-4.68 (m, 1H), 3.79 (d, J = 6.0 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.52 (t, J = 7.5 Hz, 2H), 1.67 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 149.6, 147.5, 141.8, 136.3, 136.1, 123.4, 110.8, 45.0, 37.7, 28.7, 20.2. **IR** (KBr) 3303, 3083, 2930, 1641, 1553, 1421, 1227, 892, 801, 713 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{12}H_{17}N_2O$ $[M+H]^+$:205.13354, found: 205.13317. **Rf** 0.39 (DCM/MeOH = 10/1).

4-chloro-*N*-(2-methylallyl)benzamide (148k)



To a solution of the 4-chlorobenzoly chloride or sulfonyl chloride (0.63 mL, 5 mmol) in s Et_2O (10 mL), 2-methylallylamine (0.9 mL, 10 mmol) and triethylamine (3.5 mL, 5.0 equiv., 25 mmol) were sequentially added at 0 °C. The mixture was allowed to warm to room temperature and was stirred overnight and quenched with 1 M aq. HCl. Organic material was extracted with AcOEt (x 3), and the combined organic layers were washed with brine (x 1). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the obtained crude was filtered through a short pad of silica gel using AcOEt. The obtained crude amide **148k** was used for the next step without further purification as a white solid (1.0 g, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77-7.71 (m, 2H), 7.45-7.40 (m, 2H), 6.14 (br s, 1H), 4.94-4.88 (m, 2H), 4.02 (d, J = 6.3 Hz, 2H), 1.80 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 141.7, 137.6, 132.8, 128.7, 128.4, 111.1, 45.5, 20.3. **LRMS** (ESI): $[M+Na]^+$: found: 232.06. Reported compound[13]

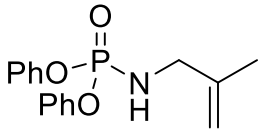
benzyl (2-methylallyl)carbamate (148l)



To a solution of 2-methylallylamine (0.45 mL, 5 mmol) in ethyl acetate (7.5 mL), potassium carbonate (1.73 g, 12.5 mmol) and water (7.5 mL) was added and cooled to 0 °C. To this solution was added dropwise benzyl chloroformate (0.74 mL, 5.25 mmol) over 30 min and the solution was stirred for 22 h. The biphasic mixture was separated, and the organic layer was washed with 1 M HCl aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =84/14 to 64/35) to give **148l** as a colorless oil (1.05 g, quant.).**^{1}H NMR** (400 MHz, CD_3CN) δ 7.39-7.27 (m, 5H), 5.77 (br s, 1H), 5.05 (s, 2H), 4.82-4.77 (m, 2H), 3.64 (d, J = 6.3 Hz, 2H),

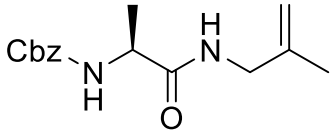
1.69 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.4, 142.1, 136.5, 128.4, 128.0, 110.6, 66.7, 46.6, 20.1. **LRMS** (ESI): $[M+Na]^+$: found: 228.07. Reported compound[14]

diphenyl (2-methylallyl)phosphoramidate (148m)



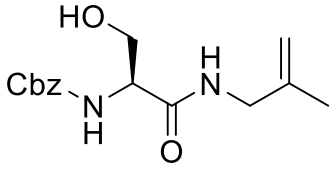
To a solution of diphenyl chlorophosphite (1.48 g, 5.5 mmol) in dry DCM (20 mL) was added dropwise 2-methylallylamine (0.36 g, 5.0 mmol) and followed by NEt_3 (0.76 g, 7.5 mmol) at 0 °C. The solution was stirred for 24 h, after which water was added. The biphasic mixture was extracted with DCM (x 3) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 76/24 to 55/45) to give **148m** as a colorless solid (1.38 g, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4H), 7.28-7.22 (m, 4H), 7.20-7.12 (m, 2H), 4.92-4.87 (m, 1H), 4.85-4.80 (m, 1H), 3.63 (dd, J = 8.4 Hz, 2H), 3.10-2.95 (m, 1H), 1.70 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.8 (d, $J_{P\text{-}C}$ = 6.7 Hz), 142.4 (d, $J_{P\text{-}C}$ = 7.7 Hz), 129.6, 124.9 (d, $J_{P\text{-}C}$ = 1.9 Hz), 120.2 (d, $J_{P\text{-}C}$ = 1.9 Hz), 111.3, 47.4, 20.0. **IR** (KBr) 3174, 1596, 1488, 1452, 1240, 1188, 1160, 933, 902, 773, 686 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{16}H_{18}NO_3PNa$ $[M+Na]^+$:326.09165, found: 326.09070. **Rf** 0.59 (hexane/AcOEt = 1/1)

benzyl (S)-(1-((2-methylallyl)amino)-1-oxopropan-2-yl)carbamate (148n)



To a solution EDC·HCl (1.24 g, 6.5 mmol) and DMAP (0.86 g, 7 mmol) in dry DCM (13 mL) was added *N*-carbobenzoxy-L-alanine (1.1 g, 5 mmol) followed by 2-methylallylamine (0.54 mL, 6 mmol) at 0 °C. The solution was stirred for 22 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by recrystallization (from hexane/AcOEt = 35/12 (mL)) to give a colorless solid (0.95 g, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 6.08 (br s, 1H), 5.24 (br s, 1H), 5.12 (s, 2H), 4.88-4.75 (m, 2 H), 4.30-4.16 (m, 1H), 3.81 (d, J = 6.0 Hz, 2H), 1.71 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 156.1, 141.6, 136.0, 128.5, 128.2, 128.0, 110.9, 67.0, 50.4, 44.9, 20.2, 18.7. **IR** (KBr) 3296, 1683, 1644, 1540, 1449, 1324, 1264, 1229, 1055, 912, 696 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{15}H_{20}N_2O_3Na$ $[M+Na]^+$:299.13661, found: 299.13568. **Rf** 0.26 (hexane/AcOEt = 1/1).

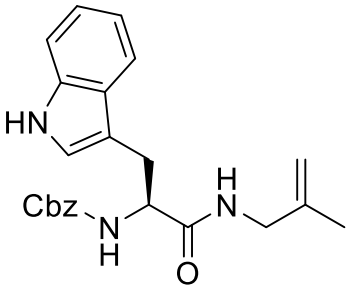
benzyl (*S*)-(3-hydroxy-1-((2-methylallyl)amino)-1-oxopropan-2-yl)carbamate (148o)



To a solution EDC·HCl (0.75 g, 3.9 mmol) and DMAP (0.51 g, 4.2 mmol) in dry DCM 7.5 mL) was added *N*-benzyloxycarbonyl-L-serine (0.72 g, 3 mmol) followed by 2-methylallylamine (0.32 mL, 3.6 mmol) at 0 °C. The solution was stirred for 22 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (3 x). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by recrystallization (from hexane/AcOEt = 70/50 (mL)) to **148o** as a colorless solid (0.95 g, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 6.68 (br s, 1H), 5.91-5.74 (m, 1H), 5.20-5.09 (m, 2H), 4.88-4.76 (m, 2 H), 4.26-4.11 (m, 2H), 3.84 (dd,

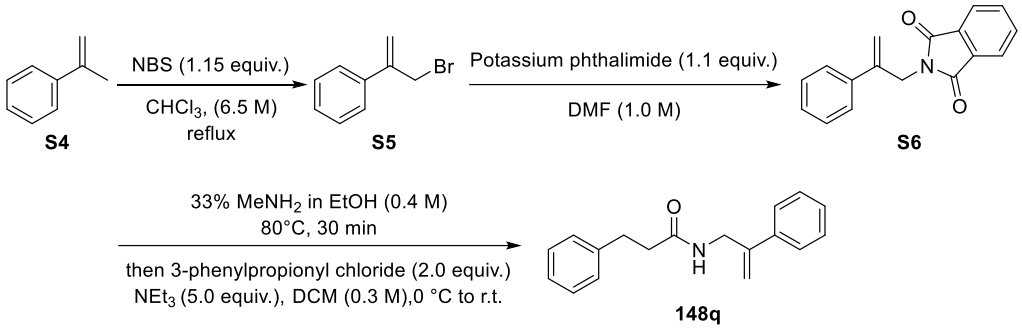
J = 16.0, 6.2 Hz, 1H), 3.77 (dd, *J* = 15.7, 5.9 Hz, 1H), 3.68 (dd, *J* = 10.8, 4.5 Hz, 1H), 1.71 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.9, 156.9, 141.2, 135.9, 128.6, 128.3, 128.1, 111.1, 67.4, 62.7, 55.3, 44.9, 20.3. **IR** (KBr) 3285, 1689, 1644, 1540, 1449, 1404, 1303, 1274, 1244, 1017, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{15}H_{20}N_2O_4Na$ $[M+Na]^+$:315.13153, found: 315.13044. **Rf** 0.68 (DCM/MeOH = 5/1).

benzyl (*S*)-(3-(1H-indol-3-yl)-1-((2-methylallyl)amino)-1-oxopropan-2-yl)carbamate (148p)



To a solution EDC·HCl (1.25 g, 6.5 mmol) and DMAP (0.86 g, 7 mmol) in dry DCM (17 mL) was added *N*-carbobenzoxy-L-tryptophan (1.7 g, 5 mmol) followed by 2-methylallylamine (0.54 mL, 6 mmol) at 0 °C. The solution was stirred for 19 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =1/1) to give **148p** as a colorless solid (1.82 g, 93%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.75-7.60 (m, 1H), 7.43-7.29 (m, 6H), 7.24-7.17 (m, 1H), 7.17-7.09 (m, 1H), 7.06-7.00 (m, 1H), 5.75 (br s, 1H), 5.44 (br s, 1H), 5.11 (s, 2H), 4.72-4.66 (m, 1H), 4.60-4.45 (m, 2H), 3.66 (d, *J* = 5.1 Hz, 2H), 3.36 (d , *J* = 14.4, 5.7 Hz, 1H), 3.19 (dd , *J* = 14.5, 7.7 Hz, 1H), 1.55 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 156.0, 141.2, 136.2, 136.1, 128.5, 128.2, 128.1, 127.3, 123.2, 122.3, 119.8, 118.8, 111.2, 111.1, 110.4, 67.0, 55.7, 45.0, 28.5, 20.1. **IR** (KBr) 3404, 3303, 3060, 2909, 1689, 1654, 1533, 1456, 1281, 1227, 1045, 902, 739 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{23}H_{25}N_3O_3Na$ $[M+Na]^+$:414.17881, found: 414.17748. **Rf** 0.22 (hexane/AcOEt = 1/1).

3-phenyl-*N*-(2-phenylallyl)propanamide (148q)



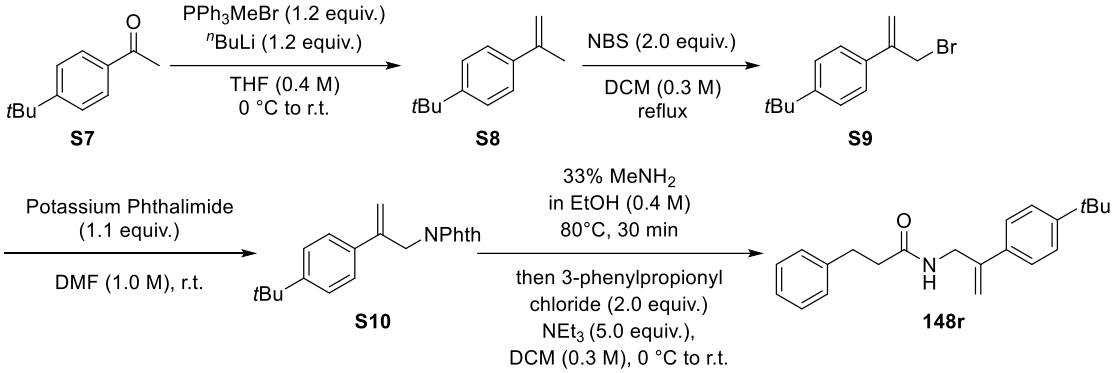
To a solution of **S4** (6.5 mL, 50 mmol) in $CHCl_3$ (7.7 mL) was added NBS (10.2 g, 34.5 mmol). The solution was refluxed for 17 h with stirring. The solution was concentrated and dissolved in hexane. The resulting precipitates were filtrated and washed with hexane. The filtrate was concentrated to give the crude mixture, which was roughly purified by flash column chromatography (silica gel, hexane) to afford **S5** as a pale yellow oil (5.56 g, 56%).

To a solution of the crude mixture of **S5** (3.9 g, 20 mmol) in DMF (20 mL) was added potassium phthalimide (4.1 g, 22 mmol). The solution was stirred for 24 h at room temperature, after which water was added. The precipitates were filtrated and washed with water to provide **S6** as a white solid (4.91 g, 93%), which was used for the next step without further purification.

The crude mixture of **S6** (1.58 g, 6 mmol) was dissolved in 33% $MeNH_2$ in EtOH (15mL), and the mixture was

stirred for 30 min at 80 °C, after which the solution was cooled to room temperature. The precipitates were removed by filtration, and the filtrate was concentrated in half volume. To the concentrated solution was added 1 M HCl in Et_2O (10 mL) and the solution was concentrated. The residue was dissolved in DCM (15 mL) and cooled to 0 °C. Then 3-phenylpropionyl chloride (1.8 mL, 12 mmol) and NEt_3 (4.1 mL, 30 mmol) were added. The solution was stirred for 52 h at room temperature, after which sat. $NaHCO_3$ aq. was added. The biphasic mixture was extracted with DCM (x 3) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude product, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 2/1 to 3/2) and recrystallization from hexane/AcOEt = 35/12.5 (mL) at 70 °C to provide **148q** as a colorless solid (0.67 g, 42%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.10 (m, 10H), 5.47-5.35 (m, 2H), 5.11 (d, J = 0.9 Hz, 1H), 4.31 (d, J = 5.4 Hz, 2H), 2.94 (d, J = 7.6 Hz, 2H), 2.46 (t, J = 7.9 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 144.1, 140.7, 138,2, 128.5, 128.4, 128.2, 128.0, 126.1, 126.0, 113.8, 43.1, 38.3, 31.5. **IR** (KBr) 3258, 3079, 3024, 1641, 1627, 1557, 1491, 1414, 1275, 1223, 1024, 892, 696 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{18}H_{19}NONa$ $[M+Na]^+$: 288.13589, found:288.13495. **Rf** 0.28 (hexane/AcOEt = 2/1).

***N*-(2-(4-(tert-butyl)phenyl)allyl)-3-phenylpropanamide (148r)**



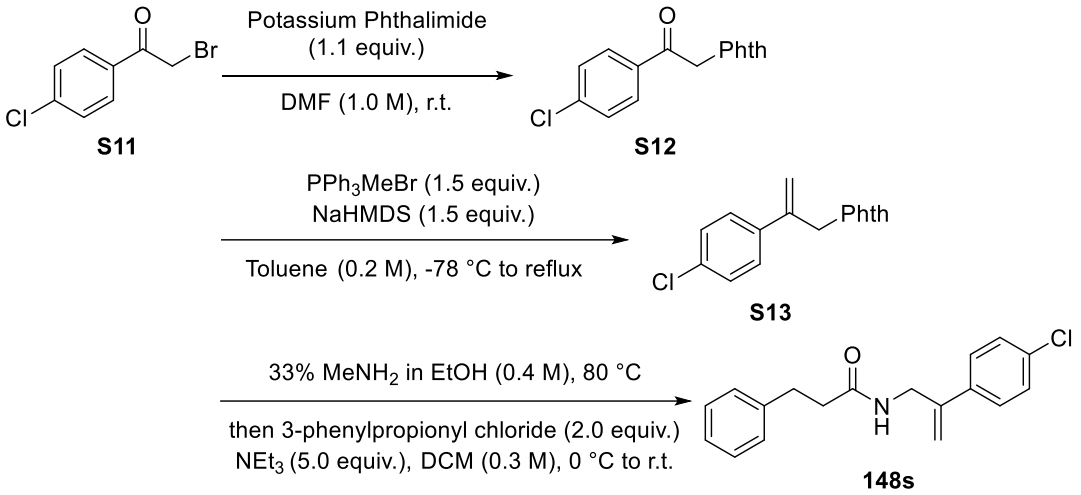
To a solution of methyltriphenylphosphonium bromide (8.57 g, 24 mmol) in THF (40 mL) was added ^{n}BuLi in hexane (1.59 M, 15 mL, 24 mmol) at 0 °C under argon atmosphere. The mixture was stirred for 1 h at the same temperature. To the mixture was added dropwise solution of **S7** (3.7 mL, 20 mmol) in THF (10 mL) at 0 °C and stirred for 19h at room temperature. The reaction mixture was filtered through a pad of silica gel and the pad was rinsed with Et_2O and the filtrate was concentrated. The crude mixture was roughly purified by flash column chromatography (silica gel, hexane) to provide **S8** as a colorless solid (3.25 g, 93%).

To a solution of crude mixture of **S8** (3.25, 18.6 mmol) in DCM (62 mL) was added NBS (6.6 g, 37.2 mmol). The solution was refluxed for 20 h with stirring. The solution was concentrated and dissolved in hexane. The resulting precipitates were filtrated and washed with hexane. The filtrate was concentrated to give the crude mixture, which was roughly purified by flash column chromatography (silica gel, hexane) to afford **S9** as a pale yellow oil (3.22 g, 68%).

To a solution of the crude mixture of **S9** (3.22 g, 12.6 mmol) in DMF (13 mL) was added potassium phthalimide (2.57 g, 13.9 mmol). The solution was stirred for 19 h at room temperature, after which water was added. The precipitates were filtrated and washed with water to provide **S10** as a colorless solid (3.60 g, 90%), which was used for the next step without further purification.

The crude mixture of **S10** (1.60 g, 5 mmol) was dissolved in 33% $MeNH_2$ in EtOH (13mL), and the mixture was stirred for 30 min at 80 °C, after which the solution was cooled to room temperature. The precipitates were removed by filtration and the filtrate was concentrated in half volume. To the concentrated solution was added 1M HCl in Et_2O (10 mL) and the solution was concentrated. The residue was dissolved in DCM (13 mL) and cooled to 0 °C. Then 3-phenylpropionyl chloride (1.5 mL, 10 mmol) and NEt_3 were added. The solution was stirred for 16 h at room temperature, after which sat. $NaHCO_3$ aq. was added. The biphasic mixture was extracted with DCM (x 3) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which product was purified by flash column chromatography (silica gel, hexane/AcOEt = 4:1 to 2:1) to provide **148r** as a colorless solid (1.27 g, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 7.25-7.09 (m, 4H), 5.42 (s, 1H), 5.36 (br s, 1H), 5.08 (s, 1H), 4.30 (d, J = 5.5 Hz, 2H), 2.94 (d, J = 7.5 Hz, 2H), 2.46 (t, J = 7.8 Hz, 2H), 1.32 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9, 151.1, 143.6, 140.8, 135.2, 128.5, 128.3, 126.2, 125.6, 125.4, 113.2, 43.2, 38.4, 34.5, 31.6, 31.2. **IR** (KBr) 3272, 3087, 2958, 2867, 1644, 1557, 1449, 1421, 1365, 1271, 1031, 892, 839, 752, 696 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{22}H_{27}NONa$ $[M+Na]^+$: 344.19849, found:344.19796. **Rf** 0.67 (hexane/AcOEt = 1/1).

***N*-(2-(4-chlorophenyl)allyl)-3-phenylpropanamide (148s)**



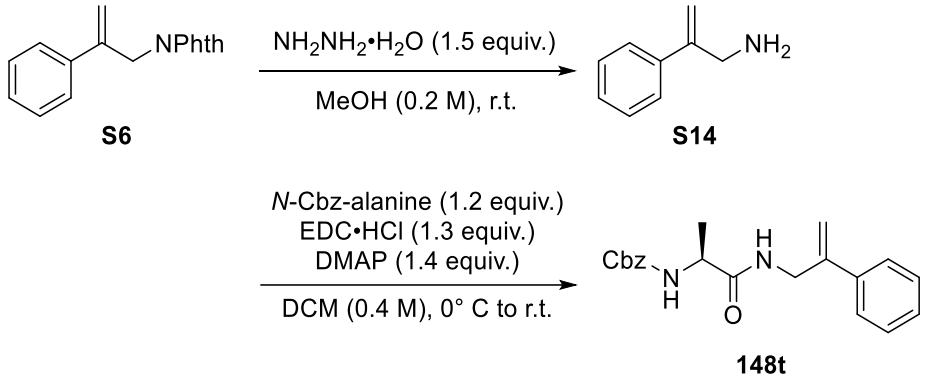
To a solution of **S11** (7.0 g, 30 mmol) in DMF (30 mL) was added potassium phthalimide (6.1 g, 33 mmol). The solution was stirred for 4 h at room temperature, after which water was added. The precipitates were filtrated and washed with water to provide **S12** as a yellow solid (8.74 g, 97%), which was used for the next step without further purification.

To a solution of methyltriphenylphosphonium bromide (5.4 g, 15 mmol) in toluene (50 mL) was added NaHMDS in THF (1.1 M, 14 mL, 15 mmol) at 0 °C under argon atmosphere. The mixture was stirred for 30 min at the same temperature. To the mixture was added the crude mixture of **S12** (3.0 g, 10 mmol) at -78 °C and stirred for 10 min at the same temperature, after which the reaction mixture was refluxed for 21 h and quenched with water. The resulting mixture was extracted with AcOEt (x 3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give the crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 5/1 to 2/1) and recrystallization (from hexane/AcOEt = 50/24 (mL), 70 °C) to provide **S13** as a pale yellow solid

(1.32 g, 44%).

The crude mixture of **S13** (1.20 g, 4 mmol) was dissolved in 33% $MeNH_2$ in EtOH (10mL), and the mixture was stirred for 30 min at 80 °C, after which the solution was cooled to room temperature. The precipitates were removed by filtration and the filtrate was concentrated in half volume. To the concentrated solution was added 1M HCl in Et_2O (10 mL) and the solution was concentrated. The residue was dissolved in DCM (10 mL) and cooled to 0 °C. Then 3-phenylpropionyl chloride (1.2 mL, 8 mmol) and NEt_3 (2.8 mL, 20 mmol) were added. The solution was stirred for 19 h at room temperature, after which sat. $NaHCO_3$ aq. was added. The biphasic mixture was extracted with DCM (x 3) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 2/1 to 3/2) to provide **148s** as a colorless solid (0.87 g, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.08 (m, 9H), 5.39 (s, 1H), 5.35 (br s, 1H), 5.12 (s, 1H), 4.27 (d, J = 5.9 Hz, 2H), 2.94 (d, J = 7.7 Hz, 2H), 2.46 (t, J = 7.7 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9, 143.2, 140.6, 136.6, 133.8, 128.6, 128.5, 128.2, 127.3, 126.2, 114.4, 42.3, 38.2, 31.5. **IR** (KBr) 3289, 3087, 3028, 2919, 1648, 1631, 1550, 1488, 1223, 1093, 1010, 895, 832, 739, 696 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{18}H_{18}ONClNa$ $[M+Na]^+$: 322.09691, found:322.09647. **Rf** 0.44 (hexane/AcOEt = 1/1)

benzyl (*S*)-(1-oxo-1-((2-phenylallyl)amino)propan-2-yl)carbamate (148t)

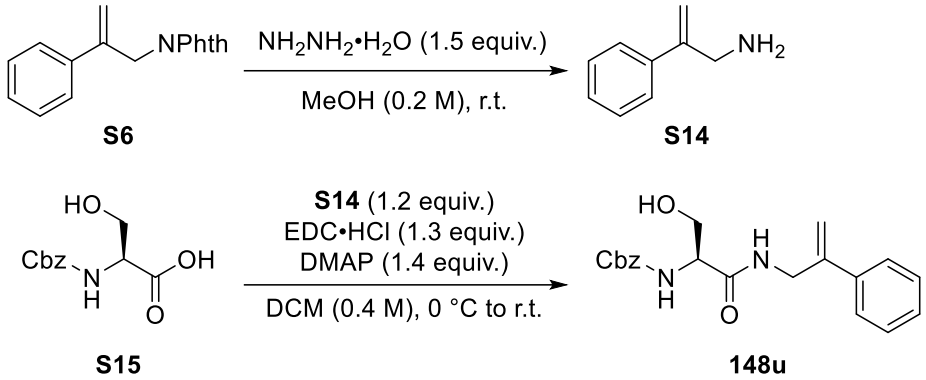


To a solution of **S6** (1.32 g, 5 mmol) in MeOH (25 mL) was added NH_2NH_2·H_2O (0.36 mL, 7.5 mmol), and the mixture was stirred for 4 h at room temperature. After the addition of water, most of MeOH was removed in vacuo. To the resulting mixture was added conc. HCl (5 mL), and the resulting suspension was stirred for further 30 min at room temperature. The precipitates were filtered, and the filter cake was washed with water. The combined filtrates were basified with solid NaOH and extracted with ether (x 3). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give the crude **S14**, which was used in the next reaction without further purification.

To a solution of EDC·HCl (0.73 g, 3.5 mmol) and DMAP (0.50 g, 4.1 mmol) in dry DCM (4 mL) was added *N*-carbobenzoxy-L-alanine (1.10 g, 5 mmol) followed by the crude **S14** (0.38 g, 2.9 mmol) in DCM (7 mL) at 0 °C. The solution was stirred for 15 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 5/4) and recrystallization (from hexane/AcOEt = 30/20 (mL), 70°C) to give **148s** as a colorless solid (0.56 g, 57%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51-7.29 (m, 10H), 6.09 (m, 1H), 5.44 (s, 1H), 5.29-5.14 (m, 2H), 5.08 (d, J = 12.1 Hz, 1H), 5.03 (d, J = 12.1 Hz, 1H), 4.42-4.26 (m, 2H), 4.24- 4.09 (m,

1H), 1.31 (d, J = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0, 155.9, 144.1, 138.3, 136.1, 128.5, 128.4, 128.2, 128.0, 128.0, 126.0, 113.7, 67.0, 50.5, 43.0, 18.5. **IR** (KBr) 3356, 3300, 3087, 3056, 3032, 2948, 2891, 1693, 1661, 1536, 1295, 1247, 1125, 1083, 1041, 899, 776, 735, 696, 592 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{20}H_{22}N_2O_3Na$ $[M+Na]^+$: 361.15226, found:361.15150. **Rf** 0.44 (hexane/AcOEt = 1/1).

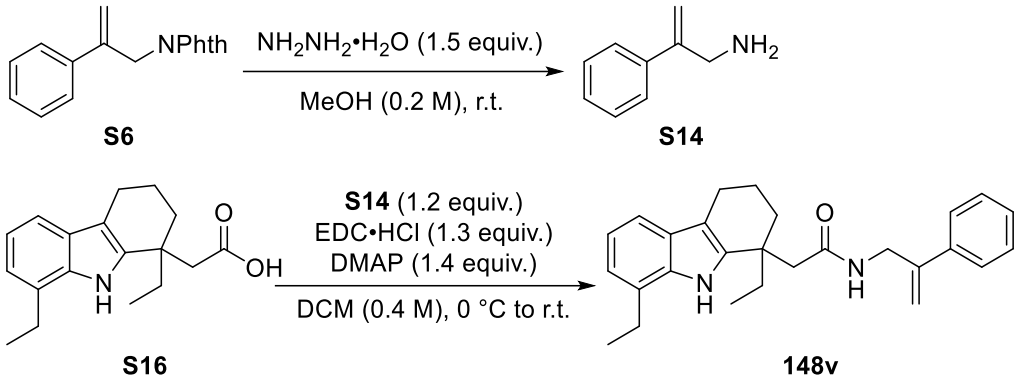
benzyl (*S*)-(1-oxo-1-((2-phenylallyl)amino)propan-2-yl)carbamate (148u)



To a solution of **S6** (1.58 g, 6 mmol) in MeOH (30 mL) was added NH_2NH_2·H_2O (0.44 mL, 9 mmol) and stirred for 24 h at room temperature. After the addition of water, most of MeOH was removed in vacuo. To the resulting mixture was added conc. HCl (5 mL), and the resulting suspension was stirred for further 30 min at room temperature. The precipitates were filtered, and the filter cake was washed with water. The combined filtrates were basified with solid NaOH and extracted with ether (3 x). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give the crude **S14**, which was used in the next reaction without further purification.

To a solution of EDC·HCl (1.07 g, 5.6 mmol) and DMAP (0.73 g, 6.0 mmol) in dry DCM (11 mL) was added **S15** (1.03 g, 5 mmol) followed by the crude **S14** (0.38 g, 6.8 mmol) at 0 °C. The solution was stirred for 15 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by recrystallization (from hexane/AcOEt = 50/63 (mL)) and flash column chromatography (silica gel, toluene/AcOEt = 1/1 to 1/2) to give **148u** as a colorless solid (0.68 g, 45%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.29 (m, 10H), 6.64 (br s, 1H), 5.73 (br s, 1H), 5.42 (s, 1H), 5.20 (s, 1H), 5.08 (d, J = 11.8 Hz, 1H), 5.04 (d, J = 11.9 Hz, 1H), 4.39 (dd, J = 15.8, 6.2 Hz, 1H), 4.28 (dd, J = 16.0, 5.9 Hz, 1H), 4.20-4.12 (m, 1H), 4.12-4.03 (m, 1H), 3.65-3.54 (m, 1H), 2.67-2.53 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7, 156.6, 143.9, 138.4, 135.9, 128.6, 128.5, 128.3, 128.1, 128.0, 126.0, 113.6, 67.3, 62.7, 55.4, 43.0. **IR** (KBr) 3293, 2937, 1693, 1655, 1543, 1303, 1279, 1240, 1020, 696 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{20}H_{22}N_2O_4Na$ $[M+Na]^+$: 377.14718, found:377.14692. **Rf** 0.17 (hexane/AcOEt = 1/1).

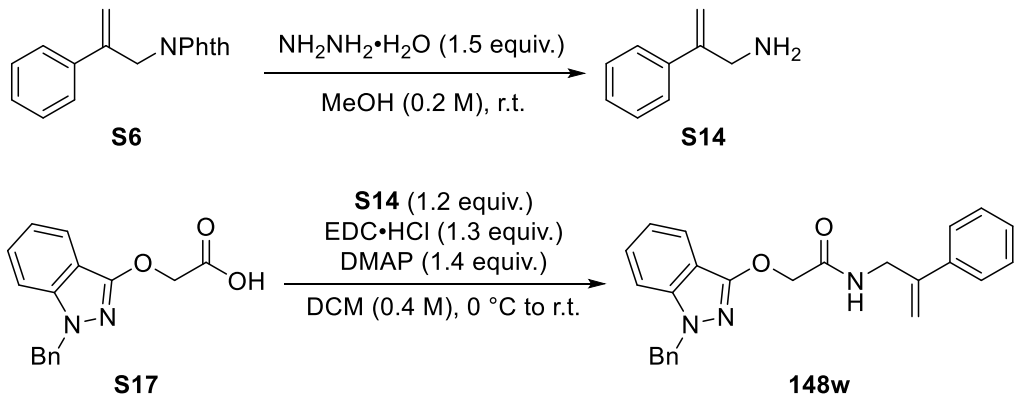
2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b] indol-1-yl)-*N*-(2-phenylallyl)acetamide (148v)



To a solution of **S6** (2.11 g, 8 mmol) in MeOH (40 mL) was added $NH_2NH_2 \cdot H_2O$ (0.60 mL, 12 mmol) and stirred for 20 h at room temperature. After the addition of water, most of MeOH was removed in vacuo. To the resulting mixture was added conc. HCl (8 mL), and the resulting suspension was stirred for further 30 min at room temperature. The precipitates were filtered, and the filter cake was washed with water. The combined filtrates were basified with solid NaOH and extracted with ether (x 3). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give the crude **S14**, which was used in the next reaction without further purification.

To a solution of EDC·HCl (1.22 g, 6.4 mmol) and DMAP (0.84 g, 6.9 mmol) in dry DCM (12 mL) was added **S16** (1.41 g, 4.9 mmol) followed by the crude **S14** (0.72 g, 5.4 mmol) at 0 °C. The solution was stirred for 38 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 3/1 to 2/1) to give **148v** as a colorless solid (1.77 g, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.43-7.36 (m, 2H), 7.36-7.28 (m, 4H), 7.10-6.97 (m, 2H), 6.22 (br s, 1H), 5.42 (s, 1H), 5.17 (s, 1H), 4.44 (dd, J = 15.3, 5.8 Hz, 2H), 4.22 (dd, J = 15.3, 5.4 Hz, 2H), 4.02-3.96 (m, 1H), 3.93-3.87 (m, 1H), 2.96-2.82 (m, 3H), 2.81-2.64 (m, 3H), 2.03 (td, J = 14.7, 7.3 Hz, 1H), 1.88 (td, J = 14.6, 7.2 Hz, 1H), 1.37 (t, J = 7.6 Hz, 3H), 0.77 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.9, 144.2, 138.4, 135.9, 134.8, 128.5, 128.0, 127.0, 126.2, 126.0, 120.1, 119.4, 115.7, 113.8, 107.6, 75.8, 60.5, 44.3, 43.1, 30.7, 24.0, 22.2, 13.9, 7.7. **IR** (KBr) 3306, 3052, 2965, 2926, 2874, 1655, 1533, 1495, 1456, 1421, 1372, 1320, 1233, 1173, 1108, 1073, 1041, 902, 776, 745, 700, 644 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{26}H_{30}N_2O_2Na$ $[M+Na]^+$: 425.21995, found:425.21907. **Rf** 0.51 (hexane/AcOEt = 1/1).

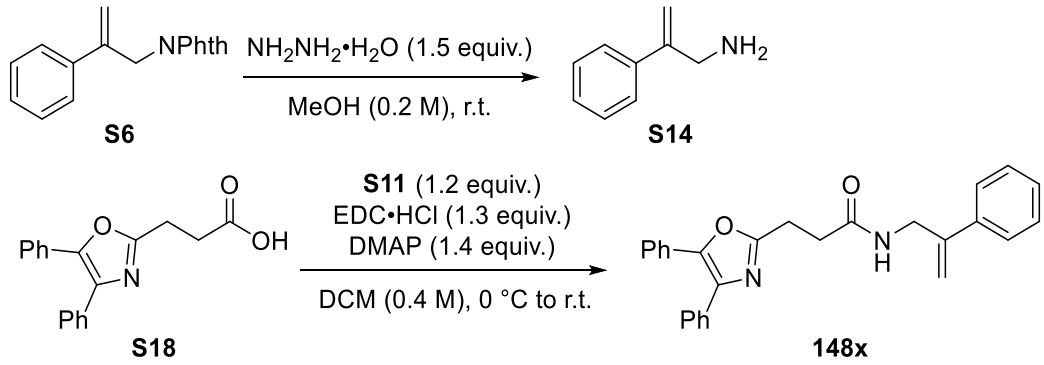
2-((1-benzyl-1H-indazol-3-yl)oxy)-*N*-(2-phenylallyl)acetamide (148w)



To a solution of **S6** (1.58 g, 6 mmol) in MeOH (30 mL) was added NH_2NH_2·H_2O (0.44 mL, 9 mmol) and stirred for 20 h at room temperature. After the addition of water, most of MeOH was removed in vacuo. To the resulting mixture was added conc. HCl (6 mL), and the resulting suspension was stirred for further 30 min at room temperature. The precipitates were filtered, and the filter cake was washed with water. The combined filtrates were basified with solid NaOH and extracted with ether (x 3). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give the crude **S14**, which was used in the next reaction without further purification.

To a solution of EDC·HCl (1.12 g, 5.9 mmol) and DMAP (0.77 g, 6.3 mmol) in dry DCM (11 mL) was added **S17** (1.27 g, 4.5 mmol) followed by the crude **S14** (0.72 g, 5.4 mmol) at 0 °C. The solution was stirred for 38 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =2/1) to give **148w** as a colorless solid (1.56 g, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.1 Hz, 1H), 7.46-7.38 (m, 2H), 7.38-7.27 (m, 6H), 7.25-7.14 (m, 4H), 7.05 (t, J = 7.4 Hz, 1H), 6.69 (br s, 1H), 5.42 (s, 1H), 5.35 (s, 2H), 5.23 (s, 1H), 4.92 (s, 2H), 4.41 (d, J = 5.8 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 154.1, 143.9, 141.5, 138.4, 136.9, 128.6, 128.5, 128.0, 127.6, 127.6, 127.2, 126.0, 119.6, 119.5, 113.5, 112.2, 109.1, 68.1, 52.4, 42.5. **IR** (KBr) 3394, 3056, 3034, 2919, 1672, 1620, 1536, 1508, 1491, 1439, 1407, 1352, 1296, 1279, 1251, 1188, 1146, 1100, 1041, 989, 909, 741, 696, 661, 592 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{25}H_{23}N_3O_2Na$ $[M+Na]^+$: 420.16825, found:420.16779. **Rf** 0.58 (hexane/AcOEt = 1/1).

3-(4,5-diphenyloxazol-2-yl)-*N*-(2-phenylallyl)propanamide (148x)

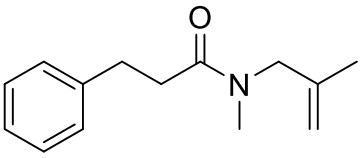


To a solution of **S6** (1.58 g, 6 mmol) in MeOH (30 mL) was added NH_2NH_2·H_2O (0.44 mL, 9 mmol) and stirred for 20 h at room temperature. After the addition of water, most of MeOH was removed in vacuo. To the resulting mixture was added conc. HCl (6 mL), and the resulting suspension was stirred for further 30 min at room temperature. The precipitates were filtered, and the filter cake was washed with water. The combined filtrates were basified with solid NaOH and extracted with ether (x 3). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give the crude **S14**, which was used in the next reaction without further purification.

To a solution of EDC·HCl (1.09 g, 5.7 mmol) and DMAP (0.76 g, 6.2 mmol) in dry DCM (11 mL) was added **S18** (1.29 g, 4.4 mmol) followed by the crude **S14** (0.70 g, 5.3 mmol) at 0 °C. The solution was stirred for 38 h, after which 1 M HCl aq. was added. The biphasic mixture was extracted with DCM (x 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (x 3) and brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent

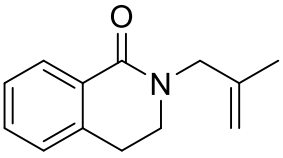
was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt = 1/1) to give **148x** as a colorless solid (1.22 g, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62-7.51 (m, 4H), 7.43-7.20 (m, 11H), 6.24 (br s, 1H), 5.41 (s, 1H), 5.23 (s, 1H), 4.36 (d, *J* = 5.8 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 162.3, 145.4, 144.2, 138.2, 134.8, 132.3, 128.8, 128.6, 128.5, 128.5, 28.4, 128.1, 128.0, 127.9, 126.4, 126.0, 113.9, 43.3, 32.9, 24.0. **IR** (KBr) 3303, 3056, 1633, 1547, 1497, 1442, 1309, 1208, 1059, 1028, 961, 920, 776, 763, 711, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{27}H_{24}N_2O_2Na$ $[M+Na]^+$: 431.17300, found: 431.17267. **Rf** 0.22 (hexane/AcOEt = 1/1).

_N_-methyl-_N_-(2-methylallyl)-3-phenylpropanamide (148y)



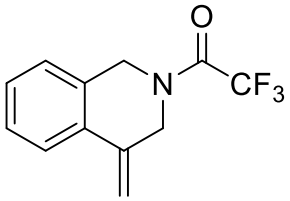
To a solution of N-methyl-3-phenylpropanamide (0.49 g, 3.0 mmol) in THF was added NaH (60%, dispersion in Paraffin Liquid) (0.18 g, 4.5 mmol) at 0 °C followed by 3-bromo-2-meyhlpropene at same temperature. The solution was stirred for 3 days, after which ice cold water was added. The biphasic mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine (x 1) and dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =85/15 to 64/36) to give **148y** as a colorless oil (0.39 g, 60%).**^{1}H NMR** (400 MHz, $CDCl_3$) mixture of rotamers in the ratio of 1/1 *δ* 7.49-7.17 (m, 5H), 4.94-4.82 (m, 1H), 4.73 (s, 1H), 3.97 (s, 1H), 3.72 (s, 1H), 3.05-2.94 (m, 2H), 2.92 (s, 1.5 H), 2.86 (s, 1.5 H), 2.66 (t, *J* = 8.0 Hz, 1H), 2.58 (t, *J* = 8.0 Hz, 1H), 1.66 (s, 1.5H), 1.65 (s, 1.5H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 172.5, 172.0, 141.4, 141.4, 140.7, 139.8, 128.4, 128.4, 126.0, 126.0, 112.1, 111.2 55.4, 52.9, 35.3, 34.7, 34.4, 33.9, 31.5, 31.3, 19.9, 19.8. **IR** (neat) 3080, 3060, 3024, 2920, 1648, 1449, 1400, 1264, 1216, 1115, 1073, 1041, 1031, 895, 752, 696 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{19}NONa$ $[M+Na]^+$:240.13589, found: 240.13511. **Rf** 0.19 (hexane/AcOEt = 4/1).

2-(2-methylallyl)-3,4-dihydroisoquinolin-1(2H)-one (148z)



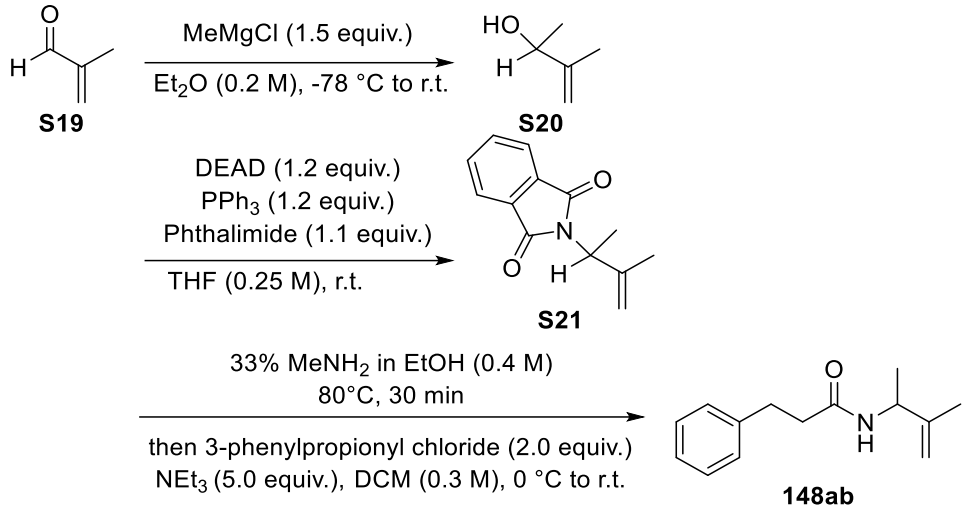
To a solution 3,4-dihydroisoquinolin-1(2H)-one (0.44 g, 3.0 mmol)) in THF (6 mL) was added NaH (60%, dispersion in Paraffin Liquid) (0.18 g, 4.5 mmol) at 0 °C followed by 3-bromo-2-methyl propene (0.6 mL, 6.0 mmol) at 0 °C. The solution was stirred for 18 h, after which ice cold water was added. The biphasic mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine (x 1) and dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =82/18 to 61/39) to give **148z** as a colorless solid (0.54 g, 90%).**^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.11 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.42 (td, *J* = 7.4, 1.5 Hz, 1H), 7.39-7.31 (m, 1H), 7.18 (dd, *J* = 7.4, 0.7 Hz, 1H), 4.98-4.92 (m, 1H), 4.92-4.86 (m, 1H), 4.16 (s, 2H), 3.55-3.44 (m, 2H), 2.99 (t, *J* = 6.6 Hz, 2H), 1.75 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 164.4, 140.9, 138.0, 131.6, 129.4, 128.4, 127.0, 126.8, 112.6, 52.5, 44.9, 28.0, 20.0. **IR** (KBr) 3293, 3073, 3028, 2971, 2937, 2913, 2867, 1648, 1603, 1575, 1480, 1456, 1439, 1421, 1337, 1302, 1261, 1160, 1052, 1028, 899, 794, 741, 703 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{23}H_{25}N_3O_3Na$ $[M+Na]^+$:224.10459, found: 224.10413. **Rf** 0.36 (hexane/AcOEt = 2/1).

2,2,2-trifluoro-1-(4-methylene-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (148aa)



To a solution of *N*-allyl-2,2,2-trifluoro-*N*-(2-iodobenzyl)acetamide (369 mg, 1.0 equiv., 1.0 mmol), Cs_2CO_3 (978 mg, 3.0 equiv., 3.0 mmol) and PPh_3 (262 mg, 1.0 equiv., 1.0 mmol) in DMF (6.7 mL, 0.15 M) was added $Pd(PPh_3)_4$ (127 mg, 11 mol%, 0.11 mmol). The solution was allowed to stir for 18 h at 80°C, after which water was added. The biphasic mixture was extracted with Et_2O (x 3). The organic layer was washed with water (x 3) brine (x 1), and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, Hexane/AcOEt =15/1) to give **148aa** as a clear oil (89.4 mg, 37%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70-7.60 (m, 1H), 7.36-7.27 (m, 2H), 7.23-7.10 (m, 1H), 5.68 (s, 0.4H, minor), 5.66 (s, 0.6H, major), 5.27 (s, 0.4H, minor), 5.18 (s, 0.6H, major), 4.88 (s, 1.2H, major), 4.78 (s, 0.8H, minor), 4.50 (s, 0.8H, minor), 4.40 (s, 1.2H, major). **^{13}C{^{1}H, ^{19}F} NMR** (100 MHz, $CDCl_3$) δ 155.6, 155.5, 136.4, 136.1, 132.4, 131.6, 131.3, 131.1, 128.8, 128.6, 127.9, 127.4, 126.6, 125.9, 124.4, 124.2, 116.5, 116.4, 111.2, 110.5, 50.0, 47.9, 47.9, 46.1. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −68.91, −69.27. **LRMS** (ESI): $[M+Na]^+$: found: 264.07. Reported compound[15]

2-((1-benzyl-1H-indazol-3-yl)oxy)-*N*-(2-phenylallyl)acetamide (148ab)



To a solution of **S19** (1.65 mL, 20 mmol) in Et_2O (100 mL) was added MeMgCl in 3M THF solution (10 mL, 30 mmol) at -78 °C. The solution was stirred for 24 h, after which sat. $NaHCO_3$ aq. was added. The biphasic mixture was extracted with Et_2O (x 3). The combined organic layers were washed with brine (x 1) and dried over Na_2SO_4. The solvent was evaporated to give the crude **S20**, which was used in the next reaction without further purification.

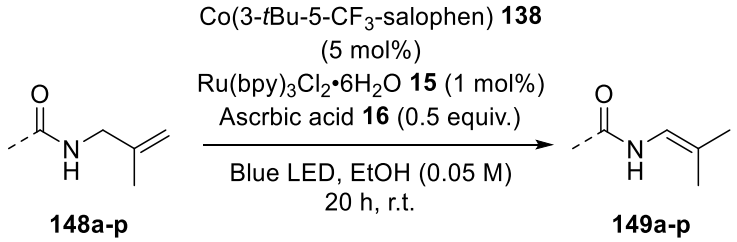
To a solution of crude **S20** (1.51 g, 17.6 mmol) in THF (70 mL) was added to PPh_3 (5.54 g, 21.1 mmol), phthalimide (2.8 g, 19.4 mmol) and DEAD in 2.2 M toluene solution (9.6 mL, 21.1 mmol) at room temperature. The solution was stirred for 24 h at the same temperature, after which the solvent was evaporated and Et_2O/hexane = 1/1 was added. The precipitates were filtered, and the filter cake was washed with Et_2O/hexane = 1/1. The organic layer was evaporated, and the crude was roughly purified by flash column chromatography (silica gel, Hexane/AcOEt =9/1) to give **S21** as a colorless solid (1.62 g, 43%).

The crude mixture of **S21** (1.62 g, 7.6 mmol) was dissolved in 33% $MeNH_2$ in EtOH (19 mL), and the mixture was

stirred for 30 min at 80 °C, after which the solution was cooled to room temperature. The precipitates were removed by filtration and the filtrate was concentrated in half volume. To the concentrated solution was added 1M HCl in Et_2O (13 mL) and the solution was concentrated. The residue was dissolved in DCM (25 mL), cooled to 0 °C. Then 3-phenylpropionyl chloride (2.2 mL, 15.2 mmol) and NEt_3 (5.3 mL, 38 mmol) were added. The solution was stirred for 22 h at room temperature, after which sat. $NaHCO_3$ aq. was added. The biphasic mixture was extracted with DCM (x 3) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which product was purified by flash column chromatography (silica gel, hexane/AcOEt = 2/1) to provide **1ab** as a colorless solid (1.31 g, 79%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.13 (m, 5H), 5.22 (br s, 1H), 4.77 (s, 2H), 4.48-4.41 (m, 1H), 2.97 (t, J = 7.7 Hz, 2H), 2.48 (t, J = 7.7 Hz, 2H), 1.66 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 146.0, 140.8, 128.5, 128.3, 126.2, 110.2, 49.4, 38.6, 31.7, 19.7, 19.5. **IR** (KBr) 3265, 3080, 3028, 2976, 2930, 2864, 1641, 1557, 1495, 1449, 1369, 1355, 1156, 895, 759, 700, 567 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{19}NONa$ $[M+Na]^+$: 240.13589, found:240.13543. **Rf** 0.22 (hexane/AcOEt = 2/1).

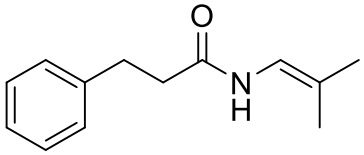
3. Isomerization of alkenes by cobalt-photoredox dual catalysis

Conditions A



In an argon filled glove box, a flame dried screw-capped vial was charged with $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1.5 mg, 0.002 mmol), **14** (6.0 mg, 0.01 mmol), ascorbic acid (17.6 mg, 0.1 mmol), **148** (0.20 mmol) and EtOH (4.0 mL). The vial was capped and removed from the glove box. The vial was placed in front of the light source (ca. 3 cm from two blue LED panels). After being stirring for 20 h, the mixture was cooled in an ice bath and sat. aq. $NaHCO_3$ was added. The mixture was extracted with DCM (x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude mixture was purified by silica gel column chromatography and reversed phase column chromatography (C18) to afford the desired emamide **149**.

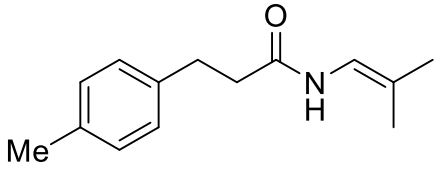
***N*-(2-methylprop-1-en-1-yl)-3-phenylpropanamide (149a)**



Prepared according to Conditions A using **148a** (40.7 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 2/1) and reverse phase chromatography ($MeOH/H_2O$ = 51/49 to 74/26). **149a** was isolated as a colorless solid (31.3 mg, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H), 7.25-7.18 (m, 3H), 6.68-6.53 (m, 1H), 6.53-6.47 (m, 0.95H, major), 6.01-5.96 (m, 0.05H, minor), 3.00 (d, J = 7.6 Hz, 2H), 2.63 (t, J = 7.8 Hz, 0.1H, minor), 2.56 (t, J = 7.6 Hz, 1.9H, major), 1.67 (s, 3H), 1.58 (s, 0.15H, minor), 1.48 (s, 2.85H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 140.6, 128.6, 128.3, 126.3, 116.8, 115.2, 38.3, 31.5, 22.4, 16.3. **IR** (KBr) 3278, 3024, 2920, 1641, 1523, 1445, 1372, 1219, 741, 700 cm^{-1}. **HRMS** (ESI): m/z

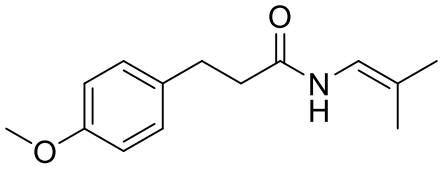
calculated for $C_{13}H_{17}NONa$ $[M+Na]^+$: 226.12024, found: 226.11955. **Rf** 0.26 (hexane/AcOEt = 3/1).

_N_-(2-methylprop-1-en-1-yl)-3-(p-tolyl)propanamide (149b)



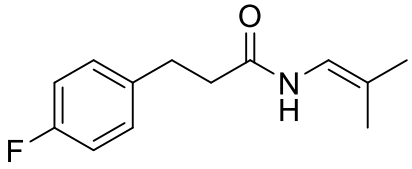
Prepared according to Conditions A using **148b** (43.5 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 76/24 to 55/45) and reverse phase chromatography ($MeOH/H_2O$ = 52/48 to 77/23). **149b** was isolated as a colorless solid (33.4 mg, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19-7.04 (m, 4H), 6.68-6.53 (m, 1H), 6.53-6.44 (m, 0.95 H, major), 6.02-5.95 (m, 0.05H, minor), 2.95 (d, J = 7.5 Hz, 2H), 2.60 (t, J = 7.9 Hz, 0.1H, minor), 2.53 (t, J = 7.6 Hz, 1.9H, major), 2.31 (s, 3H), 1.67 (s, 3H), 1.58 (s, 0.15 H, minor) 1.48 (s, 2.85 H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 137.5, 135.9, 129.3, 128.2, 116.9, 115.1, 38.5, 31.1, 22.4, 21.0, 16.3. **IR** (KBr) 3272, 3202,3020, 2916, 2864, 1689, 1633, 1516, 1442, 1369, 1212, 964, 856, 804, 728 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{19}NONa$ $[M+Na]^+$: 240.13589, found: 240.13515. **Rf** 0.56 (hexane/AcOEt = 1/1).

3-(4-methoxyphenyl)-_N_-(2-methylprop-1-en-1-yl)propanamide (149c)



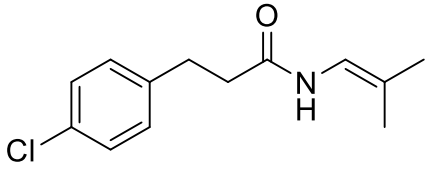
Prepared according to Conditions A using **148c** (47.6 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 2/1) and reverse phase chromatography ($MeOH/H_2O$ = 53/47 to 78/22). **149c** was isolated as a colorless solid (35.5 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16-7.10 (m, 2H), 6.87-6.80 (m, 2H), 6.63-6.52 (m, 1H), 6.52-6.47 (m, 0.95H, major), 6.00-5.96 (m, 0.05H, minor), 3.78 (s, 3H), 2.93 (d, J = 7.6 Hz, 2H), 2.59 (t, J = 7.8 Hz, 0.1H, minor), 2.52 (t, J = 7.6 Hz, 1.9H, major), 1.67 (s, 3H), 1.58 (s, 0.15H, minor), 1.49 (s, 2.85H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 158.2, 132.7, 129.3, 116.9, 115.1, 114.1, 55.3, 38.6, 30.7, 22.4, 16.3. **IR** (KBr) 3278, 3203, 2926, 1644, 1516, 1449, 1411, 1369, 1289, 1247, 1173, 1037, 961, 853, 819, 717 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{19}NO_2Na$ $[M+Na]^+$: 256.13080, found: 256.12992. **Rf** 0.48 (hexane/AcOEt = 1/1).

3-(4-fluorophenyl)-_N_-(2-methylprop-1-en-1-yl)propanamide (149d)



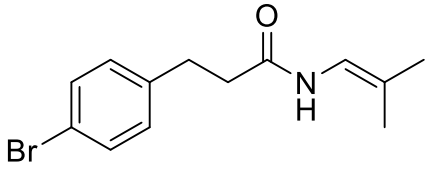
Prepared according to Conditions A using **148d** (44.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 69/31 to 48/52) and reverse phase chromatography ($MeOH/H_2O$ = 50/50 to 75/25). **149d** was isolated as a colorless solid (35.1 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23-7.09 (m, 2H), 7.03-6.90 (m, 2H), 6.73-6.55 (m, 1H), 6.54-6.45 (m, 0.95H, major), 6.00-5.95 (m, 0.05H, minor), 2.97 (d, J = 7.5 Hz, 2H), 2.60 (t, J = 7.7 Hz, 0.1H, minor), 2.52 (t, J = 7.1 Hz, 1.9H, major), 1.68 (s, 3H), 1.58 (s, 0.15H, minor) 1.52 (s, 2.85H, major). **^{13}C{^{1}H, ^{19}F }NMR** (100 MHz, $CDCl_3$) δ 168.7, 161.4, 136.3, 129.7, 116.8, 115.4, 115.3, 38.4, 30.7, 22.4, 16.3. **^{19}F NMR** (376 MHz, $CDCl_3$) [$C_6H_5CF_3$ (−63.72 as an internal standard)] δ −117.90. **IR** (KBr) 3306, 2954, 2930, 1693, 1641, 1523, 1508, 1449, 1414, 1376, 1227, 1156, 1087, 975, 829 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{16}FNONa$ $[M+Na]^+$: 244.11081 found: 244.11006. **Rf** 0.55 (hexane/AcOEt = 1/1).

3-(4-chlorophenyl)-*N*-(2-methylprop-1-en-1-yl)propanamide (149e)



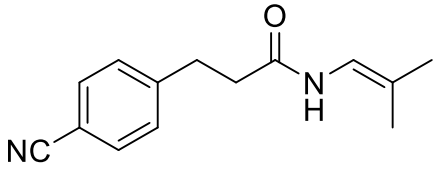
Prepared according to Conditions A using **148e** (47.5 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 5/2) and reverse phase chromatography (MeOH/H_2O = 50/50 to 75/25). **149e** was isolated as a colorless solid (36.9 mg, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.21 (m, 2H), 7.18-7.11 (m, 2H), 6.77-6.54 (m, 1H), 6.53-6.46 (m, 0.95H, major), 5.99-5.94 (m, 0.05H, minor), 2.96 (t, J = 7.5 Hz, 2H), 2.60 (t, J = 7.8 Hz, 0.1H, minor), 2.52 (t, J = 7.6 Hz, 1.9H, major), 1.70-1.65 (m, 3H), 1.58 (d, J = 0.7 Hz, 0.15H, minor), 1.52 (d, J= 0.9 Hz, 2.85H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 139.2, 132.1, 129.7, 128.7, 116.8, 115.4, 38.2, 30.8, 22.4, 16.3. **IR** (KBr) 3296, 2958, 2919, 1686, 1637, 1525, 1488, 1449, 1376, 1227, 1093, 1017, 972, 822, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{16}ClNONa$ $[M+Na]^+$: 260.08126 found: 260.08046. **Rf** 0.32 (hexane/AcOEt = 1/1).

3-(4-bromophenyl)-*N*-(2-methylprop-1-en-1-yl)propanamide (149f)



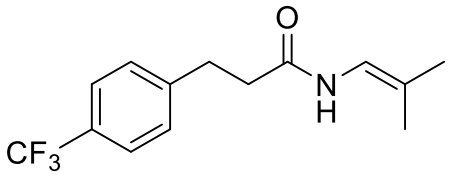
Prepared according to Conditions A using **148f** (56.4 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 2/1) and reverse phase chromatography (MeOH/H_2O = 53/47 to 78/22). **149f** was isolated as a colorless solid (40.1 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.37 (m, 2H), 7.13-7.05 (m, 2H), 6.72-6.54 (m, 1H), 6.53-6.45 (m, 0.95H, major), 5.99-5.94 (m, 0.05H, minor), 2.95 (t, J = 7.4 Hz, 2H), 2.60 (t, J = 7.6 Hz, 0.1H, minor), 2.51 (t, J = 7.4 Hz, 1.9H, major), 1.68 (s, 3H), 1.58 (s, 0.15H, minor) 1.53 (s, 2.85H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 139.7, 131.6, 130.1, 120.1, 116.7, 115.4, 38.1, 30.9, 22.4, 16.4. **IR** (KBr) 3303, 2961, 2926, 2906, 2864, 1665, 1641, 1519, 1488, 1442, 1376, 1236, 1223, 1171, 1065, 1010, 839, 815, 714 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{16}BrNONa$ $[M+Na]^+$: 304.03075 found: 304.02986. **Rf** 0.53 (hexane/AcOEt = 1/1).

3-(4-cyanophenyl)-*N*-(2-methylprop-1-en-1-yl)propanamide (149g)



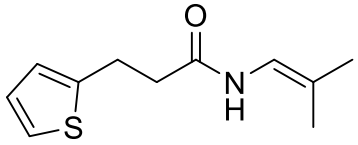
Prepared according to Conditions A using **148g** (45.7 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 58/42 to 37/63) and reverse phase chromatography (MeOH/H_2O = 49/51 to 74/26). **149g** was isolated as a colorless solid (32.3 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 6.84-6.61 (m, 1H), 6.53-6.40 (m, 0.95H, major), 6.00-5.93 (m, 0.05H, minor) 3.06 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.7 Hz, 0.1H, minor), 2.56 (t, J = 7.7 Hz, 1.9H, major), 1.69 (s, 3H), 1.59 (s, 0.15H, minor), 1.56 (s, 2.85H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 146.5, 132.3, 129.2, 118.9, 116.6, 115.7, 110.2, 37.4, 31.3, 22.4, 16.4. **IR** (KBr) 3300, 2961, 2924, 2223, 1689, 1644, 1602, 1512, 1449, 1414, 1376, 1299, 1227, 975, 825 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{16}N_2ONa$ $[M+Na]^+$: 251.11548 found: 251.11515. **Rf** 0.29 (hexane/AcOEt = 1/1).

***N*-(2-methylprop-1-en-1-yl)-3-(4-(trifluoromethyl)phenyl)propanamide (149h)**



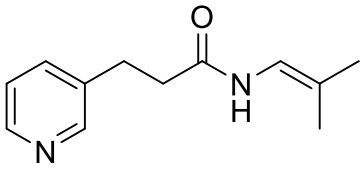
Prepared according to Conditions A using **148h** (54.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 73/27 to 52/48) and reverse phase chromatography (MeOH/H_2O = 52/48 to 73/27). **149h** was isolated as a colorless solid (42.6 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 6.74-6.54 (m, 1H), 6.53-6.44 (m, 0.95H, major), 6.00-5.94 (m, 0.05H, minor), 3.06 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.6 Hz, 0.1H, minor), 2.56 (t, J = 7.5 Hz, 1.9H, major), 1.69 (s, 3H), 1.59 (s, 0.15H, minor), 1.52 (s, 2.85H, major). **^{13}C{^{1}H, ^{19}F } NMR** (100 MHz, $CDCl_3$) δ 168.3, 144.9, 128.7, 128.7, 125.5, 124.2, 116.7, 115.6, 37.8, 31.2, 22.4, 16.3. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −62.54. **IR** (KBr) 3285, 3209, 2919, 1641, 1529, 1417, 1324, 1229, 1160, 1115, 1063, 1017, 829 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{16}F_3NONa$ $[M+Na]^+$: 294.10762 found: 294.10713. **Rf** 0.28 (hexane/AcOEt = 2/1).

***N*-(2-methylprop-1-en-1-yl)-3-(thiophen-2-yl)propanamide (149i)**



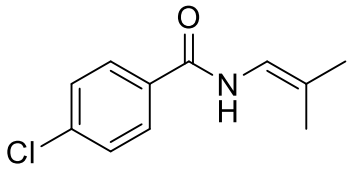
Prepared according to Conditions A using **148i** (41.9 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 78/22 to 57/43) and reverse phase chromatography (MeOH/H_2O = 48/52 to 77/23). **149i** was isolated as a colorless solid (31.3 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 5.2, 1.1 Hz, 1H), 6.92 (dd, J = 5.2, 3.4 Hz, 1H), 6.84 (dd, J = 3.4, 1.1 Hz, 1H), 6.68 (br s, 1H), 6.54-6.48 (m, 0.95H, major), 6.03-5.98 (m, 0.05H, minor), 3.21 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.7 Hz, 0.1H, minor), 2.60 (t, J = 7.2 Hz, 1.9H, major), 1.68 (s, 3H), 1.60 (s, 0.15H, minor), 1.52 (s, 2.85H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.3, 143.3, 127.0, 124.9, 123.6, 116.9, 115.4, 38.6, 25.8, 22.4, 16.3. **IR** (KBr) 3296, 3198, 2958, 2913, 2864, 1669, 1641, 1523, 1445, 1376, 1344, 1274, 1247, 1223, 1177, 1156, 689 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{11}H_{15}NOSNa$ $[M+Na]^+$: 232.07666 found: 232.07645. **Rf** 0.31 (hexane/AcOEt = 7/3).

***N*-(2-methylprop-1-en-1-yl)-3-(pyridin-3-yl)propanamide (149j)**



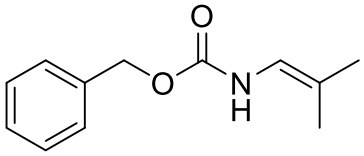
Prepared according to Conditions A using **148j** (40.9 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, DCM/MeOH = 96/4 to 89/11) and silver ion chromatography (DCM/MeOH = 20/1 to 10/1). **149j** was isolated as a brown oil (29.3 mg, 72%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.8 Hz, 1H), 8.32 (dd, J = 5.2, 1.5 Hz, 1H), 8.04 (d, J = 10.1 Hz, 1H), 7.66 (dt, J = 7.7, 1.7 Hz, 1H), 7.19 (dd, J = 7.9, 5.2 Hz, 1H), 6.51-6.42 (m, 1H), 2.96 (t, J = 7.3 Hz, 2H), 2.66 (t, J = 7.3 Hz, 2H), 1.66 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6, 151.6, 149.0, 139.0, 138.3, 124.5, 116.8, 116.4, 36.5, 28.5, 22.6, 16.6. **IR** (KBr) 3300, 2924, 1655, 1523, 1428, 1380, 1229, 711 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.13354 found: 205.13333. **Rf** 0.17 (hexane/AcOEt = 1/2)

4-chloro-*N*-(2-methylprop-1-en-1-yl)benzamide (2k)



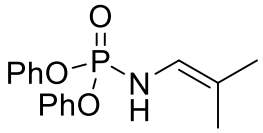
Prepared according to Conditions A using **148k** (41.9 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 83/17 to 62/38) and reverse phase chromatography (MeOH/H_2O = 50/50 to 75/25). **149k** was isolated as a colorless solid (27.3 mg, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dt, J = 8.8, 2.2 Hz, 2H), 7.46-7.33 (m, 3H), 6.72 (dt, J = 10.1, 1.4 Hz, 1H), 1.78 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.0, 138.0, 132.6, 129.0, 128.3, 117.1, 116.9, 22.5, 16.6. **LRMS** (ESI): $[M+Na]^+$: found: 232.00. Reported compound[16]

benzyl (2-methylprop-1-en-1-yl)carbamate (149l)



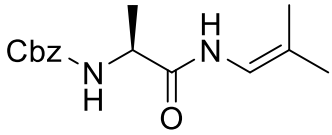
Prepared according to Conditions A using **148l** (41.1 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 93/7~72/28) and reverse phase chromatography (MeCN/H_2O = 47/53~72/28). **149l** was isolated as a white solid (24.6 mg, 60%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H), 6.27 (d, J = 10.4 Hz, 1H), 6.23-5.98 (m, 1H), 5.22-5.10 (m, 2H), 1.68 (s, 3H), 1.55 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.6, 136.1, 128.6, 128.3, 117.7, 113.2, 67.0, 22.2, 16.1. **LRMS** (ESI): $[M+Na]^+$: found: 228.09. Reported compound[17]

diphenyl (2-methylprop-1-en-1-yl)phosphoramidate (149m)



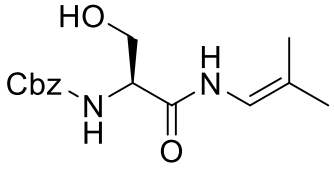
Prepared according to Conditions A using **148m** (60.7 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 78/22 to 57/43). **149m** was isolated as a colorless solid (52.9 mg, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 4H),7.28-7.22 (m, 4H), 7.21-7.15 (m, 2H), 5.96-5.83 (m, 1H), 4.92 (dd, J = 11.7, 11.7 Hz, 1H), 1.67 (s, 3H), 1.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.5 (d, $J_{P\text{-}C}$ = 6.7 Hz), 129.7, 125.1 (d, $J_{P\text{-}C}$ = 1.9 Hz), 120.4 (d, $J_{P\text{-}C}$ = 4.8 Hz), 117.4, 115.0 (d, $J_{P\text{-}C}$ = 12.5 Hz), 22.2 (d, $J_{P\text{-}C}$ = 1.0 Hz), 15.7. **IR** (KBr) 3205, 1686, 1588, 1488, 1411, 1337, 1264, 1190, 1156, 983, 933, 759, 686 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{16}H_{18}NO_3PNa$ $[M+Na]^+$: 326.09165 found: 326.09107. **Rf** 0.27 (hexane/AcOEt = 3/1).

benzyl (*S*)-(1-((2-methylprop-1-en-1-yl)amino)-1-oxopropan-2-yl)carbamate (149n)



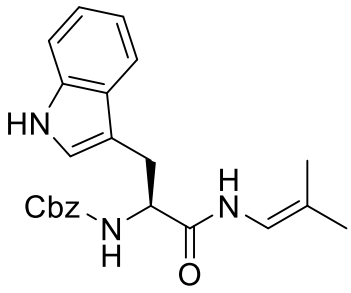
Prepared according to Conditions A using **148n** (55.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 3/2) and reverse phase chromatography (MeOH/H_2O = 50/50 to 75/25). **149n** was isolated as a colorless solid (47.4 mg, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (br s, 1H), 7.40-7.27 (m, 5H), 6.50-6.41 (m, 1H), 5.40-5.19 (m, 1H), 5.12 (s, 2H), 4.33-4.17 (m, 1H), 1.70 (d, J = 0.9 Hz 3H), 1.58 (s, 3H), 1.40 (d, J = 6.9 Hz 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 156.4, 136.0, 128.5, 128.2, 128.0, 116.7, 116.5, 67.1, 50.3, 22.4, 17.8, 16.5. **IR** (KBr) 3293, 2972, 2924, 1689, 1648, 1533, 1449, 1380, 1327, 1264, 1227, 1069, 1052, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{15}H_{20}N_2O_3Na$ $[M+Na]^+$: 299.13661 found: 299.13609. **Rf** 0.43 (Hexane/AcOEt =1/1).

benzyl (*S*)-(3-hydroxy-1-((2-methylprop-1-en-1-yl)amino)-1-oxopropan-2-yl)carbamate (149o)



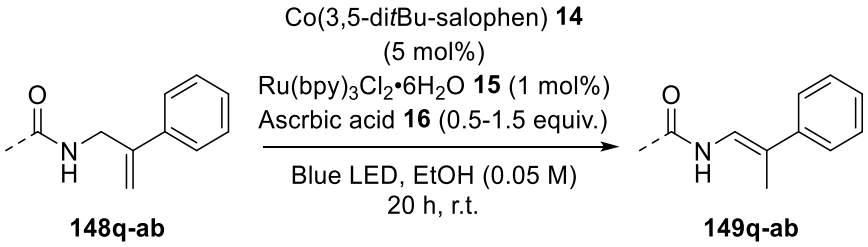
Prepared according to Conditions A using **148o** (58.5 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 43/57 to 22/78) and reverse phase chromatography (MeOH/H_2O = 49/51 to 74/26). **149o** was isolated as a colorless solid (47.4 mg, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48-8.09 (m, 1H), 7.46-7.30 (m, 5H), 6.46 (d, J = 10.3 Hz, 1H), 5.96 (d, J = 6.3 Hz, 1H), 5.16, (d, J = 12.1 Hz, 2H), 5.12 (d, J = 12.1 Hz, 2H), 4.30-4.20 (m, 1H), 4.16 (d, J = 11.2 Hz, 1H) 3.76-3.56 (br s, 1H), 3.38-3.18 (br s, 1H), 1.70 (s, 3H), 1.58 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8, 157.1, 135.9, 128.6, 128.3, 128.1, 117.6, 116.1, 67.5, 62.3, 54.8, 22.3, 16.5. IR (KBr) 3276, 1689, 1669, 1550, 1452, 1274, 1233, 1063, 1041, 741, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{15}H_{20}N_2O_4Na$ $[M+Na]^+$: 315.13153 found: 315.13096. **Rf** 0.55 (hexane/AcOEt = 1/2).

benzyl (*S*)-(3-(1H-indol-3-yl)-1-((2-methylprop-1-en-1-yl)amino)-1-oxopropan-2-yl)carbamate (149p)



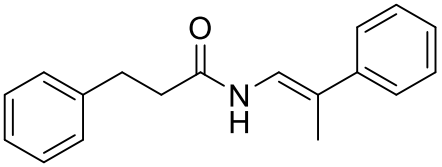
Prepared according to Conditions A, using **148p** (78.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 64/36 to 43/57) and reverse phase chromatography (MeOH/H_2O = 52/48 to 77/23). **149p** was isolated as a colorless solid (63.3 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.67 (br s, 1H), 7.37-7.30 (m, 6H), 7.23-7.16 (m, 1H), 7.15-7.03 (m, 2H), 7.01 (s, 1H), 6.43-6.32 (m, 1H), 5.60 (br s, 1H), 5.16-5.04 (m, 2H), 4.65-4.48 (m, 1H), 3.35 (dd, J = 14.2, 5.0 Hz, 1H), 3.15 (dd, J = 14.4, 8.0 Hz, 1H), 1.60 (d, J = 0.9 Hz, 3H), 1.17 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 156.3, 136.3, 136.2, 128.5, 128.2, 128.0, 127.1, 123.3, 122.4, 119.9, 118.8, 116.8, 116.1, 111.3, 110.4, 67.1, 55.3, 28.5, 22.3, 15.9. **IR** (KBr) 3404, 3317, 3056, 2916, 1700, 1658, 1516, 1456, 1341, 1227, 1055, 741 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{23}H_{25}N_3O_3Na$ $[M+Na]^+$: 414.17881 found: 414.17824. **Rf** 0.36 (hexane/AcOEt = 1/1).

Conditions B



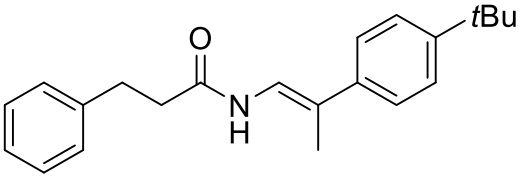
In an argon filled glove box, a flame dried screw-capped vial was charged with $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1.5 mg, 0.002 mmol), **14** (6.2 mg, 0.01 mmol), ascorbic acid (17.6 mg, 0.1 mmol), **148** (0.20 mmol) and EtOH (4 mL). The vial was capped and removed from the glove box. The vial was placed in front of the light source (ca. 3 cm from two blue LED panels). After being stirring for 20h, the mixture was cooled in an ice bath and sat. aq. $NaHCO_3$ was added. The mixture was extracted with DCM (x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude mixture was purified by silica gel column chromatography and reversed phase column chromatography (C18) to afford the desired enamide **149**.

3-phenyl-*N*-(2-phenylprop-1-en-1-yl)propanamide (149q)



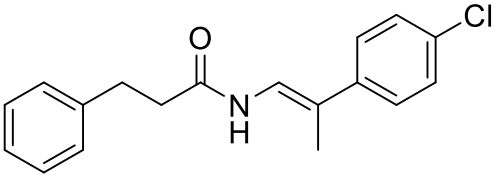
Prepared according to Conditions B using **148q** (53.1 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 4/1 to 3/1). **149q** was obtained as a pale brown solid as a mixture of isomers (39.3 mg, 75%, *E*/*Z* = 21/1). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.42-7.33 (m, 2H), 7.33-7.22 (m, 6H), 7.21-7.13 (m, 2H), 7.05 (s, 1H, *E*), 6.68 (s, 1H, *Z*), 2.96 (t, *J* = 7.7 Hz 2H, *E*), 2.88 (t, *J* = 7.5 Hz, 2H, *Z*), 2.68 (t, *J* = 7.7 Hz, 2H, *E*), 2.49 (t, *J* = 7.6 Hz, 2H, *Z*), 2.02 (d, *J* = 1.3 Hz, 3H, *E*), 1.98 (d, *J* = 1.6 Hz, 3H, *Z*). **^{13}C NMR** (100 MHz, CD_3OD) δ 173.3, 142.8, 142.2, 129.8, 129.5, 129.4, 127.6, 127.3, 126.3, 120.7, 120.6, 38.5, 32.8, 14.5. **IR** (KBr) 3293, 3198, 2961, 2909, 2863, 1665, 1644, 1523, 1445, 1372, 1344, 1275, 1223, 1177, 1156, 843, 822, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{18}H_{19}NONa$ $[M+Na]^+$: 288.13589 found: 288.13546.

(*E*)-*N*-(2-(4-(tert-butyl)phenyl)prop-1-en-1-yl)-3-phenylpropanamide (149r)



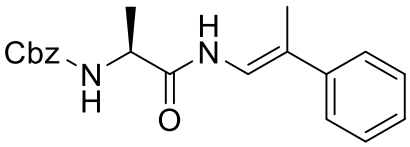
Prepared according to Conditions B using **148r** (64.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 4/1 to 3/1). **149r** was isolated as a colorless solid and as a mixture of isomers (38.0 mg, 59%, *E*/*Z* = 11/1). Careful chromatographic separation afforded analytically pure E-isomer. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.42-7.14 (m, 9H), 7.04 (s, 1H), 2.97 (t, *J* = 7.8 Hz, 1H), 2.68 (t, *J* = 7.8 Hz), 1.31 (s, 9H). **^{13}C NMR** (100 MHz, CD_3OD) δ 173.3, 150.6, 142.2, 139.7, 129.5, 129.4, 127.3, 126.3, 126.0, 120.6, 120.1, 38.6, 35.2, 32.8, 31.8, 14.5. **IR** (KBr) 3024, 2954, 2906, 2868, 1644, 1631, 1497, 1432, 1421, 1268, 1254, 825, 745, 721, 696, 571 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{22}H_{27}NONa$ $[M+Na]^+$: 344.19841 found: 344.19823. **Rf** 0.27 (hexane/AcOEt = 4/1).

(*E*)-*N*-(2-(4-chlorophenyl)prop-1-en-1-yl)-3-phenylpropanamide (149s)



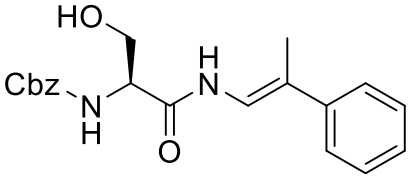
Prepared according to Conditions B using **148s** (60.0 mg, 0.20 mmol) and 1.5 equiv. ascorbic acid. The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 3/1). **149s** was isolated as a colorless solid and as a mixture of isomers (45.6 mg, 76%, *E*/*Z* = 11/1). Careful chromatographic separation afforded analytically pure E-isomer. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.40-7.32 (m, 2H), 7.32-7.14 (m, 7H), 7.07 (s, 1H), 2.96 (t, *J* = 7.6 Hz, 1H), 2.69 (t, *J* = 7.9 Hz, 1H), 2.01 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3OD) δ 173.4, 142.2, 141.5, 133.2, 129.5, 129.4, 129.4, 127.8, 127.3, 121.3, 119.3, 38.5, 32.7, 14.4. IR (KBr) 3250, 2948, 2926, 1637, 1491, 1417, 1403, 1247, 1003, 877, 822, 748, 700, 668 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{18}H_{18}NOClNa$ $[M+Na]^+$:322.09691 found: 322.09693. **Rf** 0.77 (hexane/AcOEt = 1/1).

benzyl (*S*)-(1-oxo-1-((2-phenylprop-1-en-1-yl)amino)propan-2-yl)carbamate (149t)



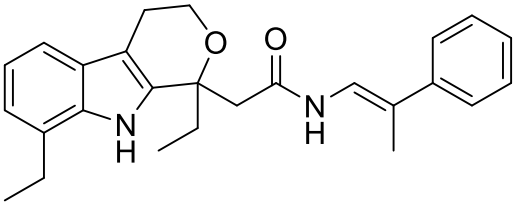
Prepared according to Conditions B using **148t** (67.7 mg, 0.20 mmol) and 1.0 equiv. ascorbic acid. The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 3/2). **149t** was isolated as a colorless solid and as a mixture of isomers (45.7 mg, 64%, *E*/*Z* = 21/1). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.38-7.18 (m, 10H), 7.03 (s, 1H, E), 6.72 (s, 1H, Z), 5.10 (s,2H, E), 5.04 (s, 2H, Z), 4.35 (q, *J* = 7.0 Hz), 2.13-1.92 (m, 3H), 1.38 (d, *J* = 6.7 Hz, E), 1.27 (d, *J* = 6.3 Hz, Z). **^{13}C NMR** (100 MHz, CD_3OD) δ 173.6, 158.4, 142.6, 138.2, 130.0, 129.5, 129.4, 129.4, 129.0, 128.9, 128.8, 128.7, 128.5, 127.7, 126.4, 121.4, 120.4, 67.7, 51.7, 18.2, 14.6. **IR** (KBr) 3421, 3306, 3032, 2982, 2456, 2410, 1724, 1686, 1655, 1449, 1425, 1362, 1261, 1160, 1069, 1030, 752, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{20}H_{22}N_2O_3Na$ $[M+Na]^+$: 361.15226 found: 361.15198. **Rf** 0.54 (hexane/AcOEt = 1/1).

(*E*)-benzyl (*S*)-(3-hydroxy-1-oxo-1-((2-phenylprop-1-en-1-yl)amino)propan-2-yl)carbamate (149u)



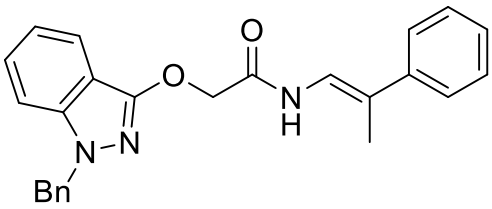
Prepared according to Conditions B using **148u** (70.9 mg, 0.20 mmol) and 1.0 equiv. ascorbic acid. The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 1/1 to 2/3). **149u** was isolated as a colorless solid and as a mixture of isomers (36.0 mg, 51%, *E*/*Z* > 20/1). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.47-7.15 (m, 10H), 7.06 (s, 1H), 5.31 (s, 1H), 4.40 (t, *J* = 5.5 Hz, 1H), 3.82 (d, *J* = 5.0 Hz, 2H), 2.07 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 168.9, 155.9, 141.2, 137.0, 128.5, 128.4, 127.8, 127.7, 126.3, 124.9, 119.9, 117.4, 65.5, 61.7, 56.7, 14.4. **IR** (KBr) 3296, 3062, 3032, 2947, 2924, 2878, 1689, 1651, 1547, 1488, 1452, 1285, 1229, 1087, 1063, 875, 763, 741, 693 cm^{-1}. HRMS (ESI): m/z calculated for $C_{20}H_{22}N_2O_4Na$ $[M+Na]^+$: 377.14718 found: 377.14693. **Rf** 0.28 (hexane/AcOEt = 1/1).

2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)-*N*-(2-phenylprop-1-en-1-yl)acetamide (149v)



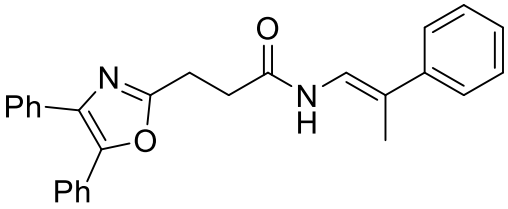
Prepared according to Conditions B, using **148v** (80.5 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 3/1). **149v** was isolated as a pale yellow solid and as a mixture of isomers containing 3% hexane on weigh basis (61.5 mg, 74%, *E*/*Z* = 6/1). **^{1}H NMR** (400 MHz, CD_3OD) δ 10.1 (s, 1H, *E*), 10.0 (s, 1H, *Z*), 7.45-7.13 (m, 6H), 7.03 (s, 1H, *E*), 7.00-6.85 (m, 2H), 6.69 (s, 1H, *Z*), 4.41 (m, 2H, *E*), 3.71-3.52 (m, 2H, *Z*), 3.08 (d, *J* = 14.6 Hz, 1H, *E*), 2.95 (d, *J* = 14.6 Hz, 1H, *E*), 2.92-2.67 (m, 4H), 2.52-2.42 (m, 1H. *Z*), 2.28-1.72 (m, 5H), 1.32 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H, *E*), 0.78 (t, *J* = 7.3 Hz, 3H, *Z*). **^{13}C NMR** (100 MHz, CD_3OD) δ 170.6, 170.1, 142.4, 136.5, 136.4, 136.4, 136.3, 130.1, 129.4, 128.8, 128.4, 128.2, 128.2, 127.8, 127.8, 127.6, 126.3, 121.4, 121.3, 121.1, 120.4, 120.1, 120.0, 116.6, 116.5, 109.2, 109.2, 77.6, 77.2, 61.9, 61.5, 45.2, 32.7, 32.3, 25.1, 25.0, 23.7, 23.2, 22.7, 22.0, 14.8, 14.4, 14.4, 8.1, 8.0. **IR** (KBr) 3358, 3048, 2961, 2920, 2874, 2857, 2505, 1651, 1421, 1376, 1313, 1274, 1244, 1173, 1069, 1041, 1024, 741, 696 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{26}H_{30}N_2O_2Na$ $[M+Na]^+$: 425.21995 found: 425.21995. **Rf** 0.37 (hexane/AcOEt = 2/1).

2-((1-benzyl-1H-indazol-3-yl)oxy)-*N*-(2-phenylprop-1-en-1-yl)acetamide 149w)



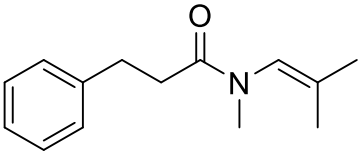
Prepared according to Conditions B using **148w** (79.5 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 4/1 to 2/1). **149w** was isolated as a colorless solid and as a mixture of isomers (61.1 mg, 77%, *E*/*Z* = 7/1). **^{1}H NMR** (400 MHz, C_6D_6) δ 8.23 (d, *J* = 11.3 Hz, 1H, *Z*), 8.01 (d, *J* = 11.3 Hz, 1H, *E*), 7.67-7.56 (m, 2H, *E*), 7.39-7.34 (m, 2H, *Z*), 7.27-6.81 (m, 12H *E*, *Z*), 4.94 (s, 2H, *E*), 4.91 (s, 2H, *E*), 4.90 (s, 2H, *Z*), 4.77 (s, 2H, *Z*), 1.77 (d, *J* = 1.4 Hz, 3H, *Z*), 1.55 (d, *J* = 1.4 Hz, 3H, *E*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.6, 165.01, 154.12, 153.7, 141.6, 141.5, 140.7, 139.0, 136.8, 128.9, 128.6, 128.5, 128.4, 127.8, 127.7, 127.6, 127.3, 127.2, 127.1, 126.8, 125.4, 120.2, 119.9, 119.5, 119.5, 119.3, 119.0, 118.4, 116.9, 112.2, 109.31. 109.1, 68.3, 67.2, 52.5, 52.4, 21.6, 14.2. **IR** (KBr) 3436, 2926, 1693, 1651, 1616, 1536, 1495, 1442, 1421, 1335, 1247, 1191, 1143, 1104, 1038, 867, 756, 745, 711, 620, 571 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{25}H_{23}N_3O_3Na$ $[M+Na]^+$: 420.16825 found: 420.16746. **Rf** 0.51 (hexane/AcOEt = 1/1).

(E)-3-(4,5-diphenyloxazol-2-yl)-*N*-(2-phenylprop-1-en-1-yl)propanamide (149x)



Prepared according to Conditions B, using **148x** (81.7 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/AcOEt = 3/2). **149x** was isolated as a colorless solid and as a mixture of isomers (59.6 mg, 73%, *E*/*Z* = 12/1). Careful chromatographic separation afforded analytically pure E-isomer. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.59-7.47 (m, 4H), 7.41-7.23 (m, 10H), 7.21-7.14 (m, 1H), 7.12-7.07 (m, 1H), 3.23 (t, *J* = 7.2 Hz, 1H), 2.96 (d, *J* = 7.2 Hz, 1H), 2.06 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3OD) δ 172.0, 164.3, 147.0, 142.8, 136.0, 133.4, 129.9, 129.8, 129.8, 129.7, 129.5, 129.4, 129.2, 127.6, 127.5, 126.4, 120.7, 120.7, 33.1, 24.7, 14.6. **IR** (KBr) 3157, 3062, 3031, 2982, 1676, 1651, 1484, 1442, 1411, 1383, 1268, 1244, 1212, 1058, 1020, 909, 735, 648 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{27}H_{24}N_2O_2Na$ $[M+Na]^+$: 431.17300 found: 431.17250. **Rf** 0.39 (hexane/AcOEt = 2/1).

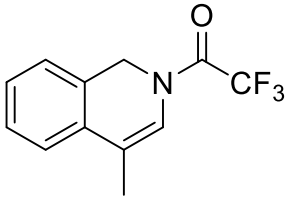
***N*-methyl-*N*-(2-methylprop-1-en-1-yl)-3-phenylpropanamide (149y)**



Prepared according to Conditions B using **148y** (43.5 mg, 0.20 mmol) and 4CzIPN (1.6 mg, 0.002 mmol) instead of $Ru(bpy)_3Cl_2 \cdot 6H_2O$. The crude mixture was purified by flash column chromatography (10%$AgNO_3$ silica gel, hexane/AcOEt = 3/2) and reverse phase column chromatography (MeCN/H_2O = 49/51~74/26). **149y** was obtained as colorless oil and as a mixture of desired product (30.2 mg, 70%) and hydrogenated product (1.3 mg, 3%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.13 (m, 5H), 6.00 (s, 0.05H, minor), 5.80 (s, 0.95H, major), 3.06-2.86 (m, 2H, minor), 2.52 (t, *J* = 7.9 Hz, 2H, major), 1.79 (s, 0.15H, minor), 1.73 (s, 0.15H, minor), 1.69 (s, 2.85H), 1.56 (s, 2.85H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 141.6, 134.8, 128.4, 128.3, 126.0, 125.0, 35.9, 34.8, 31.4, 21.7, 17.1. **IR** (neat) 3060, 3028, 2965, 2933, 1654, 1495, 1449, 1421, 1383, 1327, 1268, 1205, 1104, 1073, 832, 752, 700 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{15}NONa$ $[M+Na]^+$: 240.13589 found: 240.13538. **Rf** 0.28

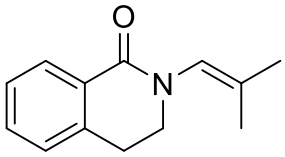
(toluene/AcOEt = 3/1).

2,2,2-trifluoro-1-(4-methylisoquinolin-2(1H)-yl)ethan-1-one (149z)



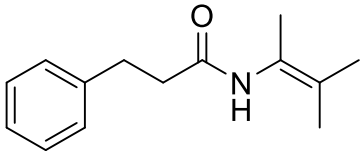
Prepared according to Conditions B using **148z** (53.1 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, Toluene). **149z** was isolated as a brown oil (28.0 mg, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.23 (m, 3H), 7.21-7.13 (m, 1H), 6.99 (s, 0.27H, minor), 6.68 (s, 0.73H, major), 4.94 (s, 1.46H, major), 4.84 (s, 0.54H, minor), 2.14 (d, J = 0.9 Hz, 0.81H, minor), 2.10 (d, J = 1.3 Hz, 2.19H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.1, 154.0, 132.1, 131.4, 129.4, 128.8, 128.7, 128.2, 128.2, 128.1, 125.7, 125.4, 122.7, 122.4, 121.2, 120.5, 119.5, 116.3, 116.2, 47.3, 45.6, 16.2, 16.0. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −69.51, -69.60. **IR** (KBr) 3073, 3032, 2969, 2937, 2916, 1686, 1641, 1599, 1575, 1477, 1421, 1380, 1324, 1233, 1173, 1153, 836, 794, 748, 721, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{12}H_{10}F_3NONa$ $[M+Na]^+$: 264.06067 found: 264.06021. **Rf** 0.43 (toluene).

2-(2-methylprop-1-en-1-yl)-3,4-dihydroisoquinolin-1(2H)-one (149aa)



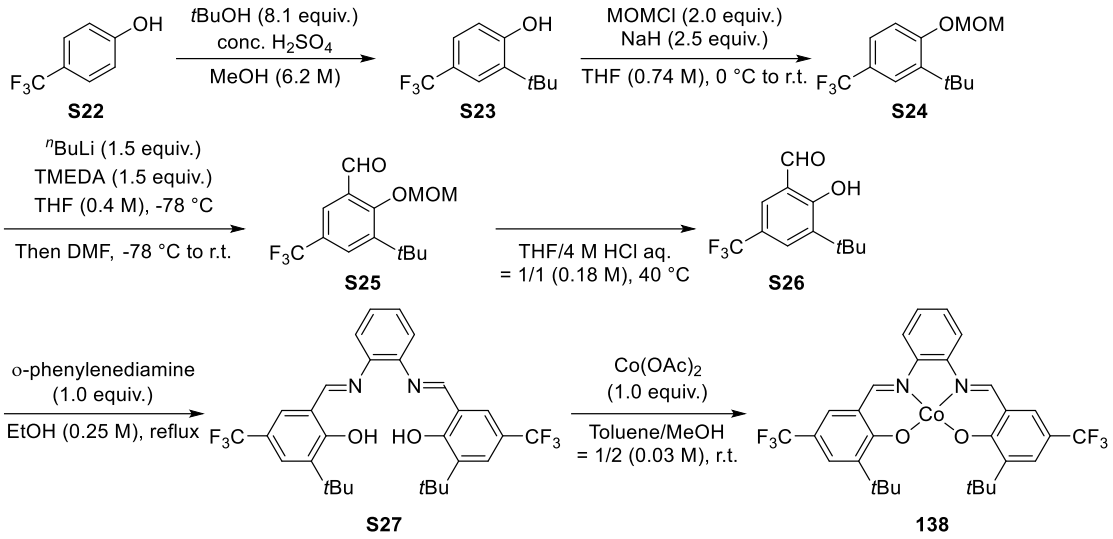
Prepared according to Conditions B, using **148aa** (53.1 mg, 0.20 mmol) and 4CzIPN (1.6 mg, 0.002 mmol) instead of $Ru(bpy)_3Cl_2{\cdot}6H_2O$. The crude mixturte was purified by flash column chromatography (silica gel, toluene/AcOEt = 8/1 to 4/1). **149aa** was isolated as a colorless solid (23.8 mg, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 6.20 (s, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.03 (t, J = 6.4 Hz, 2H), 1.80 (s, 3H), 1.71 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.3, 138.3, 131.7, 130.5, 129.5, 128.4, 127.0, 126.8, 124.4, 48.4, 28.4, 22.4, 18.3. **IR** (KBr) 3073, 3032, 2969, 2937, 2916, 1686, 1641, 1599, 1575, 1477, 1421, 1380, 1324, 1233, 1173, 1153, 836, 794, 748, 721, 693 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{15}NONa$ $[M+Na]^+$: 224.10459 found: 224.10443. **Rf** 0.30 (toluene/AcOEt = 4/1).

***N*-(3-methylbut-2-en-2-yl)-3-phenylpropanamide (149ab)**



Prepared according to Conditions B using **148ab** (43.5 mg, 0.20 mmol) and 4CzIPN (1.6 mg, 0.002 mmol) instead of $Ru(bpy)_3Cl_2{\cdot}6H_2O$. The crude mixture was purified by flash column chromatography (silica gel, toluene/AcOEt = 8/1 to 4/1) and reverse phase column chromatography ($MeCN/H_2O$ = 47/53 to 72/28). **149ab** was isolated as a colorless solid (22.5 mg, 51%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.36-7.15 (m, 5H), 6.28 (br s, 0.88H, major), 6.18 (br s, 0.12H, minor), 3.05-2.91 (m, 2H), 2.53 (t, J = 7.6 Hz, 1.75H, major), 2.43 (t, J = 7.8 Hz, 0.25H, minor), 1.82 (s, 2.61H, major), 1.71 (s, 0.39H, minor), 1.69 (s, 0.39H, minor), 1.67 (s, 2.61H, major), 1.60 (s, 0.39H, minor), 1.48 (s, 2.61H, major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4, 140.8, 128.5, 128.4, 126.2, 125.1, 124.0, 38.5, 31.8, 19.5, 19.3, 17.3. **IR** (KBr) 3273, 3059, 3028, 2912, 2863, 1652, 1523, 1449, 1372, 1302, 1278, 1226, 1142, 736, 708, 676 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{13}H_{15}NONa$ $[M+Na]^+$: 240.13589 found: 240.13555. **Rf** 0.43 (toluene/AcOEt = 1/1).

4. Synthesis of cobalt catalyst



To a solution of **S22**(2.0 g, 12.2 mmol) in methanol (2 mL) was added *tert*-butyl alcohol (10 mL) followed by conc. H_2SO_4 (10 mL) at 0℃. The solution was stirred for 18 h, after which aq. NaOH (13.5g / 90 mL) was added to pH 7. The aqueous solution was extracted with Et_2O (x3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/DCM = 3/2) to give **S23** as a purple oil (1.58 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.34 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 1.42 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.8, 136.7, 124.6, 124.5, 124.4, 122.8, 116.4, 34.7, 29.3. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −61.37. **LRMS** (ESI): [M-H]$^-$: found: 217.10. Reported compound[18]

To a solution of **S23** (1.58 g, 7.6 mmol) in THF was added to NaH (60%, dispersion in Paraffin Liquid) (0.76 g, 19 mmol) followed by chloromethyl methyl ether (1.1 mL, 15.2 mmol) at 0℃. The solution was stirred for 19 h, after which water was added. The aqueous solution was extracted with Et_2O (x3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/DCM =6/1 to 3/1) to give **S24** as a colorless oil (1.72 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 5.28 (s, 2H), 3.50 (s, 3H), 1.41 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 138.9, 124.6, 124.4, 123.9, 123.2, 113.9, 93.9, 56.3, 35.1, 29.5. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −61.59. **IR** (neat) 3000, 2961, 2913, 2833, 1609, 1501, 1359, 1331, 1285, 1233, 1195, 1139, 1119, 1080, 992, 922, 902, 829, 696, 658, 612 cm^{-1}. **HRMS** (APCI): m/z calculated for $C_{13}H_{16}F_3O_2Na$ [M-H]$^-$: 261.11079, found: 261.11052. **Rf** 0.62 (Hexane/DCM = 3/2).

To a solution of **S24** (1.42 g, 5.4 mmol) and TMEDA (1.2 mL, 8.1 mmol) in THF (13.5 mL) was added ^{n}BuLi in 1.59 M hexane solution (5.1 mL) at -78℃. The solution was stirred for 1 h after which DMF (0.98 mL, 13 mmol) was added at -78℃. The solution was stirred for 12 h at room temperature, after which NH_4Cl aq. was added. The aqueous solution was extracted with Et_2O (x3), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/DCM =1/1) to give **S25** as a colorless oil (0.97 g, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) 10.2 (s, 1H), 8.00 (s, 1H), 7.81 (s, 1H), 5.09 (s, 2H), 3.65 (s, 3H), 1.46 (s, 9H); **^{13}C**

NMR (100 MHz, $CDCl_3$) δ 189.8, 162.4, 145.2, 130.8, 129.3, 126.3, 124.9, 123.8, 102.5, 57.8, 35.3, 30.5. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −62.45. **IR** (KBr) 3007, 2965, 2902, 1696, 1613, 1467, 1362, 1335, 1233, 1167, 1121, 1073, 930, 888, 721, 661, 606 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{14}H_{17}F_3O_3Na$ $[M+Na]^+$: 313.10220, found: 313.10164. **Rf** 0.27 (hexane/DCM = 1/1).

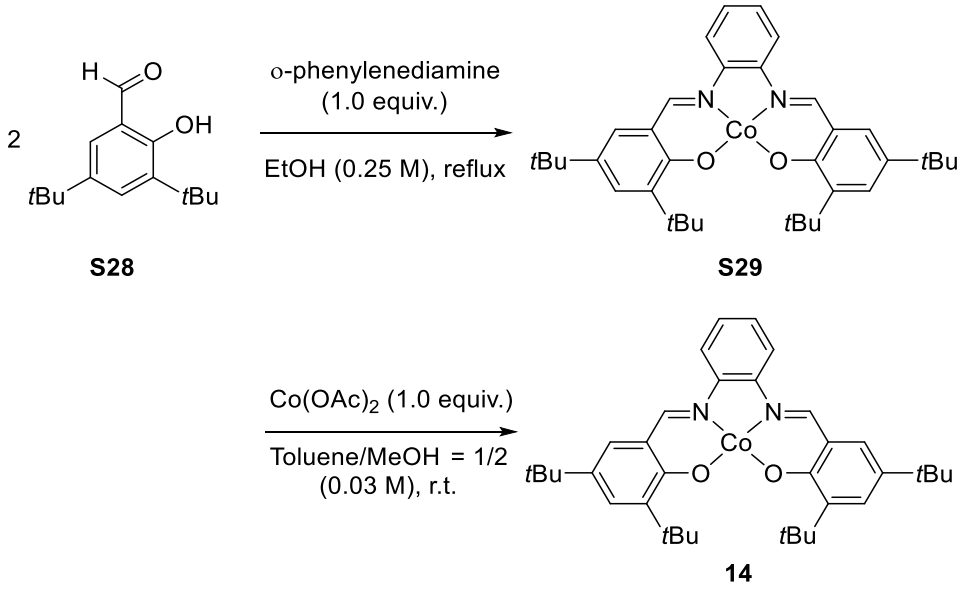
The solution of **S25** (0.92 g, 3.2 mmol) in THF/4 M HCl aq. = 1/1 (18 mL) was stirred for 19 h at 40℃, after which water was added. The aqueous solution was extracted with DCM (x3) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/DCM =12/1) to give **S26** as a colorless solid (0.76 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.1 (s, 1H), 9.93 (s, 1H), 7.71 (s, 1H), 1.44 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.5, 163.5, 139.9, 130.3, 129.2, 123.9, 121.7, 119.8, 35.1, 28.9. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.15 as an internal standard)] δ −62.07. **Rf** 0.34 (hexane/AcOEt = 8/1). **LRMS** (ESI): $[M-H]^-$: found: 245.09. Reported compound[19]

To a solution of **S26** (0.72 g, 2.9 mmol) in EtOH (6 mL) was added o-phenylenediamine (0.16 g, 1.5 mmol) at room temperature. The solution was stirred at 90℃ for 24 h. Upon cooling to room temperature, **S27** precipitated as a bright yellow powder which was isolated by filtration (0.47 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 7.57 (d, *J* = 11.0 Hz, 4H), 7.42-7.38 (m, 2H), 7.32-7.29 (m, 2H), 1.43 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.5, 163.2, 141.7, 139.1, 128.3, 127.9, 127.0, 124.4, 120.5, 119.8, 118.4, 35.2, 29.0. **^{19}F NMR** (376 MHz, $CDCl_3$) [C_6H_5F (−113.2 as an internal standard)] δ −61.65. IR (KBr) 2958, 2919, 2878, 1620, 1570, 1480, 1365, 1303, 1257, 1229, 1173, 1108, 888, 843, 745, 672 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{30}H_{30}F_6N_2O_2Na$ $[M-H]^-$: 563.21387, found: 563.21450.

To a solution od **S27** (0.68 g, 1.2 mmol) in toluene (13 mL) was added a solution of $Co(OAc)_2$•$4H_2O$ (0.30 g, 1.2 mmol) in MeOH (26 mL). The mixture was stirred for 2 h at room temperature. The precipitates were collected by filtration and washed with cold MeOH. Removal of the residual solvent in vacuo afforded **138** as a dark red solid (0.57 g, 76%). IR (KBr) 2951, 2913, 1620, 1596, 1533, 1488, 1389, 1299, 1264, 1184, 1100, 1087, 933, 902, 881, 745 cm^{-1} **HRMS** (ESI): m/z calculated for $C_{30}H_{28}CoF_6N_2O_2$ $[M]^+$: 621.13815, found: 621.13768.



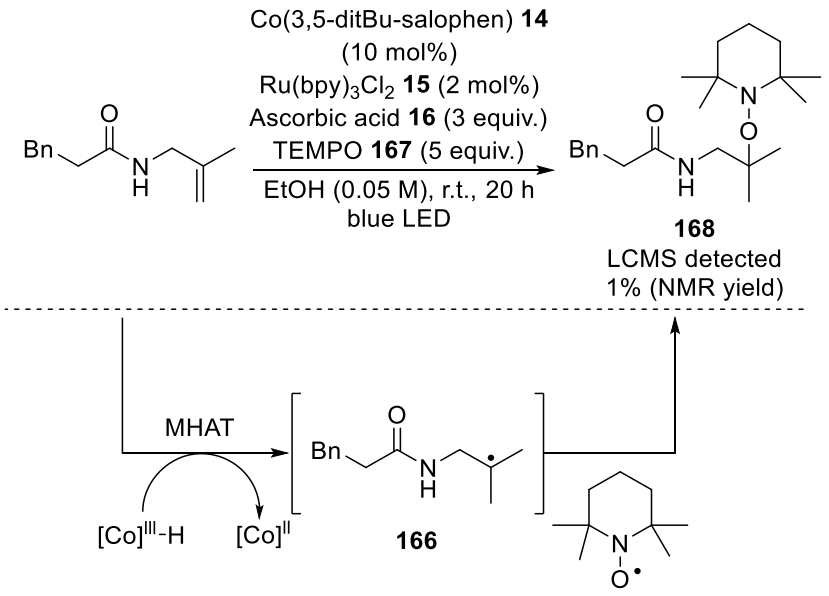
To a solution of **S28** (4.69 g, 20 mmol) in EtOH (40 mL) was added o-phenylenediamine (1.08 g, 10 mmol) at room temperature. The solution was refluxed 90℃ for 24 h with stirring. Upon cooling to room temperature, **S29** precipitated as a bright yellow powder which was isolated by filtration (4.32 g, 80%).

NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 2H), 7.44 (d, J = 2.2 Hz, 2H), 7.34-7.29 (m, 2H), 7.25-7.22 (m, 2H), 7.21 (d, J = 2.7 Hz, 2H), 1.48 (s, 18H), 1.32 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.7, 158.6, 142.7, 140.3, 137.2, 128.2, 127.3, 126.8, 119.8, 118.3, 35.1, 34.2, 31.5, 29.4. **LRMS** (ESI): $[M--H]^-$: found: 539.32. Reported compound[20]

S29 (1.08 g, 2 mmol) was dissolved in toluene (22 mL). Then, a solution of $Co(OAc)_2$•$4H_2O$ (0.50 g, 2.0 mmol) in MeOH (45 mL) was added. The mixture was stirred for 2 h and the precipitate was collected by filtration and washed with cold MeOH. Removal of the residual solvent in vacuo afforded **14** as a black solid (0.96 g, 80%).

IR (KBr) 2956, 2865, 1573, 1524, 1466, 1423, 1360, 1258 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{36}H_{46}O_2N_2Co$ $[M]^+$: 597.2886, found: 597.2890.

5. Detection of the radical intermediate by TEMPO-trapping

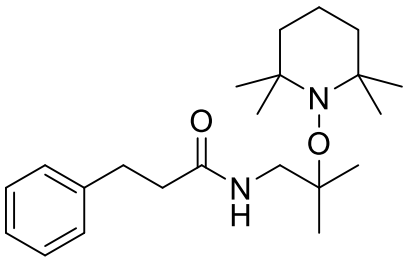


In an argon-filled glove box, a flame-dried screw-capped vial was charged with $Ru(bpy)_3Cl_2$·$6H_2O$ (0.75 mg, 0.001 mmol), **14** (3.1 mg, 0.005 mmol), ascorbic acid (52.8 mg, 0.3 mmol), **148a** (0.10 mmol), and EtOH (2.0 mL). The vial was capped and removed from the glove box. The vial was placed in front of a light source (ca. 3 cm from two blue LED panels). After being stirred for 20 h, the mixture was cooled in an ice bath and sat. aq. $NaHCO_3$ was added. The mixture was extracted with DCM (3x 2mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The solvent was removed under reduced pressure and the residue was analyzed by LS/MS. The m/z of **5** ($[M+H]^+$: 361.28) was observed by LCMS analysis of the crude mixture (Figure S38).

To estimate the yield of **5**, the crude mixture was dried in vacuo to remove the residual TEMPO and analyzed by ^{1}H NMR in $CDCl_3$ using 1,1,2,2-tetrachloroethane as an internal standard. The yield of **5** was calculated to be 1%. The

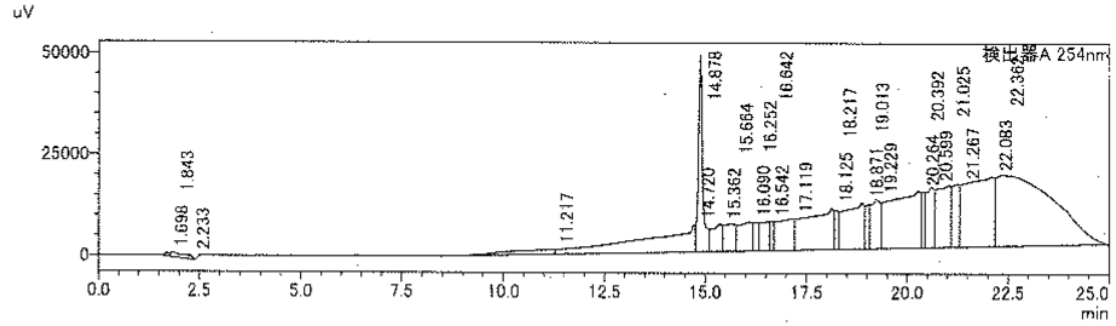
identity of **5** was further confirmed by comparing the retention time in LCMS to that of **5** independently prepared by Boger's method.[21]

Synthesis of 168



To a solution of iron(III) oxalate (604.7 mg, 1.25 mmol) in degassed water (100 mL) was added a solution of allylamide **148a** (50.8 mg, 0.25 mmol) and TEMPO (125 mg, 0.80 mmol) in MeCN (5 mL) at room temperature followed by $NaBH_4$ (30.2 mg, 0.8 mmol) at 0 °C. After 5 min, additional $NaBH_4$ (30 .2 mg, 0.8 mmol) was added at the same temperature and the solution was stirred for 30 min, after which conc. NH_3 aq. (4 mL) was added. The solution was extracted with DCM (x 3). The combined organic layers were washed with brine (x 1) and dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane/AcOEt =4/1) to give **168** as a colorless oil (33.7 mg, 37%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.14 (m, 5H), 6.11 (br s, 1H), 3.33 (d, J = 5.1 Hz, 2H), 3.00 (t, J = 7.7 Hz, 2H), 2.55 (t, J = 7.7 Hz, 2H), 1.62-1.24 (m, 6H), 1.21 (s, 6H) 1.06 (s, 6H), 1.04 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 140.7, 128.4, 126.1, 77.5, 59.3, 49.6, 40.6, 38.6, 34.4, 31.7, 24.9, 20.6, 16.9. **IR** (neat) 3442, 3316, 3087, 3062, 2930, 1739, 1648, 1553, 1452, 1372, 1257, 1240, 1156, 1132, 912, 748, 702 cm^{-1}. **HRMS** (ESI): m/z calculated for $C_{22}H_{37}N_2O_2$ $[M+H]^+$: 361.28398 found: 361.28495. **Rf** 0.28 (hexane/AcOEt = 4/1).

UV detection



LC/MS chart of crude mixture

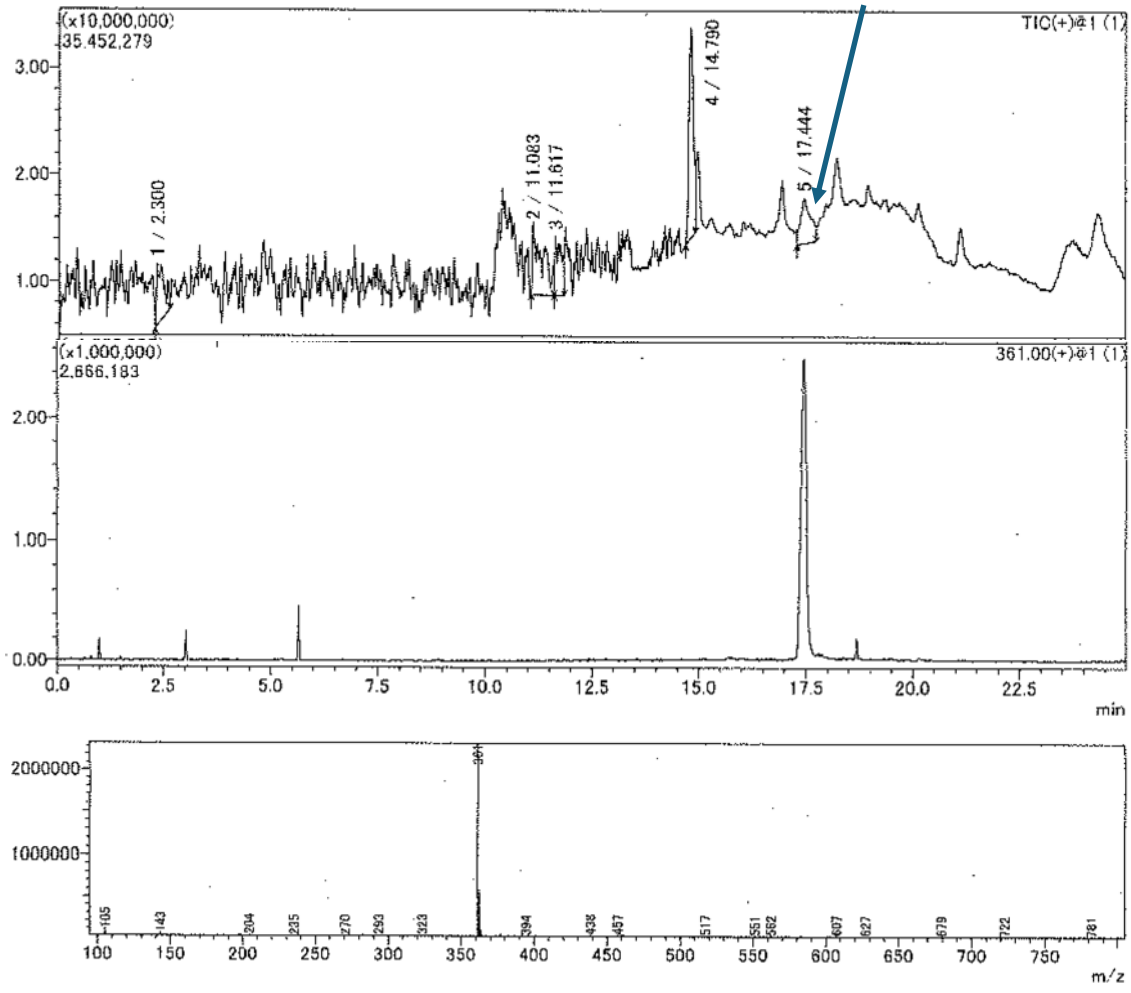
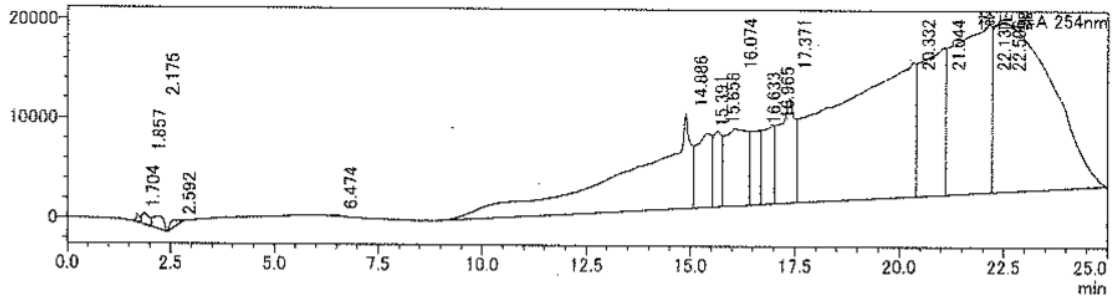


Figure S30 Detection of 5 by LCMS (TEMPO trap experiment)

LC/MS of Synthesized **168**

UV detection



LC/MS chart of synthesized **5**

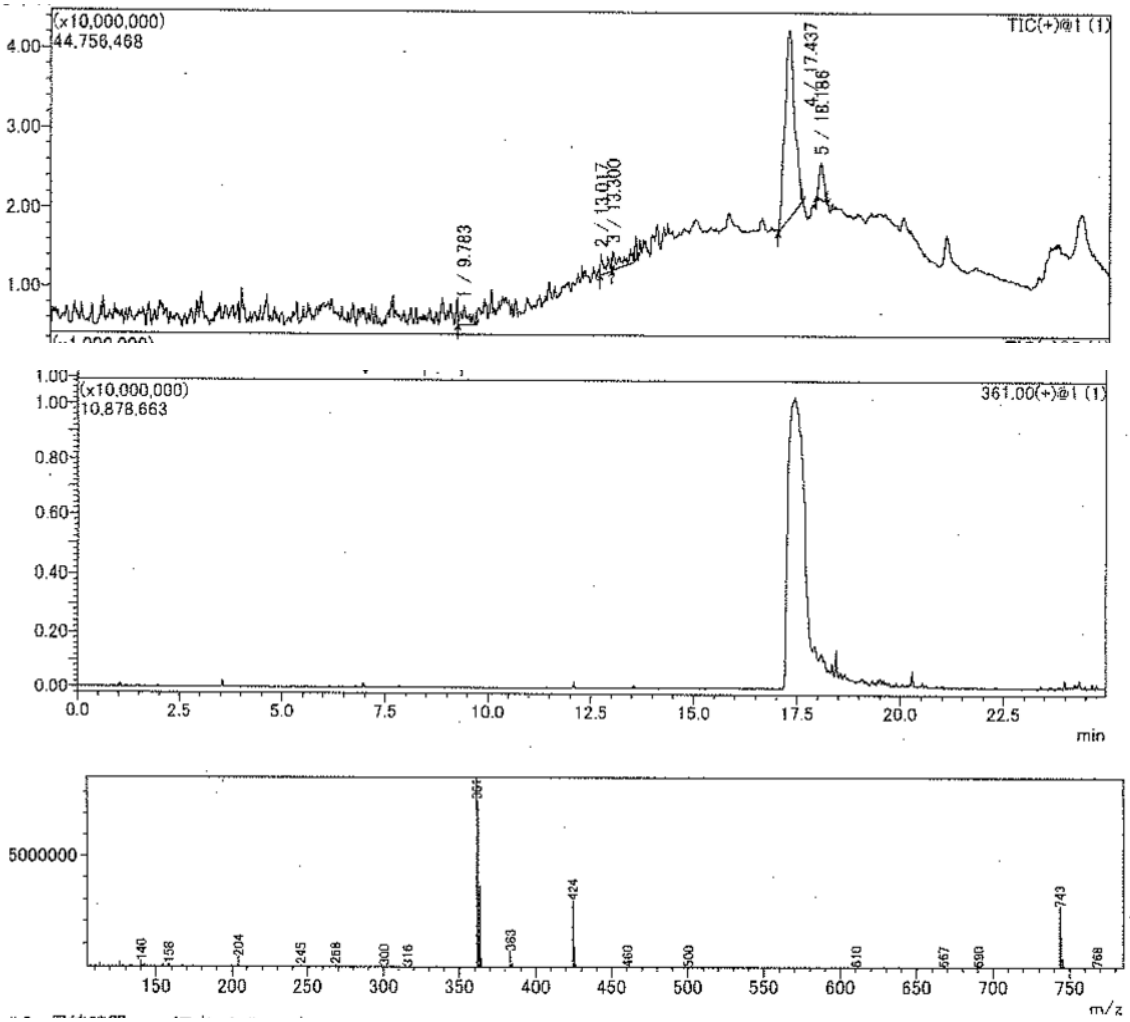


Figure S31 Detection of 5 by LCMS (Synthesized 5)

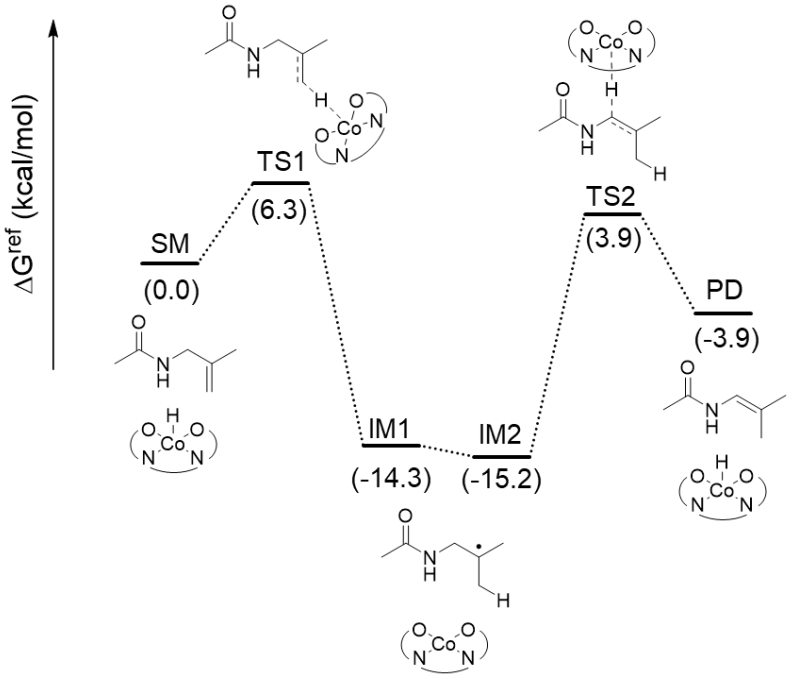
6. Computational details

General

All the equilibrium and transition structures were optimized using Gaussian 16 Rev.B.01 employing UωB97X-D density functional with inclusion of the solvent effects of ethanol by the PCM method, and the basis set of LANL2DZ(f) (LANL2DZ with added f polarization function α = 2.780) for Co and 6-31G(d,p) for the other atoms. Vibrational calculations were performed to confirm that no imaginary frequencies (equilibrium structures) or one imaginary frequency (transition structure) exist. IRC calculations were also performed to confirm the desired connection from the transition state. For more accurate electronic energies, single point calculations were performed using Gaussian 16 Rev.B.01 program employing UωB97X-D density functional with inclusion of the solvent effects of ethanol by the PCM method, and the basis set of SDD for Co and 6-311G(d,p) for the other atoms. Gibbs free energies were calculated as the sum of the electronic energies (UωB97X-D/SDD for Co, 6-311G(d,p)+PCM(ethanol)) and the thermal correction terms from the vibrational calculation (UωB97X-D/LANL2DZ(f) for Co, 6-31G(d,p)+PCM(ethanol), 298.15 K). Cobalt-mediated hydrogen atom transfer steps were calculated employing DFT with broken-symmetry formalism in singlet state in reference to previous studies. [11], [12], [13] All the unrestricted DFT calculations were performed using stable=opt option to guarantee the stability of wavefunctions throughout the calculation.

Calculated energy diagrams.

DFT calculations were performed employing the cobalt hydride complex derived from **138** and an acetamide derivative as a model substrate. The calculated reaction pathway is summarized in Figure 1. The transition state of the HAT from the cobalt hydride to the acetamide derivative (TS1 in Figure 1) was revealed to be 6.3 kcal/mol higher in free energy than the starting materials (SM), suggesting that the HAT between the two species can rapidly proceed at ambient temperature. The barrier for the following isomerization via TS2 is 19.1 kcal/mol higher in free energy than IM2. HAT between the two species proceeds via TS2, regenerating the cobalt hydride, while the isomerized product (PD) is obtained via hydrogen atom abstraction. This step was calculated to be slightly exergonic, and its energy barrier is sufficiently low (19.1 kcal/mol).



4-3-3. Optimized structures and energies

SM

Free energy correction [UωB97X-D/6-31G(d,p)+PCM(ethanol)]: 0.629876 au

EE [U ω B97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.778569 au

G [U ω B97X-D/SDD/6-311G(d,p) +PCM(ethanol)): -2530.148693 au

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TM1

Free energy correction [UωB97X-D/6-31G(d,p)+PCM(ethanol)]: 0.624734 au

EE [UωB97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.763403 au

G [UωB97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.138669 au

imaginary frequency (cm^{-1}) -1666.25*i*

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C	-3.53249200	1.76524300	1.98968200
O	-3.78676900	2.58368900	1.10800400
C	-4.40839500	0.56553500	2.27405600
H	-3.92603700	-0.33234000	1.87263700
H	-4.55881600	0.42057000	3.34718600
H	-5.37014000	0.68872400	1.77950700
F	7.68795700	0.85901900	-0.82504600
F	7.80552700	-0.59799800	0.77374300
F	7.75142200	-1.25796900	-1.27713800
F	-6.98638500	-2.19204100	-1.41634400
F	-7.03250000	-0.02916500	-1.56312300
F	-7.03034100	-0.98910600	0.37407000

IM1

Free energy correction n (UωB97X-D/6-31G(d,p)+PCM(ethanol)): 0.634822 au

E U ω B97X-D/SDD/6-311G(d,p) +PCM(ethanol)): -2530.806338 au

G U ω B97X-D/SDD/6-311G(d,p) +PCM(ethanol)): -2530.171516 au

C	0.64487400	-0.21712900	2.67508700
H	1.63768300	-0.58590000	2.41478800
C	0.40434500	1.15066200	2.08888900
C	-0.89682900	1.81606300	2.48525500
H	-0.75760500	2.16877900	3.52356000
H	-1.08668100	2.70750300	1.88517800
C	1.57139900	2.08747500	2.29192200
H	1.71059200	2.24277000	3.37214300
H	2.50015500	1.66181700	1.90622700
H	1.40798800	3.06848200	1.83843400
H	0.57723500	-0.15505200	3.77240500
C	-2.31604400	1.69534600	-0.87380700
H	-2.94135400	2.51198500	-1.23378500
N	-1.07986500	1.94876200	-0.57991200
C	-0.54526100	3.25222400	-0.70012800
C	0.85498400	3.29714800	-0.78434300
C	-1.28976900	4.43117400	-0.69069800
H	-2.36383400	4.40162900	-0.54645000
C	1.49837700	4.52886900	-0.91200900

C	-0.64001100	5.65241800	-0.82165800
H	2.57862900	4.59548400	-0.96717900
H	-1.21691100	6.57061500	-0.81051700
C	0.74806900	5.69881000	-0.94224700
H	1.25413500	6.65358700	-1.03420600
C	-2.95461300	0.42117300	-0.77924800
C	-4.32213400	0.39099800	-1.11267600
C	-2.27700000	-0.75882700	-0.32592900
H	-4.80872500	1.30702100	-1.43328300
C	-5.03314100	-0.77517000	-1.01146300
C	-3.04130700	-1.98783700	-0.24792900
C	-4.37703000	-1.94756500	-0.58285400
H	-4.96610800	-2.85484200	-0.52737200
C	2.76726300	1.88624200	-0.76541300
H	3.37331800	2.75393300	-1.02539100
N	1.48237000	2.03208600	-0.65639600
C	3.49602900	0.67824100	-0.54386700
C	2.85706200	-0.57797300	-0.28245500
C	4.90371400	0.77237600	-0.59744400
H	5.36416500	1.73649300	-0.78808000
C	3.68861800	-1.75617100	-0.14839300
C	5.67564000	-0.33967500	-0.39994300
C	5.05331700	-1.59176700	-0.18994400
H	5.69757400	-2.45532400	-0.07202500
O	-1.03186300	-0.75698100	0.00031200
O	1.58061600	-0.69366900	-0.18754000
C	-2.37830400	-3.30050000	0.19551900
C	-6.50632700	-0.80193900	-1.24797000
C	3.05063900	-3.14956900	-0.04267100
C	7.16762700	-0.27514600	-0.41696700
C	-1.19444400	-3.62834200	-0.73302400
H	-0.71794600	-4.56255400	-0.41523000
H	-1.53765400	-3.75682700	-1.76561100
H	-0.44887800	-2.83518000	-0.70293000
C	-1.87954200	-3.16663200	1.64565100
H	-1.12609600	-2.38422900	1.71739300
H	-2.70759400	-2.92924600	2.32303500
H	-1.42720100	-4.10741400	1.97788200

C	-3.35435300	-4.48610800	0.14828900
H	-2.82486400	-5.39249700	0.45726500
H	-4.20113800	-4.35287300	0.83001300
H	-3.74252200	-4.65898900	-0.86102500
C	2.31917400	-3.43914200	-1.36936600
H	1.80876700	-4.40694200	-1.31583900
H	1.57371300	-2.67120900	-1.58160100
H	3.03351000	-3.47396700	-2.19896900
C	4.10577100	-4.24820900	0.15988600
H	3.60146800	-5.21696500	0.22741100
H	4.81122300	-4.30617300	-0.67547600
H	4.67282100	-4.10417300	1.08598100
C	2.06186200	-3.23628900	1.13668200
H	1.22721300	-2.55021200	1.00423200
H	1.66860500	-4.25647000	1.20975800
H	2.56663600	-3.00093900	2.08064000
Co	0.24815400	0.64564000	-0.19064500
H	-0.07789800	-0.95398900	2.32686500
N	-2.07227000	0.97846000	2.41506700
H	-1.98828300	0.00698100	2.66954600
C	-3.30750600	1.47675700	2.16632900
O	-3.49926900	2.65849000	1.88173400
C	-4.43940000	0.48026000	2.29438900
H	-4.13034700	-0.53432000	2.03054900
H	-4.79688600	0.47695300	3.32875900
H	-5.26034500	0.78086300	1.64414900
F	7.62982800	0.95983100	-0.67858200
F	7.70248000	-0.65379800	0.76400200
F	7.69886100	-1.10035100	-1.34450300
F	-6.90417400	-1.93105600	-1.86802100
F	-6.92705100	0.23343500	-1.99703700
F	-7.20424900	-0.74608800	-0.08962600

IM2

Free energy correction [UωB97X-D/6-31G(d,p)+PCM(ethanol)]: 0.633916 au

EE [UωB97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.806803 au

G [UωB97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.172887 au

C	-2.23023100	2.11073900	-0.76679400

H	-2.83405300	2.99687400	-0.95961900
N	-0.96437200	2.25885800	-0.51780900
C	-0.35231800	3.53830800	-0.48139400
C	1.04716000	3.50646200	-0.36969900
C	-1.01956100	4.76354000	-0.49625700
H	-2.10049800	4.81309300	-0.55463200
C	1.76471900	4.69826100	-0.25926000
C	-0.29566300	5.94580700	-0.40837300
H	2.84041500	4.69081500	-0.12695200
H	-0.82019500	6.89490800	-0.41486400
C	1.09260700	5.91354900	-0.28762900
H	1.65357100	6.83719700	-0.19736800
C	-2.94046900	0.87103800	-0.81127900
C	-4.34177800	0.95178600	-0.97404400
C	-2.28716600	-0.40197000	-0.70677500
H	-4.81379300	1.92711500	-1.03726500
C	-5.09211100	-0.18985800	-1.03047500
C	-3.09382100	-1.59854600	-0.82337700
C	-4.45301400	-1.44921000	-0.96545100
H	-5.08099900	-2.32956700	-1.03360600
C	2.87551100	1.99461500	-0.48103100
H	3.52550300	2.84869700	-0.67160900
N	1.60281600	2.20466800	-0.32648100
C	3.53186000	0.72864400	-0.41736800
C	2.82812200	-0.50677700	-0.23252500
C	4.93799400	0.74483700	-0.54135700
H	5.44633700	1.69216400	-0.69013600
C	3.59977600	-1.72915300	-0.14264500
C	5.64975100	-0.42089700	-0.46609100
C	4.96690200	-1.64197800	-0.26337800
H	5.56555500	-2.54337900	-0.20255700
O	-1.02229700	-0.50658500	-0.50948700
O	1.54646300	-0.56399900	-0.15025600
C	-2.43348600	-2.98411800	-0.83066900
C	-6.58342800	-0.14288400	-1.08622200
C	2.89752600	-3.07633100	0.08322900
C	7.13787300	-0.44372600	-0.58978200
C	-1.56391100	-3.09790100	-2.09893300

H	-1.03889900	-4.05925700	-2.11043400
H	-2.18721000	-3.03720200	-2.99754500
H	-0.81849200	-2.30179300	-2.13541700
C	-1.56475800	-3.19980800	0.42418000
H	-0.72300400	-2.50993100	0.43699000
H	-2.15013700	-3.06005500	1.33944700
H	-1.17247600	-4.22294100	0.42484900
C	-3.47541100	-4.11254500	-0.86951400
H	-2.95585300	-5.07543500	-0.87267000
H	-4.13047700	-4.09211300	0.00833500
H	-4.09676900	-4.07517700	-1.77033800
C	1.91436200	-3.35500900	-1.06963300
H	1.41291900	-4.31574400	-0.90742200
H	1.15437400	-2.57712700	-1.12777300
H	2.44654200	-3.40687000	-2.02596900
C	3.89602200	-4.24240400	0.14003100
H	3.34473300	-5.17378900	0.30117700
H	4.45649900	-4.34950400	-0.79476000
H	4.60925300	-4.13563800	0.96433700
C	2.13751100	-3.04802900	1.42351200
H	1.37815800	-2.26649300	1.42173800
H	1.64020200	-4.00936200	1.59233200
H	2.82681500	-2.86964200	2.25614000
Co	0.28045000	0.83815300	-0.21438100
F	7.66145500	0.78192700	-0.76565100
F	7.72775700	-0.97164000	0.50435200
F	7.54670000	-1.20027600	-1.63109900
F	-7.08390700	-0.97987200	-2.01755100
F	-7.05247600	1.08605300	-1.36251200
F	-7.13800200	-0.51763100	0.08865300
H	-0.33597800	-1.11906500	2.01941100
C	-0.67936900	-0.22504800	2.55069800
H	-0.53427100	-0.42419700	3.62295900
C	0.18390300	0.95727900	2.18031700
C	-0.35423400	2.31742600	2.54432300
H	-1.34394500	2.52436500	2.13371900
H	-0.43856100	2.37485400	3.64017800
H	0.32567800	3.11079200	2.22582500

C	1.61826900	0.75058000	2.59815400
H	1.98520200	-0.24362000	2.34054600
H	2.28214600	1.49745100	2.15895200
H	1.68176300	0.85990800	3.69119100
N	-2.09508700	-0.01829900	2.33846000
C	-3.02093300	-0.83423300	2.89545700
O	-2.71925100	-1.71725200	3.69689700
C	-4.45277400	-0.59535700	2.46923500
H	-5.07470100	-0.48982700	3.36055500
H	-4.57744300	0.28334500	1.83355400
H	-4.80254500	-1.47105300	1.91695800
H	-2.38664700	0.59358400	1.59280000

TM2

Free energy correction [UωB97X-D/6-31G(d,p)+PCM(ethanol)]: 0.625187 au

EE [UωB97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.767688 au

G [UωB97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.142501 au

imaginary frequency (cm^{-1}) -1559.82*i*

C	-2.37744600	1.88475400	-0.86033400
H	-3.00712400	2.77078300	-0.93701100
N	-1.08617800	2.02942200	-0.87788800
C	-0.47251000	3.30414800	-0.95816300
C	0.93191900	3.27542000	-0.90862400
C	-1.13865800	4.52916500	-1.03693600
H	-2.22005800	4.57740300	-1.08370000
C	1.65053200	4.47331400	-0.89450800
C	-0.41388600	5.71358000	-1.04082300
H	2.73138000	4.47605900	-0.81577500
H	-0.93842700	6.66114100	-1.09483800
C	0.97791000	5.68599700	-0.96245100
H	1.54199200	6.61203800	-0.94807300
C	-3.08105800	0.64798200	-0.74611300
C	-4.49006800	0.72300400	-0.70657300
C	-2.41503700	-0.62048400	-0.69232700
H	-4.97071200	1.69597800	-0.72843000
C	-5.23885000	-0.41990600	-0.63767300
C	-3.22584400	-1.82169100	-0.66929500
C	-4.59319100	-1.67835400	-0.63513200

H	-5.22107300	-2.56105200	-0.60338100
C	2.77210900	1.77159500	-0.85893100
H	3.43333700	2.61628500	-1.05225200
N	1.48956400	1.97807600	-0.81498900
C	3.42542100	0.52233800	-0.64177900
C	2.70852800	-0.68687000	-0.36187700
C	4.83715900	0.52928900	-0.67079800
H	5.35877800	1.45368600	-0.89808600
C	3.46698600	-1.87703500	-0.03555300
C	5.53717300	-0.61618400	-0.40631800
C	4.83857500	-1.80263000	-0.07949800
H	5.42836100	-2.68235900	0.15171600
O	-1.13612700	-0.72320900	-0.67318200
O	1.42738700	-0.75058200	-0.39448400
C	-2.55998200	-3.20438900	-0.68907400
C	-6.72665700	-0.37701400	-0.52518400
C	2.73594700	-3.16241200	0.37583900
C	7.02962700	-0.64852300	-0.42892700
C	-1.75288000	-3.36149100	-1.99366500
H	-1.24458100	-4.33202400	-2.00232000
H	-2.41656100	-3.31706700	-2.86425800
H	-0.99943500	-2.57805000	-2.08445500
C	-1.63115400	-3.36671800	0.52930900
H	-0.81143200	-2.65171000	0.49437300
H	-2.18021500	-3.21204700	1.46354100
H	-1.20985600	-4.37854800	0.53845200
C	-3.59586000	-4.33772300	-0.64107600
H	-3.07234800	-5.29826900	-0.66769400
H	-4.18906100	-4.31129800	0.27940500
H	-4.27847600	-4.31239200	-1.49729400
C	1.81762600	-3.64658300	-0.76380800
H	1.31332200	-4.57240500	-0.46498800
H	1.05749300	-2.90266800	-0.99861400
H	2.40421400	-3.85586600	-1.66547300
C	3.71637700	-4.30025800	0.69822500
H	3.14729300	-5.18631900	0.99589400
H	4.32520100	-4.57604400	-0.16956900
H	4.38583200	-4.04583300	1.52687000

C	1.90701500	-2.88590400	1.64725400
H	1.18492500	-2.08575100	1.48245100
H	1.35880700	-3.78834200	1.93920800
H	2.56393900	-2.60343800	2.47740100
Co	0.17129500	0.62746700	-0.62543700
F	7.56958400	0.54232100	-0.74231900
F	7.54643400	-1.01313600	0.76476200
F	7.50224000	-1.54320500	-1.32369200
F	-7.32759700	-1.17371400	-1.43381500
F	-7.22375200	0.86082700	-0.69432400
F	-7.15163100	-0.80714100	0.68366500
H	0.12954100	0.92114800	0.87743100
C	-0.10768100	1.11430900	2.36868200
H	0.40804600	0.17806400	2.56638300
C	0.54900200	2.31082100	2.55773200
C	-0.15481600	3.62812600	2.65133200
H	-1.17684100	3.53580100	3.02794300
H	0.39406100	4.29817500	3.32022200
H	-0.19513400	4.12298300	1.67127600
C	2.04391900	2.33261700	2.49929600
H	2.46151600	1.34827600	2.27145800
H	2.38762800	3.03773800	1.73203800
H	2.45980400	2.67836300	3.45311300
N	-1.50811800	0.98120400	2.46409400
C	-2.09299800	-0.21273000	2.78886600
O	-1.43277400	-1.18146900	3.14314700
C	-3.59846900	-0.25273500	2.69281900
H	-4.00210700	-0.61777300	3.63939100
H	-4.04698000	0.71354000	2.45608100
H	-3.87349900	-0.96702900	1.91222500
H	-2.09148400	1.72385900	2.11180100

TM2

Free energy correction [UωB97X-D/6-31G(d,p)+PCM(ethanol)]: 0.628848 au

EE [U ω B97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.783794 au

G [U ω B97X-D/SDD/6-311G(d,p) +PCM(ethanol)]: -2530.154946 au

C	-2.34945400	1.73615300	-0.91328800
H	-2.97963500	2.62452300	-0.94414400

N	-1.06546000	1.87931500	-1.04648600
C	-0.47212100	3.14982000	-1.23614400
C	0.92432500	3.15825100	-1.10725100
C	-1.15451200	4.33088600	-1.53214600
H	-2.22800500	4.33494300	-1.68000500
C	1.62164400	4.36375100	-1.21305100
C	-0.45163600	5.52206900	-1.64922300
H	2.69827100	4.40339100	-1.09702200
H	-0.98499600	6.43832700	-1.87670400
C	0.93218700	5.54003500	-1.47765700
H	1.48006800	6.47190400	-1.56265500
C	-3.03594600	0.50051500	-0.73268100
C	-4.43726600	0.56820400	-0.58468700
C	-2.35910700	-0.76039100	-0.74252600
H	-4.92353700	1.53833800	-0.56485300
C	-5.16973400	-0.58075800	-0.46300200
C	-3.15397400	-1.96637600	-0.65831300
C	-4.51621300	-1.83258800	-0.51348500
H	-5.13245700	-2.72010100	-0.43293100
C	2.77828300	1.71360600	-0.75465700
H	3.43030800	2.57964700	-0.85980800
N	1.49483000	1.88312400	-0.87099400
C	3.44132800	0.48004200	-0.49454500
C	2.73709500	-0.75612700	-0.34376700
C	4.84956700	0.52400500	-0.39452500
H	5.36250200	1.47122700	-0.52682800
C	3.49524400	-1.94535100	-0.02003700
C	5.55491000	-0.61864000	-0.13560000
C	4.86359300	-1.83709900	0.05857700
H	5.45487600	-2.71567600	0.28957000
O	-1.07776300	-0.84988600	-0.83603300
O	1.46156100	-0.84515700	-0.49172700
C	-2.48401400	-3.34532800	-0.72070900
C	-6.63978400	-0.54283600	-0.20326300
C	2.76982400	-3.26374300	0.27995300
C	7.04509700	-0.61636800	-0.03116100
C	-1.75281000	-3.50431900	-2.06900400
H	-1.25324000	-4.47859400	-2.10701600

H	-2.46431500	-3.45461800	-2.90055800
H	-1.00006900	-2.72660600	-2.20267000
C	-1.48515000	-3.49046200	0.44173700
H	-0.69252800	-2.74874800	0.36649800
H	-1.98967800	-3.36446000	1.40547500
H	-1.03078400	-4.48738800	0.41927300
C	-3.50687500	-4.48559800	-0.60722700
H	-2.97876800	-5.44217700	-0.66533300
H	-4.04186400	-4.46310900	0.34823700
H	-4.24135900	-4.46547900	-1.41952000
C	1.91577900	-3.70653500	-0.92486200
H	1.42585600	-4.66000700	-0.69823200
H	1.14638200	-2.97164700	-1.15728400
H	2.54800100	-3.85272100	-1.80794700
C	3.75308100	-4.40229100	0.59138700
H	3.18505600	-5.31228400	0.80754700
H	4.41290800	-4.61792700	-0.25598000
H	4.37162100	-4.18634000	1.46890100
C	1.88330300	-3.05623300	1.52496100
H	1.18447400	-2.23169000	1.37906100
H	1.30692800	-3.96432500	1.73222100
H	2.50459700	-2.83877300	2.40059400
Co	0.20272700	0.50695100	-0.75508700
F	7.57551000	0.60372000	-0.22345300
F	7.46713900	-1.04437100	1.17789500
F	7.61465100	-1.44156000	-0.93541100
F	-7.31390900	-1.42606700	-0.96719000
F	-7.17358100	0.66986300	-0.43202100
F	-6.92884700	-0.85981300	1.07858500
H	0.08447600	0.73527200	0.60726400
C	-0.31544100	1.83258700	2.64842700
H	0.34894900	1.02888300	2.94389800
C	0.14458200	3.05890200	2.37262200
C	-0.72978800	4.21603200	1.97060200
H	-1.68189400	3.90427300	1.53004200
H	-0.95224000	4.85928300	2.83069400
H	-0.22026900	4.83589300	1.22608800
C	1.61634400	3.34695500	2.48170000

H	2.18678800	2.45892800	2.76662700
H	2.00610500	3.71352700	1.52395600
H	1.81117100	4.13284500	3.22177500
N	-1.65629900	1.42916900	2.60040500
C	-2.03448600	0.12658100	2.77291000
O	-1.22308100	-0.76849500	2.98312200
C	-3.52032300	-0.13871400	2.71554900
H	-3.85513300	-0.46733300	3.70298200
H	-4.10921100	0.72790000	2.41066200
H	-3.70099900	-0.95443300	2.01221800
H	-2.37318600	2.11693800	2.43054700

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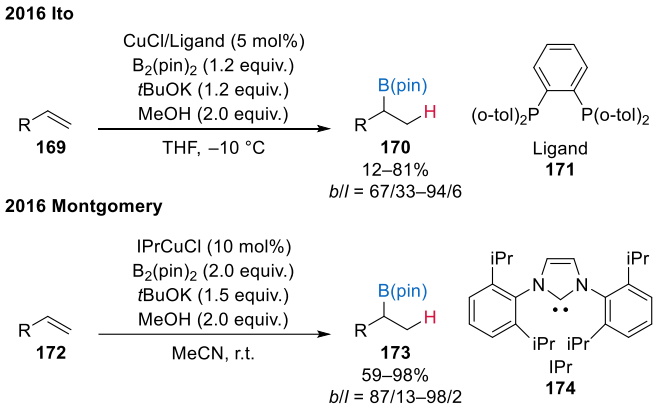
第 2 章　コバルト触媒と光酸化還元触媒の協働による MHAT を用いた不活性アルケンのマルコフニコフヒドロホウ素化反応の開発

第 1 節 背景

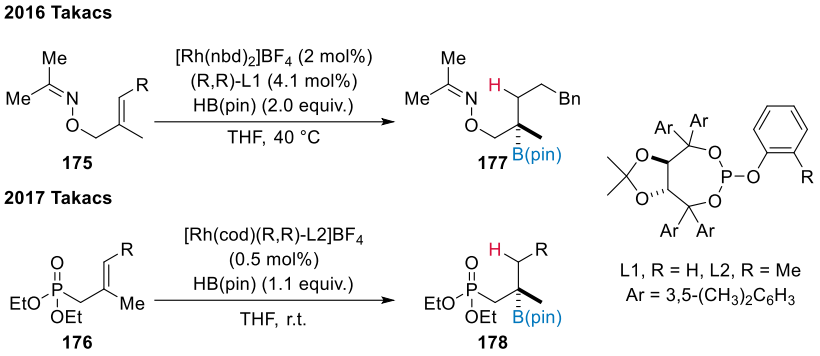
アルキルボロン酸エステルは、有機合成におけるビルディングブロックとして有用な化合物であり、多くの合成法が開発されてきた[1,2]。その中でも、アルキルボロン酸エステルを得る手法として、不活性アルケンのヒドロホウ素化反応は、多くの研究者によって研究がなされてきた。特に不活性アルケンのマルコフニコフヒドロホウ素化反応は、未だに困難な課題として研究がなされている。

2016 年に伊藤らは、銅触媒とかさ高いジホスフィン配位子 **171** を用いることにより、末端不活性アルケンのマルコフニコフヒドロホウ素化反応を達成し、2018 年にはその不斉化反応も達成した[3]。2016 年に Montgomery らは、銅触媒とかさ高い NHC 配位子 **174** を用いることによって、不活性アルケンのマルコフニコフ選択的ヒドロホウ素化反応を開発した[4]。しかしながら、これらの手法では、立体障害により選択性を発現させていることから、完全なマルコフニコフ選択的なヒドロホウ素化反応は困難な課題である。また基質に依存した選択性の低下も大きな問題となっている。さらに立体障害の大きい不活性 3 置換アルケンに対する反応性の低さも解決するべき課題となっている(Scheme 2-1.)。



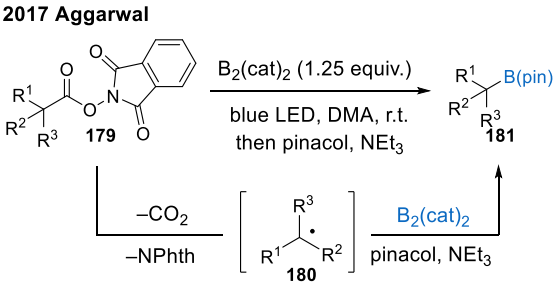
Scheme 2-1. Examples of Markovnikov hydroboration of unactivated terminal alkenes

不活性 3 置換アルケンのマルコフニコフヒドロホウ素化反応は不活性 3 置換アルケンの立体障害により困難な課題であるが、2016 年に Takacs らは、オキシム配向基を利用することで、エナンチオ選択的なマルコフニコフヒドロホウ素化反応を報告し[5]、翌年には、ホスホネート配向基を利用したエナンチオ選択的なマルコフニコフヒドロホウ素化反応を報告した[6]。しかしながら、位置選択性の発現には、配向基が必須であり、基質一般性に課題を残している(Scheme 2-2)。



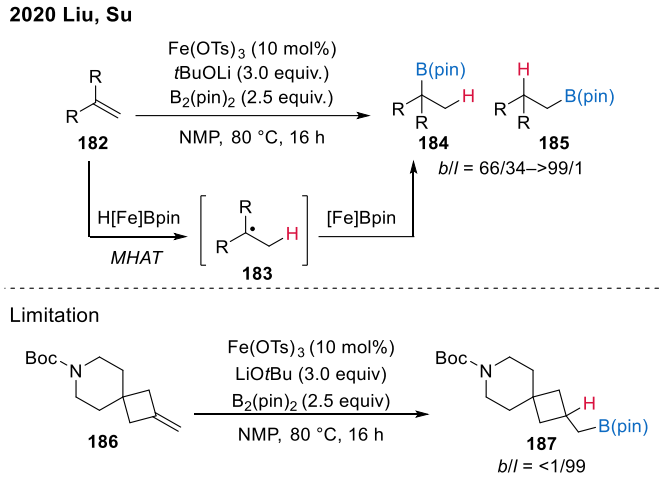
Scheme 2-2. Markovnikov hydroboration of unactivated trisubstituted alkenes

位置選択的にホウ素官能基を導入する手法として、アルキルラジカルをジボランと反応させることによるアルキルボロン酸エステル合成が報告されている。2017 年に Aggarwal らは、カルボン酸から誘導したレドックスアクティブエステル **179** から生成したアルキルラジカル **180** をビスカテコラートジボロンと反応させることにより、アルキルボロン酸エステル **181** が得られることを見出している(Scheme 2-3)[7]。これの報告に続いて様々なラジカル生成法を用いたホウ素化反応が報告されている[8]。このように、アルキルラジカルを活用することで、位置選択的にホウ素官能基の導入が可能となる。



Scheme 2-3. Regioselective boration using alkyl radical

不活性アルケンのラジカル的なマルコフニコフヒドロホウ素化反応の例として、2020 年に Liu、Su らは、鉄触媒による 1,1-2 置換アルケンのマルコフニコフヒドロホウ素化反応を報告した(Scheme 2-4)[9]。反応系中で生じる鉄ヒドリド種からのアルケン **182** に対する MHAT によりアルキルラジカル **183** が生成し、鉄ボリル種と反応することで、マルコフニコフヒドロホウ素化反応が進行すると想定されている。しかしながら、メチレンシクロブタン骨格 **186** を有する基質を用いた際には、選択性が逆転することから、基質によって反応メカニズムが変わっていることが示唆されており、さらに末端不活性アルケンを用いた場合には、選択性が低下することから、基質一般性に未だ課題を残していた。



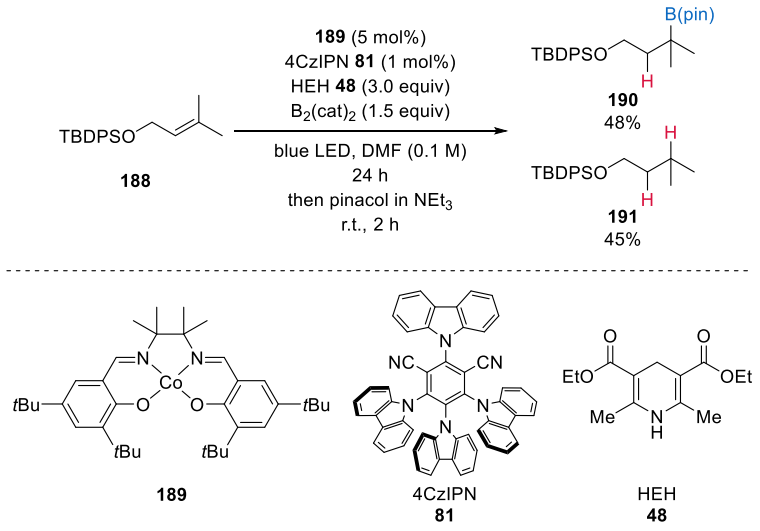
Scheme 2-4. Markovnikov hydroboration of unactivated alkenes via MHAT

これらの背景から私は、MHAT による位置選択的なアルキルラジカルの生成を活用した様々な置換パターンの不活性アルケンに対するマルコフニコフヒドロホウ素化反応を開発するべく、研究を行った。

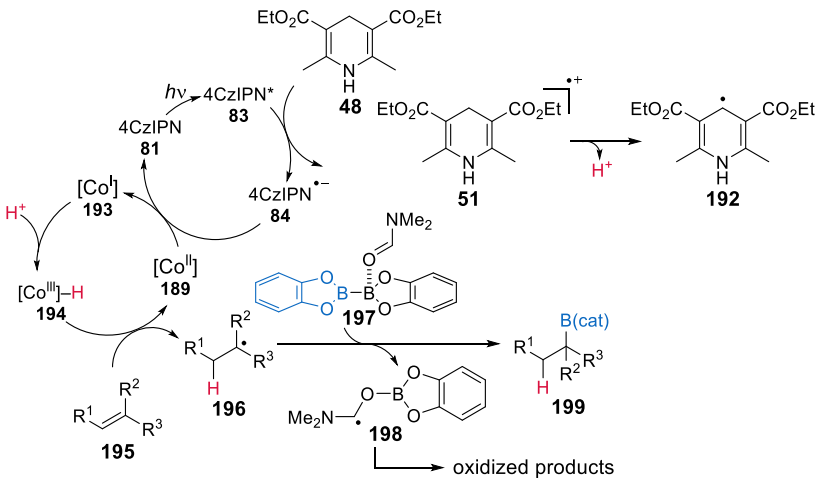
第 2 節　反応条件最適化

1.　初期検討と想定反応機構について

初期検討として、不活性 3 置換アルケン **188** を用い、コバルト触媒として **189**、光酸化還元触媒として 4CzIPN **81**、プロトン源かつ還元剤としてハンチュエステル(HEH **48**)、ホウ素化剤としてビスカテコラートジボロンを用い、DMF 溶媒中可視光照射下、反応を行い、反応後、ピナコールとトリエチルアミンで処理をすることで、目的のアルキルボロン酸ピナコールエステル **190** を収率 48%で得た。一方で、水素化体 **191** が収率 45%で得られた(Scheme 2-5)。ここで想定反応機構を以下に示す(Scheme 2-6)。光酸化還元触媒 **81** が可視光により励起され、励起種 **83** がハンチュエステル **48** による還元を受け、ラジカルアニオン種 **84** が生成する。これが 2 価のコバルト触媒 **189** を 1 電子還元することで、求核性を持ったコバルト(Ⅰ) **193** が生成する。これが反応系中に存在するプロトンを捕捉することにより、触媒活性種であるコバルト(Ⅲ)ヒドリド **194** が生成する。これがアルケン **195** へ MHAT を起こし、アルキルラジカル中間体 **196** が生成し、ビスカテコラートジボロン **197** と反応することで、目的のアルキルボロン酸エステル **199** が生成すると想定している。水素化体 **191** は生じたアルキルラジカルが HEH **48** の活性メチレンの水素原子をラジカル的に引き抜くことにより生じると想定した。



Scheme 2-5. Initial result

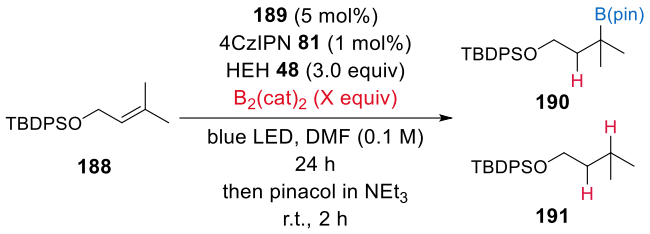


Scheme 2-6. Proposed mechanism

2.　ホウ素化剤の当量の検討

収率向上を目指し、ホウ素化剤の当量の検討を行った(Table 2-7)。ホウ素化剤の当量を増加させると収率は向上し、ホウ素化体を 5 当量用いた際に、収率 70%で目的のホウ素化体 **190** が得られたが、水素化体 **191** が未だ 19%得られた。これは、MHAT により生じる第 3 級アルキルラジカルが立体的に比較的かさ高いため、ビスカテコラートジボロンとの反応が遅く、副反応として、水素化反応が生じると考えている。

Table 2-7. Amount of $B_2(cat)_2$

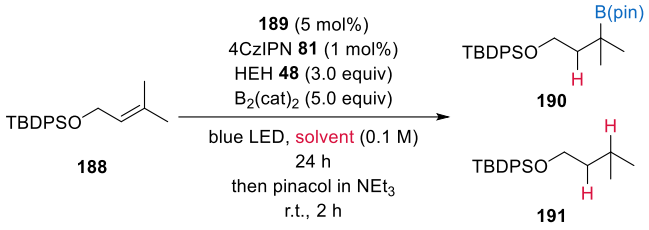


Entry	X	**190** (%)	**191** (%)
0	1.5	48	45
1	3.0	70	32
2	5.0	70	19

3.　溶媒の検討

次に溶媒の検討を行った(Scheme 2-8)。非プロトン性極性溶媒であるジメチルアセトアミド(DMA)や *N*-メチルピロリドン（NMP)を用いた際には、ホウ素化体 **190** の収率が低下し、水素化体 **191** の収率が増加した(entries 1,2)。ジメチルスルホキシド(DMSO)を用いた場合には、ほとんど反応が進行しなかった(entry 3)。アセトン、テトラヒドロフラン(THF)、トルエン、エタノールを用いた際には、基質 **188** が残存し、水素化体 **191** が主生成物として得られた(entrie 4-7)。クロロホルム($CHCl_3$)を用いると、反応はほとんど進行しなかった(entries 8)。DMF や DMA、NMP でしか反応が進行しなかった理由として、以下のことを想定している。MHAT により生じたアルキルラジカルがビスカテコラートジボロンと反応する時、非常に不安定なホウ素ラジカルが脱離をする必要があるため、熱力学的に反応の進行が不利になると考えられる。溶媒として DMF や DMA、NMP を用いることで、脱離するホウ素上にこれらの溶媒が配位し、生じるホウ素ラジカルが安定化されることで、熱力学的に反応が進行しやすくなると想定している。

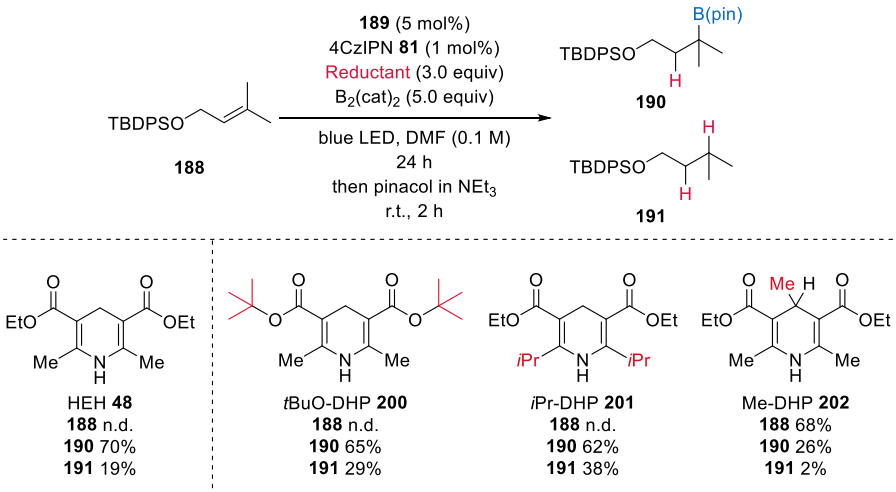
Table 2-8. Screening of solvent



Entry	solvent	**188** (%)	**190** (%)	**191** (%)
0	DMF	n.d.	70	19
1	DMA	n.d.	52	25
2	NMP	17	54	21
3	DMSO	74	trace	trace
4	Acetone	57	2	13
5	THF	56	3	26
6	Toluene	28	trace	57
7	EtOH	33	4	59
8	$CHCl_3$	85	trace	trace

4.　還元剤の検討

水素化体 **191** は生じたアルキルラジカルがハンチュエステルの活性メチレンの水素原子をラジカル的に引き抜くことにより生じると想定したため、ハンチュエステルの構造のチューニングを行った(Scheme 2-9)。ハンチュエステルのエチルエステル部分を *t*Bu エステルに変換したハンチュエステルや窒素原子近傍のメチル基をイソプロピル基に変更したハンチュエステル **200**、**201** を用いた際には、水素化反応の進行を抑えることができなかった。活性メチレンの水素をメチル基に置換したハンチュエステル **202** を用いた際には、基質 **188** が NMR 収率 68%で回収されたが、水素化体 **191** の生成が抑制された。これはメチル基を導入したことにより、活性メチン近傍の立体障害が増大したことによるものであると考察した。

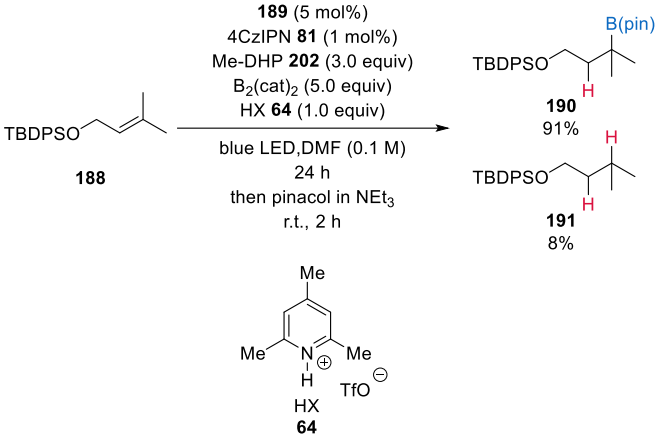


Scheme 2-9. Screening of reductant

5.　添加剤の検討

ハンチュエステルを変更した際に反応性が低下した理由として、ハンチュエステルへのメチル基の導入により、酸化されたハンチュエステルからの脱プロトン化が遅くなることで、反応系中のプロトン濃度が低下する。その結果、求核性のあるコバルト(Ⅰ)のプロトン化が進行しにくくなることにより、反応性

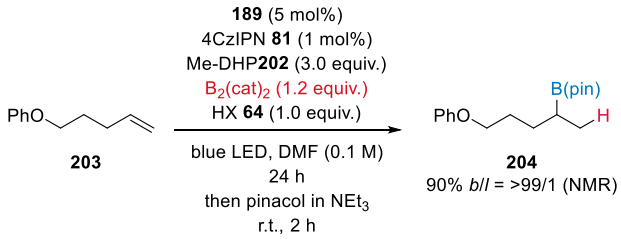
が低下したと考察した。そこで、プロトン源であるコリジニウムトリフラート **64** を 1 当量添加したところ、目的のホウ素化体が NMR 収率 91%で得られ、水素化体の生成は NMR 収率 8%まで抑制された（Scheme 2-10）。



Scheme 2-10. Addition of proton source

6.　不活性末端アルケンへの適用

上記の検討で得られた反応条件を基に不活性末端アルケンへの適用の検討を行った（Scheme 2-11）。末端アルケン **203** については、ビスカテコラートジボロンの当量を大幅に減らすことが可能であり、1.2 当量のビスカテコラートジボロンを用いて反応を行うと、NMR 収率 90%で目的のホウ素化体 **204** が得られた。

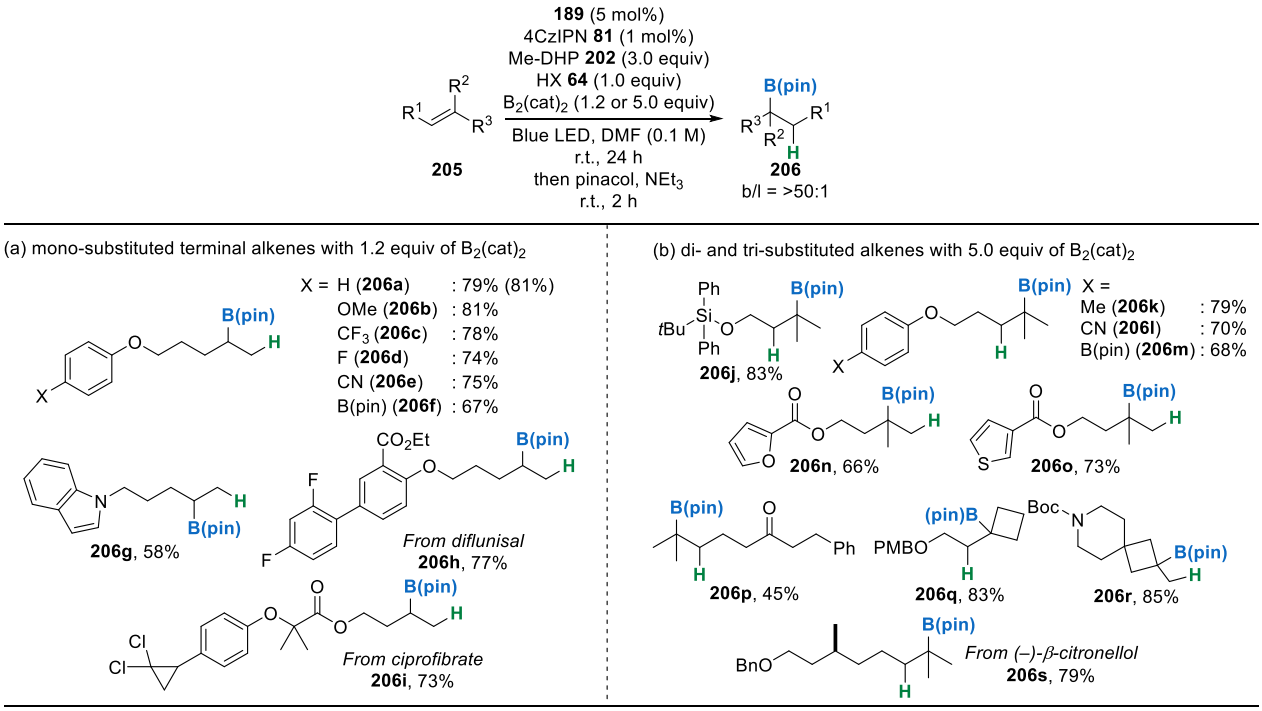


Scheme 2-11. Application to unactivated terminal alkene

第 3 節　基質適用範囲

得られた最適条件を基に基質適用範囲の検討を行った。まず不活性末端アルケンの基質適用範囲について示す(Scheme 2-12)。メトキシ基やトリフルオロメチル基、フルオロ基、シアノ基、ボロン酸ピナコールエステルを有する基質においても、良好な収率で目的のホウ素化体が得られた(**206a -206f**)。*N*-アルキルインドールを有する基質では、中程度の収率でホウ素化体が得られた(**206g**)。医薬品のジフルニサルやシプロフィブラートの誘導体においても問題なく反応が進行し、良好な収率で目的のホウ素化体を得た(**206h**, **206i**)。

次に不活性多置換アルケンの基質適用範囲について示す。メチル基やシアノ基、ボロン酸ピナコールエステルを有する基質において、良好な収率で目的のホウ素化体が得られた(**206k**-**206m**)。1,1-2 置換アルケンと複素環であるフランやチオフェンを有する基質でも、問題なく反応が進行した(**206n**, **206o**)。脂肪族ケトンを有する基質では、低収率ながら目的のホウ素化体が得られた(**206p**)。シクロブタン骨格を有する基質を用いた際には、問題なく反応が進行し、良好な収率で目的のホウ素化体が得られた(**206q**, **206r**)。天然物である β-シトロネロールの誘導体においても問題なく反応が進行した(**206s**)。

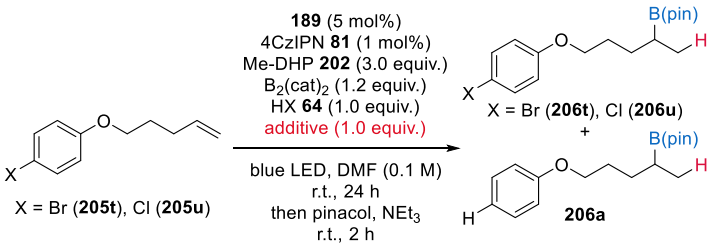


Scheme 2-12. Substrate scope

基質適用範囲の調査を行っている際に、ブロモ基を有する基質で反応を行うと、目的のホウ素化体は収率 46%得られた一方で、脱ハロゲン化が進行し、かつホウ素化反応も進行した脱ハロゲン化体が収率 41%で得られた(entry 0)。脱ハロゲン化反応が進行した原因について、MHAT により生じたアルキルラジカルがビスカテコラートジボロンと反応した際に、電子豊富なラジカル種が生成し、この電子豊富なラジカル種が、ブロモアリールからハロゲン原子引き抜きを引き起こしているのではないかと想定した。このハロゲン引き抜き反応を防ぐために、犠牲試薬の検討を行った(Scheme 2-13)。ブロモベンゼンを 1 当量添加した場合には、十分な効果が得られなかった(entry 1)。*t*BuBr を添加した場合には、NMR 収率 81%で目的のホウ素化体が得られたが、未だ水素化体が NMR 収率 8%生成した(entry 2)。ヨードベンゼンを添

加した際に、ほぼ完全に基質からの脱ハロゲン化が抑制され、良好な収率で目的のホウ素化体を得た(entry 3)。クロロ基を有する基質においても同様の結果が得られ、良好な収率で目的のホウ素化体を得た(entry 4, 5)。

Table 2-13. Screening of sacrificial reagents



Entry	additive	X	yield (%) **206a** (%)	
0	none	Br	46	41
1	PhBr	Br	73	22
2	*t*BuBr	Br	81	7
3	PhI	Br	86 (74)	n.d.
4	none	Cl	59	7
5	PhI	Cl	80 (81)	n.d.

第 4 節　位置選択性の決定について

MHAT による不活性末端アルケン、不活性多置換アルケンのマルコフニコフヒドロホウ素化反応について、マルコフニコフ選択的に反応が進行していることを確認するため、不活性末端アルケン **205a** と不活性 3 置換アルケン **205k** を用い、それぞれのアンチマルコフニコフ体の標品を合成し、^{1}H NMR 及び GCMS を用い、位置選択性の確認を行った。末端不活性末端アルケン **205a** のマルコフニコフ体 **206a** の粗生成物とアンチマルコフニコフ体 **206a'**の ^{1}H NMR チャートの比較を行ったところ、アンチマルコフニコフ体に特有の 0.75-0.90 ppm 付近のピークは全く見られなかった(Figure 2-14)。次に GCMS による解析を行った。単離した不活性末端アルケン **205a** のマルコフニコフ体 **206a** は保持時間 17.172 min にピークが見られ、アンチマルコフニコフ体 **206a'**は保持時間 17.727 min にピークが見られた。またそれぞれのホウ素化体に対応する MS のフラグメントピークを得た(Figures 2-15~18)。不活性末端アルケン **205a** のマルコフニコフ体 **206a** の粗生成物を GCMS で解析を行ったところ、マルコフニコフ体 **206a** のピークが保持時間 17.168 min に見られ、単離した不活性末端アルケン **205a** のマルコフニコフ体 **206a** の保持時間と MS のフラグメントピークが一致していることを確認した。アンチマルコフニコフ体 **206a'**のピークが 17.719 min にごく少量見られたが、マルコフニコフ体 **206a** とアンチマルコフニコフ体 **206a'**の GC の面積比は 588/1 であったため、無視できる量しか生成していないと判断した(Figures 2-19~21)。これらの結果から、マルコフニコフ体 **206a** が選択的に生成していると結論付けた。

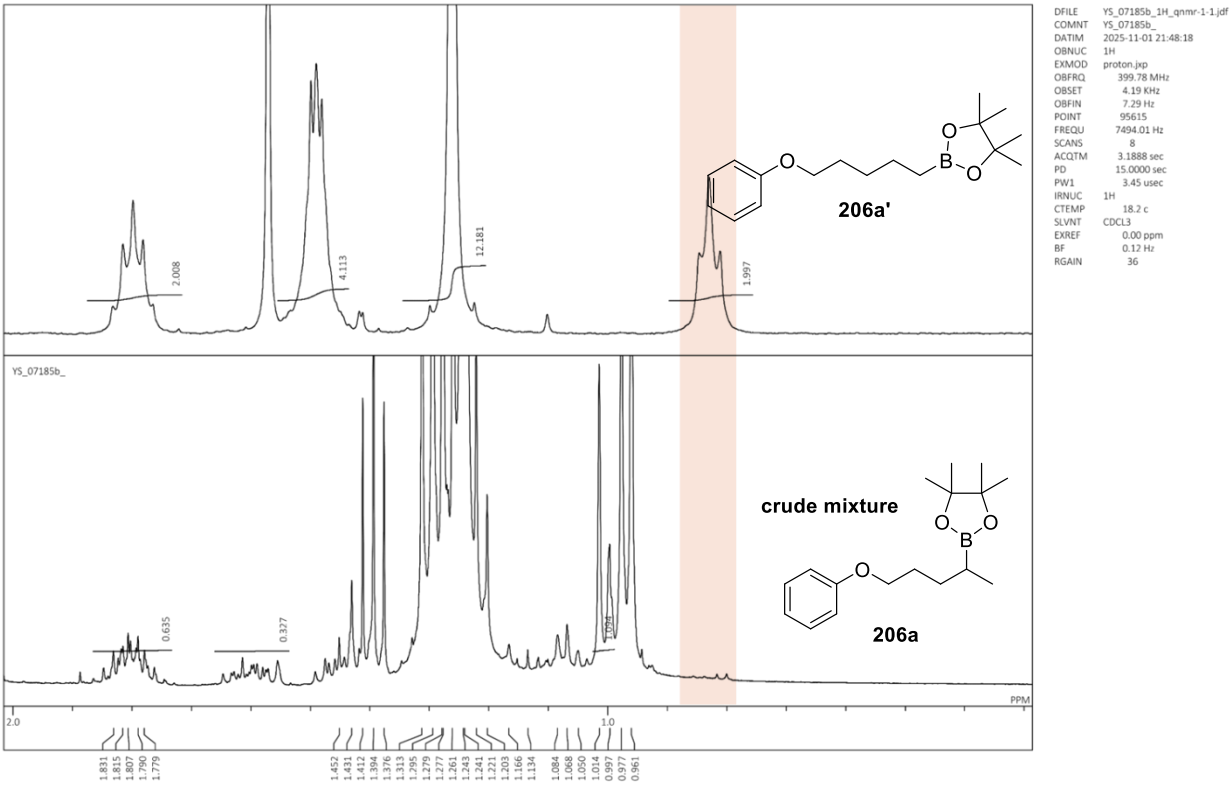


Figure 2-14. Comparison of the ^{1}H NMR spectra of the *anti*-Markovnikov product **206a'**and **206a** in crude mixture.

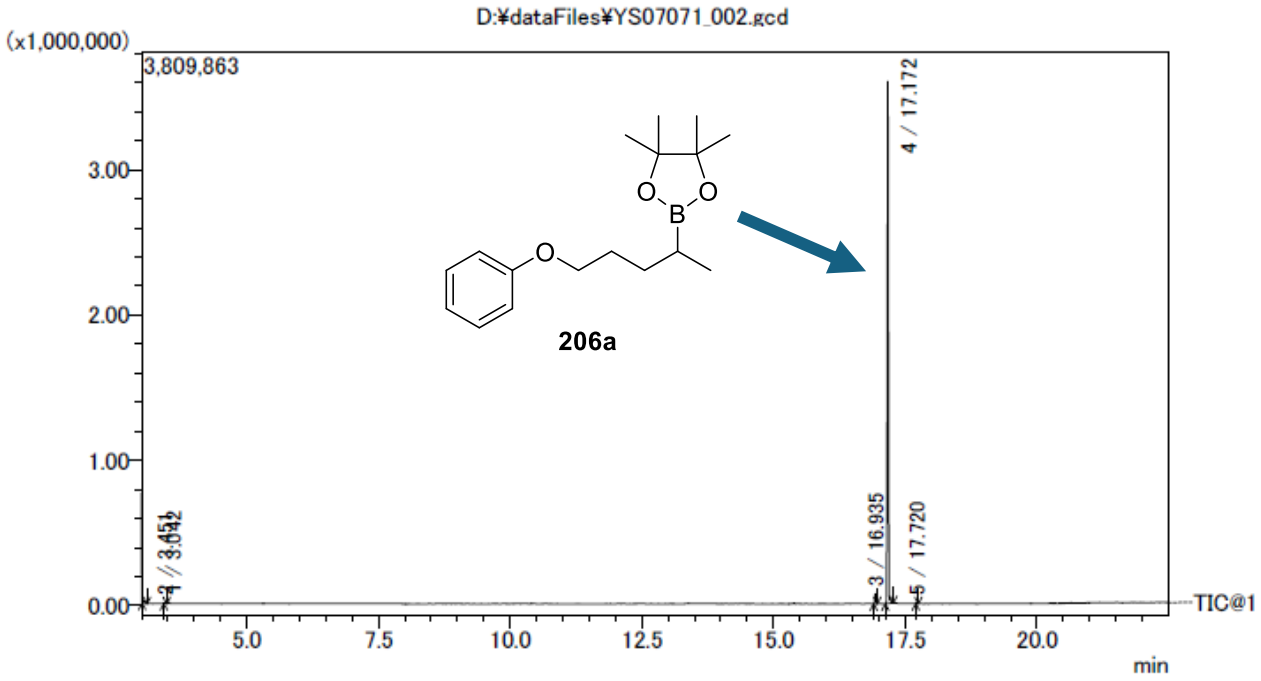


Figure 2-15. GS-MS chromatogram of isolated **206a**.

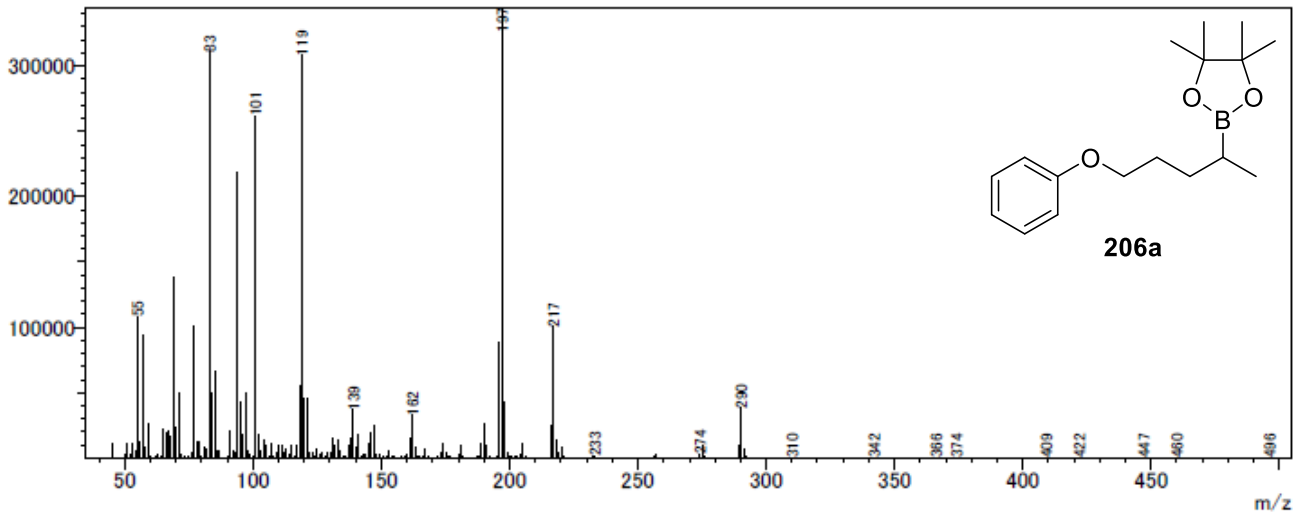


Figure 2-16. Mass spectrum of isolated **206a** (retention time: 17.172 min).

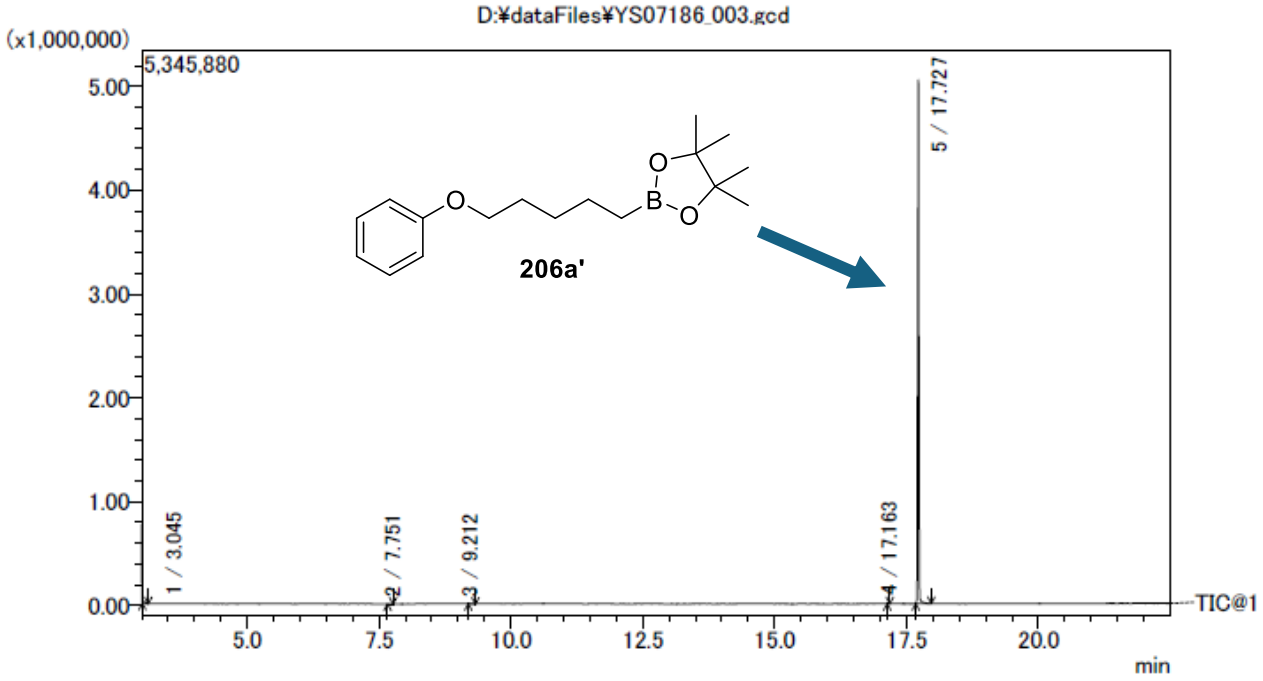


Figure 2-17. GC-MS chromatogram of isolated *anti*-Markovnikov product **206a'**

.

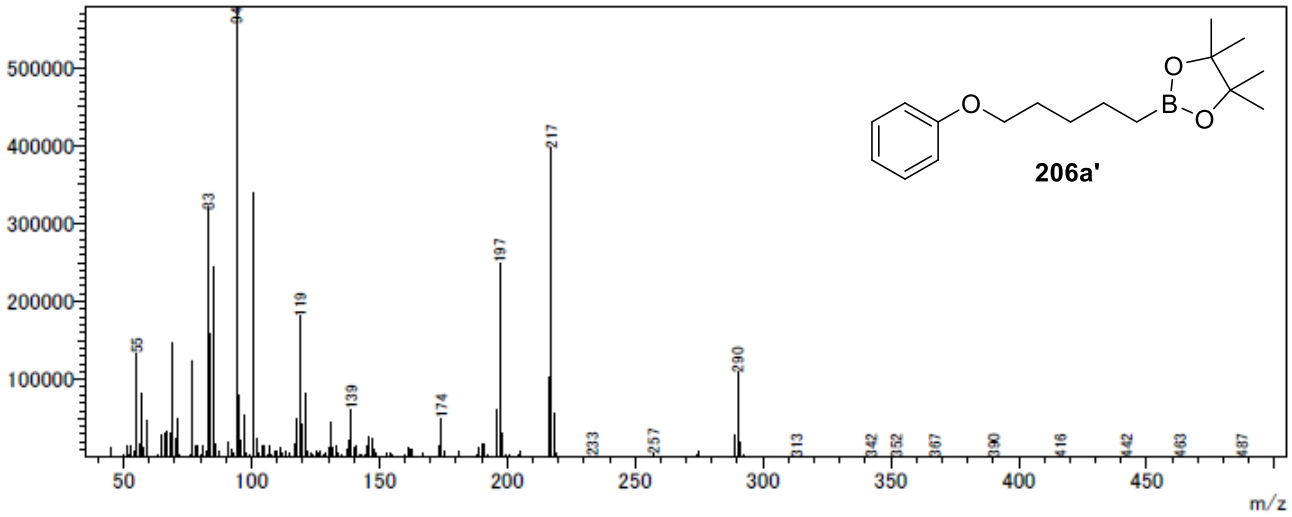
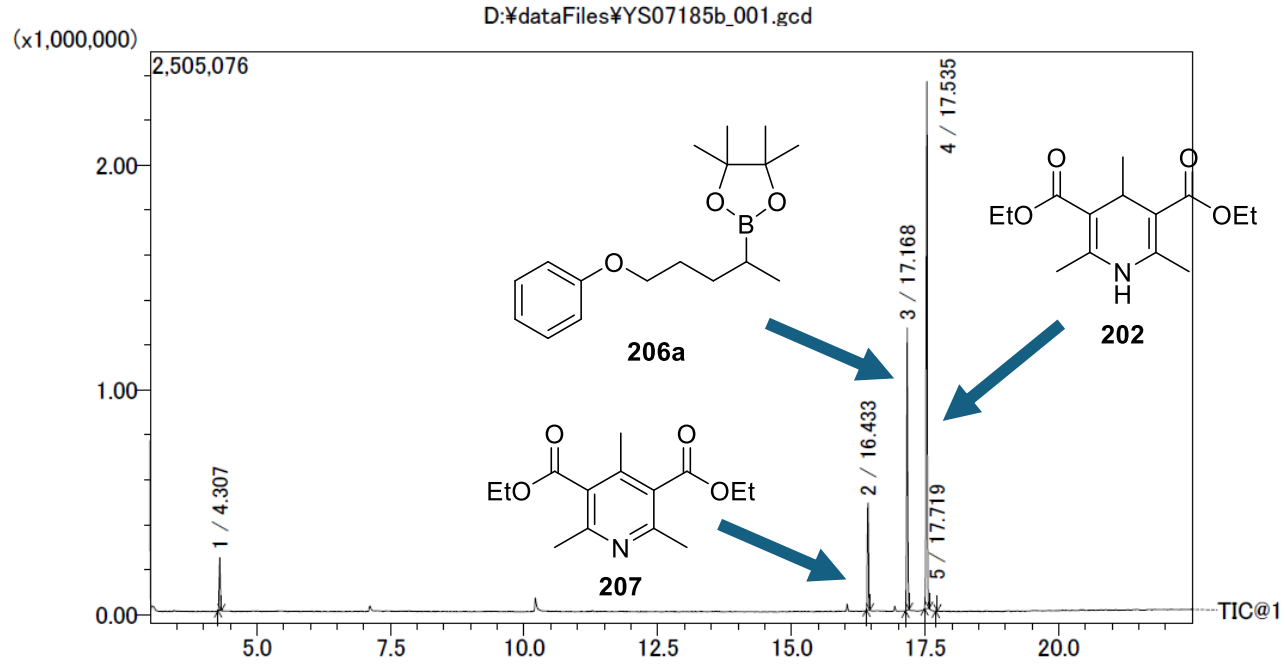


Figure 2-18. Mass spectrum of *anti*-Markovnikov product **206a'** (retention time: 17.727 min).



peak No.　Rt.　area

ピーク#	保持時間	m/z	面積	マーク	化合物名	A/H	イベント#
1	4.307	TIC	361942			1.523	1-1
2	16.433	TIC	666803			1.400	1-1
3	17.168	TIC	1728502			1.377	1-1
4	17.535	TIC	3517114			1.499	1-1
5	17.719	TIC	2940	M		1.032	1-1
合計 total			6277301				

Figure 2-19. GC-MS chromatogram of **206a** in crude mixture.

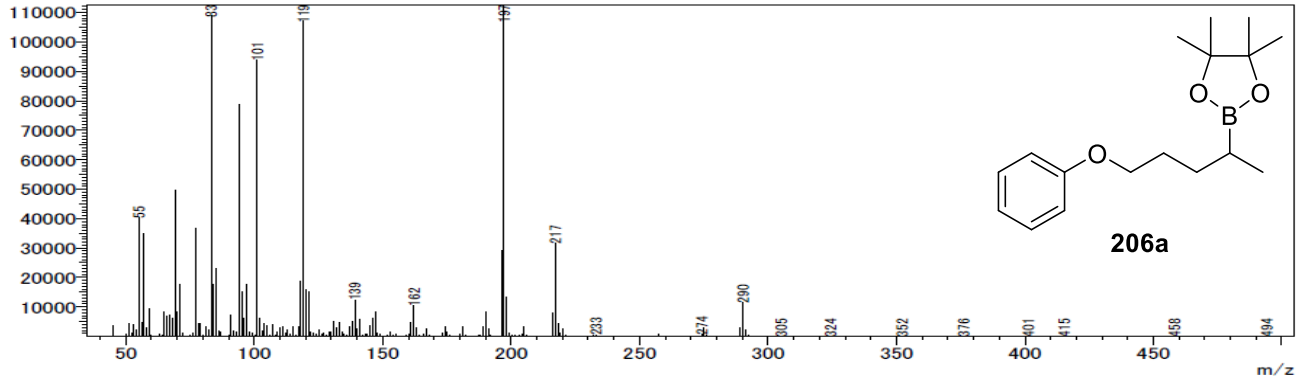


Figure 2-20. Mass spectrum of **206a** in crude mixture (retention time: 17.168 min).

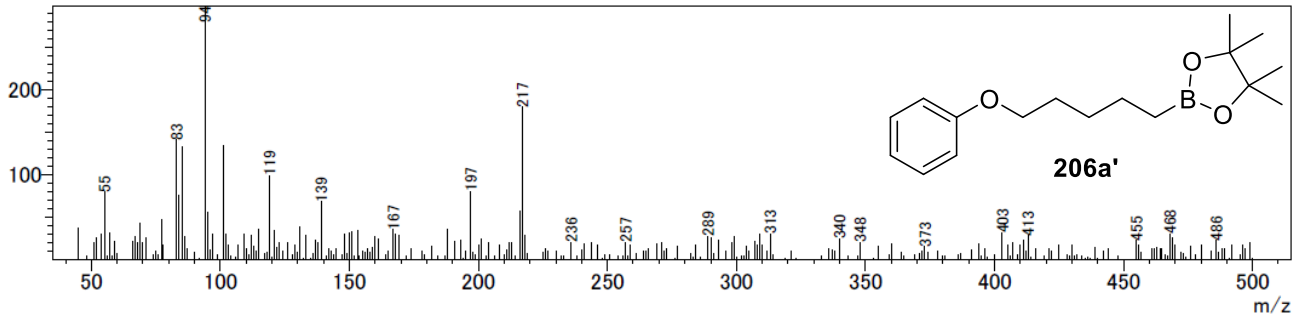


Figure 2-21. Mass spectrum of *anti*-Markovnikov product **206a'** in crude mixture (retention time: 17.719 min).

不活性 3 置換アルケン **205k** についても同様の比較を行った。不活性 3 置換アルケン **205k** のマルコフニコフ体 **206k** の粗生成物とアンチマルコフニコフ体 **206k'**の ^{1}H NMR チャートの比較を行い、アンチマルコフニコフ体に特有のピークは全く見られなかった(Figures 2-22~24)。次に GCMS による解析を行った。不活性 3 置換アルケン **205k** のマルコフニコフ体 **206k** は保持時間 17.934 min にピークが見られ、アンチマルコフニコフ体は保持時間 18.053 min にピークが見られた。またそれぞれのホウ素化体の MS のフラグメントピークを得た(Figures 2-25~29)。不活性 3 置換アルケン **205k** のマルコフニコフ体 **206k** の粗生成物を GCMS で解析を行ったところ、マルコフニコフ体 **206k** のピークが保持時間 17.947 min に見られ、アンチマルコフニコフ体 **206k'**のピークは全く観測されなかった。またマルコフニコフ体 **206k** の MS のフラグメントピークも一致した(Figure 2-30, 31)。これらの結果から、不活性 3 置換アルケン **205k** においてもマルコフニコフ体が選択的に得られていると結論付けた。

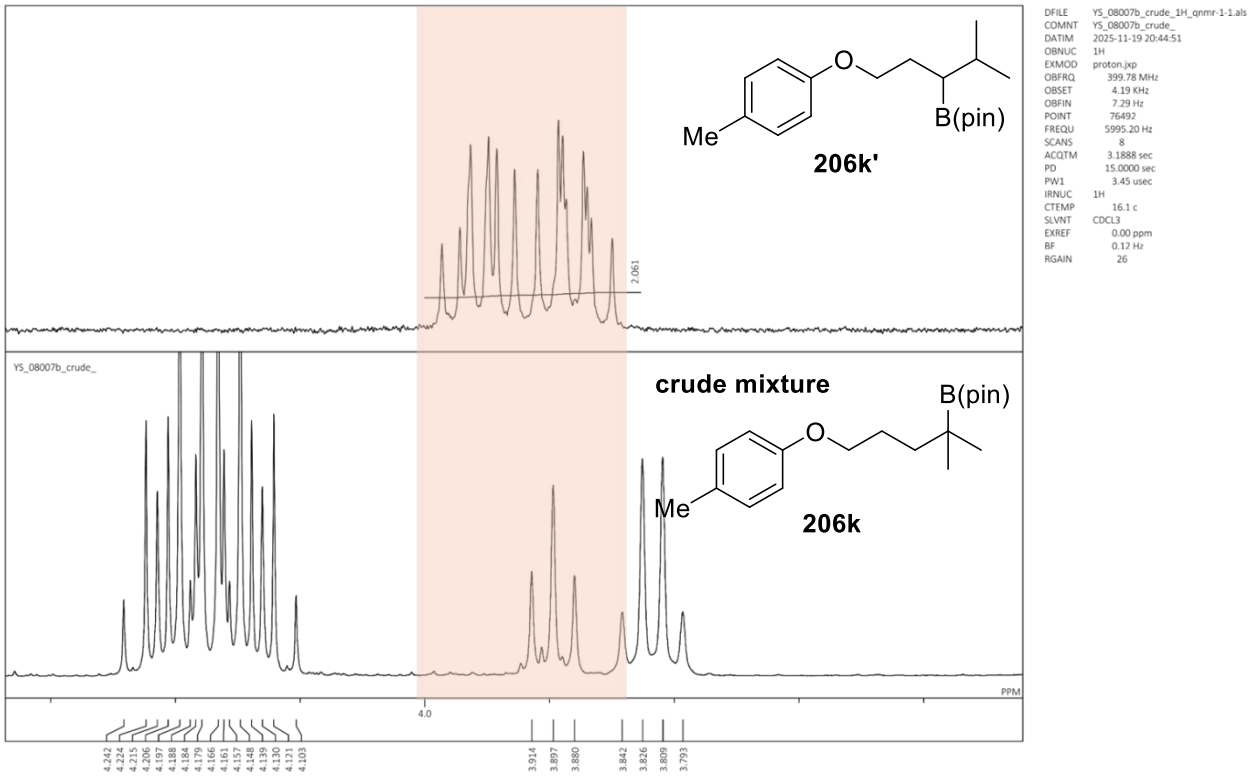


Figure 2-22. Comparison of the ^{1}H NMR spectra of the *anti*-Markovnikov product **206k'** and **206k** in crude mixture.

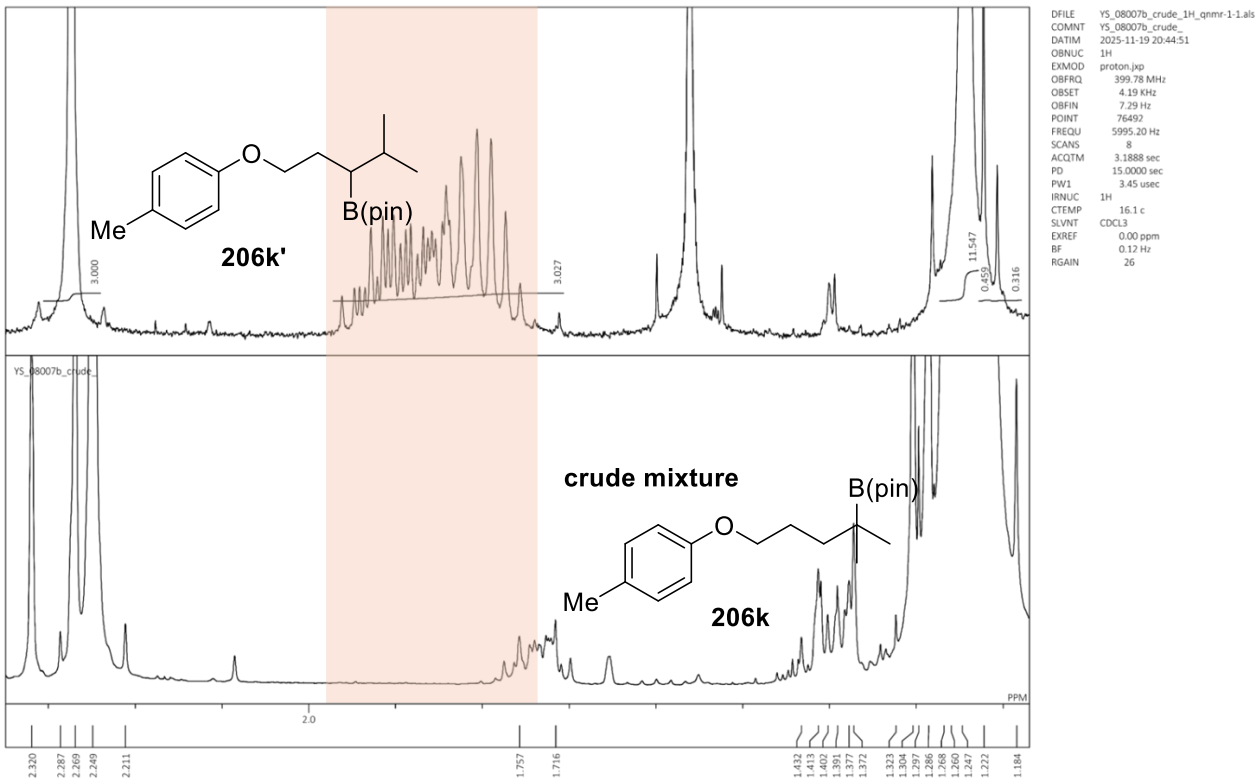


Figure 2-23. Comparison of the ^{1}H NMR spectra of the *anti*-Markovnikov product **206k'** and **206k** in crude mixture.

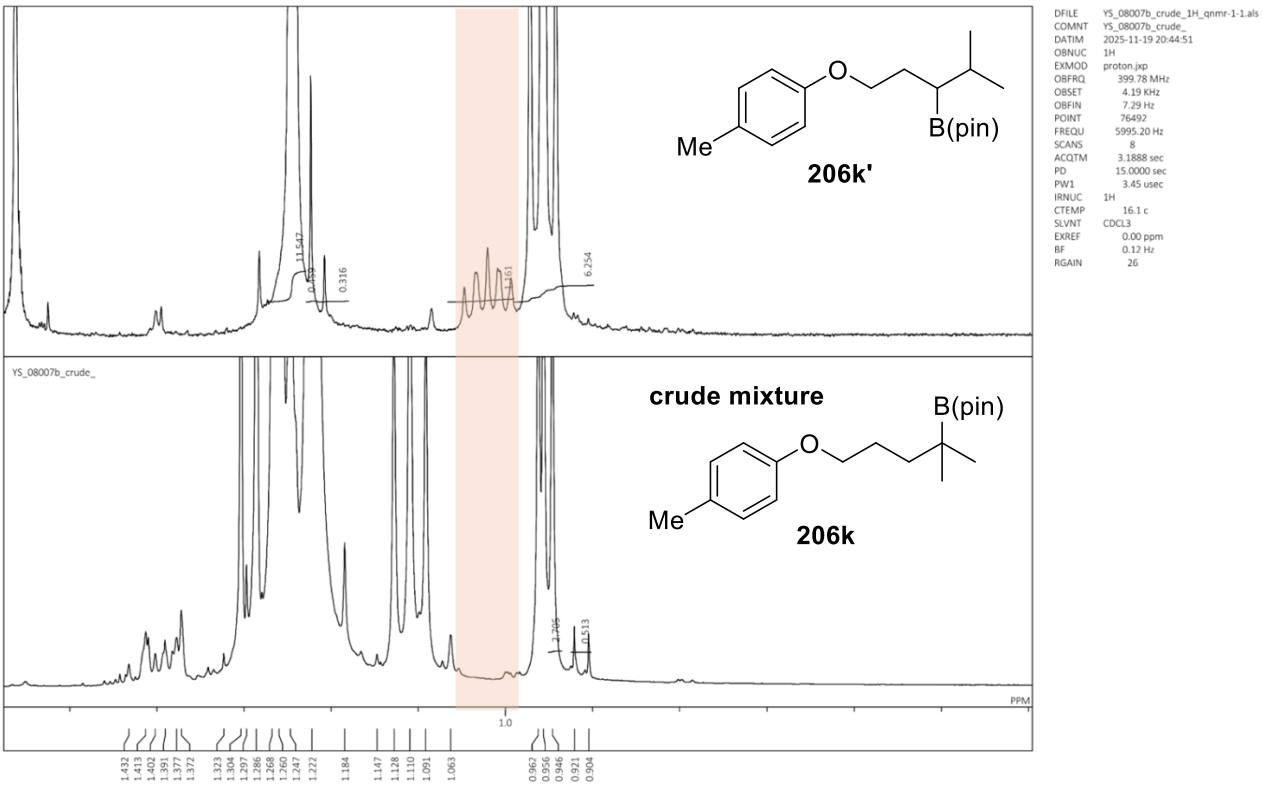


Figure 2-24. Comparison of the ^{1}H NMR spectra of the *anti*-Markovnikov product **206k'** and **206k** in crude mixture.

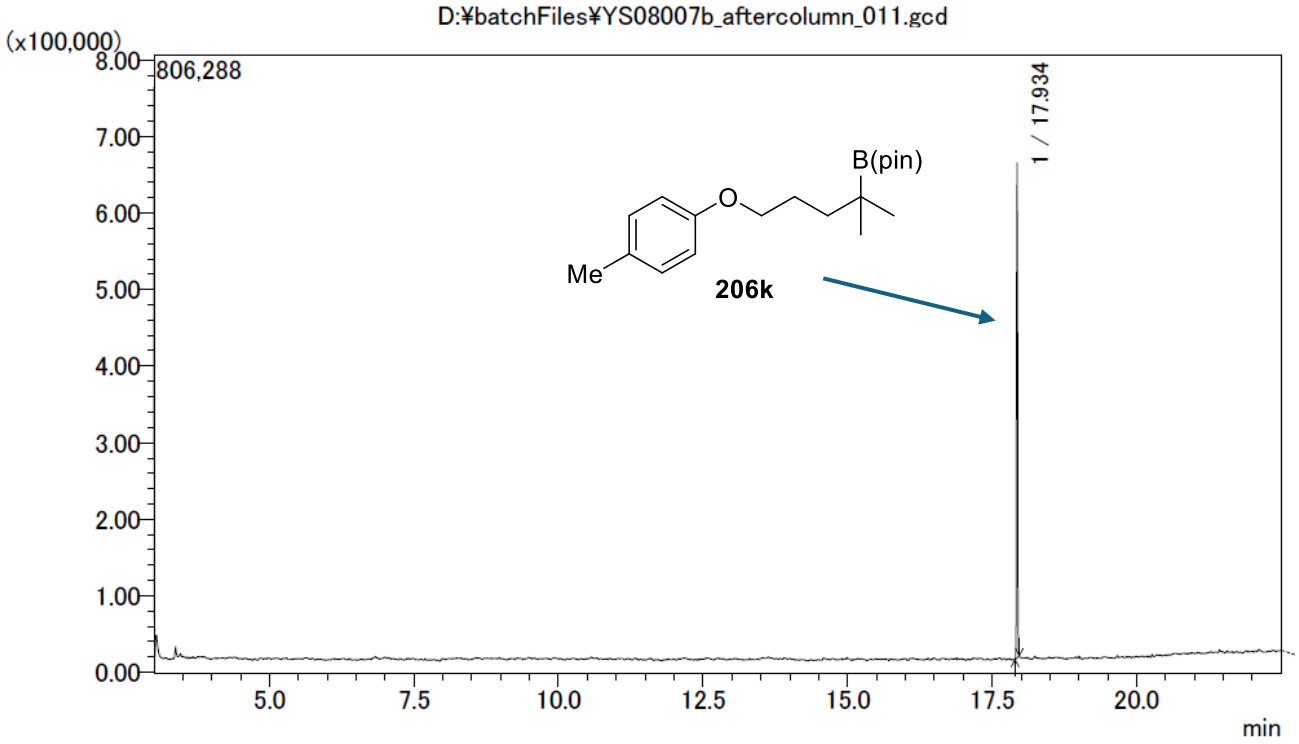


Figure 2-25. GC-MS chromatogram of isolated **206k**

.

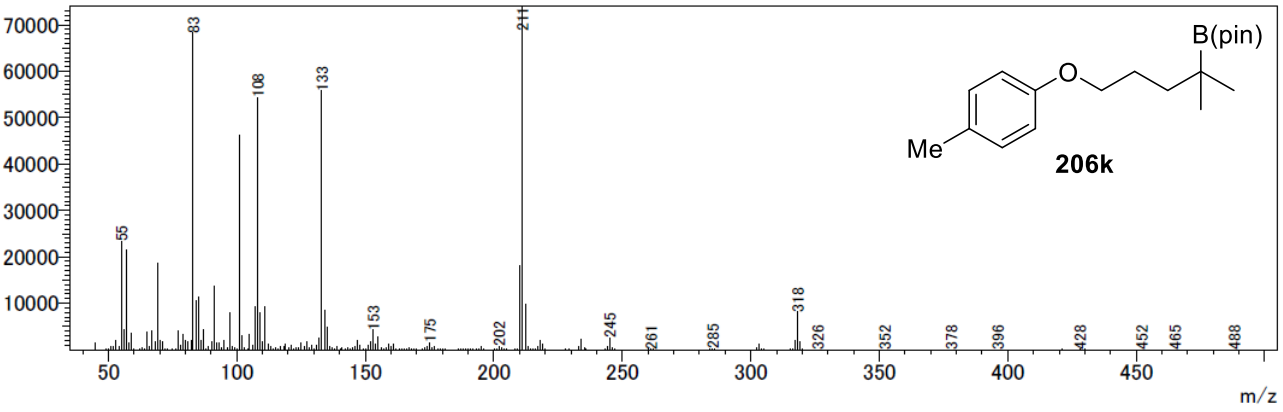
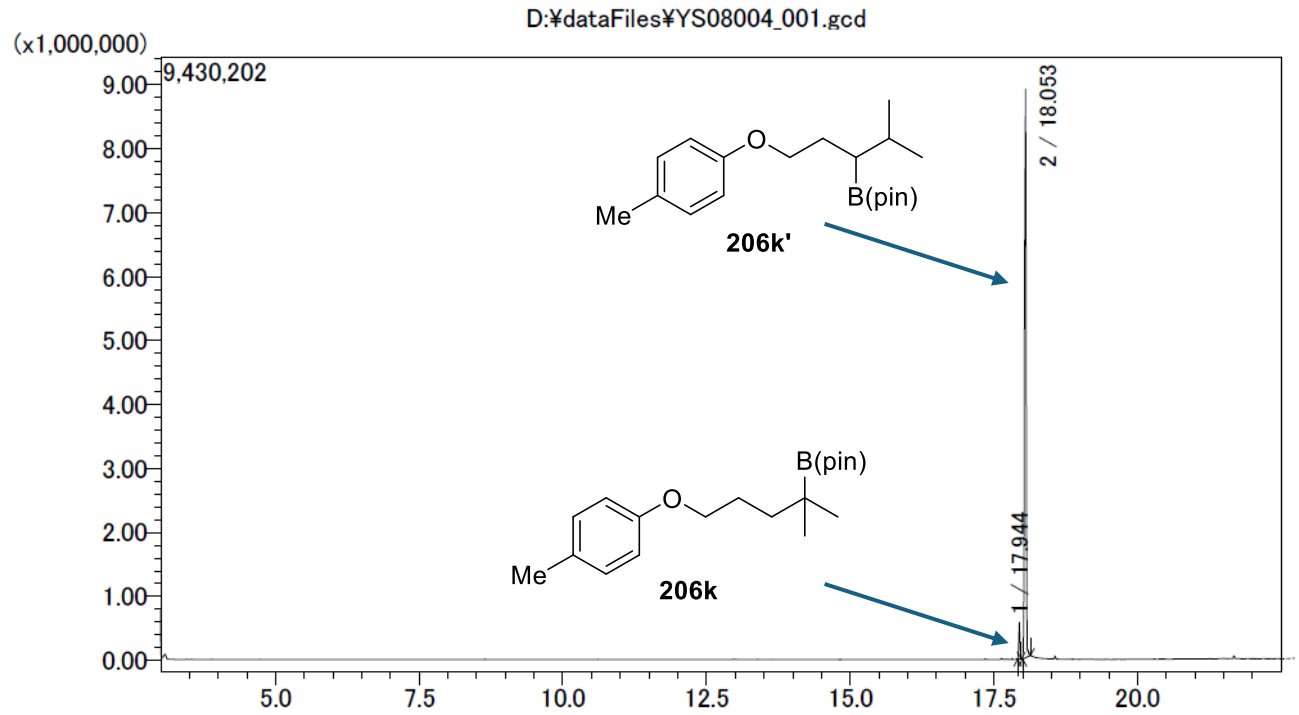


Figure 2-26. Mass Spectrum of isolated **206k** (retention time: 17.934 min).



peak No.	Rt.		area				
ピーク#	保持時間	m/z	面積	マーク	化合物名	A/H	イベント#
1	17.944	TIC	815254			1.401	1-1
2	18.053	TIC	18179979			2.045	1-1
合計			18995233				
total							

Figure 2-27. GC-MS chromatogram of isolated *anti*-Markovnikov product **206k'**.

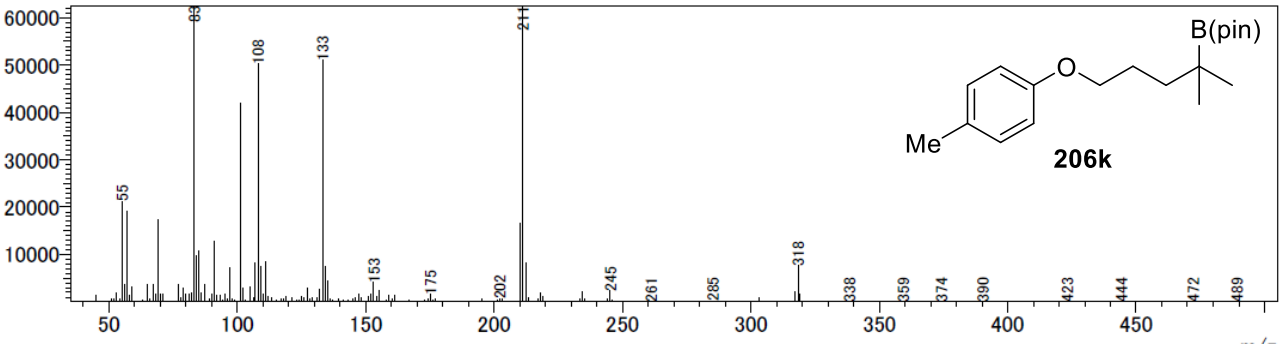


Figure 2-28. Mass spectrum of Markovnikov product **206k** (retention time: 17.944 min).

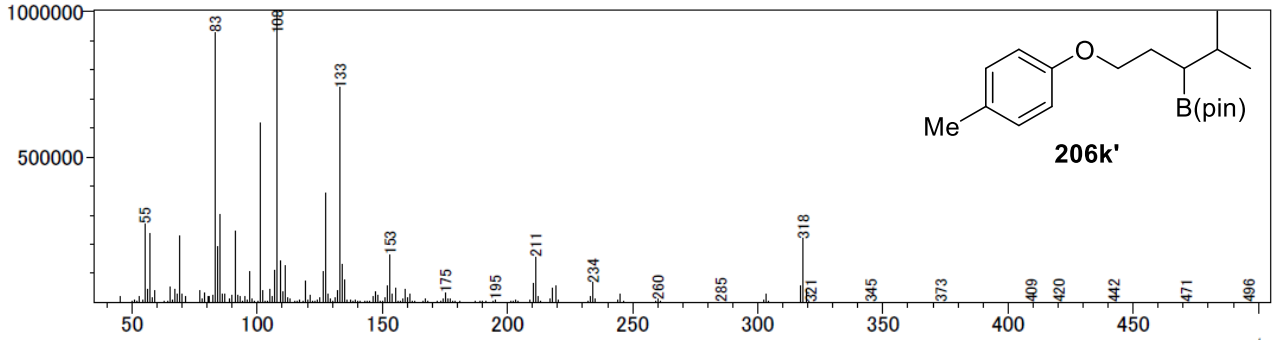


Figure 2-29. Mass Spectrum of *anti*-Markovnikov product **206k'** (retention time: 18.053 min).

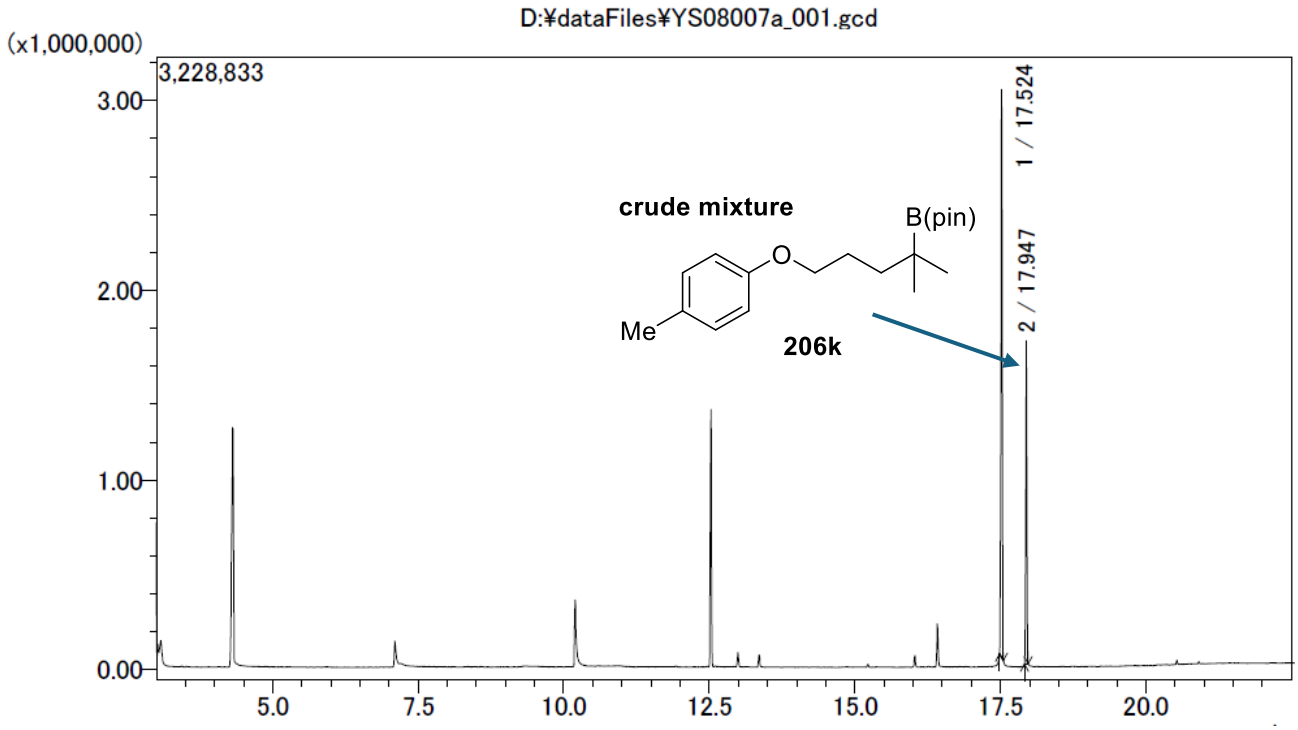


Figure 2-30. GC-MS chromatogram of **206k** in crude mixture.

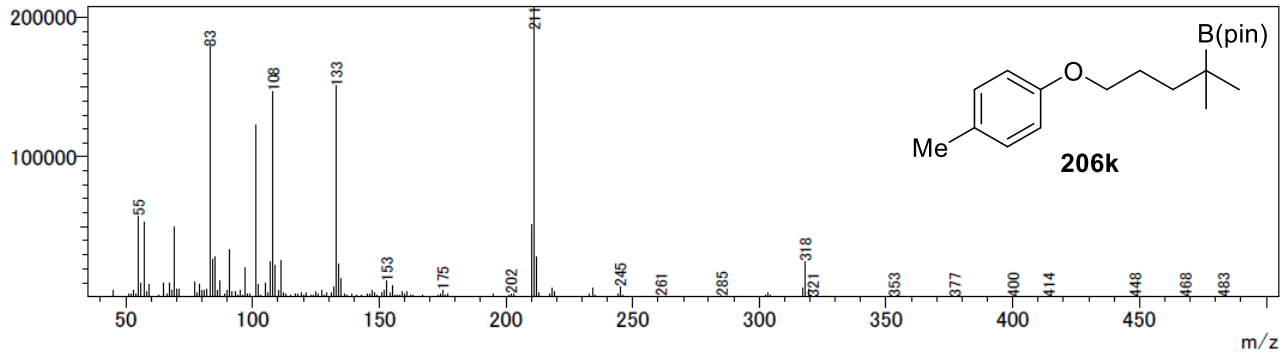
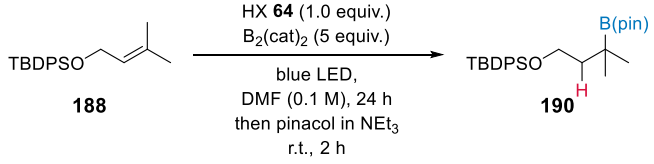


Figure 2-31. Mass spectrum of **206k** in crude mixture (retention time: 17.947 min).

第 5 節　コントロール実験

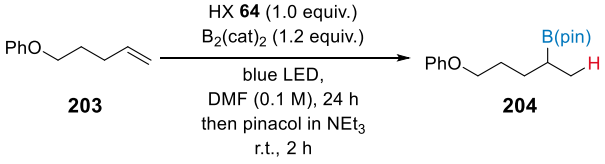
コントロール実験を行った。まず不活性多置換アルケン **188** を用いてコントロール実験を行った(Scheme 2-32)。コバルト触媒非存在下では、全く反応は進行しなかった(entry 1)。光酸化還元触媒非存在下では、低収率ながらホウ素化体 **190** が得られた(entry 2)。遮光下では、全く反応は進行しなかった(entry 3)。プロトン源非存在下では、大幅に収率が低下した(entry 4)。一方で、犠牲還元剤非存在で反応を行った際に、存在下よりも若干収率が低下したものの、NMR 収率 85%で目的物が得られた(entry 5)。次に不活性末端アルケン **203** を用いてコントロール実験を行った(Scheme 2-33)。コバルト触媒非存在下では、全く反応は進行しなかった(entry 1)。光酸化還元触媒非存在下では、NMR 収率 85%でホウ素化体 **204** が得られたが、存在下よりも収率は低下した(entry 2)。遮光下では、全く反応は進行しなかった(entry 3)。プロトン源非存在下では、大幅に収率が低下した(entry 4)。一方で、犠牲還元剤非存在で反応を行った際に、存在下よりも収率が低下したものの、NMR 収率 64%で目的物が得られ、アルケンの異性化体が ^{1}H NMR にて観測された(entry 5)。犠牲還元剤非存在下で反応が進行した理由として、アルキルラジカルがビスカテコラートジボロンに付加した際に生じる DMF によって安定化されたホウ素ラジカルが、還元剤として働いたため、反応が進行したと想定している。ビスカテコラートジボロンの当量が少ない不活性末端アルケン **203** の反応条件では、高い反応性を有すると考えられる DMF によって安定化されたホウ素ラジカルが、反応系中のビスカテコラートジボロンを分解することで、アルキルラジカルとビスカテコラートジボロンとの反応が遅くなり、副反応であるアルケンの異性化反応がホウ素化反応に競合し、収率が低下したと想定している。Me-DHP を添加することによって、コバルト(Ⅲ)ヒドリドの生成が Me-DHP により効率的に進行し、短時間でアルキルラジカル種を生成させ、速やかにビスカテコラートジボロンと反応させることが可能となるため、良好な収率でホウ素化体 **204** が得られたと想定している。

Table 2-32. Control experiment of unactivated trisubstituted alkene



entry	deviation	**188** (%)	**190**(%)
0	-	N.D.	90
1	Without Co cat.	93	N.D.
2	Without PC	50	27
3	Without blue LED	90	N.D.
4	No HX	68	26
5	No Me-DHP	N.D.	85

Table 2-33. Control experiment of unactivated terminal alkene

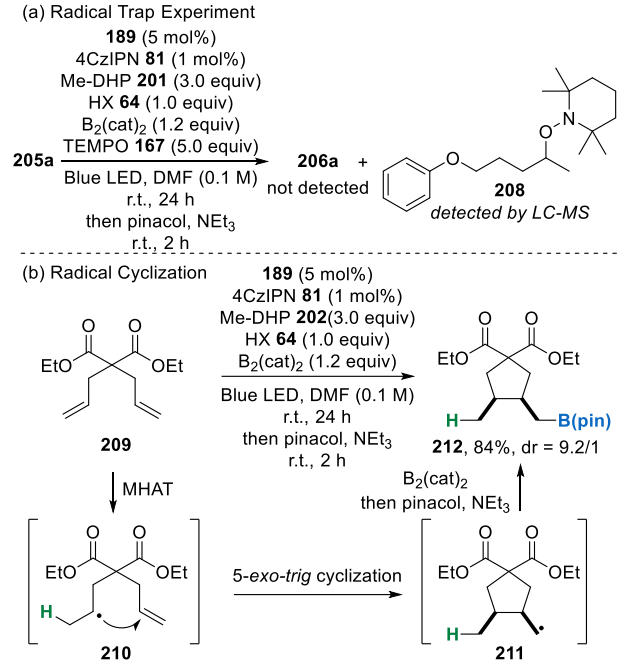


entry	deviation	**203** (%)	**204** (%)
0	-	N.D.	90
1	Without Co cat.	95	N.D.
2	Without PC	20	76
3	Without blue LED	90	N.D.
4	No HX	59	22
5	No Me-DHP	N.D.	64

第 6 節　反応機構に関する実験

反応機構について知見を得るために、TEMPO を用いたラジカル捕捉実験を行った(Scheme 2-34(a))。その結果、MHAT により生じたアルキルラジカル中間体が TEMPO と反応した TEMPO 付加体 **208** が LCMS にて観測された。このことから、MHAT によるアルキルラジカル中間体の生成が示唆された。

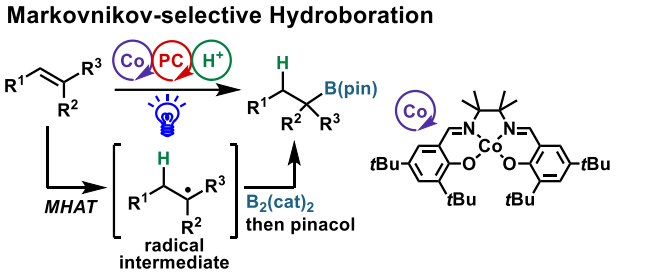
次に、ジアリルマロネート **209** を用いたラジカル環化実験を行った(Scheme 2-34(b))。その結果、MHAT により生じたアルキルラジカル **211** が 5-exo-trig 環化を起こし、生じた第 1 級アルキルラジカルがビスカテコラートジボロンと反応し、生じた第 1 級アルキルラジカル **211** がホウ素化された化合物 **212** が収率 84%で得られた。このことからも、MHAT によるアルキルラジカル中間体の生成が示唆された。ジアリルマロネート **209** を用いたラジカル環化反応ではシス体が主生成物であることや [10]、副生成物であるトランス体が ^{1}H NMR で確認できたことから [11]、この環化/ホウ素化反応においてもシス体が主生成物であると考えている。



Scheme 2-34. Radical Trap Experiment and Radical Cyclization

第 7 節　小括

ここまでの内容について小括する。筆者は、コバルトサレン触媒と光酸化還元触媒の協働による MHAT を用いた様々な置換パターンを持つ不活性アルケンのマルコフニコフヒドロホウ素化反応を開発した。MHAT を用いた位置選択的なアルキルラジカル生成を活用することで、不活性末端アルケン、不活性 1,1-2 置換アルケン、不活性 3 置換アルケンいずれにおいても完全なマルコフニコフ選択性でヒドロホウ素化反応が進行することを見出した。本成果は論文として、査読付き国際学術誌に投稿中である。



第 8 節　実験項

Contents

1. General information

Reactions were carried out under argon atmosphere unless otherwise noted. All non-aqueous reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted or in an argon-filled glove box. NMR spectra were recorded on JEOL JNM-ECZ400 spectrometers operating at 399.78 MHz for ^{1}H NMR and 100.53 MHz for ^{13}C{^{1}H} NMR, and 376.13 MHz for ^{19}F NMR, JEOL JNM-ECZ600 spectrometers operating at 190.63 MHz for ^{11}B{^{1}H} NMR. NMR tubes (super grade, Cat. No. 96938-02, borosilicate glass) were purchased from Kanto Chemical Co., Inc.. A broad signal derived from boron species in the NMR tube was observed at around 20 to –20 ppm in the ^{11}B{^{1}H} NMR spectra. Chemical shifts were reported in the scale relative to TMS (0.00 ppm for ^{1}H NMR in $CDCl_3$), $CHCl_3$ (7.26 ppm for ^{1}H NMR in $CDCl_3$), $CDCl_3$ (77.16 ppm for ^{13}C{^{1}H} NMR in $CDCl_3$), acetonitrile-d_3 (1.32 ppm for ^{13}C{^{1}H} NMR in acetonitrile-d_3), $PhCF_3$ (–62.96 ppm for ^{19}F NMR in $CDCl_3$), and C_6H_5F (–112.9 ppm for ^{19}F NMR in $CDCl_3$) as an internal reference, respectively. High resolution mass spectra (HRMS) were measured on Shimadzu LCMS-9030. Gas Chromatography Mass spectrometry (GC-MS) was measured on Shimadzu GCMS-QP2025. Liquid Chromatography Mass Spectrometry (LC-MS) was measured on Shimadzu LCMS-2020. Infrared (IR) spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrophotometer. Column chromatography was performed with silica gel Kanto Silica gel 60 N (40-50 mesh) or Yamazen YFLC AI-580 using Universal Column SiOH. TLC analysis was carried out on Wako Silicagel 70 F254 plates.

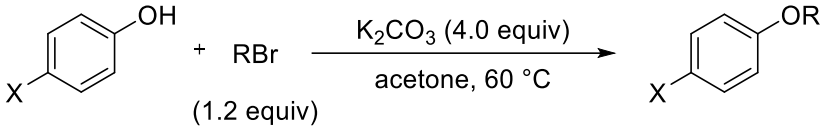
Dichloromethane (DCM), tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene were purified by Glass Contour solvent purification system (Nikko Hansen & Co., Ltd.,). Acetone (Super Dehydrated: 014-23461) and ethanol (Super Dehydrated: 014-23461) were purchased from Fujifilm Wako Pure Chemical Co.. 3,5-Diethoxycarbonyl-1,4-dihydro-2,4,6-collidine and Bis(pinacolate)diboron ($B_2(pin)_2$) were purchased from Tokyo Chemical Industry Co., Ltd. Bis(catecolate)diboron ($B_2(cat)_2$) were purchased from BLD Pharmatech Ltd.. All commercially available reagents were used as received unless otherwise noted. 4 mL glass vials (Cat. No. 1030-61060) and screw caps with a septum (Cat. No.1030-51261) were purchased from GL Sciences. Photo-irradiation was performed with A160WE TUNA Blue (purchased from Kessil; Wavelength of peak intensity = 456 nm) as a photon source, and the blue LED was equipped with PhotoRedOx Box Duo (EvoluChemTM).

Pinacol and triethylamine solution was prepared according to Baran's procedure.[12] Pinacol was added to a　100 mL round-bottom flask and dissolved in toluene, and the solvent was removed under reduced pressure. Pinacol was dried by repeating this process three times. The pinacol was further dried under high vacuum until it became crystalline, at which point it was weighed, evacuated, placed under argon gas, and then dissolved in distilled triethylamine.

Collidine triflate was prepared according to reported procedure.[13]

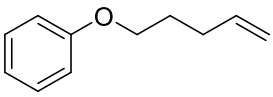
2. Substrate Preparation

General Procedure for Preparing 205a-f,k-m,t-u



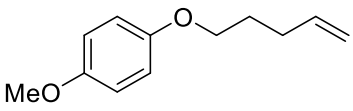
A solution of phenol derivatives (1.0 equiv) and potassium carbonate (4.0 equiv) in dry acetone (0.2 M) was placed under an argon atmosphere at room temperature, and 5-bromo-1-pentene or 5-bromo-2-methyl-2-pentene (1.2 equiv) was added to the mixture. The reaction mixture was stirred at 60 °C for 14–40 h. After completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure. The residue was diluted with water (50 mL) and extracted with diethyl ether (30 mL) three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford the desired product.

1-(pent-4-en-1-yloxy)benzene (205a)[14]



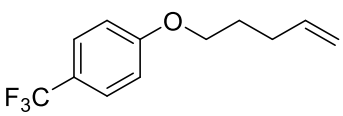
Prepared according to **General procedure** using phenol (471 mg, 5.0 mmol) and 5-bromo-1-pentene (710 μL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:DCM = 75:25). **205a** was isolated as colorless oil (708 mg, 4.37 mmol, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.24 (m, 2H), 6.97-6.87 (m, 3H), 5.86 (ddt, J = 17.2, 10.4, 6.8 Hz, 1H), 5.07 (ddt, J = 16.4, 2.0, 1.6 Hz, 1H), 5.00 (ddt, J = 9.8, 2.0, 1.2 Hz, 1H), 3.97 (t, J = 6.4 Hz, 2H), 2.29-2.19 (m, 2H), 1.95-1.82 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.2, 138.0, 129.6, 120.7, 115.3, 114.7, 67.2, 30.3, 28.6. **R_f** 0.39 (hexane:EtOAc = 50:1).

1-methoxy-4-(pent-4-en-1-yloxy)benzene (205b)[14]



Prepared according to **General procedure** using 4-methoxyphenol (621 mg, 5.0 mmol) and 5-bromo-1-pentene (710 μL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 82:18). **205b** was isolated as colorless oil (725 mg, 3.77 mmol, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89-6.75 (m, 4H), 5.84 (ddt, J = 17.0, 10.4, 6.8 Hz, 1H), 5.10-5.02 (m, 1H), 5.02-4.95 (m, 1H), 3.91 (t, J = 6.5 Hz, 2H), 3.75 (s, 3H), 2.29-2.17 (m, 2H), 1.92-1.81 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 153.9, 153.4, 138.0, 115.6, 115.2, 114.7, 68.0, 55.8, 30.3, 28.7. **R_f** 0.30 (hexane:EtOAc = 20:1).

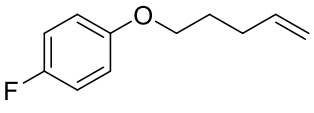
1-(pent-4-en-1-yloxy)-4-(trifluoromethyl)benzene (205c)[14]



Prepared according to **General procedure** using 4-(trifluoromethoxy)phenol (891 mg, 5.0 mmol) and 5-bromo-1-pentene (710 μL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 94:6). **205c** was isolated as colorless oil (945 mg, 4.10 mmol, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56-7.49 (m, 2H), 6.98-6.89 (m, 2H), 5.85 (ddt, J = 17.2, 10.4, 6.4 Hz, 1H), 5.07 (ddt, J = 17.2, 1.6 Hz, 1H), 5.01 (ddt, J = 10.2, 1.6, 1.2 Hz, 1H), 4.01 (t, J = 6.4 Hz, 2H), 2.29-2.19 (m, 2H), 1.96-1.85 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$)

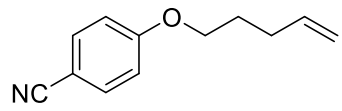
δ 161.7, 137.7, 127.0 (q, J = 3.7 Hz), 124.7 (q, J = 270.9 Hz), 122.9 (q, J = 32.1 Hz), 115.6, 114.6, 67.5, 30.2, 28.4. **R_f** 0.50 (hexane:EtOAc = 40:1).

1-fluoro-4-(pent-4-en-1-yloxy)benzene (205d)[15]



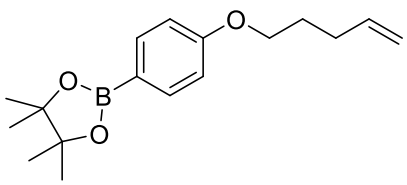
Prepared according to **General procedure** using 4-fluorophenol (561 mg, 5.0 mmol) and 5-bromo-1-pentene (710 µL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 88:12). **205d** was isolated as colorless oil (615.1 mg, 3.41 mmol, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02-6.92 (m, 2H), 6.86-6.79 (m, 2H), 5.85 (ddt, J = 17.2, 10.4, 6.4 Hz, 1H), 5.07 (m, 1H), 5.03-4.97 (m, 1H), 3.93 (t, J = 6.5 Hz, 2H), 2.29-2.18 (m, 2H), 1.93-1.82 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 157.3 (d, J = 237.9 Hz), 155.3 (d, J = 2.0 Hz), 137.9, 116.0, 115.7 (d, J = 11.0 Hz), 115.5 (d, J = 20.0 Hz), 68.0, 30.2, 28.6. **R_f** 0.34 (hexane:EtOAc = 80:1).

4-(pent-4-en-1-yloxy)benzonitrile (205e)[16]



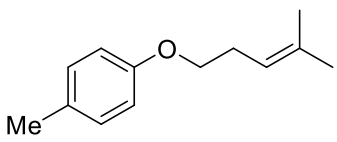
Prepared according to **General procedure** using 4-cyanophenol (596 mg, 5.0 mmol) and 5-bromo-1-pentene (710 µL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane:EtOAc =97:3 to 76:24). **205e** was isolated as colorless oil (920 mg, 4.91 mmol, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 5.84 (ddt, J = 17.2, 10.4, 6.4 Hz, 1H), 5.31-5.04 (m, 1H), 5.04-4.98 (m, 1H), 4.01 (t, J = 6.4 Hz, 2H), 2.30-2.18 (m, 2H), 1.95-1.84 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.5, 137.4, 134.0, 119.4, 115.6, 115.3. 103.8, 67.6, 30.0, 28.2. **R_f** 0.26 (hexane:EtOAc = 10:1).

4,4,5,5-tetramethyl-2-(4-(pent-4-en-1-yloxy)phenyl)-1,3,2-dioxaborolane (205f)[17]



Prepared according to **General procedure** using 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (660 mg, 3.0 mmol) and 5-bromo-1-pentene (430 µL, 3.6 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 83:17). **205f** was isolated as colorless oil (415 mg, 1.44 mmol, 48%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 2H), 6.91-6.85 (m, 2H), 5.85 (ddt, J = 17.2, 10.0, 6.8 Hz, 1H), 5.06 (ddt, J = 17.0, 2.0, 1.6 Hz, 1H), 5.06 (ddt, J = 10.0, 2.0, 1.6 Hz, 1H)), 4.00 (t, J = 6.5 Hz, 2H), 2.28-2.19 (m, 2H), 1.93-1.84 (m, 2H), 1.33 (s, 12H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.8, 137.9, 136.6, 115.3, 114.0, 83.6, 67.1, 30.2, 28.5, 25.0. **R_f** 0.24 (hexane:EtOAc = 20:1).

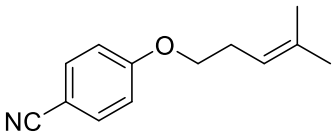
1-methyl-4-((4-methylpent-3-en-1-yl)oxy)benzene (205k)



Prepared according to **General procedure** using *p*-cresol (540 mg, 5.0 mmol) and 5-bromo-2-methyl-2-pentene (800 µL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane/DCM = 40/1). **205k** was isolated as colorless oil (358 mg, 1.88 mmol, 38%). **IR** (ATR) ν 3029, 2968, 2914, 2864, 1615, 1584, 1510, 1471, 1448, 1381, 1290, 1239, 1174, 1109, 1033, 985, 899, 816, 769, 744, 729, 703 cm^{-1};

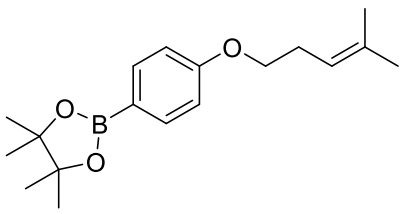
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.03 (m, 2H), 6.83-6.76 (m, 2H), 5.26-5.15 (m, 1H), 3.90 (t, J = 7.1 Hz, 2H), 2.53-2.41 (m, 2H), 2.28 (s, 3H), 1.73 (d, J = 1.1 Hz, 3H), 1.66 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 157.0, 134.5, 130.0, 129.8, 119.8, 114.5, 67.8, 28.4, 25.9, 20.6, 18.0. **R_f** 0.22 (hexane:DCM = 40:1). **HRMS (APCI):** m/z calculated for $C_{13}H_{19}O$ $[M+H]^+$: 191.1430, found: 191.1427.

4-((4-methylpent-3-en-1-yl)oxy)benzonitrile (205l)



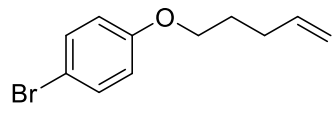
Prepared according to **General procedure** using 4-hydroxybenzonitrile (596 mg, 5.0 mmol) and 5-bromo-2-methyl-2-pentene (800 µL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane:EtOAc = 97:3 to 76:24). **205l** was isolated as colorless oil (565 mg, 2.81 mmol, 56%). **IR** (ATR) ν 2969, 2917, 2875, 2223, 1604, 1573, 1507, 1467, 1448, 1419, 1377, 1300, 1253, 1170, 1112, 1065, 1015, 899, 833, 766, 704, 680 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61-7.54(m, 2H), 6.97-6.90 (m, 2H), 5.23-5.15 (m, 1H), 3.97 (t, J = 6.9 Hz, 2H), 2.55-2.46 (m, 2H), 1.73 (d, J = 1.2 Hz, 3H), 1.66 (d, J = 0.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.5, 135.1, 134.0, 119.4, 119.1, 115.3, 103.8, 68.2, 28.1, 25.8, 18.0. **R_f** 0.31 (hexane:EtOAc = 10:1). **HRMS (APCI):** m/z calculated for $C_{13}H_{16}NO$ $[M+H]^+$: 202.1226, found: 202.1231.

4,4,5,5-tetramethyl-2-(4-((4-methylpent-3-en-1-yl)oxy)phenyl)-1,3,2-dioxaborolane (205m)



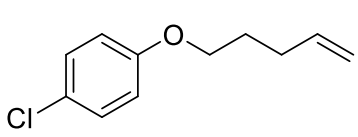
Prepared according to **General procedure** using 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (515 mg, 2.3 mmol) and 5-bromo-2-methyl-2-pentene (330 µL, 2.8 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 82:18). **205m** was isolated as colorless oil (259 mg, 0.857 mmol, 37%). **IR** (ATR) ν 2976, 2917, 2864, 1604, 1565, 1514, 1473, 1444, 1396, 1355, 1325, 1280, 1245, 1245, 1175, 1139, 1091, 1029, 1008, 964, 861, 828, 763, 735, 667 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 5.24-5.18 (m, 1H), 3.95 (t, J = 7.1 Hz, 2H), 2.53-2.45 (m, 2H), 1.73 (s, 3H), 1.66 (s, 3H). 1.33 (s, 12H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.8, 136.6, 134.6, 119.6, 114.0, 83.7, 67.6, 28.4, 25.9, 25.0, 18.0. **R_f** 0.32 (hexane:EtOAc = 15:1). **HRMS** (APCI): m/z calculated for $C_{18}H_{28}O_3B$ $[M+H]^+$: 303.2126, found: 303.2133.

1-bromo-4-(pent-4-en-1-yloxy)benzene (205t) [18]



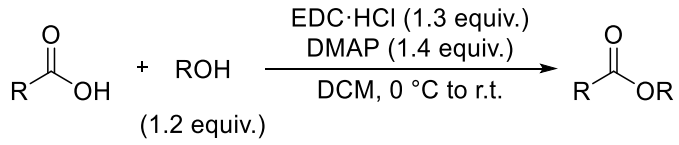
Prepared according to **General procedure** using 4-bromophenol (865 mg, 5.0 mmol) and 5-bromo-1-pentene (710 µL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:DCM = 78:22). **205t** was isolated as colorless oil (1.06 g, 4.40 mmol, 88%).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 2H), 6.82-6.74 (m, 2H), 5.84 (ddt, J = 17.2, 10.4, 6.4 Hz, 1H), 5.07 (ddt, J = 17.2, 2.0, 1.6 Hz, 1H), 5.00 (ddt, J = 10.2, 2.0, 1.2 Hz, 1H), 3.93 (t, J = 6.5 Hz, 2H), 2.28-2.18 (m, 2H), 1.93-1.82 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.3, 137.8, 132.3, 116.5, 115.4, 112.8, 67.5, 30.2, 28.4. **R_f** 0.44 (hexane:EtOAc = 40:1).

1-chloro-4-(pent-4-en-1-yloxy)benzene (205u)[14]



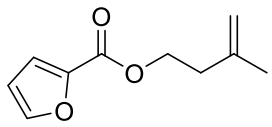
Prepared according to **General procedure** using 4-chlorophenol (495 μL, 5.0 mmol) and 5-bromo-1-pentene (710 μL, 6 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane). **205u** was isolated as colorless oil (824 mg, 4.19 mmol, 84%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.24-7.19 (m, 2H), 6.85-6.78 (m, 2H), 5.90-5.78 (m, 1H), 5.09-5.02 (m, 1H), 5.02-4.98 (m, 1H), 3.93 (t, J = 6.6 Hz, 2H), 2.27-2.19 (m, 2H), 1.92-1.83 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 157.8, 137.8, 129.4, 125.5, 115.9, 115.4, 67.6, 30.2, 28.5.

General Procedure for Preparing 205n,o



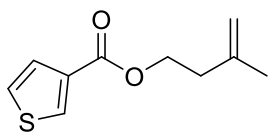
A solution of EDC·HCl (1.3 equiv) and DMAP (1.4 equiv) in dry dichloromethane (0.4 M) was placed under an argon atmosphere and cooled to 0 °C. Carboxylic acid (1.0 equiv) was added, followed by the addition of alcohol (1.2 equiv). The reaction mixture was stirred at room temperature for 16–19 h. After completion of the reaction, as monitored by TLC, the mixture was quenched with 1 M HCl aq. (50 mL). The biphasic mixture was extracted with dichloromethane (50 mL) three times. The combined organic layers were washed with 1 M HCl aq. (50 mL) three times, sat. $NaHCO_3$ aq. (50 mL) and brine (100 mL), and the organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude mixture was purified by flash column chromatography (silica gel) to afford the desired product.

3-methylbut-3-en-1-yl furan-2-carboxylate (205n)[19]



Prepared according to **General procedure** using 2-furancarboxylic acid (560 mg, 5.0 mmol) and 3-methyl-3-butene-1-ol (610 μL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 79:21). **205n** was isolated as colorless oil (787 mg, 4.37 mmol, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, 1H), 7.16 (d, J = 3.4 Hz, 1H), 6.50 (dd, J = 3.4, 1.7 Hz, 1H), 4.88-4.76 (m, 2H), 4.42 (t, J = 6.9 Hz, 2H), 2.46 (t, J = 6.9 Hz, 2H), 1.80 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.8, 146.4, 144.9, 141.6, 117.9, 112.6, 111.9, 63.3, 36.8, 22.6. **R_f** 0.24 (hexane:EtOAc = 15:1).

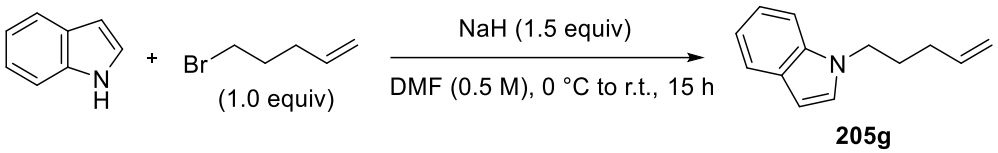
3-methylbut-3-en-1-yl thiophene-3-carboxylate (205o)



Prepared according to **General procedure** using 3-thiophencarboxylic acid (641 mg, 5.0 mmol) and 3-methyl-3-butene-1-ol (610 μL, 6.0 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 80:20). **205o** was isolated as colorless oil (863 mg, 4.40 mmol, 88%). **IR** (ATR) ν 3111, 3077, 2967, 2905, 1710, 1648, 1522, 1448, 1409, 1376, 1249, 1202, 1186, 1101, 1025, 972, 891, 872, 822, 745, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 3.0, 1.0 Hz, 1H), 7.52 (dd, J = 5.0, 1.0 Hz, 1H), 7.30 (dd, J = 5.0, 3.0 Hz, 1H), 4.88-4.74 (m, 2H), 4.39 (t, J = 6.8 Hz, 2H), 2.46 (t, J = 6.8 Hz, 2H), 1.80 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$)

δ 162.8, 141.8, 134.0, 132.7, 128.0, 126.0, 112.5, 63.0, 36.9, 22.6. **R_f** 0.31 (hexane:EtOAc = 20:1). **HRMS (APCI):** m/z calculated for $C_{10}H_{13}O_2S$ $[M+H]^+$: 197.0631, found: 197.0631.

Preparation of 1-(Pent-4-en-1-yl)-1*H*-indole (205g)

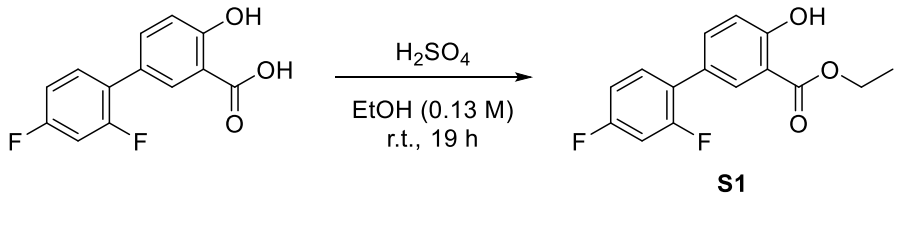


205g

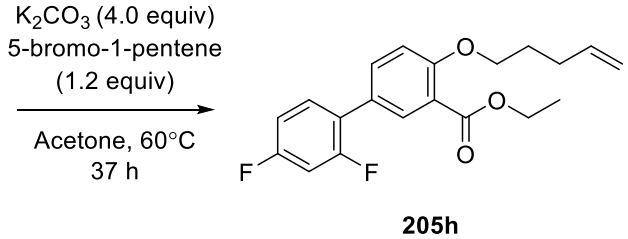
In a 50 mL round-bottom flask, NaH (300 mg, 5.0 mmol, 60% dispersion in mineral oil, 1.5 equiv) was added to a solution of indole (586 mg, 5.0 mmol) in dry DMF (10 mL) at 0 ºC under an argon atmosphere. The reaction mixture was stirred at room temperature for 30 minutes. 5-Bromo-1-pentene (590 µL, 5.0 mmol, 1.0 equiv) was added to the reaction mixture at 0 ºC under an argon atmosphere. The mixture was warmed to room temperature and stirred for 15 hours before the dropwise addition of sat. NH_4Cl aq. (5 mL) at 0 ºC. The resulting mixture was diluted with water (20 mL) and Et_2O (15 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (15 mL) three times. The combined organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 87:13) to give **205g** as clear green oil (862 mg, 4.65 mmol, 93%). The spectral data was consistent with the reported values.[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.60 (m, 1H), 7.37-7.32 (m, 1H), 7.23-7.17 (m, 1H), 7.13-7.06 (m, 2H), 6.49 (dd, J = 3.1, 0.8 Hz, 1H), 5.85 (ddt, J = 17.2, 10.4, 6.4 Hz, 1H), 5.08-5.03 (m, 1H), 5.03-5.00 (m, 1H), 4.13 (t, J = 7.0 Hz, 2H), 2.13-2.02 (m, 2H), 2.00-1.89 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.5, 136.1, 128.8, 127.9, 121.5, 121.1, 119.4, 115.8, 109.5, 101.1, 45.7, 31.0, 29.3. **R_f** 0.29 (hexane:EtOAc = 30:1).

Preparation of Ethyl 2',4'-Difluoro-4-(pent-4-en-1-yloxy)-[1,1'-biphenyl]-3-carboxylate (205h)



S1



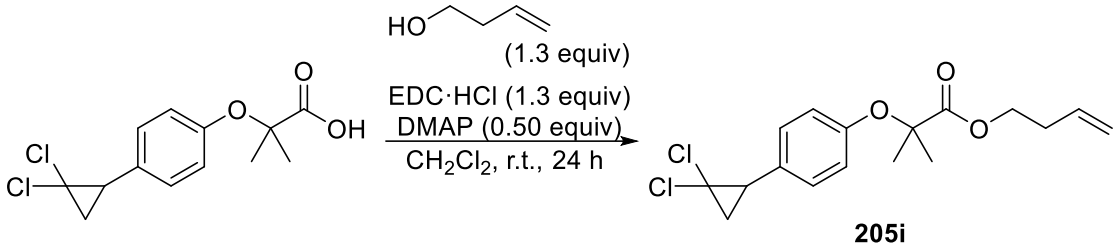
205h

In a 200 mL round flask, conc. H_2SO_4 (10 mL) was added to a solution of diflunisal (1.25 g, 5.0 mmol, 1.0 equiv.) in EtOH (38 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at 80 ºC for 19 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (100 mL) twice and brine (100 mL). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated to give **S1**, which was used for the next step without further purification.

In a 50 mL round-bottom flask, 5-bromo-1-pentene (0.28 mL, 2.4 mmol, 1.2 equiv) was added to suspension of the crude **S1** (557 mg, 2.0 mmol) and K_2CO_3 (1.11 g, 8.0 mmol, 4.0 equiv) in acetone (10 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at 60 ºC for 38 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude mixture was diluted with water (50 mL) and extracted with Et_2O (30 mL) three times, and the combined organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane:EtOAc =96:4 to 75:25) to give **205h** as colorless oil (379 mg, 1.09 mmol, 55%).

IR (ATR) ν 3077, 2978, 2937, 1726, 1701, 1609, 1489, 1466, 1434, 1388, 1365, 1313, 1271, 1252, 1216, 1160, 1140, 1094, 1077, 1044, 1013, 967, 912, 849, 809, 786, 734, 660 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 2.3, 1.1 Hz, 1H), 7.61-7.55 (m, 1H), 7.44-7.35 (m, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.98-6.86 (m, 2H), 5.87 (ddt, J = 17.2, 10.0, 6.8 Hz, 1H), 5.08 (ddt, J = 17.2, 1.6, 2.0 Hz, 1H), 5.04-4.97 (m, 1H), 4.38 (q, J = 7.2 Hz, 2H), 4.09 (t, J = 6.3 Hz, 2H), 2.36-2.27 (m, 2H), 2.01-1.91 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 166.5, 162.3 (dd, J = 248.5, 12.0 Hz), 159.8 (dd, J = 249.5, 12.0 Hz), 158.1, 137.8, 133.6 (d, J = 4.0 Hz), 132.0 (d, J = 2.0 Hz), 131.2, (dd, J = 9.5, 4.5 Hz), 127.0, 124.2 (dd, J = 14.0, 4.0 Hz), 121.2, 115.4, 113.3, 111.7 (dd, J = 21.0, 4.0 Hz), 104.5 (t, J = 25.8 Hz), 68.2, 61.1, 30.1, 28.4, 14.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –111.75-–111.88 (m, 1F), –113.86-–114/02 (m, 1F). **HRMS** (APCI): m/z calculated for $C_{20}H_{21}O_3F_2$ $[M+H]^+$: 347.1453, found: 347.1460. **R_f** 0.29 (hexane:EtOAc = 10:1).

Preparation of But-3-en-1-yl 2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methylpropanoate (205i)

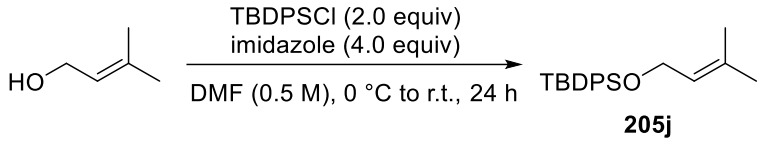


205i

In a 100 mL two necked round-bottom flask, 3-buten-1-ol (115 µL, 1.3 mmol, 1.3 equiv), EDC·HCl (256 mg, 1.3 mmol, 1.3 equiv), and DMAP (20.3 mg, 0.50 mmol, 0.50 equiv) were added to a solution of ciprofibrate (289 mg, 1.0 mmol, 1.0 equiv) in dry CH_2Cl_2 (16 mL) at 0 ºC under an argon atmosphere. After stirring the reaction mixture for 24 hours at room temperature, the resulting mixture was quenched with deionized water (50 mL) and extracted with DCM (30 mL) three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crude was purified by silica gel column chromatography (hexane:EtOAc = 15:1) to afford **205i** as colorless oil (277 mg, 0.807 mmol, 81%).

IR (ATR) ν 2932, 2829, 1734, 1611, 1509, 1381, 1286, 1241, 1141, 1122, 1092, 846, 834, 761, 675 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.13-7.08 (m, 2H), 6.84-6.78 (m, 2H), 5.69 (ddt, J = 17.2, 10.4, 6.8 Hz, 1H), 5.09-4.99 (m, 2H), 4.21 (t, J = 6.6 Hz, 2H), 2.83 (dd, J = 10.8, 8.4 Hz, 1H), 2.36 (qt, J = 6.8, 1.2 Hz, 2H), 1.93 (dd, J = 10.8, 7.6 Hz, 1H), 1.77 (dd, J = 8.4, 7.2 Hz, 1H), 1.59 (s, 6H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 174.1, 155.0, 133.6, 129.6, 128.1, 118.7, 117.4, 79.2, 64.4, 60.9, 34.8, 32.9, 25.8, 25.5, 25.4. **HRMS** (ESI): m/z calculated for $C_{17}H_{20}Cl_2O_3Na$ $[M+Na]^+$: 365.0682, found: 365.0683.

Preparation of *tert*-Butyl((3-methylbut-2-en-1-yl)oxy)diphenylsilane (205j)

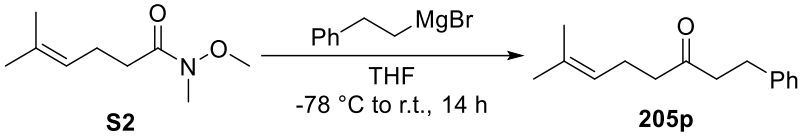


205j

In a 200 mL round-bottom flask, *tert*-butyldiphenylchlorosilane (2.6 mL, 10 mmol, 2.0 equiv) was added to a solution of 3-methyl-2-buten-1-ol (0.50 mL, 5.0 mmol) and imidazole (1.36 g, 20 mmol, 4.0 equiv) in DMF (20 mL) at 0 ºC under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with water (100 mL) and extracted with hexane/EtOAc = 4/1 (50 mL x 3), and the combined organic layer was dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 20:1) to give **205j** as colorless oil (1.47 g, 4.53 mmol, 91%). The spectral data was consistent with the reported values.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.64 (m, 4H), 7.46-7.36 (m, 6H), 5.44-5.35 (m, 1H), 4.19 (d, J = 6.1 Hz, 2H), 1.69 (s, 3H), 1.45 (s, 3H). 1.04 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 135.8, 134.3, 133.9, 129.6, 127.7, 124.4, 61.3, 27.0, 25.8, 19.3, 18.1. **R_f** 0.52 (hexane:EtOAc = 20:1).

Synthesis of 7-Methyl-1-phenyloct-6-en-3-one (205p)

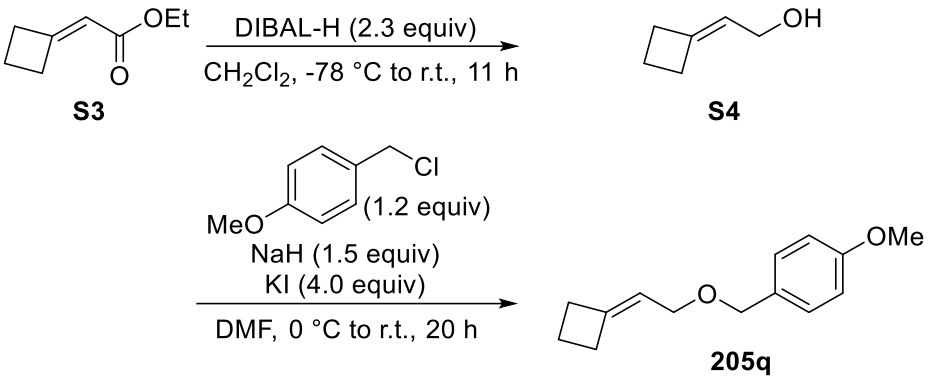


S2 **205p**

A 30 mL round-bottom flask containing stirring bar and Mg turnings (319 mg, 13 mmol, 2.6 equiv) was flame-dried under reduced pressure. Dry THF (5 mL) and dibromoethane (10 µL) were added to the flask under an argon atmosphere, and the mixture was stirred for 15 minutes. The solution of (2-bromoethyl)benzene (880 µL, 6.5 mmol, 1.3 equiv) in dry THF (3 mL) was added dropwise to the solution. The resulting solution was warmed by heat gun to launch the reaction. After 5 minutes, the reaction was completed, and *N*-methoxy-*N*,5-dimethylhex-4-enamide (**S2**) (860 mg, 5 mmol, 1.0 equiv) in dry THF (13 mL) was added dropwise to the Grignard reagent at -78 ºC. The resulting solution was stirred for 3 hours at -78 ºC, then slowly warmed to room temperature. After stirring the mixture for 14 hours, the resulting mixture was quenched with sat. NH_4Cl aq. (20 mL) and deionized water (20 mL). The aqueous layer was extracted with diethyl ether (50 mL) three times. The combined organic layer was washed with brine and dried over Na_2SO_4. All volatiles were removed under reduced pressure, and the crude was purified by silica gel column chromatography (hexane to hexane:EtOAc = 10:1) to afford **205p** as colorless oil (1.03 g, 4.75 mmol, 95%). The NMR spectra of **205p** was matched with the reported data.[22]

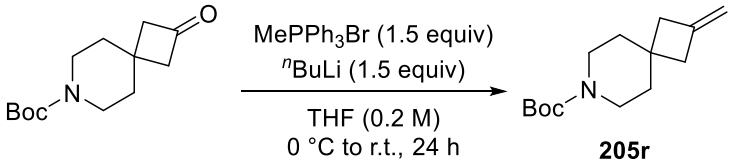
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31-7.24 (m, 2H), 7.21-7.15 (m, 3H), 5.07-5.00 (m, 1H), 2.90 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.41 (t, J = 7.6 Hz, 2H), 2.28-2.19 (m, 2H), 1.66 (d, J = 1.2 Hz, 3H), 1.60 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 210.0, 141.3, 132.9, 128.6, 128.5, 126.2, 122.9, 44.5, 43.2, 29.9, 25.8, 22.7, 17.8.

Preparation of 1-((2-Cyclobutylideneethoxy)methyl)-4-methoxybenzene (205q)



In a 200 mL round-bottom flask, diisobutylaluminum hydride (1.0 M solution in hexane, 23 mL, 23 mmol, 2.3 equiv) was added dropwise to a solution of ethyl 2-cyclobutylideneacetate (**S3**) (1.41 g, 10 mmol, 1.0 equiv) in dry CH_2Cl_2 (50 mL) at -78 ºC under an argon atmosphere. The reaction mixture was stirred at room temperature for 11 hours. The resulting mixture was quenched with deionized water (30 mL) at 0 ºC, and the suspended white solid was removed through Celite eluting with CH_2Cl_2. The filtrate was concentrated, dissolved in diethyl ether, and washed with brine. The organic layer was dried over Na_2SO_4 and evaporated. The crude product was obtained as colorless oil (172.2 mg) containing a small amount of impurity, which was used for the next step without further purification.
In a 100 mL Schlenk flask, 2-cyclobutylideneethan-1-ol (**S4**) (489 mg, approx. 5 mmol) was dissolved in dry dimethylformamide (25 mL) under an argon atmosphere at 0 ºC. After addition of NaH (60 wt% in mineral oil, 300 mg, 7.5 mmol, 1.5 equiv), the resulting mixture was stirred for 1.5 hours at 0 ºC. KI (3.35 g, 20 mmol, 4.0 equiv) and *p*-methoxybenzyl chloride (817 µL, 6.0 mmol, 1.2 equiv) were added to the mixture, and the mixture was stirred at room temperature for 20 hours. The resulting mixture was quenched with deionized water (20 mL) and extracted with diethyl ether (50 mL) three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crude was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to afford **205q** as colorless oil (725 mg, 3.32 mmol, 66%).
IR (ATR) ν 2933, 2914, 2835, 1611, 1585, 1510, 1464, 1299, 1242, 1171, 1142, 1088, 1031, 817, 755 cm^{-1} ; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29-7.24 (m, 2H), 6.90-6.84 (m, 2H), 5.33-5.27 (m, 1H), 4.42 (s, 2H), 3.89-3.84 (m, 2H), 3.80 (s, 3H), 2.73-2.64 (m, 4H), 2.01-1.91 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 159.2, 146.1, 130.7, 129.4, 116.7, 113.7, 71.5, 66.3, 55.3, 31.2, 29.5, 17.1. **HRMS** (ESI): m/z calculated for $C_{14}H_{18}O_2Na^+$ $[M+Na]^+$: 241.1199, found: 241.1195.

Preparation of *tert*-Butyl 2-Methylene-7-azaspiro[3.5]nonane-7-carboxylate (205r)

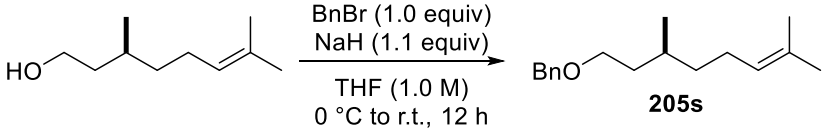


In a 100 mL round-bottom flask, ^{n}BuLi (1.53 M solution in hexane, 4.9 mL, 7.5 mmol, 1.5 equiv) was added dropwise to a solution of $MePPh_3Br$ (2.68 g, 7.5 mmol, 1.5 equiv) in dry THF (15 mL) at 0 ºC under an argon atmosphere. The

reaction mixture was stirred at room temperature for 30 minutes. *tert*-Butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (1.20 g, 5.0 mmol) in dry THF (10 mL) was added dropwise to reaction mixture at 0 ºC under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with sat. NH_4Cl aq. (50 mL) and extracted with EtOAc (50 mL) three times. The combined organic layer was dried over Na_2SO_4. The solvent was evaporated to give crude **205r**, which was purified by flash column chromatography (silica gel, hexane/EtOAc = 20/1 to 10/1) to afford **205r** as colorless oil (946 mg, 3.99 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87-4.79 (m, 2H), 3.38-3.26 (m, 4H), 2.48-2.40 (m, 4H), 1.60-1.52 (m, 4H), 1.45 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 154.9, 144.5, 107.7, 79.2, 41.7, 41.1, 36.5, 33.6, 28.4. **R_f** 0.37 (hexane:EtOAc = 8:1). The spectral data was consistent with the reported values.[23]

Preparation of (*S*)-(((3,7-Dimethyloct-6-en-1-yl)oxy)methyl)benzene (205s)



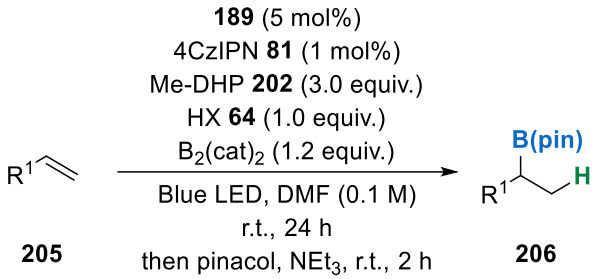
205s

In a 30 mL round-bottom flask, (-)-β-citronellol (1.82 mL, 10 mmol) was added to a solution of NaH (440 mg, 11 mmol, 60% dispersion in mineral oil, 1.1 equiv) in dry THF (10 mL) at 0 ºC under an argon atmosphere. The reaction mixture was stirred at 0 ºC for 30 minutes. Benzyl bromide (1.19 mL, 10 mmol, 1.0 equiv) was added to the reaction mixture at 0 ºC under an argon atmosphere. The mixture was warmed to room temperature and stirred for 12 hours before the dropwise addition of sat. NH_4Cl aq.. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 98:2 to 95:5) to give **205s** as clear green oil (2.21 mg, 8.96 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 4H), 7.30-7.23 (m, 1H), 5.15-5.04 (m, 1H), 4.50 (s, 2H), 3.58-3.44 (m, 2H), 2.08-1.87 (m, 2H), 1.73-1.63 (m, 4H), 1.63-1.54 (m, 4H), 1.48-1.29 (m, 2H), 1.22-1.10 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 138.8, 131.3, 128.5, 127.7, 127.6, 125.0, 73.0, 68.9, 37.3, 36.9, 29.7, 25.9, 25.6, 19.7, 17.8. **R_f** 0.26 (hexane:EtOAc = 40:1). The spectral data was consistent with the reported values.[24]

3. Markovnikov Hydroboration

General Procedure for Markovnikov Hydroboration of mono-substituted Alkenes



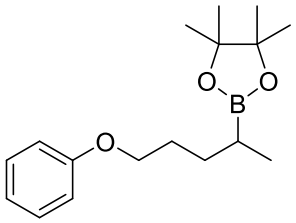
In an argon-filled glove box, a flame dried screw-capped vial was charged with alkene **205** (0.2 mmol), DMF (2 mL, 0.1 M), 4CzIPN **81** (1.6 mg, 0.002 mmol, 1 mol%), **189** (6.1 mg, 0.01 mmol, 5 mol%), Me-DHP **202** (160.4 mg, 0.6 mmol, 3.0 equiv), collidinium triflate **64** (54.3 mg, 0.2 mmol, 1.0 equiv), and bis(catecolate)diboron ($B_2(cat)_2$) (57.1 mg, 0.24 mmol, 1.2 equiv). The vial was capped with a screw-cap septum and removed from the glove box. The reaction vial was placed in the photoreactor with a cooling fan. The temperature of the reactor was kept at approximately 25 ºC. After stirring for 24 hours under photo-irradiation, pinacol in triethylamine (1.6 mL, ca. 1.6 M, ca. 2.56 mmol) was added to the mixture. After stirring for additional 2 hours at room temperature, EtOAc (10 mL), water (10 mL), and sat. NH_4Cl aq. were added to the resulting mixture. The mixture was extracted with EtOAc (10 mL) three times, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford the desired alkyl boronic esters **206**.

General Procedure for Markovnikov Hydroboration of di- and tri-substituted Alkenes

In an argon-filled glove box, a flame dried screw-capped vial was charged with alkene **205** (0.2 mmol), DMF (2 mL, 0.1 M), 4CzIPN **81** (1.6 mg, 0.002 mmol, 1 mol%), **189** (6.1 mg, 0.01 mmol, 5 mol%), Me-DHP **202** (160.4 mg, 0.6 mmol, 3.0 equiv.), collidinium triflate **64** (54.3 mg, 0.2 mmol, 1.0 equiv), and bis(catecolate)diboron ($B_2(cat)_2$) (237.8 mg, 1.0 mmol, 5.0 equiv). The vial was capped with a screw-cap septum and removed from the glove box. The reaction vial was placed in the photoreactor with a cooling fan. The temperature of the reactor was kept at approximately 25 ºC. After stirring for 24 hours under photo-irradiation, pinacol in triethylamine (1.6 mL, ca. 1.6 M, ca. 2.56 mmol) was added to the mixture. After stirring for additional 2 hours at room temperature, EtOAc (10 mL), water (10 mL), and sat. NH_4Cl aq. were added to the resulting mixture. The mixture was extracted with EtOAc (10 mL) three times, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced

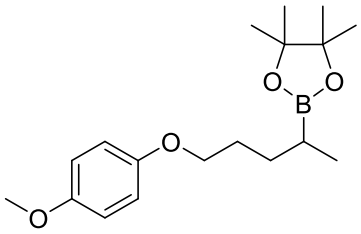
pressure. The crude mixture was purified by silica gel column chromatography to afford the desired alkyl boronic esters **206**.

4,4,5,5-tetramethyl-2-(5-phenoxypentan-2-yl)-1,3,2-dioxaborolane (206a)[25]



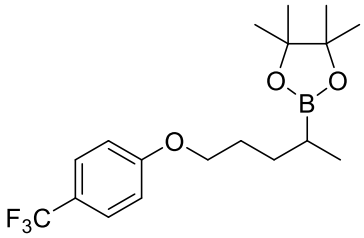
Prepared according to **General procedure** using **205a** (32.4 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane to hexane:EtOAc = 87:13). **206a** was isolated as colorless oil (46.1 mg, 0.159 mmol, 79%). **IR** (ATR) ν 2976, 2930, 2870, 1599, 1496, 1466, 1370, 1313, 1242, 1168, 1142. 1078, 1034, 966, 918, 855, 812, 751, 690 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.21 (m, 2H), 6.95-6.84 (m, 3H), 3.94 (t, J = 6.7 Hz, 2H), 1.88-1.74 (m, 2H), 1.67-1.54 (m, 1H), 1.51-1.37 (m, 1H), 1.23 (s, 12H), 1.11-0.98 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.3, 129.5, 120.5, 114.7, 83.0, 68.2, 29.6, 28.7, 24.9, 24.8, 15.6. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.9. **R_f** 0.24 (hexane:EtOAc = 20:1). **HRMS (APCI):** m/z calculated for $C_{17}H_{28}O_3B$ $[M+H]^+$: 291.2126, found: 291.2123.

2-(5-(4-methoxyphenoxy)pentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (206b)



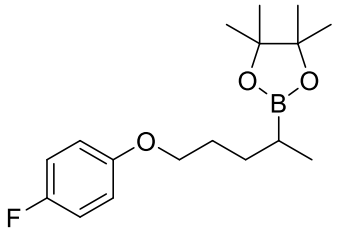
Prepared according to **General procedure** using **205b** (38.5 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 77:23 and hexane:EtOAc = 12:1). **206b** was isolated as a colorless solid (52.1 mg, 0.163 mmol, 81%). **IR** (ATR) ν 2975, 2931, 2869, 1507, 1464, 1370, 1313, 1228, 1142, 1107, 1039, 966, 919, 855, 823, 741, 687, 670 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87-6.77 (m, 4H), 3.89 (t, J = 6.6 Hz, 2H), 3.75 (s, 3H), 1.84-1.73 (m, 2H), 1.65-1.54 (m, 1H), 1.49-1.36 (m, 1H), 1.23 (s, 12H), 1.12-0.97 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 153.8, 153.4, 115.6, 114.7, 83.0, 69.0, 55.9, 29.6, 28.8, 24.9, 24.8, 15.6. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.6. **R_f** 0.21 (hexane:EtOAc = 15:1). **HRMS (APCI):** m/z calculated for $C_{18}H_{30}O_4B$ $[M+H]^+$: 321.2232, found: 321.2231.

4,4,5,5-tetramethyl-2-(5-(4-(trifluoromethyl)phenoxy)pentan-2-yl)-1,3,2-dioxaborolane (206c)



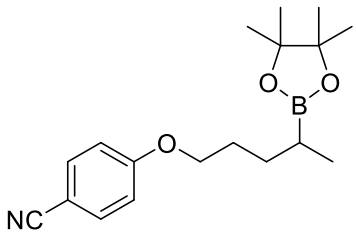
Prepared according to **General procedure** using **205c** (46.0 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 4:1 and hexane:EtOAc = 20:1). **206c** was isolated as a colorless solid (55.7 mg, 0.155 mmol, 78%). **IR** (ATR) ν 2948, 2920, 2877, 2845, 1614, 1590, 1520, 1464, 1372, 1359, 1317, 1247, 1176, 1159, 1132, 1111, 1067, 1008, 987, 966, 913, 842, 705, 686, 671 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 3.98 (t, J = 6.6 Hz, 2H), 1.89-1.76 (m, 2H), 1.66-1.56 (m, 1H), 1.52-1.38 (m, 1H), 1.24 (s, 12H), 1.12-0.98 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.8, 126.9 (q, J = 3.7 Hz), 124.7 (q, J = 270.9 Hz), 122.7 (q, J = 32.7 Hz), 114.6, 83.1, 68.6, 29.6, 28.5, 24.9, 24.8, 15.6. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –61.23. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.5. **R_f** 0.20 (hexane:EtOAc = 20:1). **HRMS (APCI):** m/z calculated for $C_{18}H_{27}O_3BF_3$ $[M+H]^+$: 359.2000, found: 359.2002.

2-(5-(4-fluorophenoxy)pentan-2-yl)-4,4,5,5-textramethyl-1,3,2-dioxaborolane (206d)



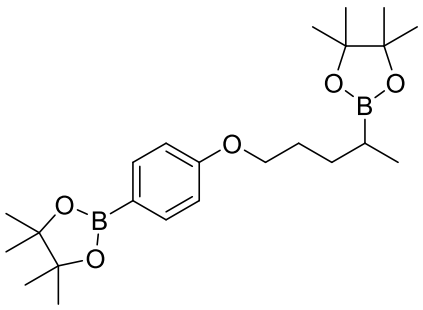
Prepared according to **General procedure** using **205d** (36.0 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 4:1 and hexane:EtOAc = 20:1). **206d** was isolated as colorless oil (45.8 mg, 0.149 mmol, 74%). **IR** (ATR) ν 2973, 2939, 2864, 1604, 1506, 1462, 1370, 1313, 1248, 1204, 1165, 1140, 1100, 1018, 966, 909, 854, 833, 753, 704, 670 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98-6.90 (m, 2H), 6.85-6.78 (m, 2H), 3.90 (t, J = 6.6 Hz, 2H), 1.85-1.72 (m, 2H), 1.65-1.53 (m, 1H), 1.49-1.37 (m, 1H), 1.23 (s, 12H), 1.12-0.97 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 157.2 (d, J = 238.0 Hz), 155.4 (d, J = 2.0 Hz), 115.8 (d, J = 23.0 Hz), 115.6 (d, J = 8.0 Hz), 83.1, 69.0, 29.6, 28.7, 24.9, 24.8, 15.6. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –124.82- –124.94 (m, 1F). **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.5. **R_f** 0.24 (hexane:EtOAc = 20:1). **HRMS (APCI):** m/z calculated for $C_{17}H_{27}O_3BF$ $[M+H]^+$: 309.2032, found: 309.2031.

4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)benzonitrile (206e)



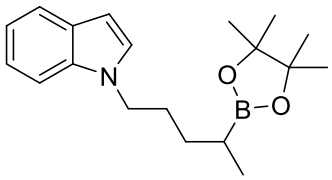
Prepared according to **General procedure** using **205e** (37.4 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane:EtOAc = 96:4 to 3:1 and hexane:AcOEt = 7:1). **206e** was isolated as a colorless solid (47.0 mg, 0.149 mmol, 75%). **IR** (ATR) ν 2976, 2933, 2861, 2220, 1604, 1573, 1507, 1463, 1384, 1370, 1304, 1257, 1206, 1173, 1142, 1008, 965, 909, 855, 838, 761, 710, 670 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.52 (m, 2H), 6.97-6.89 (m, 2H), 3.99 (t, J = 6.6 Hz, 2H), 1.88-1.76 (m, 2H), 1.66-1.55 (m, 1H), 1.50-1.38 (m, 1H), 1.24 (s, 12H), 1.11-0.97 (m, 4H). **^{13}C{^{1}H}NMR** (101 MHz, $CDCl_3$) δ 162.6, 134.0, 119.5, 115.3, 103.7, 83.1, 68.8, 29.5, 28.4, 24.9, 24.8, 15.6. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.5. **R_f** 0.23 (hexane:EtOAc = 7:1). **HRMS (APCI):** m/z calculated for $C_{18}H_{27}NO_3B$ $[M+H]^+$: 316.2079, found: 316.2077.

4,4,5,5-tetramethyl-2-(4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)phenyl)-1,3,2-dioxaborolane (206f)



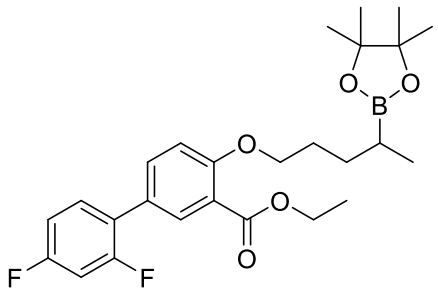
Prepared according to **General procedure** using **205f** (57.6 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane:EtOAc = 99:1 to 78:22 and hexane:EtOAc = 10:1). **206f** was isolated as a colorless solid (55.4 mg, 0.133 mmol, 67%). **IR** (ATR) ν 2977, 2920, 2867, 1604, 1567, 1518, 1458, 1398, 1354, 1310, 1277, 1251, 1214, 1174, 1141, 1090, 1050, 1010, 987, 965, 915, 855, 837, 736, 694, 670 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz 2H), 6.88 (d, J = 8.2 Hz 2H), 3.97 (t, J = 6.6 Hz, 2H), 1.88-1.74 (m, 2H), 1.66-1.53 (m, 1H), 1.51-1.38 (m, 1H), 1.33 (s, 12H), 1.23 (s, 12H), 1.11-0.97 (m, 4H). **^{13}C {^{1}H }NMR** (101 MHz, $CDCl_3$) δ 161.9, 136.6, 114.0, 83.6, 83.0, 68.2, 29.6, 28.6, 25.0, 24.9, 24.9, 15.6. **^{11}B {^{1}H } NMR** (191 MHz, $CDCl_3$) δ 33.6, 30.2. **R_f** 0.24 (hexane:EtOAc = 10:1). **HRMS (APCI):** m/z calculated for $C_{23}H_{38}O_5B_2Na$ $[M+Na]^+$: 439.2798, found: 439.2803.

1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)-1*H*-indole (206g)



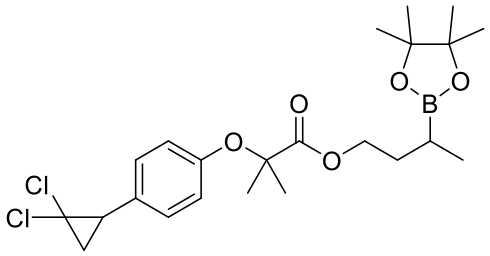
Prepared according to **General procedure** using **205g** (37.1 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 15:1 and hexane:EtOAc = 19:1). **206g** was isolated as a colorless solid (36.6 mg, 0.116 mmol, 58%). **IR** (ATR) ν 3127, 3101, 3053, 2972, 2950, 2928, 2865, 1509, 1460, 1388, 1370, 1305, 1249, 1220, 1167, 1131, 1043, 1011, 990, 968, 930, 883, 858, 831, 763, 744, 729, 702, 686, 670 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.21-7.14 (m, 1H), 7.11-7.03 (m, 2H), 6.46 (d, J = 2.7 Hz, 1H), 4.09 (t, J = 7.3 Hz, 2H), 1.93-1.81 (m, 2H), 1.56-1.45 (m, 1H), 1.41-1.29 (m, 1H), 1.20 (s, 12H), 1.08-0.99 (m, 1H), 0.96 (d, J = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 136.1, 128.7, 127.9, 121.3, 121.0, 119.2, 109.6, 100.9, 83.1, 46.8, 30.6, 29.7, 24.9, 24.8, 15.7. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.5. **R_f** 0.26 (hexane:EtOAc = 15:1). **HRMS (APCI):** m/z calculated for $C_{19}H_{29}NO_2B$ $[M+H]^+$: 314.2286, found: 314.2289.

ethyl-2',4'-difluoro-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)-[1,1'-biphenyl]-3-carboxylate (206h)



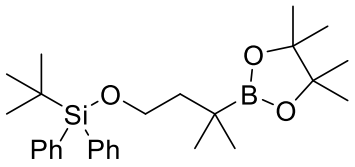
Prepared according to **General procedure** using **205h** (69.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 6:1 and hexane:EtOAc = 9:1). **206h** was isolated as a colorless solid (73.5 mg, 0.155 mmol, 77%). **IR** (ATR) ν 2976, 2931, 2871, 1728, 1702, 1610, 1490, 1465, 1435, 1404, 1386, 1370, 1313, 1271, 1254, 1216, 1140, 1096, 1077, 1044, 1012, 967, 850, 809, 734, 686, 669 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91-7.86 (s, 1H), 7.60-7.53 (m, 1H), 7.43-7.33 (m, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.97-6.84 (m, 2H), 4.38 (q, J = 7.0 Hz, 2H), 4.07 (t, J = 6.6 Hz, 2H), 1.93-1.83 (m, 2H), 1.72-1.58 (m,1H), 1.57-1.44 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.24 (s, 12H), 1.12-0.98 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 166.7, 162.2 (dd, J = 248.0 Hz, 12.1 Hz), 159.8 (dd, J = 250.0 Hz, 12.1 Hz), 158.2, 133.5 (d, J = 4.0 Hz), 131.9 (d, J = 2.0 Hz), 131.2 (dd, J = 9.0 Hz, 5.0 Hz), 126.8, 124.3 (dd, J = 13.0 Hz, 4.0 Hz), 121.3, 113.3, 111.7 (dd, J = 21.0 Hz, 4.0 Hz), 104.4 (dd, J = 26.9 Hz), 83.0, 69.4, 61.1, 29.5, 28.6, 24.9, 24.8, 15.6, 14.5. **^{19}F NMR** (376 MHz, $CDCl_3$): δ –111.88- –111.99 (m, 1F), –113.86- –113.97 (m, 1F). **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.6. **R_f** 0.29 (hexane/EtOAc = 6:1). **HRMS (APCI):** m/z calculated for $C_{26}H_{33}O_5BF_2Na$ $[M+Na]^+$: 497.2281, found: 497.2287.

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl 2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methylpropanoate (206i)



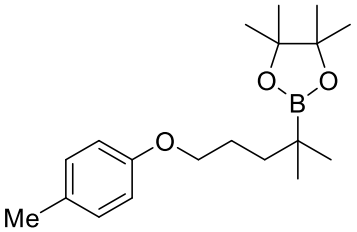
Prepared according to **General procedure** using **205i** (68.6 mg, 0.20 mmol). Purification by silica gel column chromatography twice (hexane to hexane:EtOAc = 9:1 and hexane:EtOAc = 10:1) afforded **206i** as pale brown oil (68.9 mg, 0.146 mmol, 73%). **IR** (ATR) ν 2976, 2932, 2866, 1731, 1610, 1510, 1465, 1380, 1291, 1175, 1141, 1122, 1093, 1058, 1028, 966, 847, 760, 675 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz; mixture of two diastereomers) δ 7.13-7.67 (m, 2H), 6.84-6.79 (m, 2H), 4.19 (t, 2H, J = 7.0 Hz), 2.82 (dd, 1H, J = 5.4, 4.2 Hz), 1.93 (dd, 1H, J = 10.8, 7.2 Hz), 1.84-1.73 (m, 2H), 1.63-1.52 (m, 7H), 1.23, (s, 12H), 1.09-0.98 (m, 1H), 0.98-0.93 (m, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz; mixture of two diastereomers) δ 174.2, 155.0, 129.6, 128.1, 118.9, 118.8, 83.1, 79.3, 65.0, 60.9, 34.9, 31.5, 25.8, 25.5, 25.4, 24.8, 24.7, 15.2. **^{11}B{^{1}H} NMR** ($CDCl_3$, 128 MHz) 33.7. **R_f** 0.27 (hexane/EtOAc = 10:1). **HRMS** (ESI): *m/z* calculated for $C_{23}H_{33}O_5BCl_2Na^+$ $[M+Na]^+$: 493.1690, found: 493.1692.

***tert*-butyl(2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)diphenylsilane (206j)[9]**



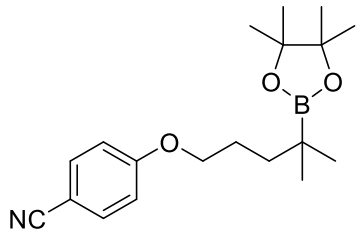
Prepared according to **General procedure** using **205j** (64.9 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane:DCM = 97:3 to 63:37). **206j** was isolated as a colorless solid (74.7 mg, 0.165 mmol, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72-7.63 (m, 4H), 7.42-7.32 (m, 6H), 3.72-3.65 (m, 2H), 1.70-1.64 (m, 2H), 1.11 (s, 12H), 1.04 (s, 9H), 0.90 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 135.7, 134.4, 129.5, 127.7, 83.0, 62.7, 43.7, 27.1, 25.4, 24.7, 19.3. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.9. **R_f** 0.26 (hexane:EtOAc = 20:1). **HRMS (APCI):** m/z calculated for $C_{27}H_{42}O_3BSi$ $[M+H]^+$: 453.2991, found: 453.2993.

4,4,5,5-tetramethyl-2-(2-methyl-5-(p-tolyloxy)pentan-2-yl)-1,3,2-dioxaborolane (206k)



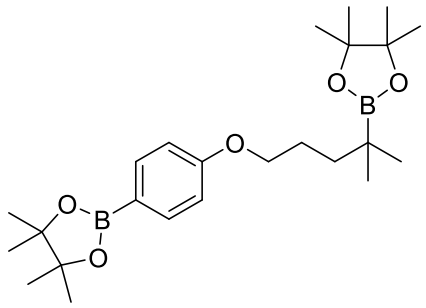
Prepared according to **General procedure** using **205k** (38.1 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 20:1 and hexane:EtOAc = 20:1). **206k** was isolated as a colorless solid (50.6 mg, 0.159 mmol, 79%). **IR** (ATR) ν 2955, 2864, 1615, 1583, 1514, 1474, 1389, 1366, 1345, 1309, 1241, 1204, 1178, 1138, 1061, 1030, 966, 937, 849, 805, 750, 718, 694, 669 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 8.3 Hz, 2H), 3.89 (t, J = 6.9 Hz, 2H), 2.27 (s, 3H), 1.83-1.66 (m, 2H), 1.46-1.34 (m, 2H), 1.22 (s, 12H), 0.96 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.9, 129.8, 129.5, 114.3, 82.9, 68.8, 37.0, 26.2, 24.8, 24.7, 20.4. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 34.0. **R_f** 0.20 (hexane:EtOAc = 30:1). **HRMS (APCI):** m/z calculated for $C_{19}H_{31}O_3BNa$ $[M+Na]^+$: 341.2259, found: 341.2256.

4-((4-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)benzonitrile (206l)



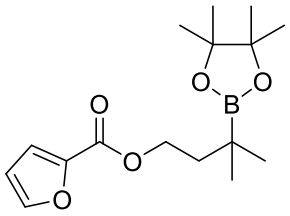
Prepared according to **General procedure** using **205l** (40.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography (silica gel, hexane:EtOAc = 8:1, twice). **206l** was isolated as a colorless solid (46.0 mg, 0.140 mmol, 70%). **IR** (ATR) ν 2976, 2935, 2862, 2217, 1605, 1573, 1509, 1472, 1388, 1366, 1342, 1304, 1266, 1202, 1175, 1140, 1111, 1022, 964, 935, 849, 829, 760, 716 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59-7.53 (m, 2H), 6.97-6.90 (m, 2H), 3.98 (t, J = 6.7 Hz, 2H), 1.83-1.72 (m, 2H), 1.44-1.36 (m, 2H), 1.22 (s, 12H), 0.96 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.6, 134.0, 119.5, 115.3, 103.7, 83.2, 69.3, 37.0, 26.0, 24.9, 24.8. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.9. **R_f** 0.23 (hexane:EtOAc = 8:1). **HRMS (APCI):** m/z calculated for $C_{19}H_{28}NO_3BNa$ $[M+Na]^+$: 352.2054, found: 352.2059.

4,4,5,5-tetramethyl-2-(4-((4-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)phenyl)-1,3,2-dioxaborolane (206m)



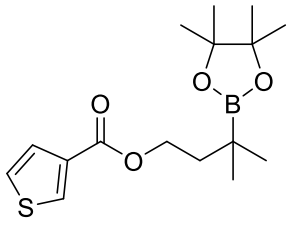
Prepared according to **General procedure** using **205m** (60.4 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane:EtOAc = 95:5 to 74:26 and hexane:EtOAc = 10:1). **206m** was isolated as a colorless solid (58.1 mg, 0.135 mmol, 68%). **IR** (ATR) ν 2978, 2949, 2909, 2862, 1603, 1567, 1473, 1389, 1355, 1306, 1266, 1247, 1208, 1139, 1107, 1091, 1018, 965, 861, 849, 837, 820, 762, 736, 717, 692, 670, 654 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 3.95 (t, J = 6.8 Hz, 2H), 1.82-1.70 (m, 2H), 1.45-1.36 (m, 2H), 1.32 (s, 12H), 1.22 (s, 12H), 0.95 (s, 6H). **^{13}C{^{1}H} NMR** (101MHz, $CDCl_3$) δ 161.9, 136.6, 114.0, 83.6, 83.1, 68.7, 37.1, 26.3, 25.0, 24.9, 24.8. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 34.1, 30.3. **R_f** 0.29 (hexane:EtOAc = 12:1). **HRMS (APCI):** m/z calculated for $C_{24}H_{40}O_5B_2Na$ $[M+Na]^+$: 453.2954, found: 453.2963.

3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl furan-2-carboxylate (206n)



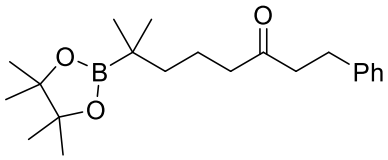
Prepared according to **General procedure** using **205n** (36.0 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 8:1 and hexane:EtOAc = 10:1). **206n** was isolated as a colorless solid (40.8 mg, 0.132 mmol, 66%). **IR** (ATR) ν 2975, 2939, 2863, 1717, 1580, 1474, 1390, 1358, 1298, 1230, 1168, 1138, 1115, 1077, 1013, 965, 885, 852, 762, 717, 693, 670 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, J = 0.9 Hz, 1H), 7.15 (d, J = 3.4 Hz, 1H), 6.49 (dd, J = 3.4, 1.7 Hz, 1H), 4.35 (t, J = 7.7 Hz, 2H), 1.76 (t, J = 7.7 Hz, 2H), 1.22 (s, 12H), 1.01 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.9, 146.2, 145.2, 117.7, 111.8, 83.3, 63.7, 39.1, 25.1, 24.8. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.6. **R_f** 0.25 (hexane/EtOAc = 8:1). **HRMS (APCI):** m/z calculated for $C_{16}H_{26}O_5B$ $[M+H]^+$: 309.1868, found: 309.1868.

3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl thiophene-3-carboxylate (206o)



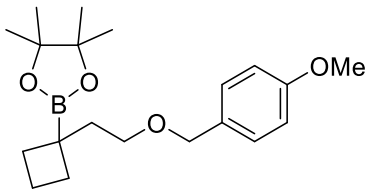
Prepared according to **General procedure** using **205o** (39.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 10:1 and hexane:EtOAc = 24:1). **206o** was isolated as a colorless solid (47.5 mg, 0.146 mmol, 73%). **IR** (ATR) ν 3098, 2975, 2940, 2861, 1712, 1520, 1474, 1410, 1373, 1355, 1298, 1262, 1191, 1165, 1135, 1106, 953, 868, 850, 834, 749, 710, 686 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 3.0, 1.0 Hz, 1H), 7.52 (dd, J = 5.1, 1.0 Hz, 1H), 7.28 (dd, J = 5.1, 3.1 Hz, 1H), 4.31 (t, J = 7.6 Hz, 2H), 1.76 (t, J = 7.6 Hz, 2H), 1.23 (s, 12H), 1.02 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 163.0, 134.3, 132.5, 128.1, 125.9, 83.3, 63.5, 39.2, 25.2, 24.8. **R_f** 0.27 (hexane:EtOAc = 10:1). **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.7. **HRMS (APCI):** m/z calculated for $C_{16}H_{26}O_4BS$ $[M+H]^+$: 325.1639, found: 325.1644.

7-methyl-1-phenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octan-3-one (206p)



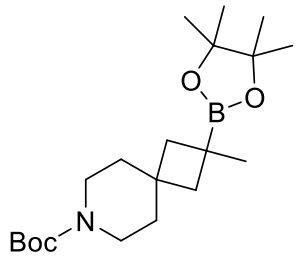
Prepared according to **General procedure** using **205p** (43.3 mg, 0.20 mmol). Purification by silica gel column chromatography (hexane to hexane:EtOAc = 9:1) afforded **206p** as pale brown oil (31.2 mg, 0.0902 mmol, 45%). **IR** (ATR) ν 2975, 2935, 2861, 1712, 1474, 1369, 1305, 1137, 966, 853, 747, 694 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30-7.23 (m, 2H), 7.21-7.14 (m, 3H), 2.89 (t, J = 7.8 Hz, 2H), 2.72 (t, 2H, J = 7.8 Hz), 2.36 (t, J = 7.4 Hz, 2H), 1.58-1.47 (m, 2H), 1.27-1.17 (m, 14H), 0.91 (s, 6H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 210.3, 141.2, 128.5, 128.3, 126.0, 83.0, 44.1, 44.0, 40.6, 29.8, 24.73, 24.69, 20.8. **^{11}B NMR** ($CDCl_3$, 128 MHz) 34.1. **R_f** 0.24 (hexane:EtOAc = 10:1). **HRMS** (ESI): *m/z* calculated for $C_{21}H_{33}O_3BNa^+$ $[M+Na]^+$: 367.2415, found: 367.2413.

2-(1-(2-((4-methoxybenzyl)oxy)ethyl)cyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (206q)



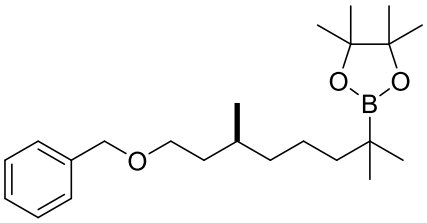
Prepared according to **General procedure** using **205q** (43.7 mg, 0.20 mmol). Purification by silica gel column chromatography twice (hexane to hexane:EtOAc = 9:1 and hexane:EtOAc = 20:1) afforded **206q** as pale brown oil (57.8 mg, 0.167 mmol, 83%). **IR** (ATR) ν 2969, 2926, 2854, 1609, 1512, 1379, 1294, 1240, 1142, 1121, 1092, 1060, 1028, 965, 846, 675 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28-7.22 (m, 2H), 6.88-6.83 (m, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.33 (t, J = 7.0 Hz, 2H), 2.16-2.07 (m, 2H), 1.99-1.82 (m, 4H), 1.77-1.66 (m, 2H), 1.22 (s, 12H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 159.1, 131.1, 129.4, 113.8, 83.1, 72.5, 67.7, 55.4, 39.6, 30.4, 24.8, 18.5. **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 34.1. **R_f** 0.13 (hexane:EtOAc = 20:1). **HRMS** (ESI): *m/z* calculated for $C_{20}H_{31}O_4BNa^+$ $[M+Na^+]^+$: 369.2208, found: 369.2209.

tert-butyl 2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate (206r)



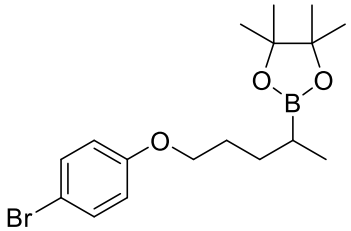
Prepared according to **General procedure** using **205r** (47.5 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 8:1). **206r** was isolated as a colorless solid (62.4 mg, 0.155 mmol, 85%). **IR** (ATR) ν 2972, 2916, 2850, 1685, 1459, 1426, 1364, 1311, 1271, 1245, 1177, 1140, 1077, 1008, 969, 858, 831, 767, 711, 689, 671 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.36-3.18 (m, 4H), 2.14-1.99 (m, 2H), 1.55-1.42 (m, 15H), 1.24 (s, 12H), 1.20 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 155.0, 83.1, 79.0, 41.5, 40.0, 36.9, 32.3, 28.4, 26.5, 24.6. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.8. **R_f** 0.29 (hexane:EtOAc = 8:1). **HRMS (APCI):** m/z calculated for $C_{20}H_{36}BNO_4Na$ $[M+Na]^+$: 388.2630, found: 388.2629.

(*S*)-2-(8-(benzyloxy)-2,6-dimethyloctan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (206s)



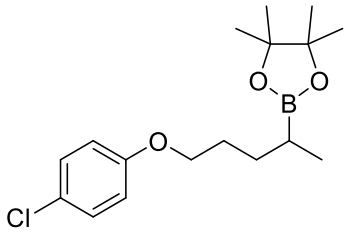
Prepared according to **General procedure** using **205s** (49.3 mg, 0.20 mmol). The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 4:1 and hexane:EtOAc = 20:1). **206s** was isolated as a colorless solid (58.3 mg, 0.156 mmol, 79%). **IR** (ATR) ν 2927, 2859, 1474, 1454, 1388, 1363, 1304, 1197, 1139, 1099, 1028, 966, 855, 733, 694, 671 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 4H), 7.30-7.23 (m, 1H), 4.49 (s, 2H), 3.55-3.44 (m, 2H), 1.71-1.61 (m, 1H), 1.60-1.52 (m, 1H), 1.47-1.36 (m, 1H), 1.32-1.17 (m, 17H), 1.14-1.04 (m, 1H), 0.91 (s, 6H), 0.86 (d, J = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 138.9, 128.5, 127.7, 127.6, 83.0, 73.0, 68.9, 41.6, 38.1, 37.0, 29.9, 25.1, 25.0, 24.8, 23.9, 19.8. **R_f** 0.21 (hexane:EtOAc = 20:1). **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 34.1. **HRMS (APCI):** m/z calculated for $C_{23}H_{39}O_3BNa$ $[M+Na]^+$: 397.2885, found: 397.2892.

2-(5-(4-bromophenoxy)pentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (206t)



Prepared according to **General procedure** using **205t** (48.2 mg, 0.20 mmol) and PhI (22.3 μL, 0.20 mmol, 1.0 equiv) as an additive. The crude mixture was purified by flash column chromatography twice (silica gel, hexane to hexane:EtOAc = 82:18 and hexane:EtOAc = 20:1). **206t** was isolated as a colorless solid (54.4 mg, 0.147 mmol, 74%). **IR** (ATR) ν 2976, 2935, 2862, 2217, 1605, 1573, 1509, 1472, 1388, 1366, 1342, 1304, 1266, 1202, 1175, 1140, 1111, 1071, 1022, 964, 935, 849, 829, 760, 716, 693, 673 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 2H), 6.82-6.71 (m, 2H), 3.90 (t, J = 6.6 Hz, 2H), 1.86-1.72 (m, 2H), 1.64-1.53 (m, 1H), 1.49-1.37 (m, 1H), 1.23 (s, 12H), 1.10-0.97 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.4, 132.3, 116.5, 112.6, 83.1, 68.6, 29.5, 28.6, 24.9, 24.8, 15.6. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.5. **R_f** 0.21 (hexane/EtOAc = 20:1). **HRMS** (APCI): *m/z* calculated for $C_{17}H_{27}O_3BBr$ $[M+H]^+$: 369.1231, found: 369.1233.

2-(5-(4-chlorophenoxy)pentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (206u)



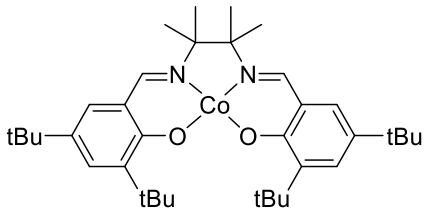
Prepared according to **General procedure** using **205u** (39.3 mg, 0.20 mmol) and PhI (22.3 μL, 0.20 mmol, 1.0 equiv) as an additive. Purification by silica gel column chromatography twice (hexane to hexane:EtOAc = 9:1 and hexane:EtOAc = 40:1) afforded **206u** as colorless oil (51.0 mg, 0.162 mmol, 81%). **IR** (ATR) ν 2974, 2926, 2874, 1596, 1579, 1493, 1472, 1369, 1316, 1281, 1241, 1206, 1142, 1130, 1015, 965, 855, 840, 756, 705, 665 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.23-7.16 (m, 2H), 6.83-6.76 (m, 2H), 3.91 (t, J = 6.6 Hz, 2H), 1.84-1.71 (m, 2H), 1.63-1.52 (m, 1H), 1.47-1.35 (m, 1H), 1.24 (s, 12H), 1.10-0.97 (m, 4H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 157.8, 129.2, 125.2, 115.8, 82.9, 68.6, 29.4, 28.5, 24.8, 24.7, 15.5. **^{11}B{^{1}H} NMR** ($CDCl_3$, 128 MHz) δ 33.8. **R_f** 0.22 (hexane/EtOAc = 40:1). **HRMS** (ESI): *m/z* calculated for $C_{17}H_{26}O_3BClNa^+$ $[M]^+$: 347.1556, found: 347.1557.

Procedure for Markovnikov Hydroboration of 206a on a 1 mmol Scale

In an argon-filled glove box, a flame dried screw-capped vial was charged with alkene **205a** (162.2 mg, 1.0 mmol), DMF (10 mL, 0.1 M), 4CzIPN **81** (7.9 mg, 0.01 mmol, 1 mol%), **189** (30.3 mg, 0.05 mmol, 5 mol%), Me-DHP **202** (802.0 mg, 3.0 mmol, 3.0 equiv), collidinium triflate **64** (271.3 mg, 1.0 mmol, 1.0 equiv), and bis(catecolate)diboron ($B_2(cat)_2$) (285.4 mg, 1.2 mmol, 1.2 equiv). The vial was capped with a screw-cap and removed from the glove box. The reaction vial was placed in the photoreactor with a cooling fan. The temperature of the reactor was kept at approximately 25 °C. After stirring for 24 hours under photo-irradiation, pinacol in triethylamine (8.0 mL, ca. 1.6 M, ca. 12.8 mmol) was added to the mixture. After stirring for additional 2 hours at room temperature, EtOAc (50 mL), water (50 mL), and sat. NH_4Cl aq. were added to the resulting mixture. The mixture was extracted with EtOAc (50 mL) three times, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (silica gel, hexane to hexane:EtOAc = 20:1 and hexane:EtOAc = 19:1) to afford the desired alkyl boronic esters **206a** as a colorless oil (237.8 mg, 0.819 mmol, 82%).

4. Preparation for Cobalt Complexes

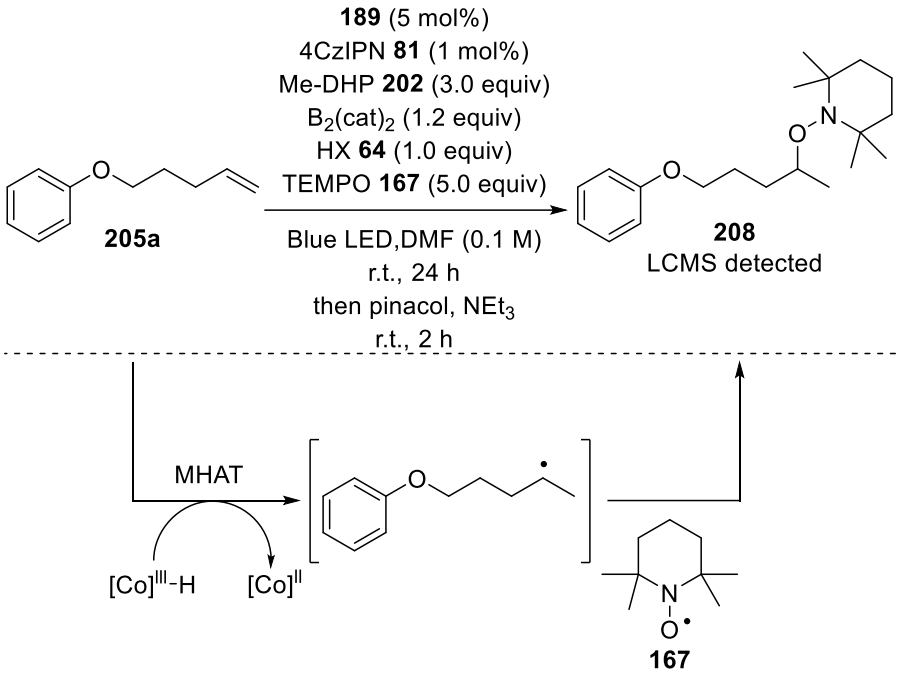
189[26]and the corresponding ligand[26] for the cobalt complexes were prepared according to the reported procedure.



189

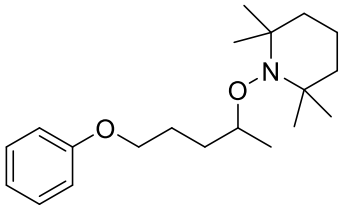
Figure S21. Structure of cobalt catalysts.

5. Detection of Radical Intermediate by TEMPO-trapping



In an argon-filled glove box, a flame dried screw-capped vial was charged with alkene **205a** (16.2 mg, 0.1 mmol), DMF (1 mL, 0.1 M), 4CzIPN (0.79 mg, 0.001 mmol, 1 mol%), **189** (3.0 mg, 0.01 mmol, 5 mol%), Me-DHP **202** (80.2 mg, 0.3 mmol, 3.0 equiv), collidine triflate **64** (27.1 mg, 0.1 mmol, 1.0 equiv), and bis(catecolate)diboron ($B_2(cat)_2$) (28.5 mg, 0.12 mmol, 1.2 equiv). The vial was capped and removed from the glove box. The reaction vial was placed in the photoreactor with a cooling fan so that the temperature of the reaction mixture was kept approximately at 25 ºC. After stirring for 24 hours under photo-irradiation, pinacol in triethylamine (0.8 mL, ca. 1.6 M, ca. 12.8 mmol) was added. After stirring for 2 hours at room temperature, EtOAc (5 mL), water (5 mL) and sat. NH_4Cl aq. (5 mL) was added. The mixture was extracted with EtOAc (5 mL x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was subjected to LC-MS analysis. The m/z of **208** ($[M+Na]^+$: 341.95) was observed by LC-MS analysis of the crude mixture (Figure S22). The identity of **208** was further confirmed by comparing the retention time in LC-MS to that of **6** independently prepared by Norton's method.[27]

2,2,6,6-tetramethyl-1-((5-phenoxypentan-2-yl)oxy)piperidine (208)



In a 100 mL round-bottom flask, TBHP (0.18 mL, approx. 5 M solution in decane) was added to solution of **205a** (162 mg, 1.0 mmol, 1.0 equiv), **189** (15.1 mg, 0.025 mmol, 2.5 mol%), $NaBH_4$ (75.7 mg, 2.0 mmol, 2.0 equiv), and TEMPO (156.3 mg, 1.0 mmol, 1.0 equiv) in EtOH/H_2O = 10/1 (22 mL) under an argon atmosphere at room temperature. The resulting mixture was stirred for 1 hour at room temperature. The crude reaction mixture was loaded on top of a silica gel plug, and the plug was washed with DCM (using a volume of solvent approximately equal to that of the silica gel) six times, and the resulting filtrate was concentrated. The crude was purified by silica gel column chromatography (hexane:EtOAc = 49:1) to afford **208** as colorless oil (36.5 mg, 0.114 mmol, 11%).

IR (ATR) ν 2968, 2927, 2868, 1600, 1586, 1496, 1470, 1374, 1360, 1301, 1242, 1207, 1172, 1131, 1078, 1034, 1003, 991, 956, 939, 926, 879, 828, 802, 750, 712, 690 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29-7.24 (m, 2H), 6.98-6.85 (m, 3H), 4.04-3.90 (m, 3H), 1.95-1.83 (m, 2H), 1.83-1.70 (m, 1H), 1.64-1.52 (m, 2H), 1.52-1.38 (m, 4H), 1.37 (m, 1H), 1.20 (d, J = 6.2 Hz, 3H), 1.17-1.00 (m, 12H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 101 MHz) δ 159.1, 129.4, 120.4, 114.5, 77.9, 68.2, 60.1, 59.1, 40.3, 34.4, 32.7, 25.6, 20.4, 19.8, 17.3. **HRMS** (APCI): *m/z* calculated for $C_{20}H_{34}NO_2Na$ $[M+Na]^+$: 320.2584, found: 320.2579.

UV-detection of TEMPO-trapping experiment

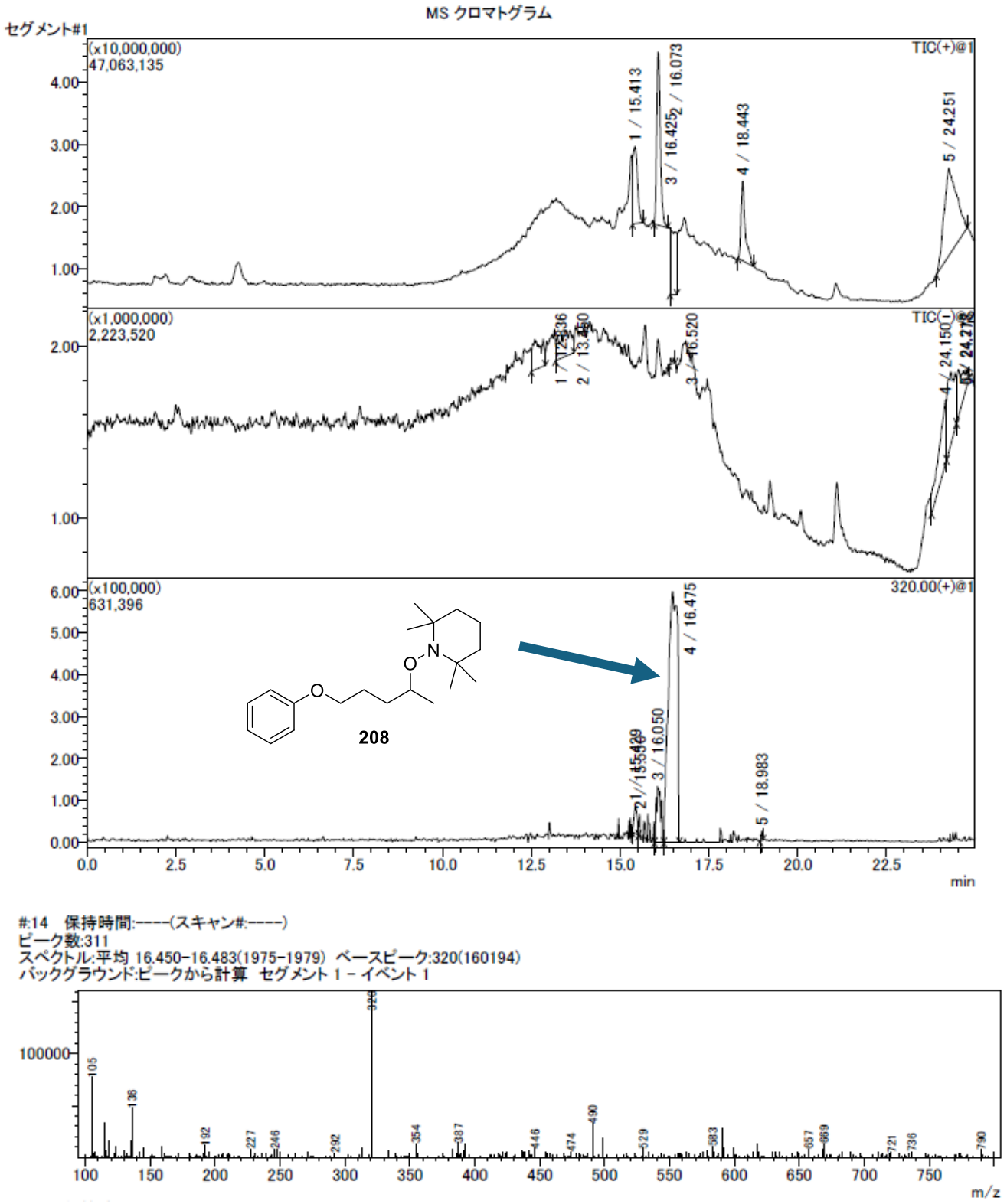


Figure S22. LC-MS measurements for the reaction mixture of TEMPO-trapping experiment.

LC/MS of authentic sample **208**

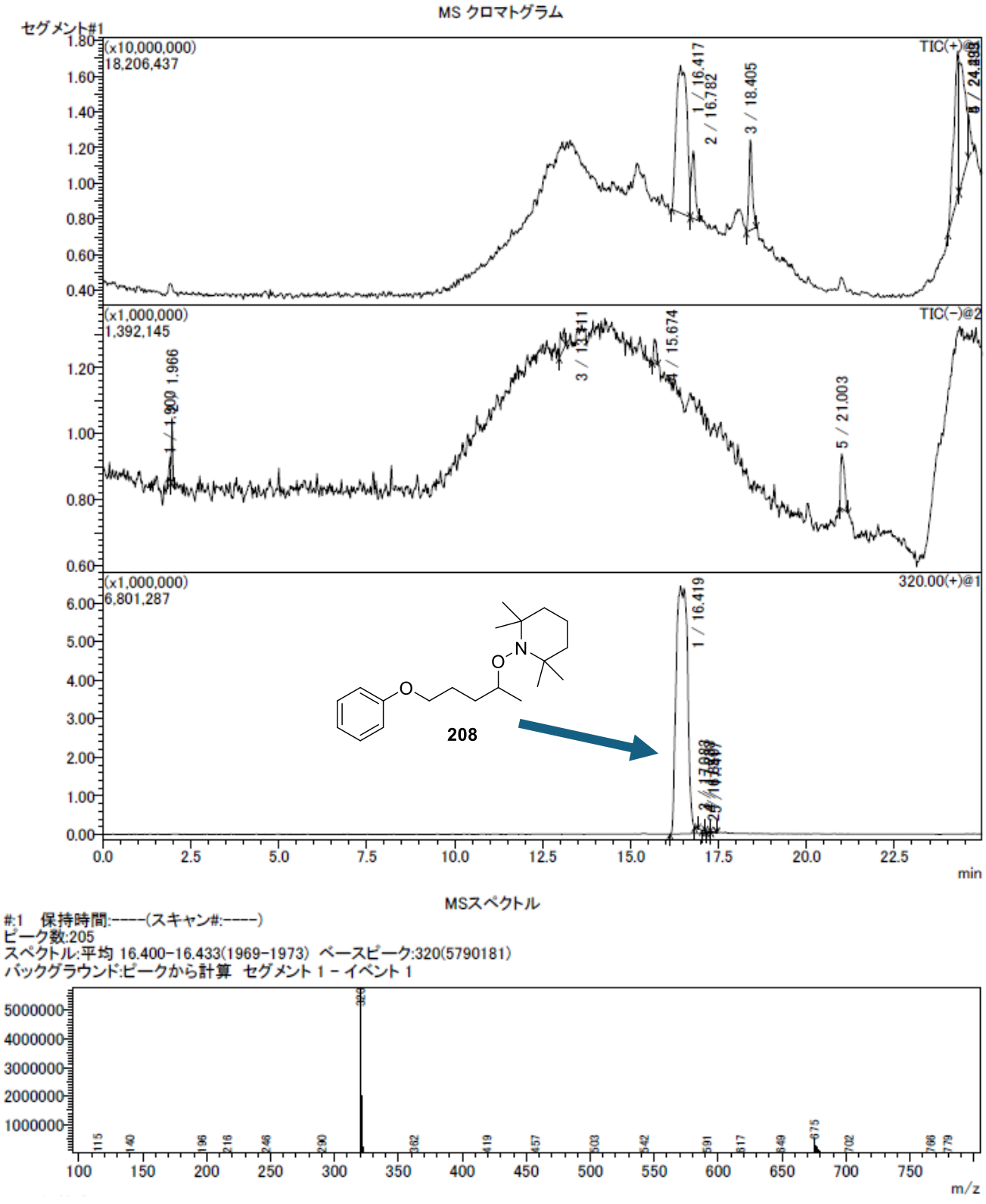
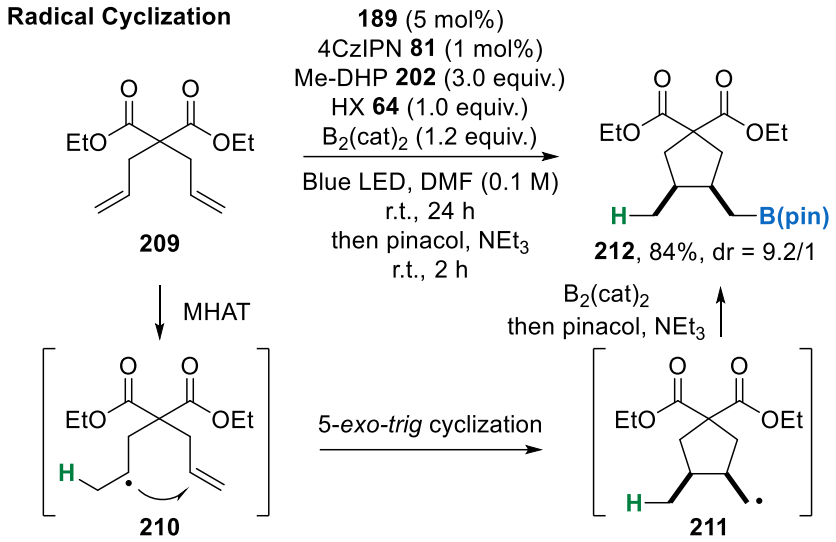


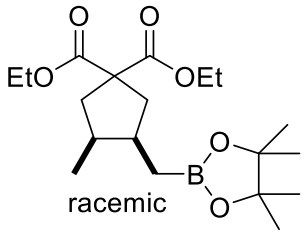
Figure S23. LC-MS measurements for the authentic sample **208**.

4.2. Radical Cyclization of 212



In an argon filled glove box, a flame dried screw-capped vial was charged with alkene **209** (48.0 mg, 0.2 mmol), DMF (2 mL, 0.1 M), 4CzIPN **81** (1.6 mg, 0.002 mmol, 1 mol%), **189** (6.1 mg, 0.01 mmol, 5 mol%), Me-DHP **202** (160.4 mg, 0.6 mmol, 3.0 equiv), collidine triflate **64** (54.3 mg, 0.2 mmol, 1.0 equiv), and bis(catecolate)diboron ($B_2(cat)_2$) (57.1 mg, 0.24 mmol, 1.2 equiv). The vial was capped and removed from the glove box. The reaction vial was placed in the photoreactor with a cooling fan so that the temperature of the reaction mixture was kept approximately at 25 °C. After stirring for 24 hours under the photo-irradiation conditions, pinacol in triethylamine (1.6 mL, ca. 1.6 M, ca. 12.8 mmol) was added. After stirring for 2 hours at room temperature, EtOAc (10 mL), water (10 mL), and sat. NH_4Cl aq. (10 mL). were added to the mixture. The mixture was extracted with EtOAc (10 mL) three times, and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude mixture was purified by silica gel column chromatography twice (silica gel, hexane to hexane:EtOAc = 8:1 and hexane:EtOAc = 8:1) to afford alkyl boronic esters **212** (61.4 mg, 0.167 mmol, 84%).

diethyl 3-methyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclopentane-1,1-dicarboxylate (212)



Isolated as *cis*:*trans* = 9.2:1 mixture of stereoisomers. The stereochemistry was determined with the reported spectral data of *trans*-**212**.[11b] **IR** (ATR) ν 2977, 2933, 1727, 1464, 1445, 1368, 1345, 1316, 1246, 1200, 1177, 1143, 1109, 1051, 967, 885, 846, 675 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 594 MHz) major isomer: δ 4.23-4.11 (m, 4H), 2.45-2.36 (m, 2H), 2.26-2.12 (m, 2H), 2.01-1.93 (m, 2H), 1.29-1.23 (m, 18H), 0.83 (d, J = 7.0 Hz, 3H), 0.81-0.69 (m, 2H). minor isomer: δ 4.23-4.11 (m, 4H), 2.60 (dd, J = 13.5, 7.1 Hz, 1H), 2.48 (dd, J = 13.3, 6.9 Hz, 1H), 1.79-1.68 (m, 2H), 1.64-1.47 (m, 2H), 1.23-1.22 (m, 18H), 1.02 (dd, J = 15.4, 4.5 Hz, 1H), 0.97 (d, J = 7.0 Hz, 3H), 0.62 (dd, J = 15.3, 9.2 Hz, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 149 MHz) major isomer: δ 173.2, 173.0, 83.05, 61.29, 59.2, 41.2, 40.9, 38.7, 36.9, 24.9, 24.8, 17.4, 15.2, 14.1, 11.8. minor isomer: δ 173.1, 83.11, 61.24, 58.2, 43.1, 42.6, 42.44, 42.38, 25.0, 17.4. **^{11}B{^{1}H} NMR** (191 MHz, $CDCl_3$) δ 33.0. **HRMS** (ESI): *m/z* calculated for $C_{19}H_{33}BO_6Na^+$ $[M+Na]^+$: 391.2262, found: 391.2268.

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結語

以上筆者は、コバルトサレン触媒と光酸化還元触媒の協働系による MHAT を用いたアルケンの分子変換の反応系の更なる拡張と、合成化学的に有用な化合物合成を目指した反応開発研究を行った。得られた結果の総括を以下に述べる。

・コバルトサレン触媒と光酸化還元触媒の協働による MHAT を用いたアルケン異性化反応による多置換エナミド合成法を開発した。この多置換エナミド合成法は、MHAT 特有の高い官能基許容性を持ち、還元的に脱離しやすいブロモ基や無保護アミノ酸の誘導体、医薬品の誘導体においても適用が可能であった。さらに、先行例では適用できなかった第 3 級アミドにも適用が可能であった。
・コバルトサレン触媒と光酸化還元触媒の協働による MHAT を用いた様々な置換パターンを持つ不活性アルケンのマルコフニコフヒドロホウ素化反応を開発した。MHAT を用いた位置選択的なアルキルラジカル生成を活用することで、不活性末端アルケン、不活性 1,1-2 置換アルケン、不活性 3 置換アルケンいずれにおいても完全なマルコフニコフ選択性でヒドロホウ素化反応が進行することを見出した。

以上の結果は、1) MHAT を用いたアルケン異性化反応が、合成化学的に有用なヘテロ原子置換アルケンの合成に有用な手法であること、2) MHAT による位置選択的なアルキルラジカル生成が、位置選択性の完全な制御が困難なアルケンのヒドロ官能基化反応を可能とすることを、を示し、MHAT を用いたアルケンの分子変換の有用性を示す例となる。

本研究がコバルトサレン触媒と光酸化還元触媒の協働系による MHAT を用いたアルケンの分子変換の反応系の更なる拡張と、合成化学的に有用な化合物合成を目指した反応開発研究の発展の一助になることを願う。

公表論文

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公表予定論文

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