Mannich 反応を利用した β-アミノ-α-ケト酸誘導体の触媒的不斉合成法の開発とペプチドへの合成展開

２０２２年度

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目次

略語表

Ac	acetyl
Alloc	allyloxycarbonyl
aq.	aqueous
AZADO	2-azaadamantane-*N*-oxyl
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
Bz	benzoyl
c	cyclic
Cbz	benzyloxycarbonyl
conc.	concentrated
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,8-diazabicylo[5,4,0]undec-7-ene
DFT	density functional theory
DIC	*N*,*N'*-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DODT	3,6-dioxa-1,8-octanedithiol
dr	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EE	1-ethoxyethyl
er	enantiomeric ratio
Et	ethyl
Fmoc	fluorenylmethoxycarbonyl
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide

	hexafluorophosphate
HBTU	1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium 3-oxide hexafluorophosphate
HPLC	high performance liquid chromatography
i	*iso*
Lg	leaving group
LiHMDS	lithium hexamethyldisilazide
L-Selectride	lithium tri-*sec*-butylborohydride
Me	methyl
MOM	methoxymethyl
MS	molecular sieve
n	*normal*
NBD	2,5-norbornadiene
o	*ortho*
p	*para*
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
Pg	protecting group
Ph	phenyl
Pr	propyl
rsm	recovered starting material
sat.	saturated
SFC	supercritical fluid chromatography
SPPS	solid-phase peptide synthesis
t	*tertiary*
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Trt	triphenylmethyl
Ts	toluenesulfonyl

序論

第一節 β-アミノ-α-ケト酸の性質と利用

α-アミノ酸の主鎖が一炭素増炭されたβ-アミノ酸は、それ自身の持つ興味深い生物活性や、側鎖の置換様式に応じて 8, 10, 12, 14-ヘリックスといったα-ペプチドとは異なる多様な二次構造を生じることを特徴とする特殊アミノ酸であり、その合成も含め古くから研究がなされてきた[1,2]。また、α-ペプチドに対する構造の差異から β-ペプチドがプロテアーゼへの加水分解耐性を有することも近年明らかとされるなど、依然精力的に研究されている[1]。

そのような β-アミノ酸の内、特に α 位にカルボニル基を有する β-アミノ-α-ケト酸は、カルボキシ基に隣接する求電子性の高い α 位が求核性官能基と共有結合を容易に形成する性質からいくつかの生物活性物質や医薬品の活性部位を担っており、他のアミノ酸には見られない特有の生物活性を発現する重要な構造である (Figure 1)[3]。例えば海産天然物である Cyclotheonamide 類は、ホモケトアルギニン残基の α 位において、セリンプロテアーゼの活性中心とヘミアセタールを形成することがトリプシンなどとの複合体の X 線結晶構造解析から明らかとされている[4]。また抗ウイルス薬として開発された Telaprevir は、C 型肝炎ウイルスの NS3/4A プロテアーゼの活性中心である Ser^{139} と結合することで阻害活性を発現する[5]。近年では更に多様な生物活性を有する化合物群が新たに見出されており、β-アミノ-α-ケト酸誘導体は依然創薬シーズとして期待される[6]。

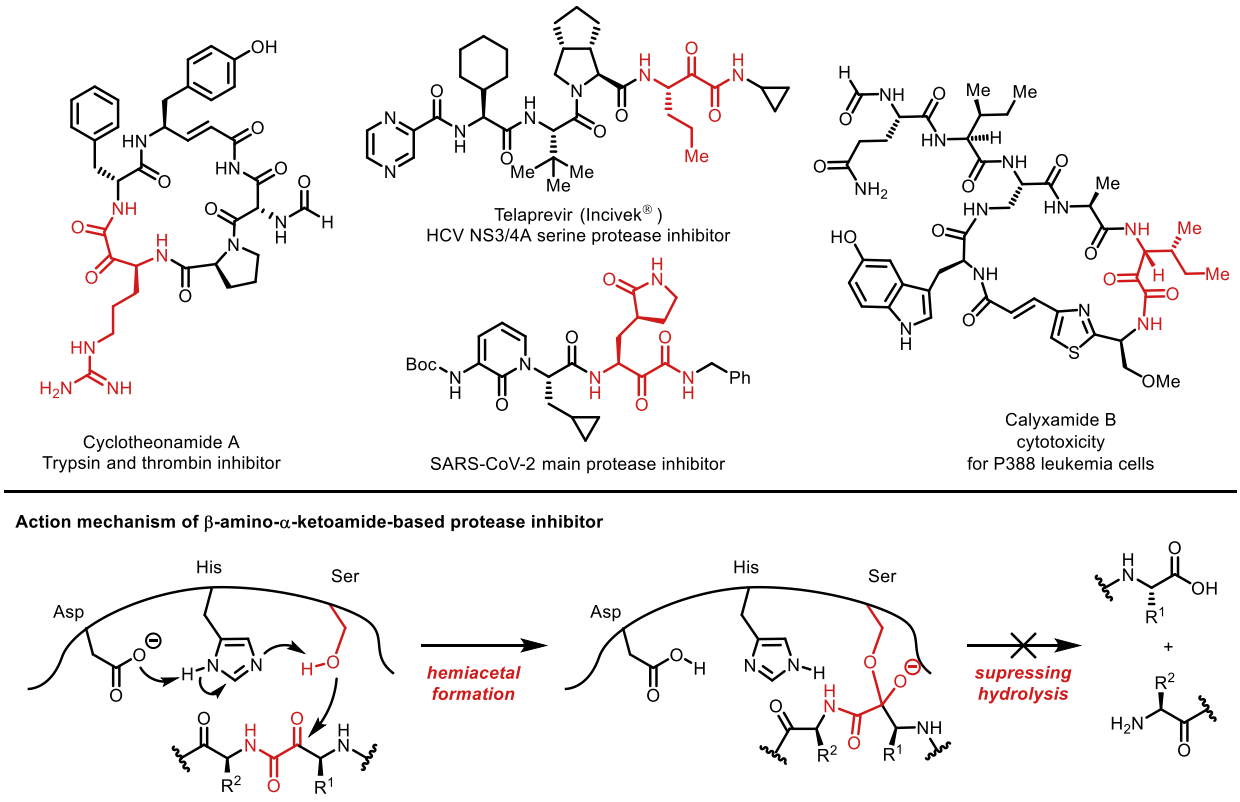
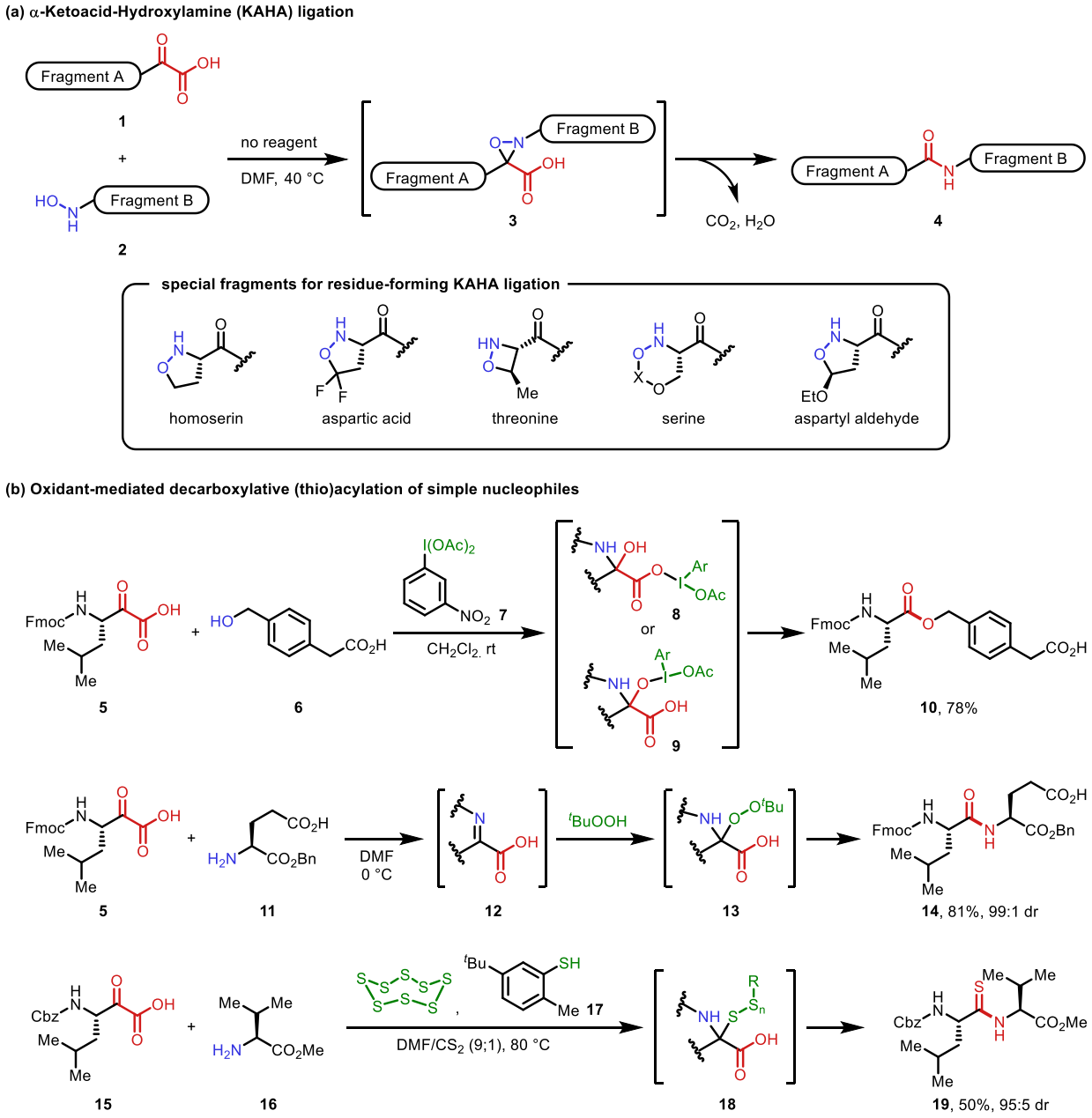


Figure 1. Bioactive natural products and pharmaceuticals containing β-amino-α-ketoamide motif

一方、酸化と脱炭酸を伴うことで β-アミノ-α-ケト酸を α-アミノ酸ユニットの化学選択的な導入に利用する例が報告されている。2006 年 Bode らは、β-アミノ-α-ケト酸 **1** とヒドロキシルアミン **2** を DMF 中 40 °C で撹拌するのみで、オキサジリジン中間体 **3** を経て対応するアミド **4** を与える α-Ketoacid-Hydroxylamine (KAHA) ligation を報告した (Scheme 1a)[7]。従来ペプチド N 末端の酸化によってカップリングフラグメントであるヒドロキシルアミンが調製されてきたが [8]、近年側鎖に酸素官能基を有するアミノ酸残基に相当する特殊なビルディングブロックが種々開発され [9]、フラグメントカップリングによるタンパク質の化学合成へ応用されている。また 2018 年竹本らは、β-アミノ-α-ケト酸に対し求電子的な酸化剤である超原子価ヨウ素 **7** を作用させることで、α 位でのヘミアセタール形成を利用

Scheme 1. Decarboxylative Condensation Using β-Amino-α-ketoacids

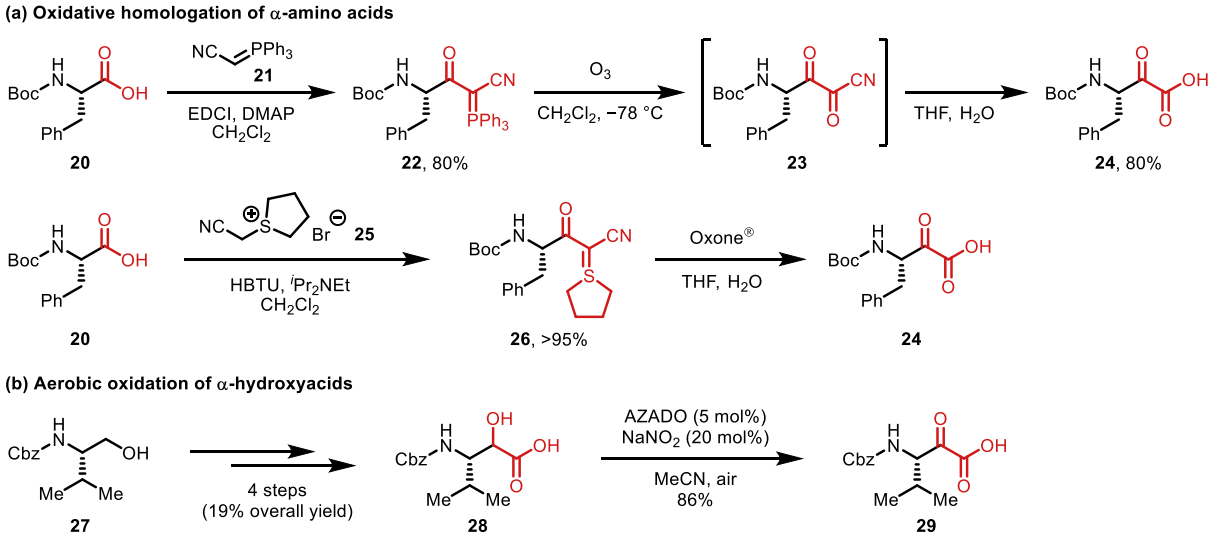


したアルコールの化学選択的なアシル化を達成し[10a]、2019 年、2020 年にはヒドロペルオキシドや単体硫黄とチオール **17** から生じるヒドロポリスルフィドといった求核的な酸化剤を用いることで、単純なアミンの(チオ)アシル化にも成功している (Scheme 1b)[10b,c]。これらの脱炭酸型縮合は縮合剤を用いる一般的な縮合とは異なり **12** のような α 位でのイミン形成を経由する機構で進行するため、従来の手法とは異なる反応性、化学選択性を示す点が特徴である。

第二節 β−アミノ−α−ケト酸の合成

β-アミノ-α-ケト酸の不斉合成法としては、入手容易な α-アミノ酸の増炭と酸化を伴う手法が一般的に用いられる (Scheme 2a)。1994 年 Wasserman らは、α-アミノ酸 **20** とリンイリド **21** を縮合し、得られた α-アシルシアノホスホラン **22** の O_3 による酸化とアシルシアニド **23** の加水分解によって対応する β-アミノ-α-ケト酸 **24** が得られることを報告した[11a]。また、O_3酸化によって得られるアシルシアニドを利用することで種々の β-アミノ-α-ケトアミド構造を含有する天然物の合成へと展開した[11b]。また 2006 年 Bode らは、上述のリンイリド **21** に代わりより酸化されやすい硫黄イリド **25** を利用することで、Oxone®を用いるより穏和な酸化条件で β-アミノ-α-ケト酸を得る改良法を報告した[12]。これらはキラルプールを利用した手法であり、高い光学純度、変換効率で β-アミノ-α-ケト酸を得ることができるため現在最も一般性の高い方法論に位置付けられているが、キラルプールに存在しない非タンパク質構成アミノ酸への展開は困難であり、また依然強力な酸化剤の使用が不可欠であるため、官能基共存性にも制限がある。一方、α-アミノ酸を直接用いない合成例も 1 例のみ報告されている。2016 年澁谷らは、β-アミノアルコール **27** から調製した β-アミノ-α-ヒドロキシ酸 **28** に対し、AZADO と亜硝

Scheme 2. Preparation of Enantio-enriched β-Amino-α-ketoacids

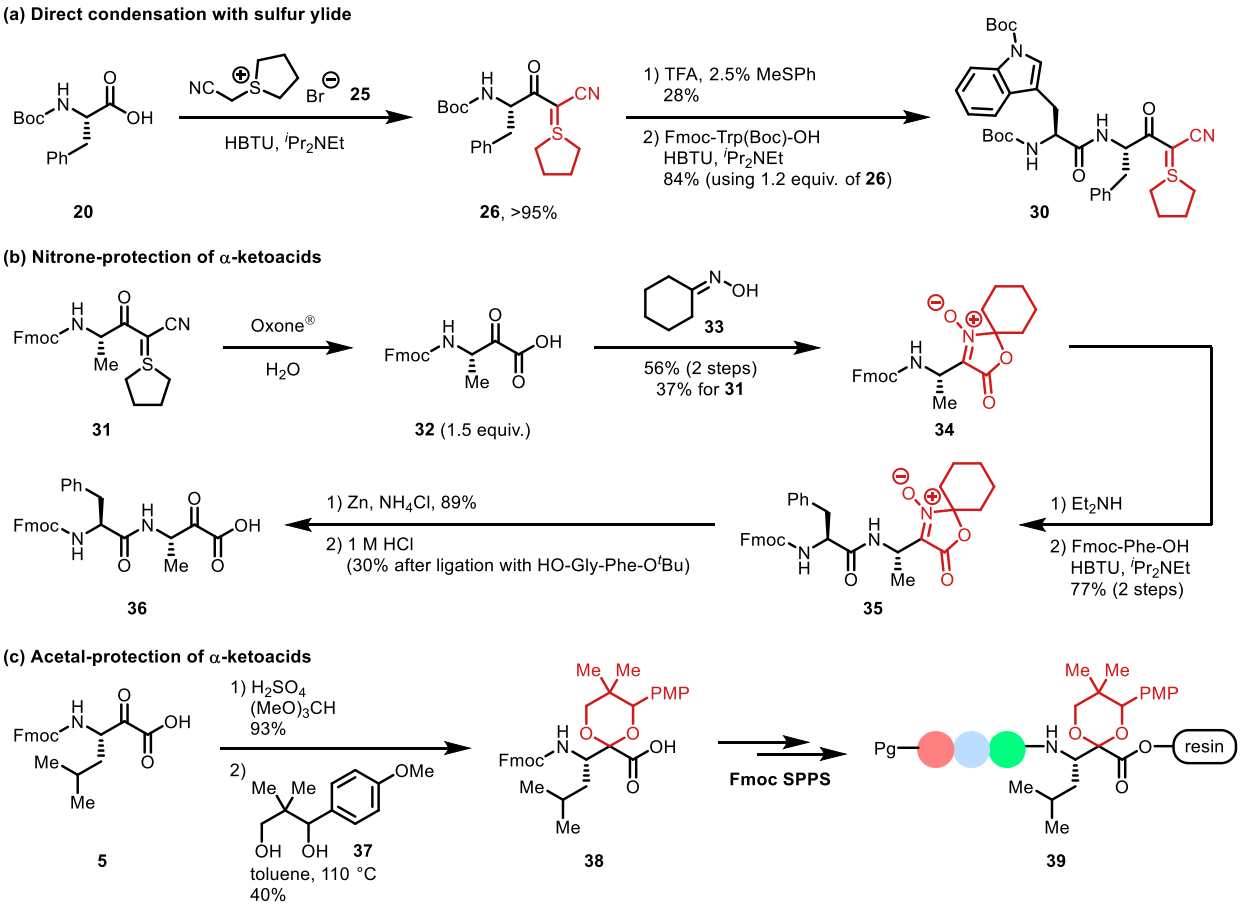


酸ナトリウムを触媒とする化学選択的な空気酸化を行うことにより β-アミノ-α-ケト酸 **29** が得られることを報告したが (Scheme 2b)[13]、光学純度の高い β-アミノ-α-ヒドロキシ酸の入手にはキラルプールが利用されている点は共通の特徴であり、また β-アミノ-α-ヒドロキシ酸の調製にはエピメリ化が進行しやすい α-アミノアルデヒドを経由する複数工程を要するため、変換効率にも課題が残る。

第三節 ペプチド−α−ケト酸、ペプチド−α−ケトアミドの合成

β-アミノ-α-ケト酸を用いた脱炭酸型縮合は、活性エステルを経由する従来の縮合とは異なる反応機構で進行するため、一般に困難なフラグメントカップリングへと応用し得る点で魅力的な反応である。そのため N 末端側にペプチド鎖を伸長したペプチド-α-ケト酸の効率的合成法の開発は重要な研究課題であるが、β-アミノ-α-ケト酸構造の潜在的高反応性のために直接的にペプチド鎖を伸長することは困難であり、通常 β 位の保護を必要とする [14]。Bode らによる硫黄イリドを直接利用するペプチド-α-ケト酸の合成は固相合成では信頼性の高い手法であるが [12b]、液相合成においては極性が高く取り扱いの困難なイリドの性質のために脱保護の効率に課題があり、実用的とは言い難い (Scheme 3a)[12a]。

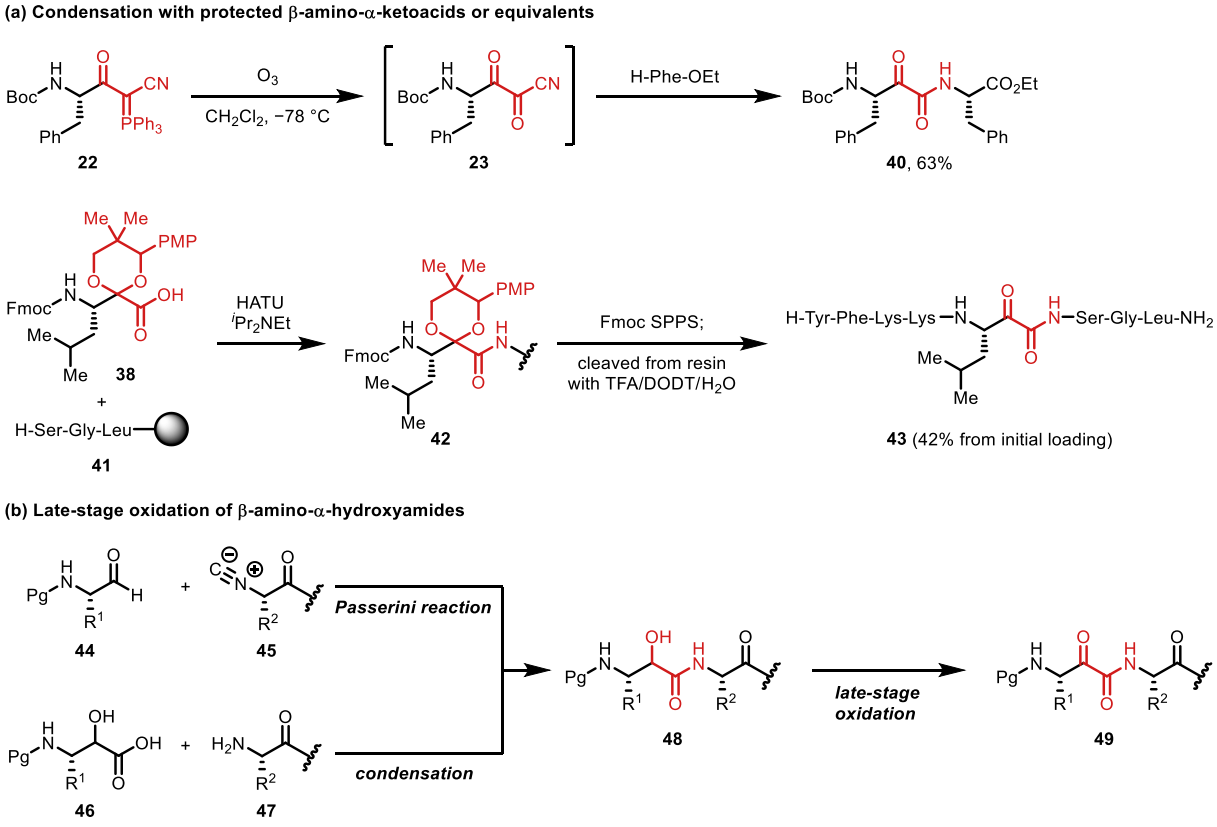
Scheme 3. Synthesis of Peptide-α-ketoacids



2008 年同著者らは、β-アミノ-α-ケト酸に対しオキシム **33** を作用させることで、α-ケト酸構造をニトロンとして化学選択的に保護できることを報告したが、保護工程において過剰量の β-アミノ-α-ケト酸を用いても収率が中程度に留まる点は課題であり、脱保護も円滑ではない (Scheme 3b)[14d]。α 位のカルボニル基を環状アセタール **38** として保護することでペプチド-α-ケト酸を得る手法も確立されているが、やはり保護工程の収率は低く、また固相合成に用いられる合成素子であるため液相合成での利用は検討されていない (Scheme 3c)[14f]。このように、液相におけるペプチド-α-ケト酸の合成法の開発は発展途上な領域である。

また、生物活性物質にみられるペプチド-α-ケトアミドの合成法も同様に限られている。Wasserman らは β-アミノ-α-ケト酸の合成と同様にアシルシアニド **23** を活性中間体としたペプチド-α-ケトアミド合成を [11b]、Bode らはアセタール保護された β-アミノ-α-ケト酸 **38** を用いた Fmoc 固相合成法によるペプチド-α-ケトアミド合成 [15] を達成しているが (Scheme 4a)、現在最も頻用される手法は Passerini 反応や β-アミノ-α-ヒドロキシ酸とアミンの縮合によって得た β-アミノ-α-ヒドロキシアミド **48** の α 位水酸基を酸化する方法である (Scheme 4b)[16]。しかし、ケトアミド β 位でのエピメリ化を抑制するために電子不足かつ込み合った位置にある水酸基を合成最終盤で酸化する必要があるため、酸化されやすい官能基を含む分子に適用することは困難であり、新たな効率的合成法の開発が依然望まれる。

Scheme 4. Construction of Peptide-α-ketoamide Motif

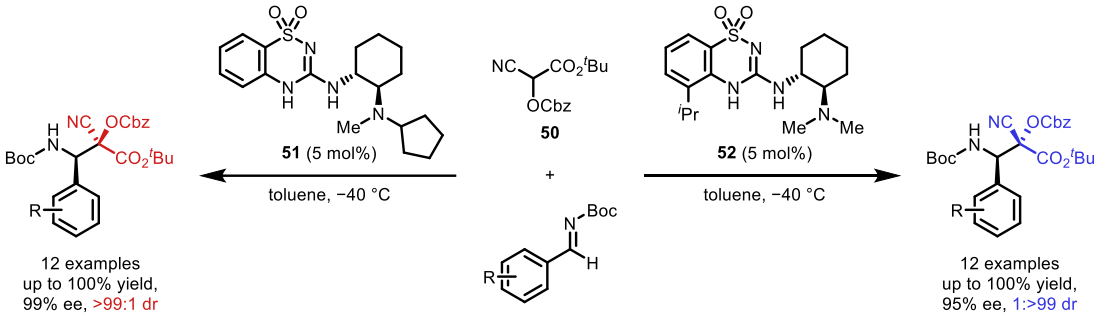


第四節　本研究の概要と構成

前述のように、実用的といえる既存の β-アミノ-α-ケト酸の合成法は α-アミノ酸の酸化的増炭反応に限られており、原料の入手容易性への依存や酸化条件下での官能基共存性がこの手法の適用範囲を制限する大きな課題である。加えて、ペプチド α-ケト酸やペプチド α-ケトアミドの合成には合成中間体である硫黄イリドを直接用いるか、一度 β-アミノ-α-ケト酸を調製した上で反応性の高い α 位を新たな保護基で抑える必要があるが、いずれの方法も保護・脱保護工程の収率が低く変換効率に課題を残す。そこで著者は、立体選択的 Mannich 反応を基盤とする β-アミノ-α-ケト酸等価体の触媒的不斉合成法を開発し、分岐的な誘導体化によって β-アミノ-α-ケト酸や関連するペプチドの効率的合成法を確立することを目指し研究を行った。以下にその概要と構成を述べる。

まず、ベンゾチアジアジン触媒によるジアステレオ分岐的不斉 Mannich 反応の開発について第一章第二節で述べる。α-ケトカルボニル構造に等価なグリオキシル酸シアノヒドリン **50** は、イミンへの求核付加によって β-アミノ-α-ケト酸の等価体を与えるため、β-アミノ-α-ケト酸や関連するペプチドの合成に有用なビルディングブロックである。著者はこの求核剤を用いる不斉 Mannich 反応の開発に取り組み、嵩高いアミン部位を持つベンゾチアジアジン触媒 **51** が芳香族イミンへの付加を高いエナンチオ選択性、ジアステレオ選択性で進行させることを見出した。加えて、置換基を調整した触媒 **52** を用いることでもう一方のジアステレオマーを選択的に得ることにも成功し、すべての立体異性体にアクセスできる立体制御法を確立した。エナンチオ選択的に得られた Mannich 成績体は、脱保護や還元などによって α 位に酸化度を持つ β-アミノ酸誘導体へ変換することが可能であった。

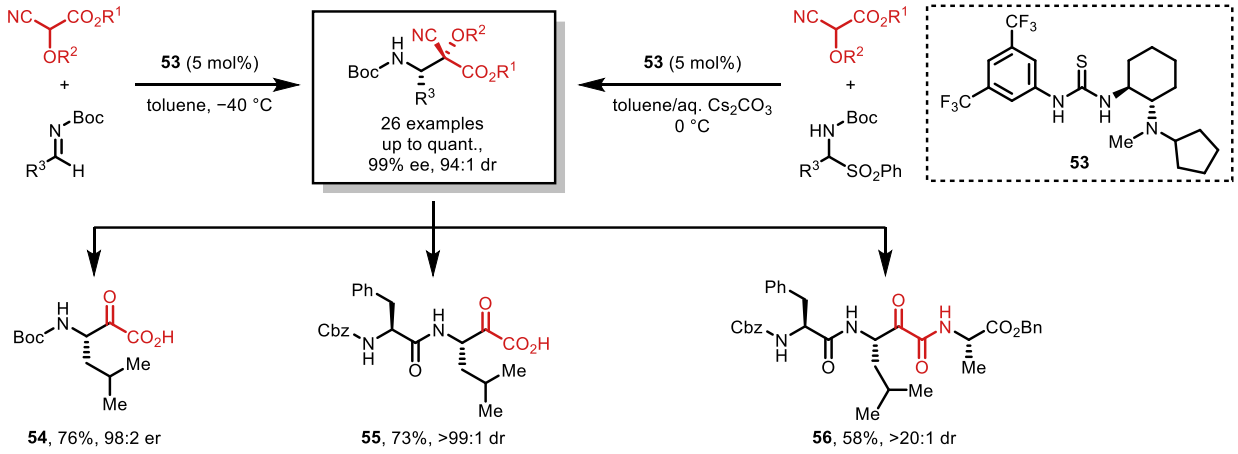
Scheme 5. Chapter 1, Section 2: Catalyst-controlled Diastereodivergent Asymmetric Mannich Reaction



次に、Mannich 反応を基盤とする β-アミノ-α-ケト酸の合成とペプチド合成への展開について第一章第三節、第四節で述べる。前述の触媒系は脂肪族イミンへ適用するには立体選択性が不十分であった。そこで触媒構造を再度精査し、立体的、電子的に設計されたチオ尿素 **53** が芳香族、脂肪族を問わず様々なイミンへの付加を高い立体選択性で触媒することを見出した。イミンの前駆体である α-アミド

スルホンを直接用いる反応条件を併用することで、既存法では合成困難な多様な β-アミノ-α-ケト酸の合成を可能とした。更に、シアノヒドリンを保護基とする新たな合成戦略によってペプチド-α-ケト酸 **55** への誘導や、エピメリ化を抑制しつつペプチド-α-ケト酸とアミンを縮合しペプチド-α-ケトアミド **56** を立体選択的に得ることにも成功し、脱炭酸型縮合によるフラグメントカップリングや医薬品の合成を達成した。

Scheme 6. Chapter 1, Sections 3 and 4: Organocatalytic Synthesis and Application of β-Amino-α-ketoacids



最後に、DFT 計算による Mannich 反応の機構解析について第二章で述べる。本反応の律速段階は炭素–炭素結合形成過程であり、その遷移状態において水素結合供与部位の構造の違いが基質を認識する空間の大きさに差異を生じさせること、またアミン部位への嵩高い置換基の導入によって反応点の位置が制御され基質–触媒間で新たな水素結合が生じることなど、立体選択性の発現に重要な幾つかの要因を見出した。またベンゾチアジアジンを用いた際のジアステレオ選択性の逆転現象が、5 位に導入した置換基と求核剤のエステル部位との立体反発に起因することを明らかにした。

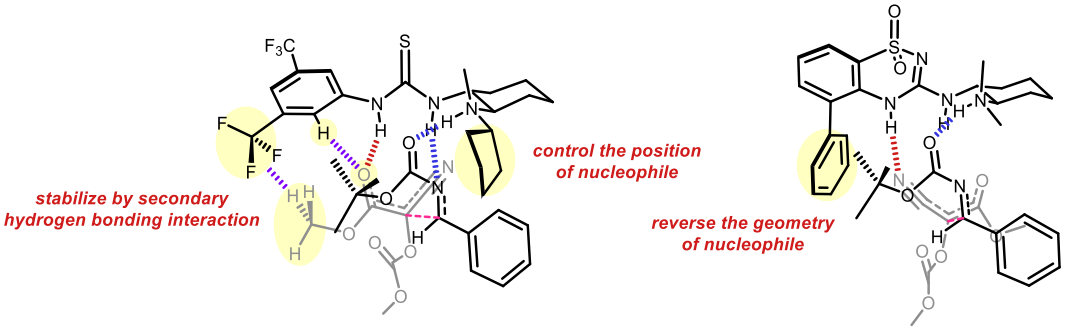


Figure 2. Chapter 2: Theoretical insights into stereoselectivity

続く第一章、第二章でその詳細を述べる。

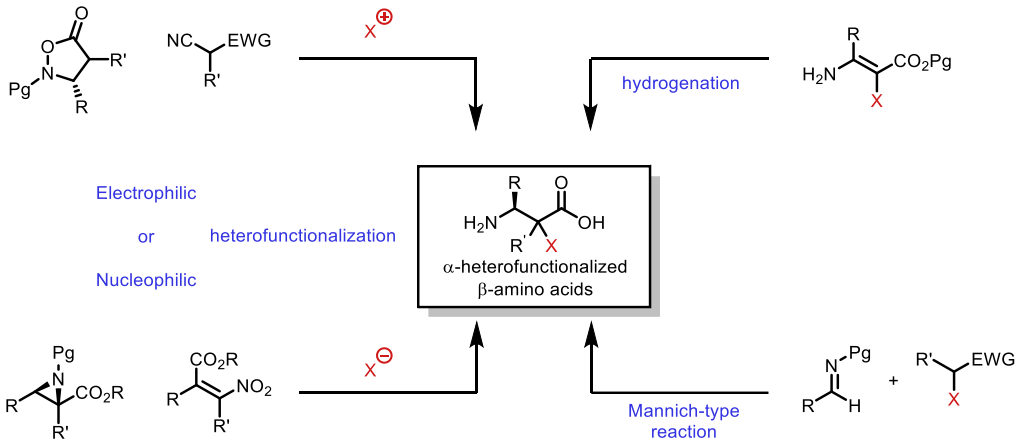
第一章 Mannich 反応を基盤とする β-アミノ-α-ケト酸の合成と応用

第一節 不斉 Mannich 反応による β-アミノ-α-ケト酸の合成計画

1-1-1. α 位に酸化度を持つ β-アミノ酸誘導体の触媒的不斉合成例

特殊アミノ酸として重要な β-アミノ酸の不斉合成法の開発は古くから精力的に研究されている分野であり、特に α 位に酸化度を持つ β-アミノ酸の不斉合成法も多数報告がなされている [2c,d]。それらは、① α 位の求電子的ヘテロ官能基化、② α 位の求核的ヘテロ官能基化、③ β-エナミノエステルの不斉水素化、④ Mannich 型付加反応 の 4 つに大別される (Scheme 7)。それらの内 Mannich 型付加反応は、アミノ酸側鎖に対応するイミンと適切な酸化度を持つエノラート前駆体の独立した 2 つの単純なフラグメントを用いることができるため、多様な β-アミノ酸類の効率的な合成において特に強力な手法である。

Scheme 7. Synthetic Approach of α-Heterofunctionalized β-Amino Acids

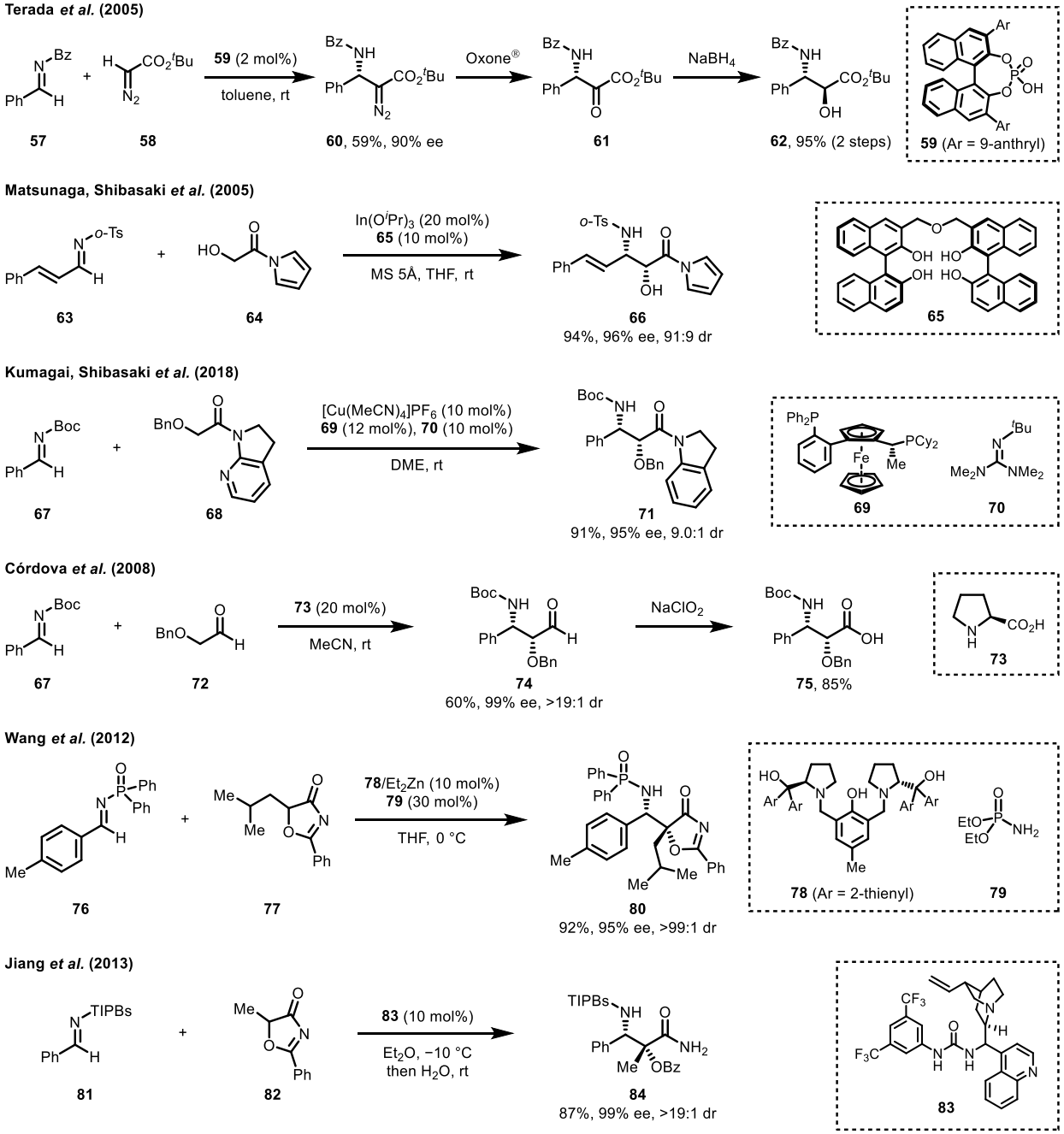


Mannich 型反応による β-アミノ-α-ケト酸誘導体の直接的合成例はないものの、酸化によって β-アミノ-α-ケト酸や β-アミノ-α-ケトアミドへ導くことが可能な β-アミノ-α-ヒドロキシ酸の触媒的不斉合成法が報告されているので [17,18]、主なものを以下に示す (Scheme 8)。

2005 年寺田らは、BINOL 骨格を有するキラルリン酸触媒 **59** を用いた *N*-ベンゾイルイミン **57** と α-ジアゾエステル **58** との不斉 Friedel-Crafts 型アルキル化を達成し、生成物 **60** のジアゾ部分を Oxone® によって酸化することで β-アミノ-α-ケトエステル **61** としたのち、水素化ホウ素ナトリウムで還元することで β-アミノ-α-ヒドロキシエステル **62** が高収率で得られることを報告した [17a]。一方松永、柴崎らは、BINOL 由来のキラル配位子 **65** からなるインジウム錯体を触媒とすることで、2-ヒドロキシアセチルピロール **64** を用いた *syn*-選択的な不斉 Mannich 型反応を報告した [17b]。その後熊谷、柴崎らによってキラルビスホスフィン配位子 **69** を有するカチオン性銅錯体を触媒とした α-オキシアザインド

リンアミド **68** の不斉 Mannich 型反応も報告された[17g]。2008 年 Córdova らは、*L*-プロリン **73** を触媒とした α-オキシアルデヒド **72** の不斉 Mannich 反応によって β-アミノ-α-ヒドロキシアルデヒド **74** を高いエナンチオ、およびジアステレオ選択性で得ることに成功し、生成物を Pinnick 酸化条件に付すことで β-アミノ-α-ヒドロキシ酸 **75** へと導き Docetaxel の側鎖構造を合成している[17c]。また Wang らはビスピロリジンフェノール配位子 **78** を含む二核亜鉛錯体、Jiang らはシンコナアルカロイド-尿素触媒 **83** を用いることで、オキサゾリジノン **77**、**82** の不斉 Mannich 反応をそれぞれ同時期に報告している[17d,f]。

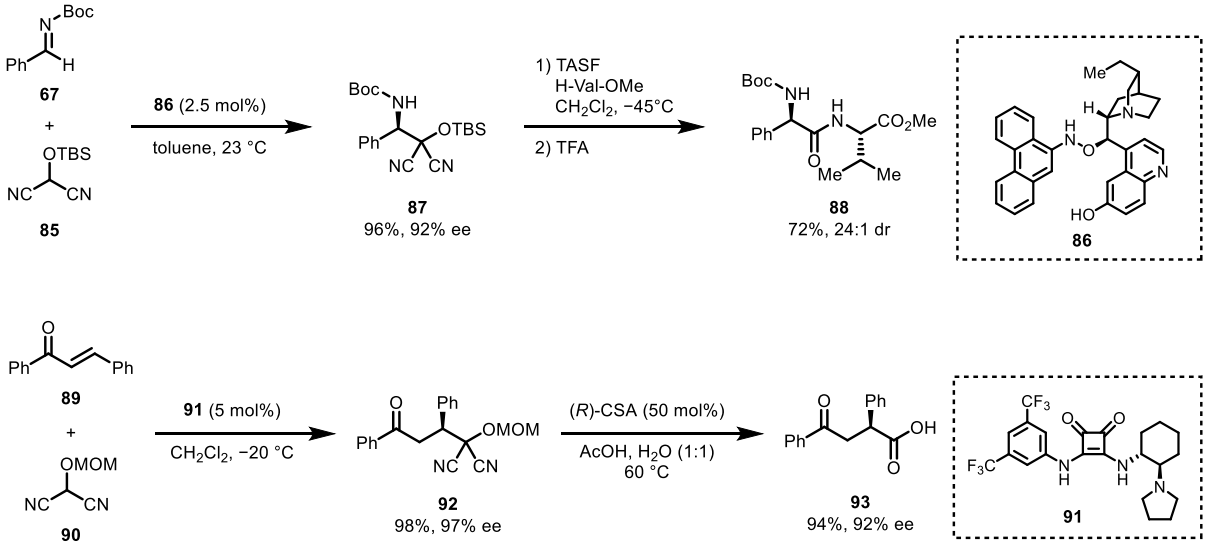
Scheme 8. Catalytic Synthesis of β-Amino-α-hydroxyacid Derivatives by Asymmetric Mannich Reaction



1-1-2. グリオキシル酸シアノヒドリンを用いるβ-アミノ-α-ケト酸の合成戦略

第一項に不斉合成例を挙げたβ-アミノ-α-ヒドロキシ酸に比べ更に酸化度の高いβ-アミノ-α-ケト酸を直接的に合成するには求電子的なα-ケトカルボニル基を求核的にイミンに付加させる必要があることから、著者はアシルアニオン等価体を用いたMannich反応を開発することとした。特にアシルアニオン等価体の一つであるシアノヒドリン[19]に対しもう一つ電子求引基を導入すれば、酸性度が高い活性メチンが生じるために温和な条件下でエノラートとして求核付加反応に利用できるとともに、適切な脱保護によってα-ケトカルボニル化合物へと変換することも可能と期待した。そのような構造の求核剤を用いた不斉反応の最近の例として、Rawalらはキラルな第三級アミン**86**、**91**を触媒とすることで一酸化炭素の等価体であるmasked acyl cyanide (MAC試薬)[20]のエナンチオ選択的な求核付加反応を開発し、脱保護によって生じるアシルシアニドを利用したアルコールやアミンのアシル化へと応用している (Scheme 9)[21]。**87**から生じるアシルシアニドに対してシアノ基を加水分解することができればβ-アミノ-α-ケト酸を与えるが、Rawalらは**92**から誘導体化したアシルシアニドを酸性条件下加水分解することでアシル置換された単純なカルボン酸を高収率で得ており、実際にはβ-アミノ-α-ケト酸への変換は困難である。またMannich成績体の時点で一方のシアノ基のみを選択的に加水分解することも極めて挑戦的な課題であり、β-アミノ-α-ケト酸の合成を達成するにはMAC試薬ではない新たな求核剤の設計が求められる。

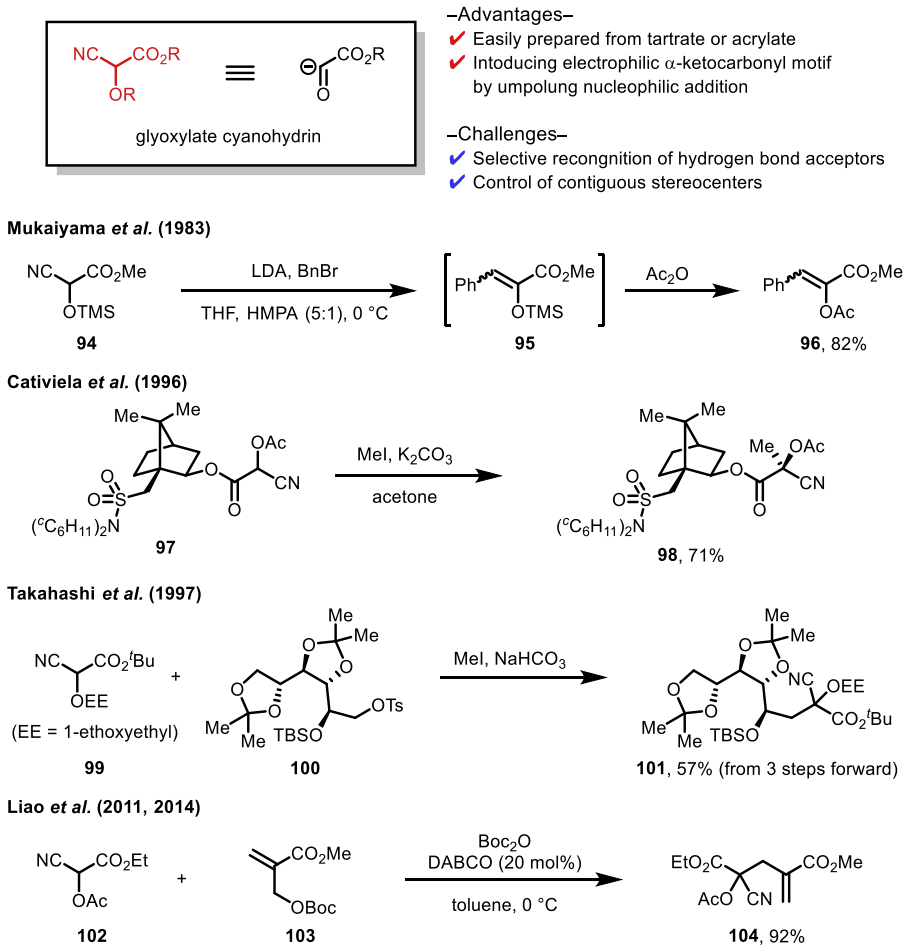
Scheme 9. Asymmetric Nucleophilic Addition of Masked Acyl Cyanide (MAC Reagent)



そこで著者は、酒石酸やアクリル酸誘導体から容易に調製可能なグリオキシル酸シアノヒドリンが、極性転換によってα-ケトカルボニル構造を求核的にイミンへと導入する試薬として利用できると期

待した (Scheme 10)。グリオキシル酸シアノヒドリンを求核剤とするアルキルハライドとの S_N2 反応や α,β-不飽和エステルへの 1,4-付加反応がこれまでに 5 例報告されているが [22]、環境の似たルイス塩基性官能基を複数有する構造的特徴や、MAC 試薬のような対称な求核剤とは異なり付加反応後に 2 つの不斉点を生じることから遷移状態における立体の制御は容易ではない。そのため、不斉反応への展開は化学量論量の不斉補助基を用いた Cativiela らの例のみであり [22b]、エナンチオ選択的な反応は未だ達成されていない。また、シアノヒドリン水酸基の保護基には脱保護に強い塩基性条件を必要とするアセチル基や、シリカゲル上で分解するような安定性の低い TMS 基、1-エトキシエチル基しか用いられておらず、β-アミノ-α-ケト酸等への誘導体化を行うには適切な保護基の選択と合成法の確立も必要である。

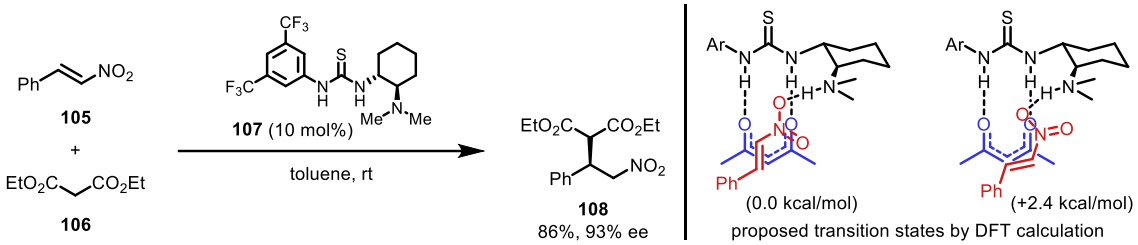
Scheme 10. Characteristics and Alkylation Reaction of Glyoxylate Cyanohydrin



2003 年、竹本らは第三級アミンを有するキラルチオ尿素 **107** を触媒としたマロン酸誘導体 **106** のニトロオレフィン **105** へのエナンチオ選択的 1,4-付加反応を報告し [23]、それ以降同様の触媒設計により数多くの不斉触媒反応が達成されてきた (Scheme 11)[24]。これらの反応は酵素のような酸塩基協働型の触媒作用によって進行しており、求核剤の活性メチレンを第三級アミンが脱プロトン化し、生じた

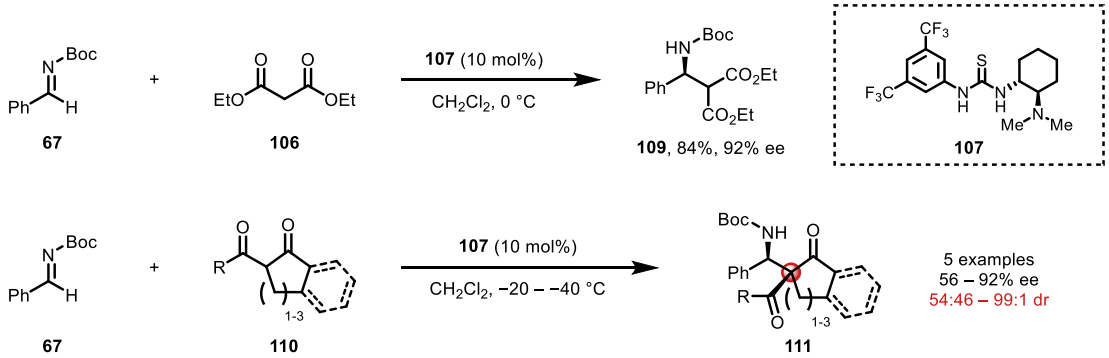
アンモニウムと(チオ)尿素上の酸性プロトンによって求核剤、求電子剤を多点同時認識することで、付加反応の立体選択性を高度に制御している [25]。

Scheme 11. Chiral Aminothiourea-catalyzed Asymmetric Michael Addition of Malonates to Nitoroolefines



また竹本らは 2007 年、アミノチオ尿素を触媒とする Mannich 反応も達成している (Scheme 12)[26]。対称な求核剤であるマロン酸ジエチル **106** の種々の *N*-Boc イミンへの付加は 90% ee 以上のエナンチオ選択性で進行し、水素結合による多点認識が Mannich 反応の立体を制御する強力な手法であることが示されている。一方ジアステレオマーを生じる非対称な求核剤は構造の固定された環状の 1,3-ジカルボニル化合物に限られ、ジアステレオ選択性にも大きなばらつきがみられるなど高いエナンチオ選択性とジアステレオ選択性を両立するには依然触媒設計に改善を必要としている。

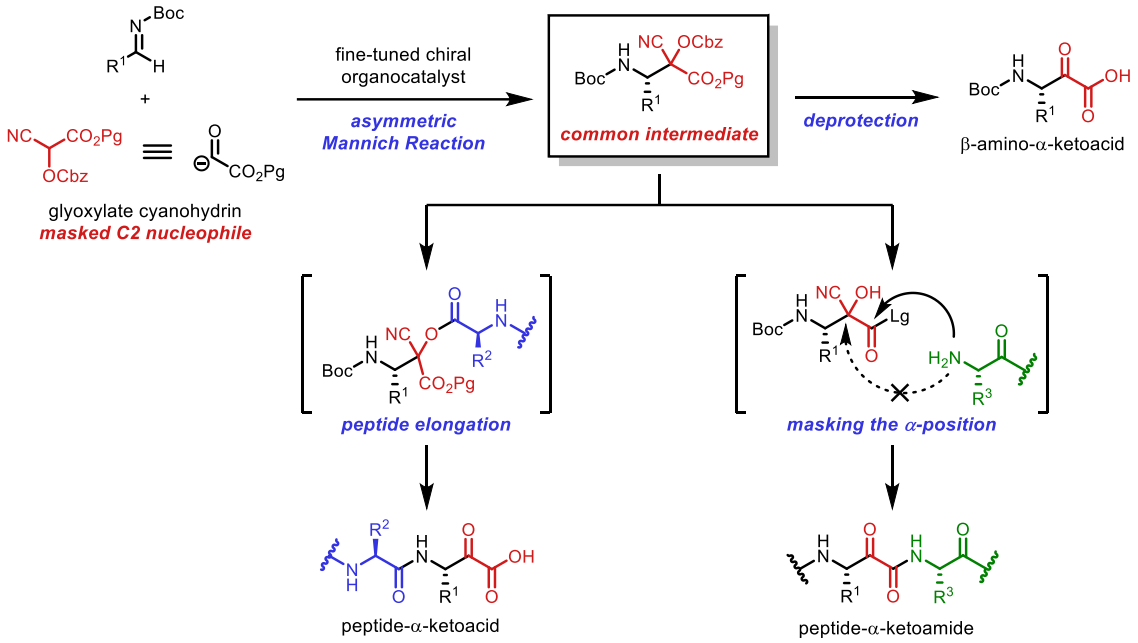
Scheme 12. Aminothiourea-catalyzed Asymmtertic Mannich Reaction of 1,3-Dicarbonyl Compounds



以上を踏まえ著者は、エナンチオ選択性とジアステレオ選択性を高度に制御できるチオウレア型触媒を設計し、複数の水素結合受容部位をもつグリオキシル酸シアノヒドリンの立体選択的 Mannich を開発することを計画した (Scheme 13)。不斉 Mannich 反応により得られる生成物は β-アミノ-α-ケト酸と等価な酸化度を有しており、適切な脱保護によって容易に β-アミノ-α-ケト酸へ導けると期待される。また α 位のシアノヒドリンはカルボニル基の保護基とみなせることから、既存法のように β-アミノ-α-ケト酸を経由することなく直接的かつ分岐的にペプチド-α-ケト酸やペプチド-α-ケトアミドを合成できることも期待できる。先述した要件を満たすグリオキシル酸シアノヒドリンの保護基は様々な

ものが利用可能ではあるが、本研究では、水酸基の保護基には安定性が高い一方で脱保護の容易なカルボナート保護基、特にイミンの保護基である Boc 基との直交性がある Cbz 基を用い、エステル部分はその後の変換に応じていくつかの保護基を使い分けることを考え、それら新規なグリオキシル酸シアノヒドリンの合成法の確立についても取り組むこととした。

Scheme 13. Synthetic Strategy of β-Amino-α-ketoacids and Peptide-derivatives by the Enantioselective Mannich-type Addition of Glyoxylate Cyanohydrin to Imines



第二節 グリオキシル酸シアノヒドリンを用いたジアステレオ分岐型不斉Mannich反応の開発

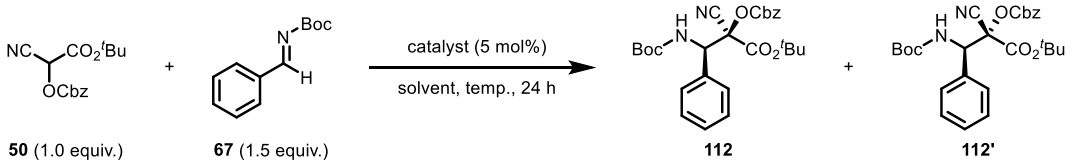
1-2-1. 反応条件の最適化

第一章第一節に述べた戦略に基づき、グリオキシル酸シアノヒドリンを用いるエナンチオ選択的Mannich反応の反応条件を検討した (Table 1)。ここでは不斉発現に有効な触媒骨格を効率的に探索するため、立体選択性が発現しやすいと考えられる嵩高い *t*-ブチル基で保護されたシアノヒドリン **50** と共役系により構造の固定された芳香族イミン **67** を基質とした。シアノヒドリン **50** とイミン **67** に対し 5 mol%のアミノチオ尿素触媒 **107** をジクロロメタン中−20 °C で 24 時間反応させたところ、所望の付加生成物 **112** と **112′**がジアステレオ比 1.6:1 の混合物として 100%収率で得られたが、エナンチオ過剰率はそれぞれ 57% ee、16% ee と低いものであった (entry 1)。なお、両ジアステレオマーの絶対立体配置の決定については本節第四項で述べる。立体選択性の向上を期待し水素結合供与部位について検討したところ、スクアリン酸アミド **113**[27] を用いると 75% ee で付加体 **112** が得られ (entry 2)、特にベンゾチアジアジン **114**[28] を用いた際に **112** を 87% ee で得ることができたため (entry 3)、ベンゾチアジアジンを水素結合供与体に固定しさらなる検討を行うこととした。触媒構造の最適化に先立ち、反応溶媒と反応温度について検討したところ、トルエン中で反応を行うことでエナンチオ選択性は 97% ee まで向上し (entry 4)、また反応温度を−40 °C とすることで若干のジアステレオ選択性の向上が見られ、付加体 **112** を 97% ee、ジアステレオ比 2.3:1 の混合物としてほぼ定量的に与えた (entry 5)。

次に、ジアステレオ選択性の向上を目指し、触媒中のキラルアミン部位について検討したが不斉触媒反応によく用いられるシンコナアルカロイド由来の触媒 **115** や 1,2-ジフェニルエチレンジアミン型の触媒 **116** では期待した結果は得られなかった (entries 6, 7)。そこで著者は、竹本らが触媒–基質複合体モデル **121** を用いた反応機構解析から提案した Mannich 反応の遷移状態構造 **122** において求核剤の嵩高い環状ケトン部位が触媒の芳香環側に位置していることに着想を得て[29]、触媒のアミン部位へ嵩高い置換基を導入することで主異性体を与える遷移状態を更にとりやすくなるのではないかと考えた。この想定の下、触媒 **114** のジメチルアミノ基について一方のメチル基をベンジル基へと置換すると、期待通りエナンチオ選択性を維持したまま顕著にジアステレオ選択性が向上することを見出した (entry 8)。さらにこの位置の置換基を嵩高くするにつれ生成物のジアステレオ選択性は向上し、特にシクロペンチル基とした触媒 **51** は **112** を 97% ee、31:1 dr とほぼ単一の立体異性体として定量的に与えたため、本条件を最適な反応条件とした (entries 9, 10)。

触媒への置換基導入がジアステレオ選択性の制御に極めて効果的であったことから、著者は触媒の芳香環側へ置換基を導入すれば、ジアステレオ選択性が逆転し、**112′**を選択的に得ることも可能ではないかと考えた。そこでシアノヒドリン **50** とイミン **67** に対し芳香環上の 5 位を臭素に置換した触媒 **119** をトルエン中−40 °C で作用させると、確かに Mannich 反応のジアステレオ選択性が逆転し **112′**が

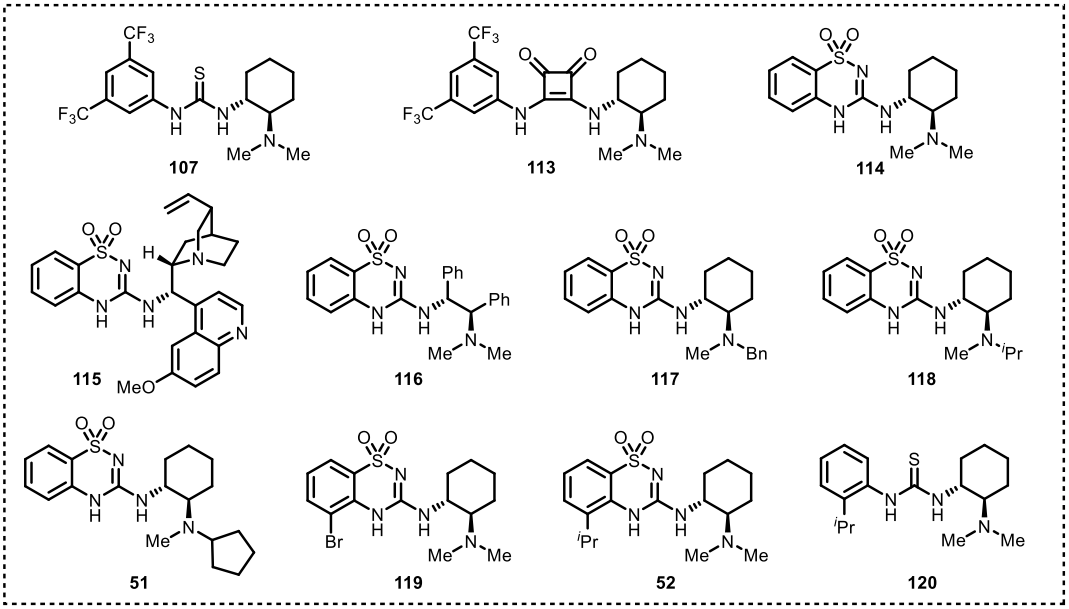
Table 1. Optimization of Reaction Conditions



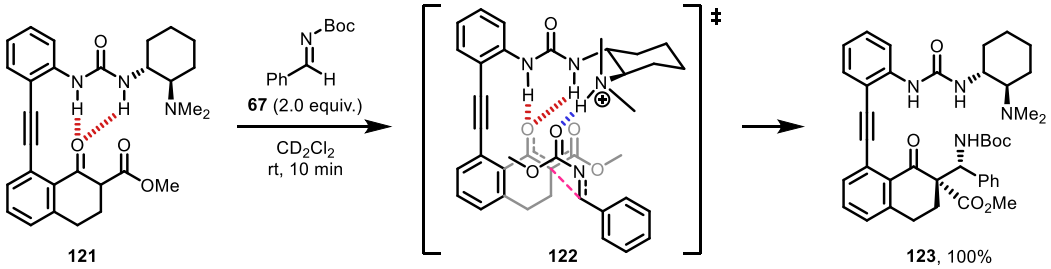
50 (1.0 equiv.) **67** (1.5 equiv.) **112** **112'**

entry	catalyst	solvent	temp. (°C)	yield[a] (%)	ee[b] (%) **112**	ee[b] (%) **112'**	dr[c] (**112**:**112'**)
1	**107**	CH_2Cl_2	−20	100	57	16	1.6:1
2	**113**	CH_2Cl_2	−20	70	75	59	1.6:1
3	**114**	CH_2Cl_2	−20	100	87	43	2.4:1
4	**114**	toluene	−20	99	95	63	1.6:1
5	**114**	toluene	−40	94	97	66	2.3:1
6[c]	**115**	toluene	−40	100	67	79	3.9:1
7	**116**	toluene	−40	91	89	89	2.1:1
8	**117**	toluene	−40	90	96	52	9.4:1
9	**118**	toluene	−40	93	96	33	15:1
10	**51**	toluene	−40	97	97	2	31:1
11	**119**	toluene	−40	82	59	85	1:3.6
12	**52**	toluene	−40	92	81	92	1:14
13	**120**	toluene	−40	87	66	42	1:2.3

(a) Isolated yields are shown. (b) Ratio of stereoisomers was determined by chiral HPLC analysis.
(c) ***Ent*-112** and ***ent*-112'** were obtained as major enantiomers.

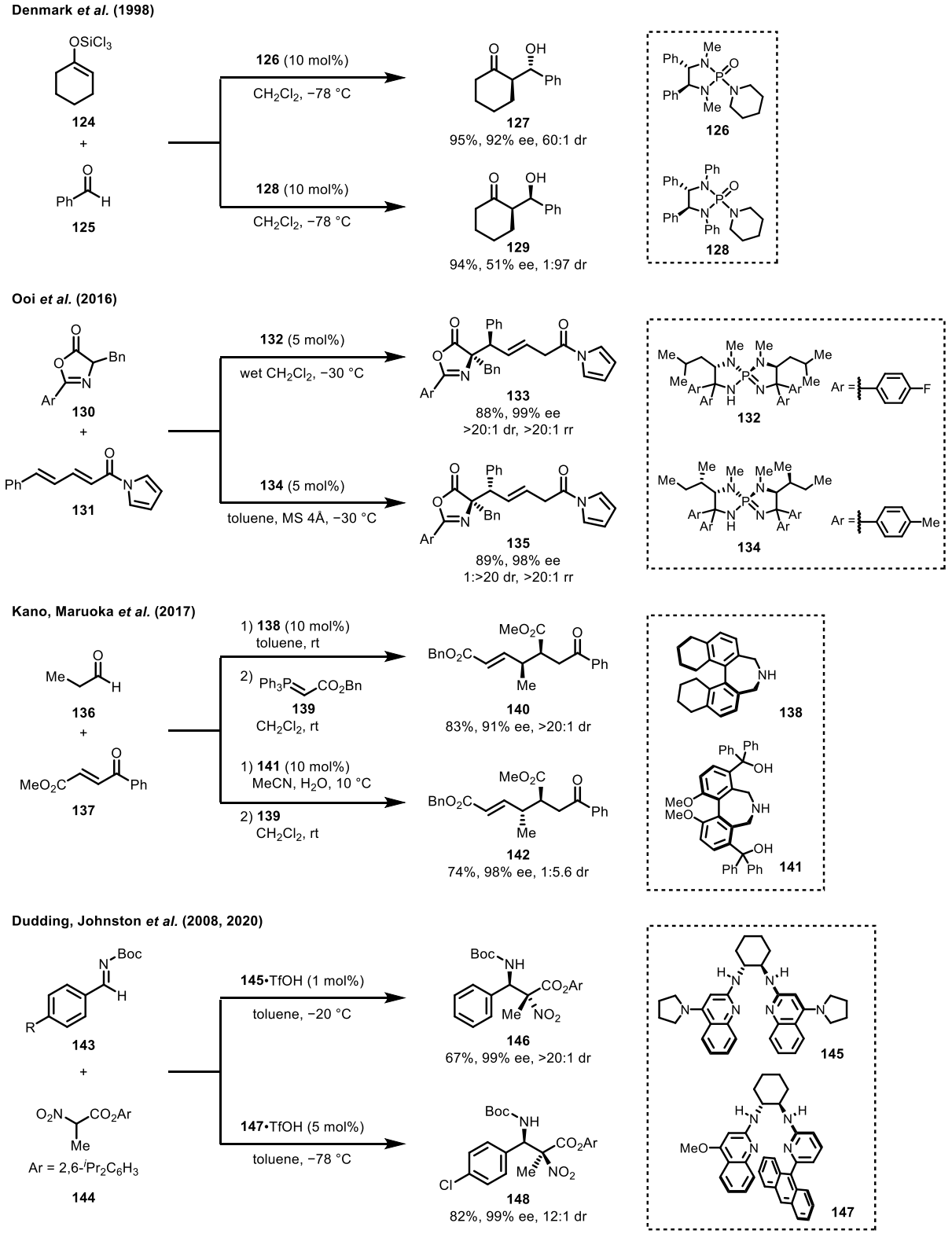


• **Snapshot analysis of aminothiourea-catalyzed Mannich reaction**



主ジアステレオマーとして 3.6:1 の比で得られることを見出した (entry 11)。溶媒効果や添加剤を利用したジアステレオ分岐的な有機分子触媒反応は数多く報告されているが、同一の骨格を有する触媒の置換基効果によってその選択性を制御している例は、Denmark のルイス塩基触媒によるアルドール反

Scheme 14. Organocatalytic Diastereodivergent Reactions Controlled by Substituent Effects of Catalysts

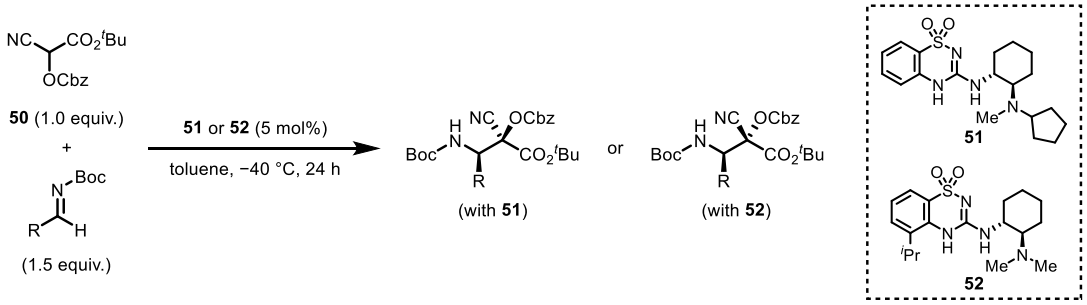


応[30]や、著者らと同時期に報告された大井、加納・丸岡らの共役付加反応[31,32]、Dudding・Johnston らの aza-Henry 反応[33]の数例しかなく、未だ類例の少ない現象である (Scheme 14)[34]。β-アミノ-α-ケト酸を合成する際にはシアノヒドリン部分の不斉点は消失するものの、著者はジアステレオ選択性の逆転を可能とするベンゾチアジアジン触媒の性質に興味を持ち、更なる選択性の向上のためにこの位置の置換基効果について検討することとした。その結果、イソプロピル基を導入した **52** を用いた際に 92% ee、14:1 dr と高い立体選択性で **112′**が得られることを見出し、本反応によって生じ得る 4 つの立体異性体全てを高いエナンチオ、およびジアステレオ選択性で作り分けることが可能となった (entry 12)。**52** と同様に芳香環上にイソプロピル基を有するチオ尿素 **120** を用いた場合には、ジアステレオ選択性の逆転は起こるもののジアステレオ比は 2.3:1 と十分な選択性は発現せず、大きなジアステレオ選択性の逆転がベンゾチアジアジン型触媒に特徴的な現象であることが示された (entry 13)。

1-2-2. 基質適用範囲の検討

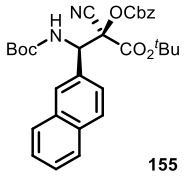
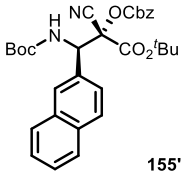
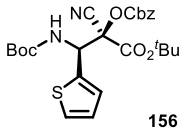
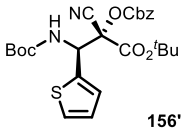
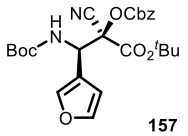
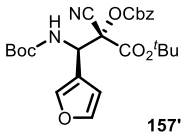
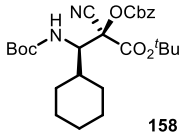
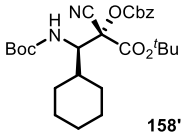
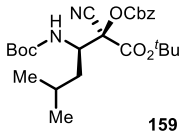
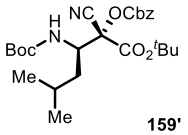
第一項で見出した最適条件を用いて、両ジアステレオマーについて基質適用範囲を調査した (Table 2)。まず電子状態の異なる種々の *p*-置換芳香族イミンについて検討したところ、触媒 **51** を用いた場合にはイミンが電子豊富になるにつれ僅かではあるがエナンチオ選択性が増大する傾向が見られた。一方で触媒 **52** を用いる系では、芳香環が電子豊富になることで若干のエナンチオ選択性の低下がみられた (entries 1–3)。イミンが電子不足になった際も同様の傾向がみられたが、総じて非常に高い立体選択性が発現していることから、本反応においてイミンの電子状態は立体選択性に大きな影響を及ぼさないことが示された (entries 4, 5)。次にイミン上の置換基の位置について検討したところ、メタ位、オルト位にそれぞれメチル基を有していても、触媒 **51**、**52** ともに優れた収率でそれぞれ付加体をジアステレオ選択性良く与えた (entries 6, 7)。2-ナフチルイミンやチオフェン、フラン環を含有するイミンについても、単純な芳香族イミンと同様に高い立体選択性が発現した (entries 8–10)。本反応の脂肪族イミンへの適用についても検討し、シクロヘキシルイミンを用いることで付加体 **158** が 93% ee で得られたが、ジアステレオ選択性は 5.9:1 と中程度にとどまった。触媒 **52** を用いると単一のジアステレオマーとして付加体 **158′**を与えたが、その一方でエナンチオ選択性は 41% ee と顕著に低下し、収率も 52%と低い結果となった (entry 11)。反応点がより立体的に空いているイソブチル基を側鎖とするイミンは、両付加体 **159**、**159′**をそれぞれ 12:1、1:>99 と良好なジアステレオ選択性で与えたが、エナンチオ選択性に関しては 82% ee、74% ee と芳香族イミンに比べて低下する結果となった (entry 12)。これらの結果から、脂肪族イミンへの付加において高い立体選択性を達成するためには、ベンゾチアジアジン触媒 **51**、**52** に比べ更に厳密に遷移状態構造を制御できる触媒が必要であることが明らかとなった。

Table 2. Substrate Scope of Diastereodivergent Mannich Reaction



	catalyst **51**				catalyst **52**			
entry	product	yield (%)	ee (%)	dr	product	yield (%)	ee (%)	dr
1	**112**	97	97	31:1	**112'**	92	92	1:14
2	**149**	98	98	48:1	**149'**	100	89	1:10
3	**150**	85	99	>99:1	**150'**	74	87	1:18
4	**151**	91	95	>99:1	**151'**	93	92	1:10
5	**152**	100	94	18:1	**152'**	100	93	1:7.9
6	**153**	98	88	11:1	**153'**	84	95	1:23
7	**154**	100	94	9.7:1	**154'**	94	89	1:27

Table 2. Continued.

8	 **155**	84	92	16:1	 **155'**	84	93	1:52
9	 **156**	100	86	9.6:1	 **156'**	99	86	1:21
10	 **157**	100	97	39:1	 **157'**	94	91	1:16
11	 **158**	100	93	5.9:1	 **158'**	52	41	1:>99
12	 **159**	quant.	82	12:1	 **159'**	100	74	1:>99

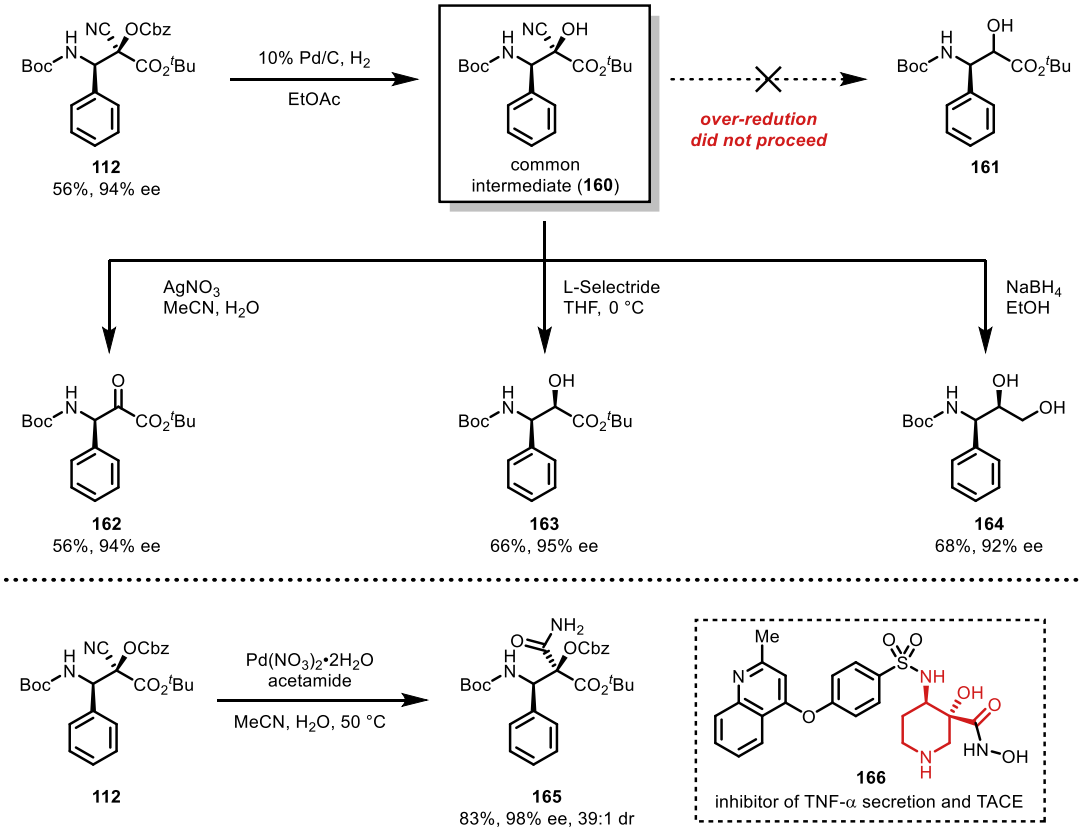
Isolated yields are shown. Ratio of stereoisomers was determined by chiral HPLC analysis.

1-2-3. 付加体の誘導体化

得られた付加体 **112** の α-オキシ-β-アミノ酸類縁体への誘導体化を行った (Scheme 15)。まず α 位のシアノヒドリンの変換を行うために、接触水素化による Cbz 基の脱保護を試みた。すなわち、酢酸エチル中パラジウム炭素を水素雰囲気下作用させることで、脱保護の進行したシアノヒドリン **160** を定量的に得た。この変換の際、過剰還元の進行した α-ヒドロキシ酸 **161** の生成は確認されなかった。α-ケト酸誘導体の α 位カルボニル基は接触還元条件で水酸基へと容易に還元されることが知られているが、Mannich 反応によって得られる付加体においては α 位のシアノヒドリン構造が熱力学的に安定であることで過剰還元を抑制しており、α 位の酸化度を維持する上で重要な役割を果たしている。この粗生成物にアセトニトリル/水中、硝酸銀を作用させると、シアニドの除去された β-アミノ-α-ケトエステル **162** を 2 工程収率 56%、94% ee と光学純度を損なうことなく良好な収率で与えた。一方で、α 位の還元的な官能基変換についても検討した。接触還元によって得られたシアノヒドリン **160** に対し THF 中 0 °C で L-Selectride を作用させると、系中で一時的に生じるカルボニル基の還元が進行し、いくつかの生物活性物質に含まれる骨格である β-アミノ-α-ヒドロキシエステル **163** が 2 工程収率 66%

で単一のジアステレオマーとして *anti*-選択的に得られた[35]。また還元剤を水素化ホウ素ナトリウムに変更し、エタノール中室温で反応を行うと、α 位のシアノヒドリンに加え *t*-ブチルエステルの還元も進行したアミノジオール **164** がやはり *anti*-選択的に得られた。これらの還元的変換においても、Mannich 反応によって生じた窒素原子 α 位の不斉情報は損なわれなかった。さらに異なる変換として、シアノ基の変換を行った。ジアステレオ分岐的 Mannich 型反応によって得られた付加体 **112** について、中らによって報告された Pd 触媒による水移動型水和反応[36]に付すと、良好な収率で対応する第一級アミド **165** をほぼ単一の立体異性体として与えた。この多置換型 β-アミノ酸構造は例えば抗ガン活性化合物 **166** に含まれる骨格であり[37]、創薬への応用が期待できるビルディングブロックである。

Scheme 15. Derivatization of Mannich Adducts **112**



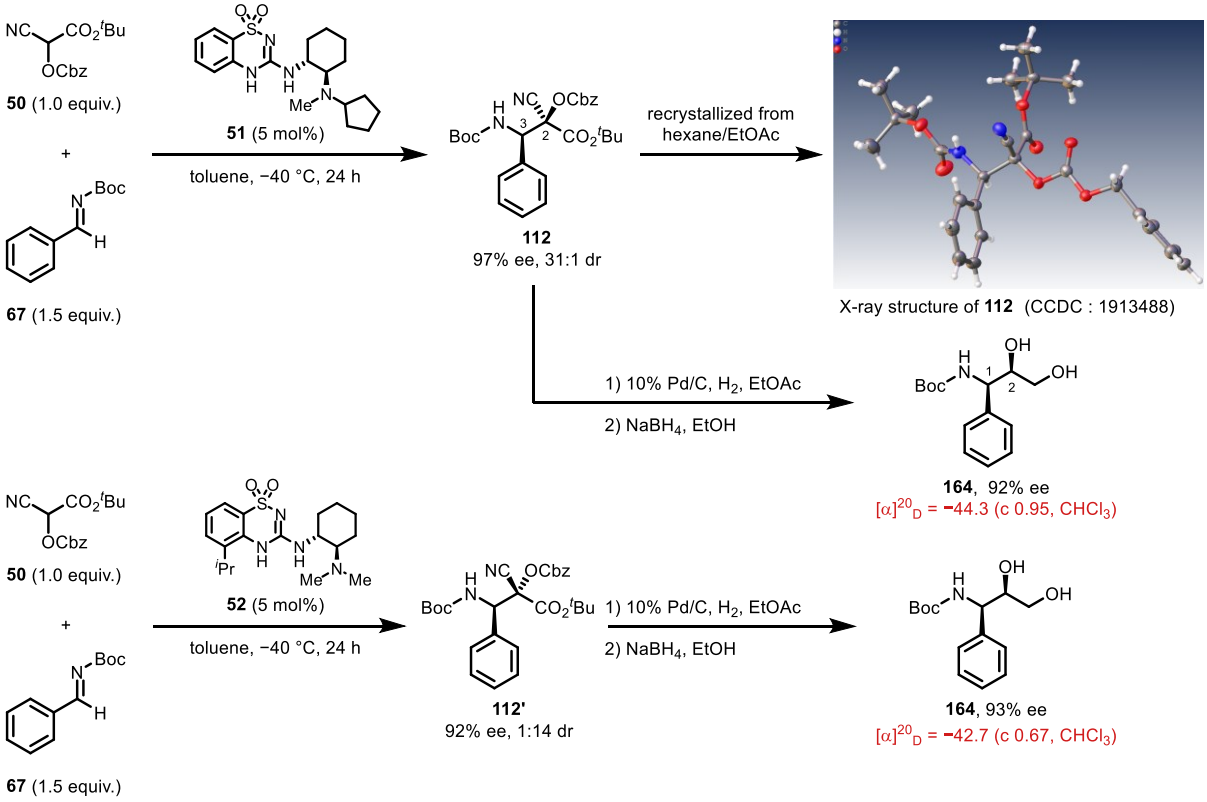
1-2-4. 付加生成物の絶対立体配置の決定

ここで、ベンゾチアジアジン触媒を用いるジアステレオ分岐的 Mannich 反応によって得られた 2 つのジアステレオマーの絶対立体配置の決定方法について述べる (Scheme 16)。触媒 **51** によって得られる付加体 **112** は安定な白色固体であり、*n*-ヘキサン/酢酸エチルを用いた再結晶により単結晶を得ることが可能であった。この単結晶に対して X 線結晶構造解析を行うことで、付加体 **112** の絶対立体配置は(2*S*,3*R*)であると決定した。なお、ここで決定した絶対立体配置は、**112** の還元によって得られたア

ミノジオール **164** の比旋光度 $[\alpha]_D^{24} = -44.3$ (c 0.95, $CHCl_3$)が(1*R*,2*R*)-**164** の文献値 $[\alpha]_D^{24} = -25.8$ (c 1.0, $CHCl_3$)[38] と良く一致することからも支持される。

一方、触媒 **52** によって与えられる付加体 **112′**は白色のアモルファスであり、X 線結晶構造解析を行うための単結晶を得ることが困難であった。そのため、付加体 **112** からアミノジオール **164** へと変換する際と同様の処理を行い、その比旋光度を比較することで絶対立体配置を決定することとした。すなわち、92% ee、1:14 dr で得られた付加体 **112′**に対し水素雰囲気化パラジウム炭素を作用させ Cbz 基を除去した後、水素化ホウ素ナトリウムで処理することでアミノジオールを 2 工程収率 68%、93% ee で得た。この化合物の比旋光度は $[\alpha]_D^{23} = -42.7$ (*c* 0.67, $CHCl_3$)であり、付加体 **112** から調製したアミノジオール **164** のものと良い一致を示した。両ジアステレオマーから同一のアミノジオールが得られたことから 3 位の絶対立体配置は同一であることが示されたため、付加体 **112′**の絶対立体配置は(2*R*,3*R*)であると決定した。

Scheme 16. Determination of the Absolute Configuration of Adducts **112** and **112′**



1-2-5. 置換基効果の検討

ベンゾチアジアジン触媒に特徴的なジアステレオ分岐性について知見を得るため、求核剤であるグリオキシル酸シアノヒドリンの保護基の影響について調査した (Scheme 17)。水酸基の保護基を Cbz 基に代わり嵩の小さいメトキシカルボニル基とした求核剤 **167** を用いて、触媒 **51**、**52** の両触媒系で

イミン **67** への Mannich 反応を行ったところ、これまでの結果と同様に付加体 **168**、**168′**がそれぞれ 16:1、1:17 と高いジアステレオ選択性で得られた。エナンチオ選択性の顕著な変化も見られておらず、シアノヒドリン水酸基上の置換基の立体効果は付加反応の立体選択性にほとんど影響を及ぼさないと考えられる。対して、*t*-ブチルエステルに代わりメチルエステルとした求核剤 **169** を用いたところ、触媒 **51** は依然高いエナンチオ、ジアステレオ選択性を発現した一方で、触媒 **52** を用いた場合はエナンチオ選択性、ジアステレオ選択性ともに低下し、エステル保護基の立体要因が立体制御に影響することが明らかとなった。この結果は、第二章で述べる遷移状態の解析結果を強く支持している。

Scheme 17. Steric Effects of Protecting Group on Cyanohydrin Moiety

catalyst	yield[a] (%)	ee[b,c] (%)	dr[b] (**168**:**168'**)
51	77	95	16:1
52	90	92	1:17

(a) Isolated yields. (b) Determined by chiral HPLC analysis.
(c) Ee of major diastereomer was shown.

catalyst	yield[a] (%)	ee[b,c] (%)	dr[b] (**170**:**170'**)
51	77	96	21:1
52	97	81	1:5.5

(a) Isolated yields. (b) Determined by chiral HPLC analysis.
(c) Ee of major diastereomer was shown.

第三節 脂肪族イミンへの高立体選択的 Mannich 型付加反応の開発

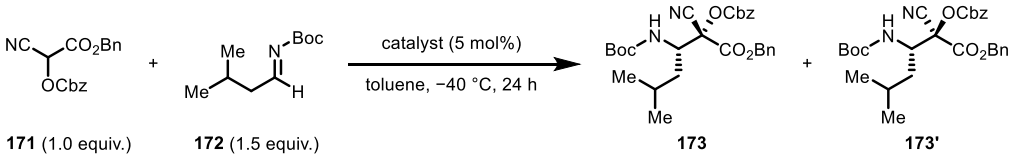
1-3-1. 触媒構造の最適化

第一章第二節で述べたように、ベンゾチアジアジン触媒 **51** もしくは **52** を用いた Mannich 反応は、種々の芳香族イミンへのグリオキシル酸シアノヒドリンの付加について高いエナンチオ、ジアステレオ選択性を発現したが、脂肪族イミンへの付加では側鎖の構造的自由度の高さから立体選択性が低下する傾向が見られた。アミノ酸の多くは脂肪族側鎖を有しており、本反応の実用性を示すためには多様な脂肪族イミンへの付加反応を高い立体選択性で行うことが求められる。そのため、更なる立体選択性の向上を目指し、第二節の反応条件を基に再度触媒構造の精査を行った。

触媒構造の再検討に際し、単量体の β-アミノ-α-ケト酸への変換を志向した脱保護の観点から、一挙に除去可能な Bn 基と Cbz 基をそれぞれ保護基とした求核剤 **171** を用いることとした。求核剤のエステル部位が *t*-ブチルエステルからベンジルエステルとなったことで、ベンゾチアジアジン **51** や **52** を用いる条件では脂肪族イミン **172** への付加における立体選択性は第二節で述べたものから僅かに低下し、それぞれ 69% ee、77% ee で付加体 **173** と **173′**を優先して与えた (entries 1, 2)。また、5 位にフェニル基を導入したベンゾチアジアジン **174** は芳香族イミン **67** への付加に対してより優れた活性を示した (93%、96% ee、1:71 dr)が、脂肪族イミン **172** への付加には有効ではなく、**52** と同程度の結果を与えるのみであった (entry 3)。そこで、ジアステレオ選択性の向上に効果的であったシクロペンチル基の置換したシクロヘキシルアミン構造は維持し、水素結合供与部位についてスクリーニングを行った。スクアリン酸アミド **175** ではエナンチオ選択性が大幅に低下したもののジアステレオ比は 20:1 まで向上した一方で (entry 4)、キナゾリノン **176**[28] ではエナンチオ選択性も若干改善され、84% ee、20:1 dr で **173** を与えた (entry 5)。最終的に、3,5-ビストリフルオロメチルフェニル基を持つチオ尿素触媒 **53** を用いた際に、98% ee、49:1 dr で付加体 **173** をほぼ定量的に与えることを見出した (entry 6)。

高活性なチオ尿素触媒を見出せたため、次に触媒の置換基効果と立体選択性の関係について調査した。アミン部位のシクロペンチル基をメチル基に置換すると、エナンチオ選択性を維持したままジアステレオ選択性は 7.3:1 まで顕著に低下した (entry 7)。また興味深いことに、チオ尿素芳香環上の置換基を変更した際も同様の傾向が見られた。すなわち、4 位にトリフルオロメチル基を持つ **177** や、3,5 位にメチル基を持つ **178** を用いた際、それぞれ 93% ee で **173** を与えたもののジアステレオマーである **173′**との比は 9.7:1、6.1:1 まで低下した (entries 8, 9)。これらの結果から、アミン部位の嵩高さと芳香環上 3,5 位の電気陰性なトリフルオロメチル基の両方が高いジアステレオ選択性の発現に重要であり、一方でエナンチオ選択性は置換基効果にはほとんど影響されず、水素結合供与部位の環境に大きく依存することが示唆された。

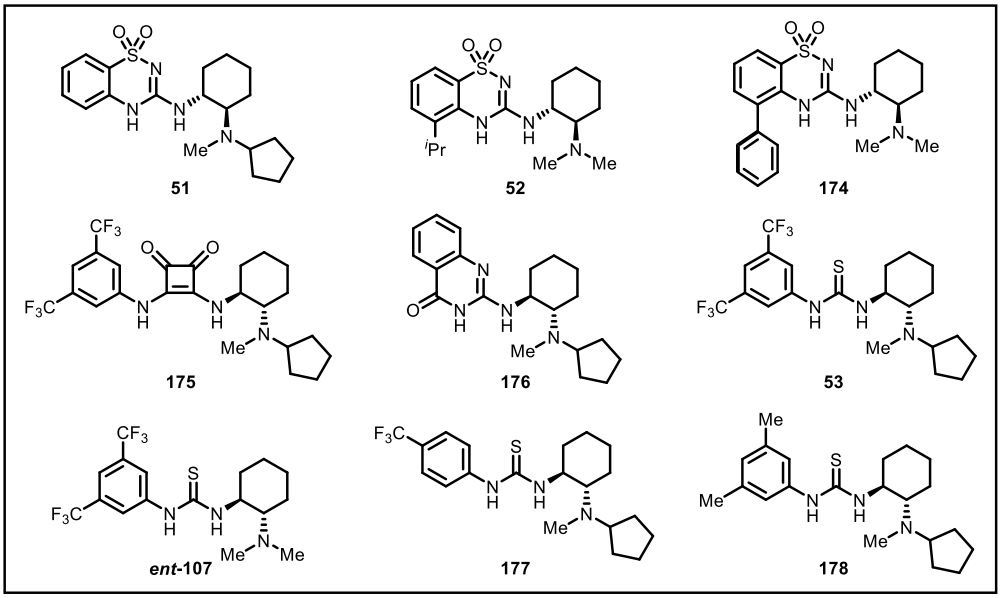
Table 3. Catalyst Screening for Addition to Aliphatic Imine



171 (1.0 equiv.) **172** (1.5 equiv.) **173** **173'**

entry	catalyst	yield[a] (%)	ee[b] (%) **173**	ee[b] (%) **173'**	dr[b] (**173**:**173'**)
1[c]	**51**	97	69	71	7.3:1
2[c]	**52**	100	69	77	1:3.3
3[c]	**174**	95	28	80	1:2.8
4	**175**	99	25	8	20:1
5	**176**	94	84	57	20:1
6	**53**	96	98	33	49:1
7	***ent*-107**	quant.	95	20	7.3:1
8	**177**	98	93	74	9.7:1
9	**178**	96	93	76	6.1:1

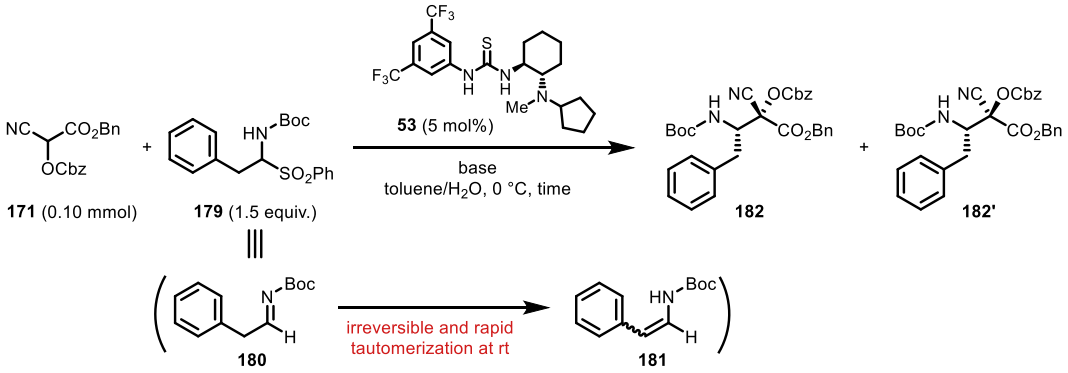
(a) Isolated yields are shown. (b) Ratio of stereoisomers was determined by chira HPLC analysis. (c) ***Ent*-173** and ***ent*-173'** were obtained as major diastereomers.



ところで、α 位に芳香環をもつものやイミンの近傍に電子求引基をもつようないくつかの *N*-Boc イミンは室温条件下より熱力学的に安定なエンカルバマートへと異性化することが知られている [39c]。これらをイミンへと再度異性化させるには比較的強いブレンステッド酸やルイス酸を作用させる必要があるため [40]、塩基を触媒とした Mannich 反応にこれらの基質を直接用いることは困難である。一方これらの不安定なイミンの利用に関して、*N*-アシルイミンの前駆体である α-アミドスルホンを塩基性条件下用いることで対応するイミンを系中で発生させる手法がしばしば用いられる [39]。そこで、α-アミドスルホンを用いる反応条件についても検討した。

グリオキシル酸シアノヒドリン **171** と α-アミドスルホン **179** に対し、最適触媒(***ent*-**)**53** と種々の炭酸塩をトルエン/水溶媒中作用させたところ、エンカルバマート **181** への異性化はほとんどみられず、期待通りイミン **180** との Mannich 反応が進行した (entry 1)。また僅かな差ではあるが炭酸セシウムを塩基とした際に最も良い収率、立体選択性で付加体 **182** を与えた (entries 2, 3)。炭酸セシウムの当量を増やしても立体選択性に大きな変化はなかったものの、収率は向上する傾向が見られた (entries 4, 5)。共溶媒である水の量を 0.10 mL に減らすと、イミンの生成に伴って生じるスルフィン酸セシウムが十分に水層に移行しないためかエナンチオ選択性、ジアステレオ選択性ともに低下し、73% ee、12:1 dr で **182** を与えた (entry 6)。最後に、4.5 当量の炭酸セシウムを用いて 48 時間反応を行った際に 7.5 当量の塩基を用いた際と同程度の収率、立体選択性で目的物を得たため、本条件を最適条件とした (entry 7)。

Table 4. Optimization of Reaction Conditions Using α-Amido Sulfone as an Imine Precursor



entry	base (equiv.)	toluene/H_2O (mL)	time (h)	yield[a] (%)	ee[b] (%) **182**	ee[b] (%) **182'**	dr[b] (**182**:**182'**)	rsm (%)
1[c]	Na_2CO_3 (2.0)	1.0/1.0	24	53	93	5	17:1	19
2[c]	K_2CO_3 (2.0)	1.0/1.0	24	45	93	10	21:1	15
3[c]	Cs_2CO_3 (2.0)	1.0/1.0	24	58	94	15	23:1	19
4[c]	Cs_2CO_3 (4.5)	1.0/1.0	24	65	92	6	17:1	27
5[c]	Cs_2CO_3 (7.5)	1.0/1.0	24	76	93	14	17:1	0
6[c]	Cs_2CO_3 (4.5)	1.0/0.10	24	67	73	9	12:1	20
7	Cs_2CO_3 (4.5)	1.0/1.0	48	76	93	8	23:1	0

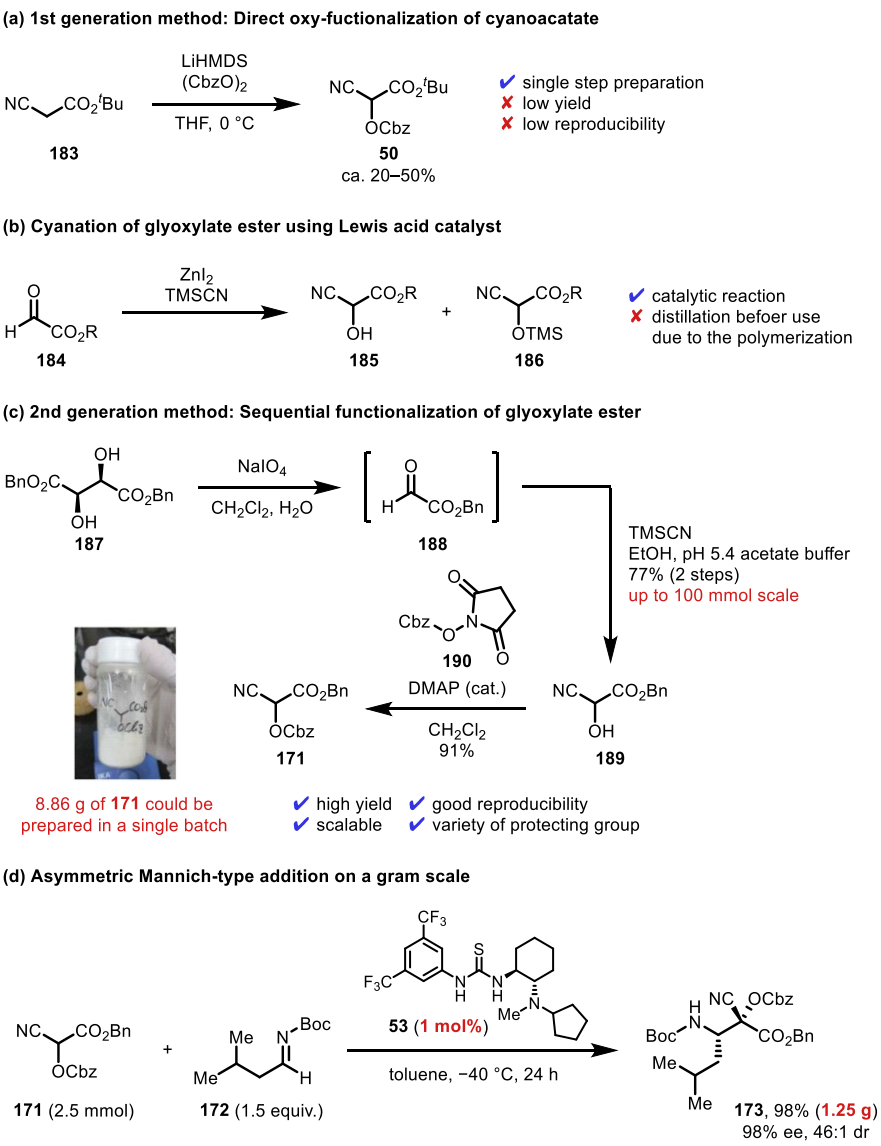
(a) Isolated yields are shown. (b) Ratio of stereoisomers was determined by chiral HPLC analysis. (c) ***Ent*-182** and ***ent*-182'** were obtained as major enantiomers by using ***ent*-53** as a catalyst.

1-3-2. 求核剤の改良合成法の確立

本研究では *O*-カルボナート保護したグリオキシル酸シアノヒドリンを高い化学直交性と脱保護の簡便さから用いているが、そのような化合物はこれまで合成例がなく、合成経路の検討も必要であった。第一章第二節に述べた検討の時点では、シアノ酢酸エステル **183** の活性メチレンを強塩基で脱プロトン化し、これに $(CbzO)_2$[41] を作用させベンジルオキシカルボニル基を直接導入することで求核剤 **50** を得ていた (Scheme 18a)。この合成経路は 1 工程で保護されたグリオキシル酸シアノヒドリンを与える点では優れているが、ペルオキシドの潜在的不安定性のために収率が低く、特に再現性に乏しいことが大きな問題であったため、スケールアップを可能とする収率、再現性に優れた合成経路を開発するため検討を行った。酒石酸ジエステルは様々なものが市販されており、また合成も容易であるが、これを過ヨウ素酸ナトリウムで処理してジオールを酸化的に開裂すれば二分子のグリオキシル酸エステルを得ることができる。このものの官能基化を利用すれば、様々な求核剤を合成できると期待した。グリオキシル酸エステルへの TMSCN の付加にはルイス酸による活性化がしばしば利用されるが、ポリメリ化しやすいグリオキシル酸の性質から使用前に蒸留精製を必要とする点は実用上の大きな課題であった (Scheme 18b)[22a]。そこで酒石酸ジベンジル **187** を用いて種々検討した結果、**187** の酸化開裂によって得たアルデヒド **188** の粗生成物にエタノール/酢酸バッファー溶液中 TMSCN を作用させることで、アルデヒドのシアノシリル化と TMS 基の除去が一挙に進行し、共通中間体となる無保護のシアノヒドリン **189** が 77%で得られた。これに触媒量の DMAP 存在下 *O*-Cbz-スクシンイミド **190** を反応させると、シアノヒドリンのアシル化が 91%収率で進行し、目的の求核剤 **171** を総収率 70%で得ることに成功した (Scheme 18c)。本合成経路は再現性も良く、また 1 段階目の過ヨウ素酸分解とシアノ化を 100 mmol スケール、2 段階目の水酸基の保護を 30 mmol スケールで実施できるなど前法に比べ容易にスケールアップすることが可能であった。また、一般的な試薬で水酸基の保護を行えるため、目的に応じて様々なグリオキシル酸シアノヒドリンを調整できることも本法の特徴である。

求核剤の量的供給法が確立できたため、グラムスケールでの Mannich 反応を実施した。2.5 mmol のグリオキシル酸シアノヒドリン **171** と 1.5 当量のイミン **172** に対し 1 mol%のチオ尿素触媒 **53** を作用させると、ほぼ定量的かつ立体選択的に付加反応が進行し、1.25 g の Mannich 成績体 **173** が得られ、本手法が β-アミノ-α-ケト酸の大量供給へ応用できる可能性が示された。

Scheme 18. Improvement of the Preparation Method of Glyoxylate Cyanohydrin



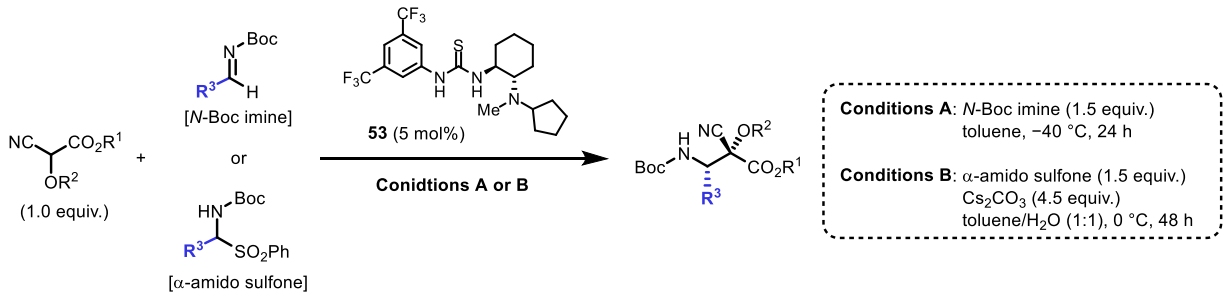
1-3-3. 基質適用範囲の検討

脂肪族イミンへの付加における最適条件を見出したため、基質適用範囲を調査した (Table 5a)。なお、より低温で実施可能な Condition A を標準条件とし、エンカルバマートへの異性化のために調製できなかったイミンに対してのみ Condition B を用いている。まず、求核剤の保護基の一般性を調査した。エステル部位をベンジルエステルからエチルエステルとした求核剤を用いると、僅かにジアステレオ比が低下したものの、高い立体選択性で定量的に **191** を与えた。シアノヒドリン部位の保護基を Alloc 基としたものも、良好な収率、立体選択性で **192** を与え、また BOM 基のようなアシル基以外の保護基も利用可能であったが、活性メチン炭素の酸性度が低下するためか反応性の低下が見られた (**193**)。

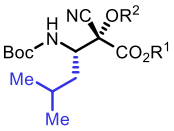
次に、タンパク質構成アミノ酸に対応するイミンの側鎖について検討した。条件検討で述べた **173** や **192** の他、メチル基やイソプロピル基のような単純な脂肪鎖を側鎖とするイミンを用いた場合、その嵩高さとジアステレオ選択性の間に相関がみられたが、いずれも単一の付加体をほぼ選択的に与えた (**194**, **195**)。特にいずれの基質を用いても 97% ee 以上のエナンチオ選択性が発現しており、チオ尿素 **53** を触媒とした場合基質の嵩高さの影響をほとんど受けないことが明らかとなった。また、アルコールやカルボン酸、アミンのような極性官能基は、適切に保護することで適用可能であった (**196**–**198**)。特にアルコールは用いる保護基によっては触媒との相互作用に影響するためか立体選択性の低下がみられたが、嵩高く電子不足な TBDPS 基で保護することで 90% ee, 14:1 dr で付加体 **196** を得ることが可能であった。さらに、酸化的増炭反応を経る既存法[11,12]では合成できないメチル、トリチルスルフィドを含む側鎖の立体選択的な導入も可能であり、本反応の優位性の 1 つである (**199**, **200**)。同様に、酸化されやすいトリプトファンやチロシンに対応する付加体 **201**, **202** も良い収率、立体選択性で合成可能であった。

非タンパク質構成アミノ酸についても検討を行った (Table 5b)。エチル基、*n*-プロピル基、*n*-ブチル基および 2-フェニルエチル基といった鎖長の異なる側鎖を持つ種々の脂肪族イミンはいずれも 98% ee、32:1 dr 以上の非常に高い立体選択性で付加体を与え (**203**–**206**)、α 位、β 位に嵩高いシクロヘキシル環を有する基質を用いても円滑に付加反応が進行した (**207**, **208**)。さらに、チオ尿素触媒 **53** は脂肪族イミンのみならず芳香族イミンへの付加にも適用可能であり、付加体 **209** を 99% ee で定量的に与えた。また、ホモセリンに対応する付加体 **210** も立体選択的に得ることができた。アスパラギン酸やアスパラギンに対応するイミンは、1,3-ジカルボニル構造を持つためイミンとして反応させることは困難であるが、**210** の側鎖を酸化することでそれらの化合物へと変換できると考えられる。最後に本反応の最大の特徴として、入手が容易でないアミノ酸に対応する側鎖を簡便に導入できることが挙げられる。例えば *N*-Boc シクロプロピルグリシン (¥19,100/1 g from TCI)[42] やアリシンエチレンアセタール (¥31,600/250 mg from Sigma Aldrich)[43] といった高価なアミノ酸や、トリフルオロメチル基、シアノ基を持つ市販されていないアミノ酸に対応する付加体を対応するイミンから高収率、高立体選択的に合成することが可能であり、本反応は既存法では直接的に得ることが困難な β-アミノ-α-ケト酸の合成に特に有用である (**211**–**214**)。

Table 5. Substrate Scope

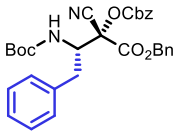


(a) For proteinogenic amino acids

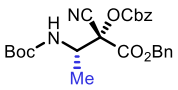


(for Leu, A)

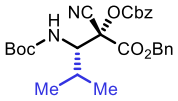
173 (R^1 = Bn, R^2 = Cbz)
96%, 98% ee, 49:1 dr
191 (R^1 = Et, R^2 = Cbz)
quant., 98% ee, 30:1 dr
192 (R^1 = Bn, R^2 = Alloc)
100%, 97% ee, 35:1 dr
193 (R^1 = Bn, R^2 = BOM)
81%, 94% ee, 34:1 dr



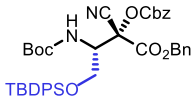
182 (for Phe, B)
76%
93% ee, 23:1 dr



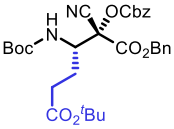
194 (for Ala, A)
quant.
97% ee, 13:1 dr



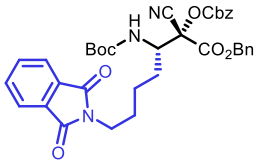
195 (for Val, A)
quant.
99% ee, 53:1 dr



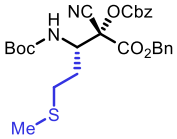
196 (for Ser, B[a])
94%
90% ee, 14:1 dr



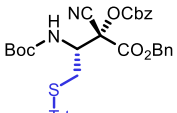
197 (for Glu, A)
quant.
91% ee, 25:1 dr



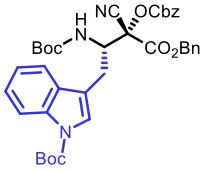
198 (for Lys, B)
89%
90% ee, 12:1 dr



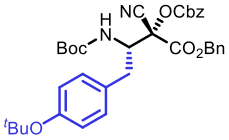
199 (for Met, A)
61%
97% ee, 49:1 dr



200 (for Cys, B[a])
85%
91% ee, 7.9:1 dr

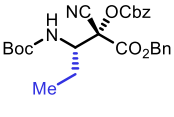


201 (for Trp, B)
82%
88% ee, 12:1 dr

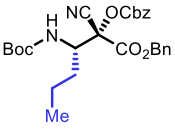


202 (for Tyr, B)
92%.
94% ee, 27:1 dr

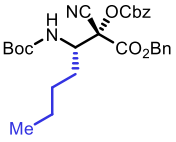
(b) For non-proteinogenic amino acids



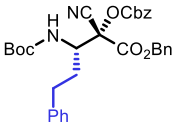
203 (for Abu, A)
80%
99% ee, 37:1 dr



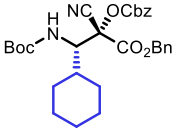
204 (for Nva, A)
98%
98% ee, 32:1 dr



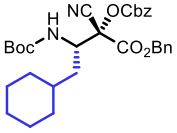
205 (for Nle, A)
99%
98% ee, 37:1 dr



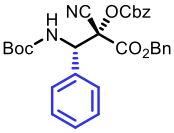
206 (for Hph, A)
96%
98% ee, 32:1 dr



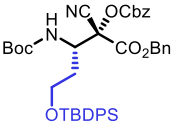
207 (for Chg, A)
93%
99% ee, 94:1 dr



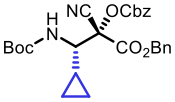
208 (for Cha, A)
96%
98% ee, 76:1 dr



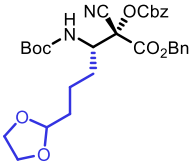
209 (for Phg, A)
99%
99% ee, 46:1 dr



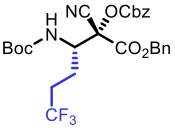
210 (for Hse, B[a])
92%
94% ee, 11:1 dr



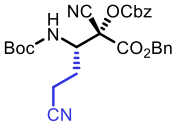
211 (A)
90%
99% ee, 36:1 dr



212 (for Aea, A)
96%
98% ee, 43:1 dr



213 (B[a])
94%
95% ee, 23:1 dr



214 (B[a])
73%
85% ee, 8.0:1 dr

Isolated yields are shown. Ratio of stereoisomers was determined by chiral HPLC analysis. Conditions are specified in parentheses as (A) or (B).
(a) The reaction was performed for 24 h.

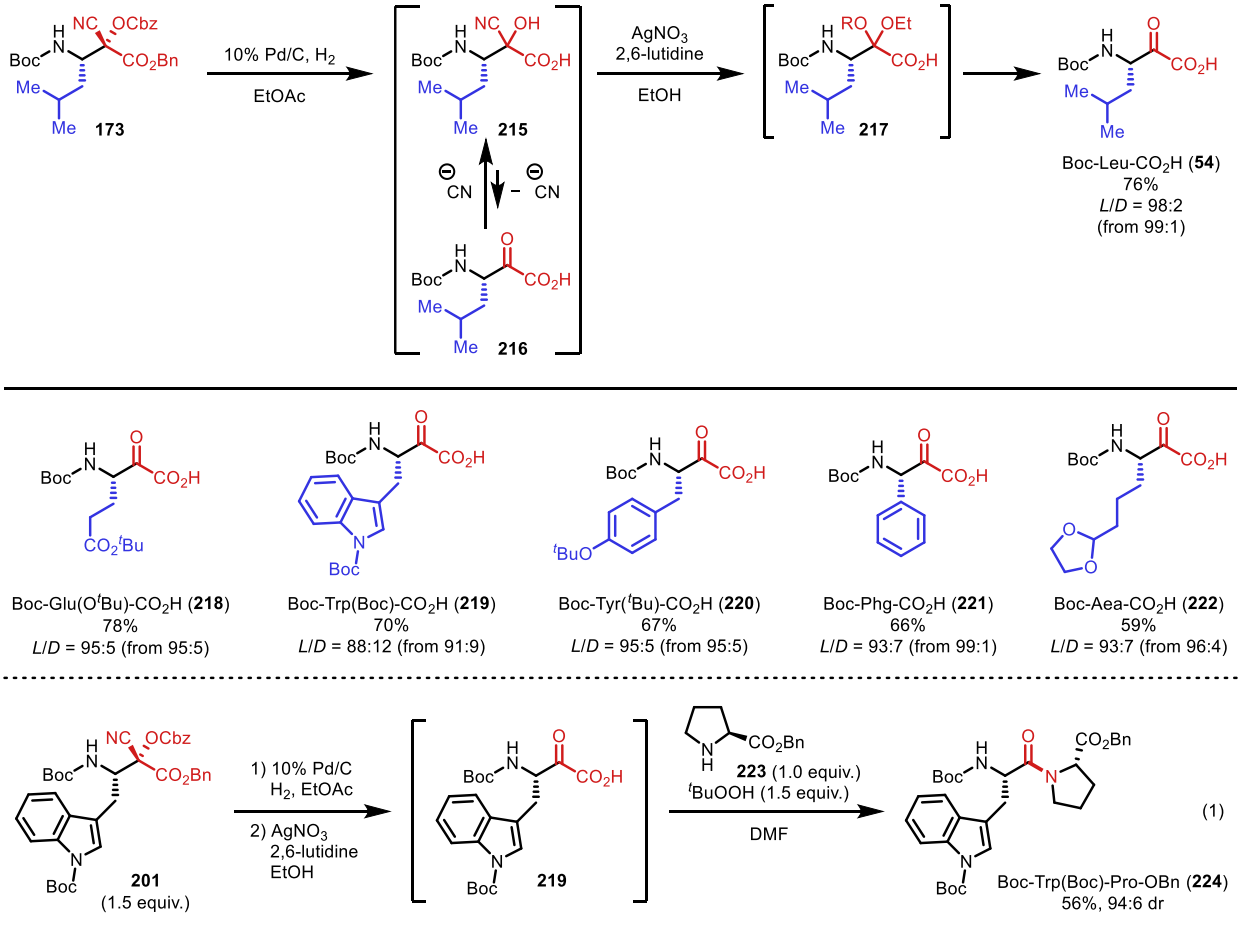
第四節 β-アミノ-α-ケト酸および関連するペプチドの合成と利用

1-4-1. β-アミノ-α-ケト酸の合成

前節で脂肪族、芳香族イミンへのグリオキシル酸シアノヒドリンの高立体選択的付加反応が確立できたため、Mannich 成績体を利用した β-アミノ-α-ケト酸や関連する特殊ペプチドの合成を検討した。

まず、脱保護による β-アミノ-α-ケト酸の合成を試みた (Scheme 19)。第一章第二節でそれぞれ立体選択的に得た 2 つのジアステレオマーはいずれも β-アミノ-α-ケト酸へ変換可能と期待できるが、ここでは第一章第三節に述べたようにより高い立体選択性で得ることが可能な(2*R*,3*S*)体の付加体を用いて検討を行った。まず、付加体 **173** に対し水素雰囲気化パラジウム炭素を用いて接触水素化を行うと、当初の期待通り Bn 基と Cbz 基の脱保護が一挙に進行した **215** が得られた。カルボン酸の露出した状態においても第二節と同様に α 位のシアノヒドリンは保持されており α-ヒドロキシ酸への過剰還元は見られなかった。一方でこのシアノヒドリン中心のエピメリ化が進行していることが確認されたため、シアノヒドリンの着脱は接触水素化条件では可逆であり、ジアステレオ比は熱力学的安定性

Scheme 19. Transformation of Mannich Adducts to β-Amino-α-ketoacids



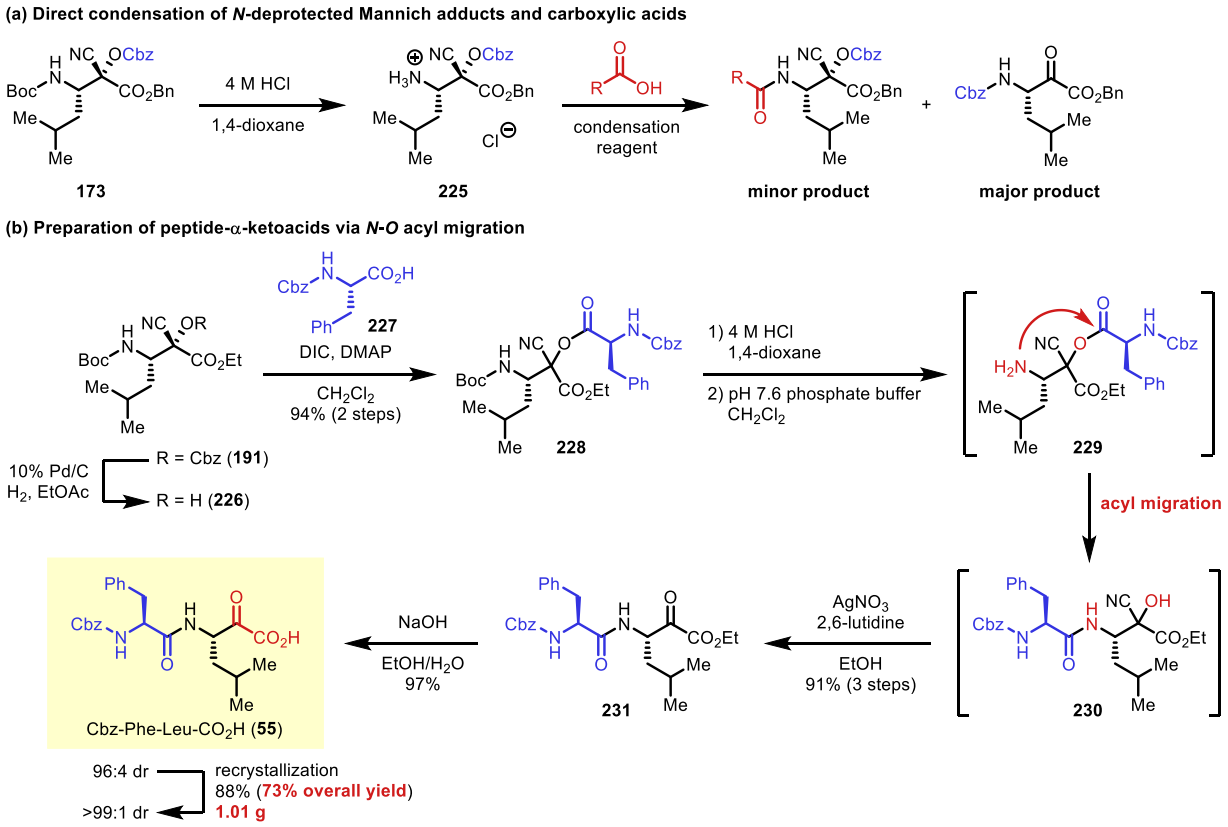
Isolated yields are shown. Ratio of stereoisomer was determined by chiral HPLC or SFC analysis after decarboxylative derivatization if necessary.

に支配されていることが示唆された。このシアノヒドリン **215** に対しエタノール溶媒中硝酸銀と 2,6-ルチジンを作用させると、シアノ基の脱離が 12 時間で円滑に進行し、カルボン酸担持型シリカゲルを用いたカラムクロマトグラフィーでの精製を行うことで目的の β-アミノ-α-ケト酸 **54** を 76%収率、*L*/*D* 比 98:2 で得ることに成功した。また **54** の不斉情報は Mannich 付加体からほとんど損なわれておらず、これは反応系中の様子から、脱シアノ化の際に溶媒としたエタノールが α 位で(ヘミ)アセタール **217** を一時的に形成しエノール化を抑制したためと考察している。これら 2 工程の変換によってグルタミン酸、トリプトファン、チロシンに対応する β-アミノ-α-ケト酸 **218**–**220** が良好な収率で得られた他、、フェニルグリシンやアリシンエチレンアセタールのような非タンパク質構成アミノ酸に対応する β-アミノ-α-ケト酸 **221**、**222** も高いエナンチオ比で得ることに成功した。また、2 段階の脱保護によって得られた β-アミノ-α-ケト酸は粗生成物のまま *t*-ブチルヒドロペルオキシドを用いた脱炭酸型縮合 [10b] に直接適用可能であり、Mannich 付加体 **201** とプロリン **223** から対応するジペプチド **224** を 56%収率、94:6 dr で与えた (eq. 1)。この結果から、脱炭酸型縮合によって本 Mannich 成績体が α-アミノ酸モチーフの効率的な導入に有用なビルディングブロックとして利用できることが示される。

1-4-2. ペプチド-α-ケト酸の合成と脱炭酸型フラグメントカップリングへの応用

次に、ペプチド-α-ケト酸の合成を試みた。最初に Boc 基の除去と縮合による単純なペプチド鎖の伸長を試みた (Scheme 20a)。しかし、付加体 **173** の *N* 末端の Boc 基の脱保護によって生じるアミン **225** を通常の脱水縮合条件に付すと、望みの縮合ではなくシアノヒドリン上の Cbz 基の分子内転移が優先して進行し、目的のアミドは低収率でしか得ることができなかった。分子内反応の抑制は困難であると考えた著者は、木曽らの開発した *O*-アシルイソペプチド法 [44] に着想を得てこのアシル基転移を利用しペプチドた-α-ケト酸の合成を計画した (Scheme 20b)。まず付加体 **191** に対し接触水素化を行いシアノヒドリン上の Cbz 基を脱保護した後、DIC、DMAP を用いて **226** の水酸基のアシル化を行った。電子不足なシアノヒドリンの求核性の低さが懸念されたものの、実際には *N*-Cbz フェニルアラニン **227** との縮合が良好に進行し、イソペプチド様のエステル **228** を 94%収率で得た。ここで塩酸を用いて Boc 基を脱保護し生じたアミンの塩酸塩を中和すると、**229** からの分子内 *O*–*N* アシル基転移が進行しアミド **230** が得られた。さらに硝酸銀と 2,6-ルチジンでの処理によってシアノ基を除去することで、ペプチド-α-ケトエステル **231** を 3 工程収率 91%で与えた。最後に C 末端のエチルエステルを加水分解することで、所望のペプチド-α-ケト酸 **55** を 96:4 で得ることに成功した。加えてジエチルエーテルを用いた再結晶によって、ジアステレオ比が>99:1 まで向上し、ペプチド-α-ケト酸 **55** を単一のジアステレオマーとしてグラムスケール、総収率 73%で得ることも可能であった。既存法が保護基の着脱効率に課題を抱え、また比較的過酷な条件を必要とするのに対し、本合成経路は多少の工程数を要

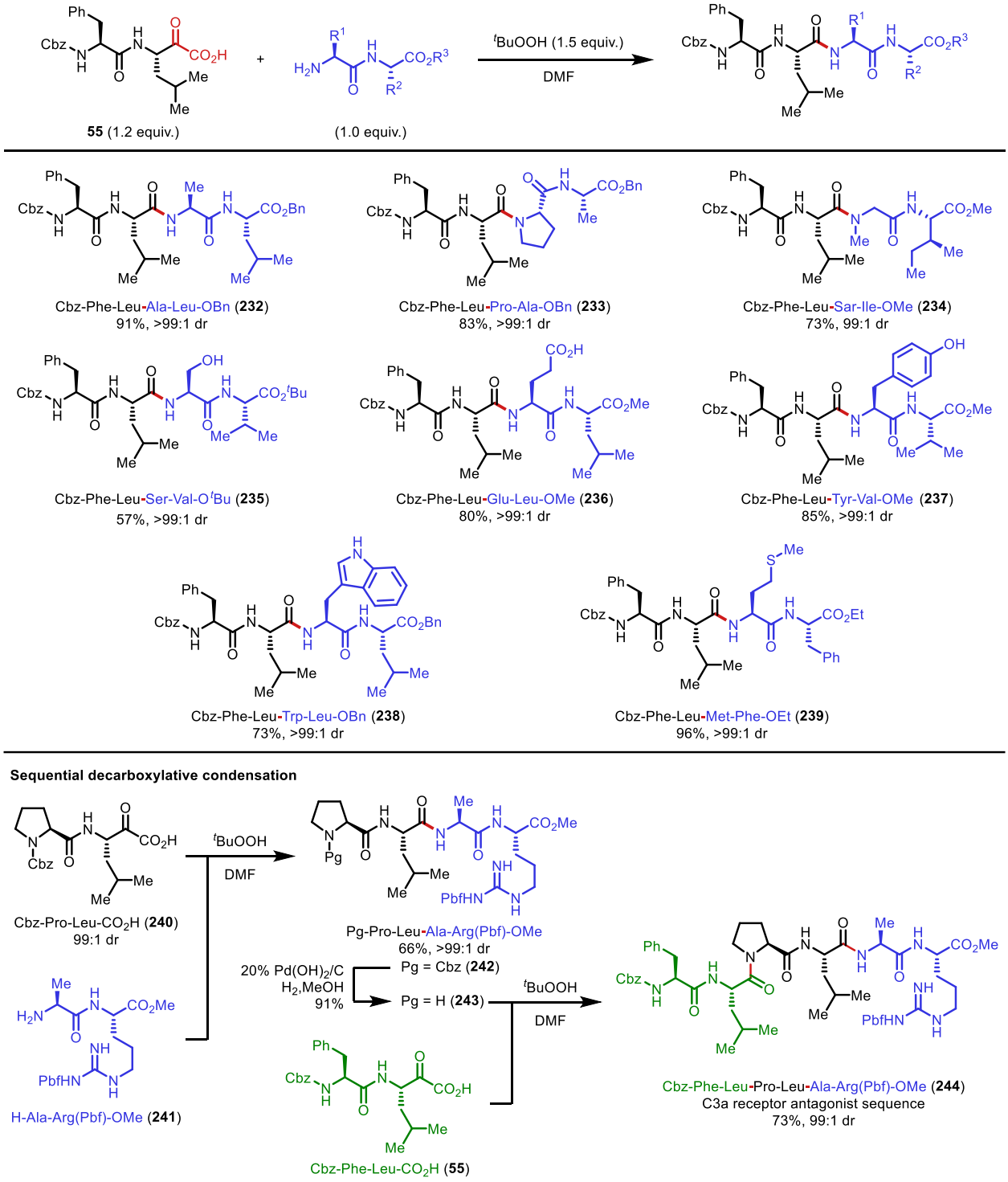
Scheme 20. Preparation of Peptide-α-ketoacid



するもののそのすべてがほぼ定量的に進行しており、効率的にペプチド-α-ケト酸を供給することが可能であった。

縮合剤を用いる一般的なアミド化反応では、ペプチド鎖同士を縮合するフラグメントカップリング[45]はアズラクトンを経由したエピメリ化が深刻な問題となるために、グリシンやプロリンのようなエピメリ化が問題とならない特定の残基で実施することが好まれる。一方著者の所属研究室ではヒドロペルオキシドを用いた脱炭酸アミド化反応を開発しており[10b]、縮合剤の機構とは異なるメカニズムで進行することからフラグメントカップリングにおいても従来の傾向とは異なる反応性を示す相補的な手法となり得ると期待される。しかし、ペプチド-α-ケト酸のラージスケールでの効率的な合成法がないためにその検討は未だ行えていなかった。そこで今回上述のペプチド-α-ケト酸のグラムスケールでの供給法が確立できたため、**55** を用いた脱炭酸型ペプチドカップリングを検討した (Scheme 21)。単純なジペプチドである H-Ala-Leu-OBn との縮合はエピメリ化を起こすことなく進行し、91%収率でテトラペプチド **232** を与えた。ヒドロキシルアミンを使用する KAHA ligation では用いることのできない第二級アミンであるプロリンやサルコシンを N 末端の残基とするジペプチドとの縮合も可能であり、対応するテトラペプチド **233**、**234** をそれぞれ良い収率で与えた。また、単純な基質でのアミド化と同様の高い化学選択性がフラグメントカップリングにおいても確認され、側鎖が無保護のセリ

Scheme 21. Decarboxylative Peptide Coupling Using Peptide-α-ketoacids



Isolated yields are shown. Ratio of stereosimers was determined by chiral SFC analysis.

ン、グルタミン酸、チロシン、トリプトファン残基や、酸化を受けやすいメチオニン残基を含むジペプチドとのカップリングによってテトラペプチド **235**–**239** を良好な収率で得ることに成功した。

さらに、本脱炭酸型フラグメント縮合を応用して、連続的な[2＋2＋2]での縮合も可能であった。**55** と同様にして調製したペプチド-α-ケト酸 **240** とジペプチド **241** に *t*-BuOOH を作用させることで、テトラペプチド **242** を 66%収率、>99:1 dr で得た。続けて N 末端の Cbz 基を脱保護し、再度 **55** を用い

た脱炭酸型縮合を行うことで、補体 3a 受容体へのアンタゴニスト活性を示すヘキサペプチドの保護体 **244**[46] を 73%収率で得ることに成功し、この脱炭酸型アミド化がオリゴペプチドの収束型合成に利用できることを示した。

1-4-3. シアノヒドリンの活用を鍵とするペプチド-α-ケトアミドの合成

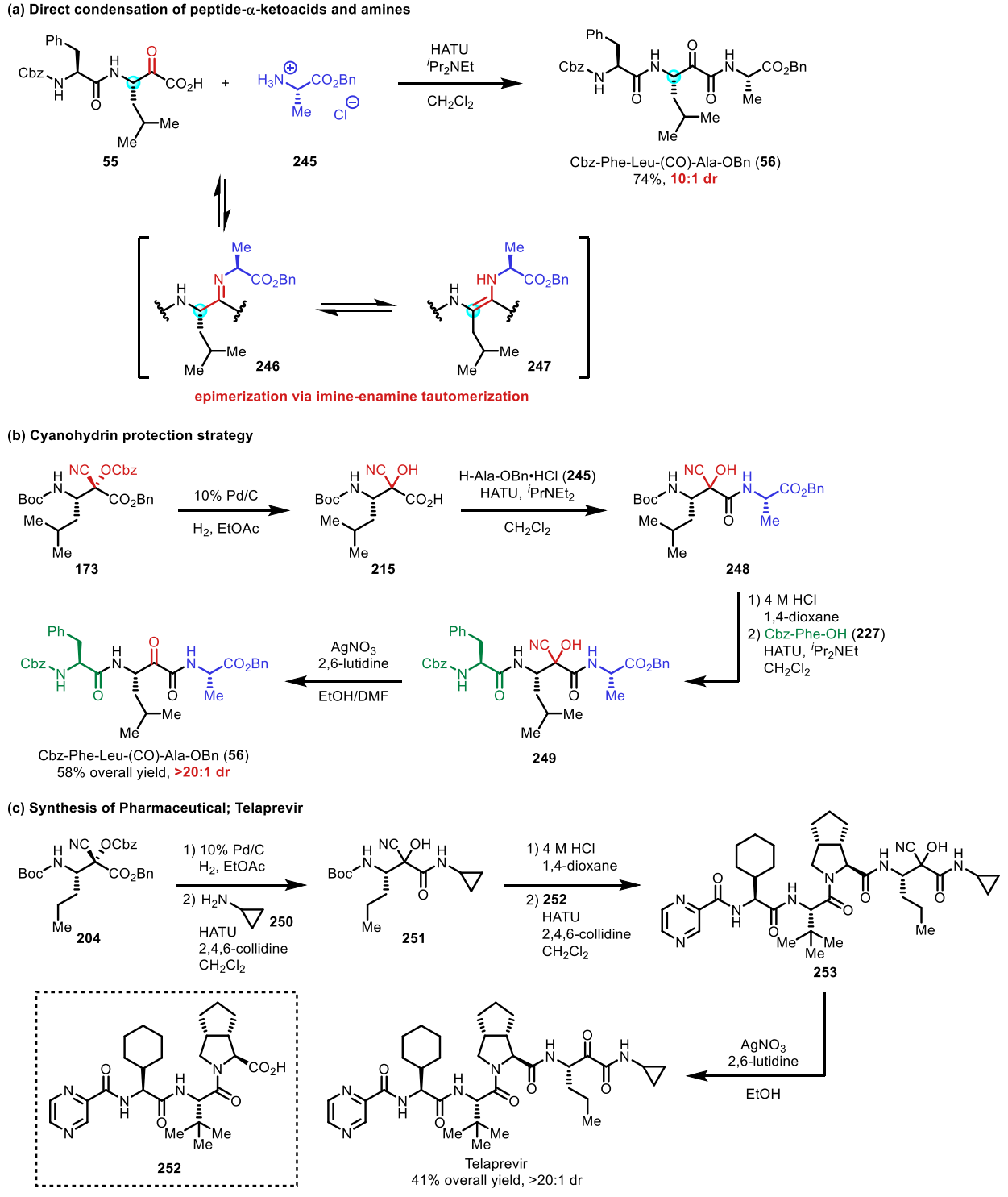
最後に、Mannich 付加体を利用したペプチド-α-ケトアミドの合成を検討した。α-ケトアミドを経る最も直接的な手法は α-ケト酸とアミンとの脱水縮合である。しかし β 位に不斉点を持つ β-アミノ-α-ケト酸やペプチド-α-ケト酸を用いた縮合では、原料と生成物のいずれにおいても求電子性の高い α 位でのイミン形成とエナミンへの異性化との平衡が存在するため、β 位の不斉情報が損なわれることが常に問題となり得る。実際、単一のジアステレオマーとして合成したペプチド-α-ケト酸 **55** とアラニン誘導体 **245** を一般的な縮合条件に付すと、目的のペプチド-α-ケトアミド **56** は良好な収率で得られるものの、ケトアミド β 位におけるジアステレオ比は 10:1 まで低下した (Scheme 22a)。そのため α-ケトアミド構造は合成最終盤に構築することが求められ、ペプチド-α-ケトアミドの合成には新たな保護基の着脱にかかる変換効率の低下や多工程を要する異なる合成経路を経ることが避けられない [16]。

このような状況の下、著者は、Mannich 成績体が持つシアノヒドリンを反応性の高い α 位の保護基として活用する合成戦略が実現すれば、β-アミノ-α-ケト酸合成の中間体から直接的にペプチド-α-ケトアミドに導くことができる効率的な手法となると期待し検討を行った (Scheme 22b)。付加体 **173** から接触水素化によって簡便に得られるカルボン酸 **215** に対して HATU、*i*-Pr_2NEt を用いてアラニン誘導体 **245** との縮合を行うと、ジペプチド **248** が良好な収率で生成していることが確認された。シリカゲルカラムクロマトグラフィーによる精製を行うことなく N 末端の Boc 基を塩酸によって除去し、続けて同様の条件でフェニルアラニン誘導体 **227** との縮合を行いトリペプチド **249** を合成した。これらの変換の過程で α 位のシアノヒドリンの大部分は保持されており、酸性条件や縮合に必要な最低限の塩基存在下では安定であることが示唆された。一方で硝酸銀を作用させた場合にはこれまでの Mannich 付加体の誘導体化と同様にシアノヒドリンはケトンへと速やかに変換され、ペプチド-α-ケトアミド **56** を総収率 58%で得ることに成功した [47]。また著者の想定した通り、β 位におけるジアステレオ比は>20:1 を維持しており、シアノヒドリン構造の活用が、α 位ケトカルボニル基の導入と保護の両面で有用であることが示された。

本手法を応用し、C 型肝炎ウイルスの NS3/4A セリンプロテアーゼ阻害活性を示す Telaprevir の合成を行った (Scheme 22c)[48]。まずノルバリンに相当する付加体 **204** を脱保護、シクロプロピルアミン **250** との縮合に付し、アミド **251** とした。その後 Boc 基を酸性条件によって脱保護し、文献既知のトリペプチド **252** との縮合を行うことでシアノヒドリン保護体 **253** を得た。最後に銀塩で処理し、テト

ラペプチドを含む Telaprevir を 41%収率、単一のジアステレオマーとして得ることに成功した。キラルプールを用いず、また酸化条件を一切経ない本手法は、既存法では合成困難なペプチド-α-ケトアミドの効率的な合成に有用と期待される。

Scheme 22. Synthetic Application of Peptide-α-ketoamides Using Cyanohydrin-protection Strategy



Isolated yield are shown. Ratio of diastereomers was determined by ^{1}H NMR spectroscopy.

第二章 DFT 計算による反応機構解析

第一節 Mannich 反応の想定反応機構

第一章第二節に述べたように、今回開発した Mannich 反応では 「ベンゾチアジアジンの置換基効果によってジアステレオ選択性が逆転する」 という興味深い結果が得られ、また第三節では「チオ尿素骨格がエナンチオ選択性の発現に有利である」 ことや「芳香環上の置換基とアミン部位の嵩高さの協奏的な効果がジアステレオ選択性の発現に重要である」 ことが明らかとなった。本触媒系に特徴的なこれらの性質が発現する理由について考察するため、DFT 計算による遷移状態の解析を行うこととした。

キラルアミンを不斉場とするチオ尿素触媒を用いた活性メチレンの不斉付加反応の機構解析はこれまで多数行われてきたが [49]、シクロヘキサンジアミンを不斉場とするチオ尿素触媒が特に詳細に議論されている (Figure 3)。竹本らはニトロオレフィンへの不斉 1,4-付加反応の開発当時、遷移状態モデルとして以下 **Model A** を提唱した [23]。すなわち、チオ尿素は弱い Brønsted 酸としてニトロオレフィンを求電子的に活性化し、第三級アミンがエノール化した 1,3-ジカルボニル化合物の脱プロトン化を促進しつつ求核的な活性化を行うものである。一方、2006 年 Pápai らは DFT 計算による遷移状態の解析を行い、ニトロオレフィンと 1,3-ジカルボニル化合物の配置は逆であり、チオ尿素によるエノラートの安定化とより酸性度の高いアンモニウムによる求電子剤の活性化を経る遷移状態 **Model B** が 1.6 kcal/mol 有利な遷移状態であると報告した [25]。また 2019 年 Hirschi、Vetticatt らは、最も安定なものではないものの、チオ尿素の一方の酸性プロトンとアンモニウムプロトンによってニトロオレフィ

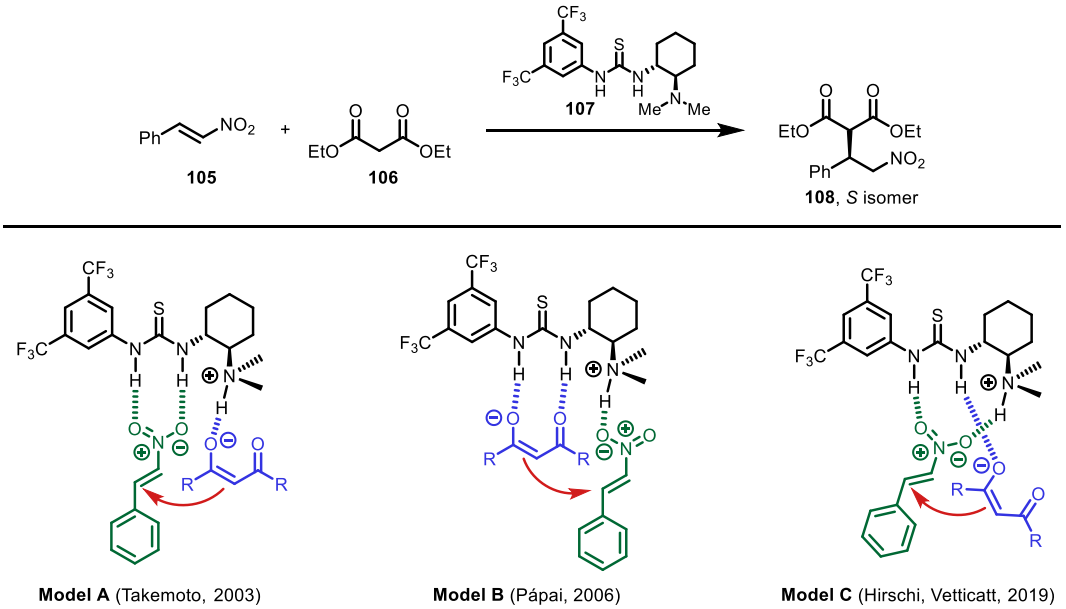


Figure 3. Proposed transition state models of amino-thiourea catalyzed asymmetric 1,4-addition of 1,3-dicarbonyl compounds to nitroolefins

ンを活性化する構造である **Model C** が比較的安定な遷移状態として存在することを計算科学の結果から提唱している[49g]。最近行われた複数の汎関数を用いたベンチマーク[49i]や速度論解析[49g]の結果からも Pápai らのモデルが最も妥当な反応機構とされているが、立体選択性を説明するためには Hirschi、Vetticatt らのモデルを考慮する必要があることが強調されている。

また第一章第二節にも述べたように、1,3-ジカルボニル化合物のイミンへの 1,2-付加反応に対して、竹本らはジアリールアセチレンをリンカーとした触媒–基質複合体モデルを設計し、Mannich 反応について実験的考察行っている (Table 1, bottom)[29]。アミノ尿素構造と β-ケトエステル構造を分子内に持つ複合体モデル **121** は、尿素上の 2 つの酸性プロトンがケトンのカルボニル酸素と水素結合を形成している状態を最安定とすることが DFT 計算によって示されている。**121** に対しジクロロメタン-d_2 中イミン **67** を室温条件下作用させると、僅か 10 分で反応が完結し、遷移状態 **122** を経て Mannich 成績体 **123** をモデル反応と同一の絶対立体配置をもつ単一のジアステレオマーとして与える[29]。この結果は、アミノ(チオ)尿素触媒による Mannich 反応が、Pápai らの提唱した複合体 **Model B** を介して進行することを支持している。

以上の背景を踏まえ、著者の行ったグリオキシル酸シアノヒドリンの Mannich 反応は以下の触媒サイクルで進行していると想定した (Figure 4)。まず、触媒のアミン部位が酸素官能基の置換した酸性度の高い活性メチンを脱プロトン化し、求核剤との複合体 **IM1** を与える。ここにイミンが取り込まれ ternary complex **IM2** が生じ、適切な配座から $\mathbf{TS_{Add}}$ を経て立体選択的に炭素–炭素結合が形成されイオ

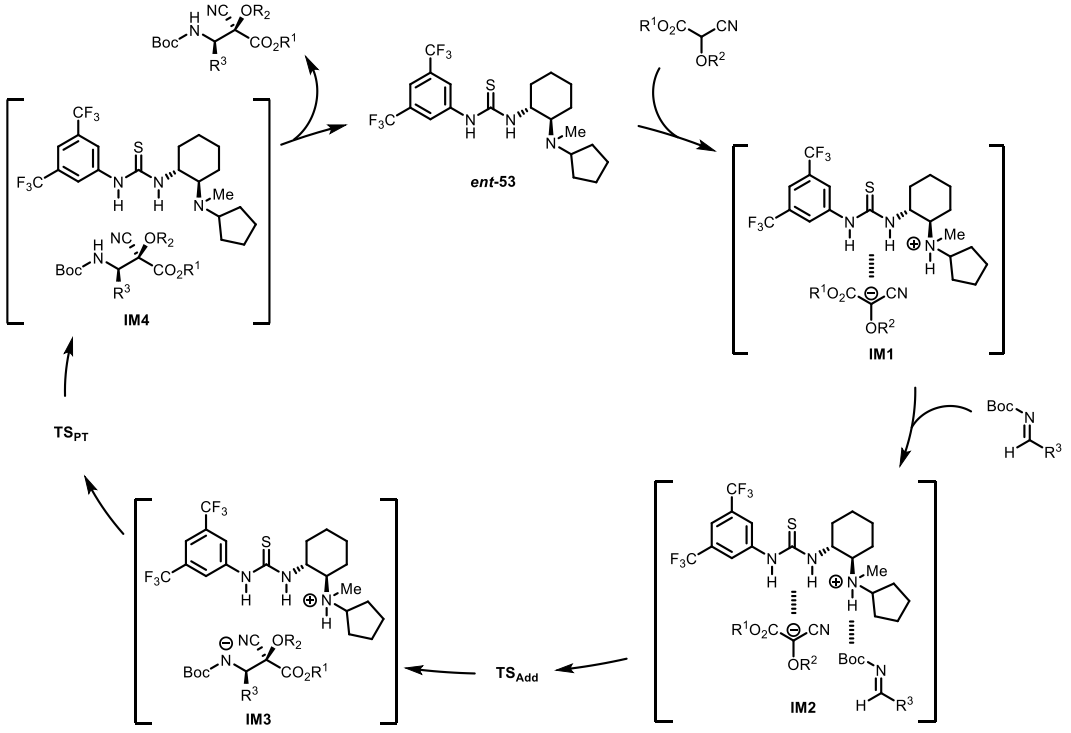
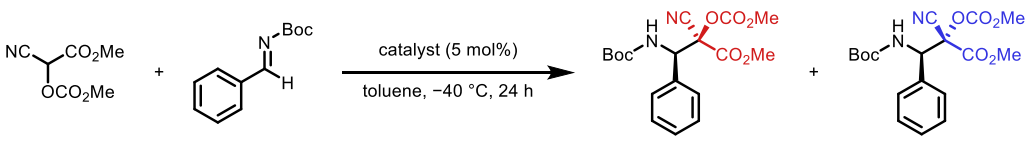


Figure 4. Plausible catalytic cycle of Mannich addition of glyoxylate cyanohydrin with aminothiourea catalyst

ン対 **IM3** を与える。最後に触媒のプロトンが $\mathbf{TS_{PT}}$ を介して生成物のアニオンへと移動し、触媒サイクルが完結する。

先行研究を鑑みると、脱プロトン化された求核剤はチオ尿素の酸性プロトンに、*N*-Boc イミンはアンモニウムによってそれぞれ認識される構造が最も安定と考えられる。しかし、アミン部位に異なる 2 つの置換基を持つ触媒や、多数の水素結合受容部位を持ち、また非対称な構造のグリオキシル酸シアノヒドリンを用いているために、マロン酸誘導体のニトロオレフィンへの 1,4-付加反応と同様に多くの配座異性体が存在する可能性は無視できない。さらに、非対称なアミン置換基を持つアミノチオウレアを対象とした機構解析はこれまで行われたことがなく、反応のエネルギー推移も不明である。そのため著者はまず、触媒サイクル全体のエネルギープロファイルを DFT 計算によって得ることとした。なお、本章で行う DFT 計算では計算コストの都合から求核剤の保護基をそれぞれメチルエステル、メトキシカルボニル基とした **254** を用いたが、Table 6 に示すようにそれぞれの触媒に対して第一章第二節、第三節の結果と矛盾しない立体選択性が発現することを実験的に確認した。

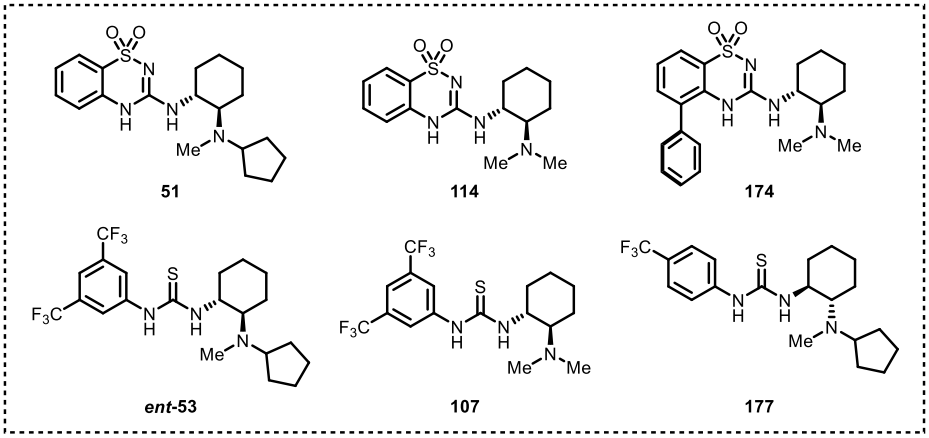
Table 6. Mannich-type Addition of Model Nucleophile **254**



254 **67** **255** **255'**

entry	catalyst	yield[a] (%)	er[b] **255**:***ent*-255**	er[b] **255'**:***ent*-255'**	dr[b] **255**:**255'**
1	**51**	95	36:1	3.4:1	33:1
2	**114**	80	41:1	3.2:1	10:1
3	**174**	98	4.1:1	15:1	1:21
4	***ent*-53**	92	>99:1	3.7:1	34:1
5	**107**	97	43:1	1.1:1	7.5:1
6	**177**	96	1:37.5	1:3.8	16:1

(a) Isolated yields are shown. (b) Ratio of stereoisomers was determined by chiral HPLC analysis.



第二節 触媒サイクルのエネルギー計算と律速段階の決定

Mannich 反応の立体選択性を考察するために、まず本反応の律速段階を決定することとした。本章で行った DFT 計算はすべて Gaussian 09[50,51] を用いて行った。遷移状態を含む各構造のギブス自由エネルギーは B3LYP-D3/6-311G(d,p)[52,53,54] で構造最適化と振動解析を行った後、B3LYP-D3/6-311+G(3d,3p)で一点計算を行うことで得た。また、構造最適化と同じ汎関数、基底関数のもとで Truhlar らの開発した SMD solvation model[55,56] を用いて、トルエン中での溶媒効果も考慮した。なお、本節で括弧内に表記した各構造のギブス自由エネルギーはそれぞれ独立に計算したシアノヒドリン **254**、イミン **67**、チオ尿素 ***ent*-53** のギブス自由エネルギーの総和と比較した値を示しており、各構造に含まれていない成分は無限遠に存在するものとして考慮している。

まず、原料系である求核剤 **254**、イミン **67**、チオ尿素 ***ent*-53** の安定配座を探索した。グリオキシル酸シアノヒドリン **254** は、双極子モーメントを小さくするためにエステルのカルボニル酸素とニトリルが逆方向を向いた構造が最安定であり、またイミン **67** は先行研究と同様に *s*-cis 配座がより安定であった (Figure 5)。

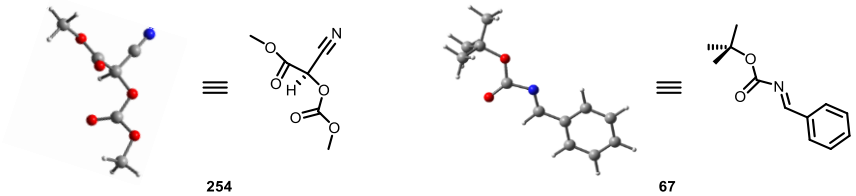


Figure 5. Optimized structure of glyoxylate cyanohydrin **254** and *N*-Boc imine **67**

チオ尿素触媒のアミン窒素上の置換基が異なる場合は sp^3 窒素原子上に不斉点が生じるため、2 つの異性体のエネルギーを比較した (Figure 6)。どちらの構造でも塩基性のアミン窒素はチオ尿素の酸性プロトンの 1 つと分子内で水素結合を形成しているが、嵩高いシクロペンチル基がシクロヘキサン環に対してエクアトリアル方向に向いた **53_A** が僅かに安定であった。これらの構造を基に求核剤とのイオン対である **IM1** の構造を探索し、エノラートがアンモニウムと、カルボナートがチオ尿素と水素結合を形成したものが最も安定な中間体構造として得られた。

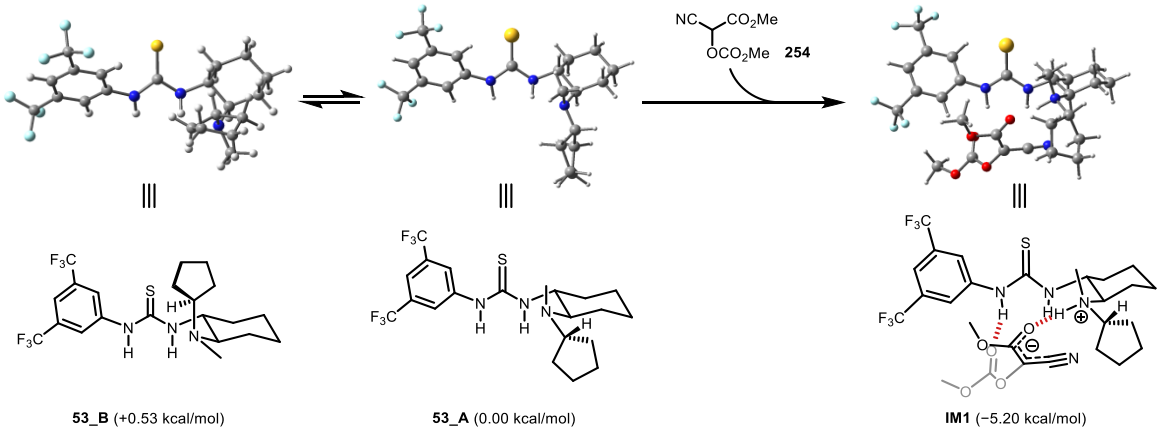


Figure 6. Stable conformation of thiourea catalyst ***ent*-53** and formation of binary complex **IM1**

次に、炭素–炭素結合形成の遷移状態を調査した (Figure 7)。グリオキシル酸シアノヒドリン **254** はエステル、ニトリル、カルボナートの 3 つの水素結合受容性官能基を有していることや、基質の配座、位置関係を考慮して種々の遷移状態構造を検討した結果、図に示す $\mathbf{TS_{Add}\_1}$ が主異性体を与える最も安定な遷移状態として得られ、また原料系からの相対的なエネルギーは+5.18 kcal/mol であった。この遷移状態においては、脱プロトン化された求核剤がエステルを介してチオ尿素と相互作用し、*s-trans* 配座のイミンがカルボニル酸素を介してアンモニウムによって活性化されている。またこの遷移状態に対して IRC 計算 [57] を行うことで、付加前の中間体 **IM2**、付加後の中間体 **IM3** がそれぞれ得られた。

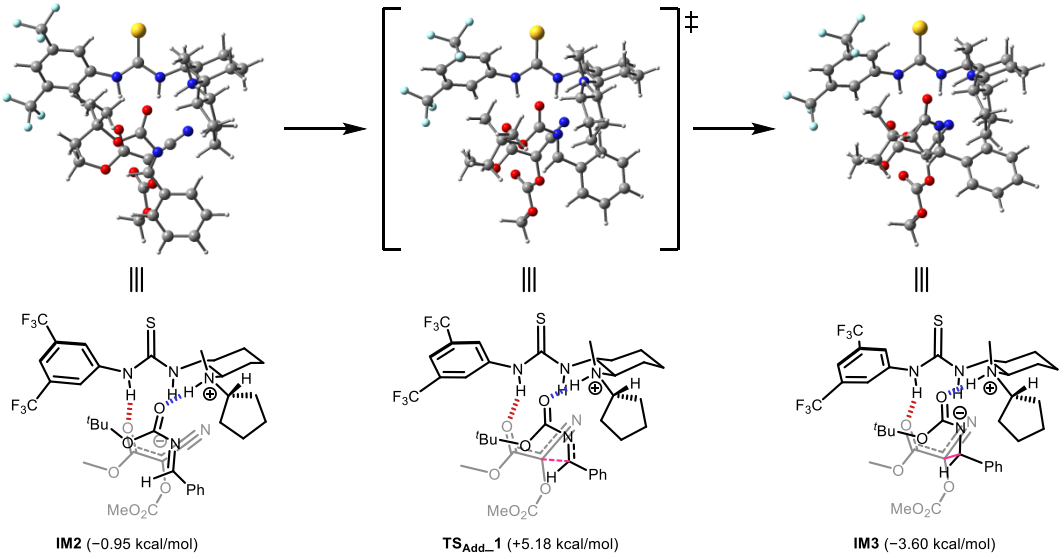


Figure 7. Reaction pathway of carbon–carbon bond formation step to afford major stereoisomer **255**

同様にして、ジアステレオマー、エナンチオマーを与える遷移状態である **TS$_{Add}$_2**、**TS$_{Add}$_3** を得た (Figure 8)。チオ尿素のような水素結合供与体を用いた 1,2-付加反応においては、一般的に求核剤、求電子剤両方の面選択性が逆転した **TS$_{Add}$_4** がエナンチオマーを与える遷移状態とされるが、興味深いことに本系ではこの遷移状態のエネルギーは基質同士の重なりのために非常に高く、シクロヘキサン環がチオ尿素に対して紙面裏側に 180°反転した **TS$_{Add}$_3** の方が 5 kcal/mol 程度安定であることが明らかとなった [58]。

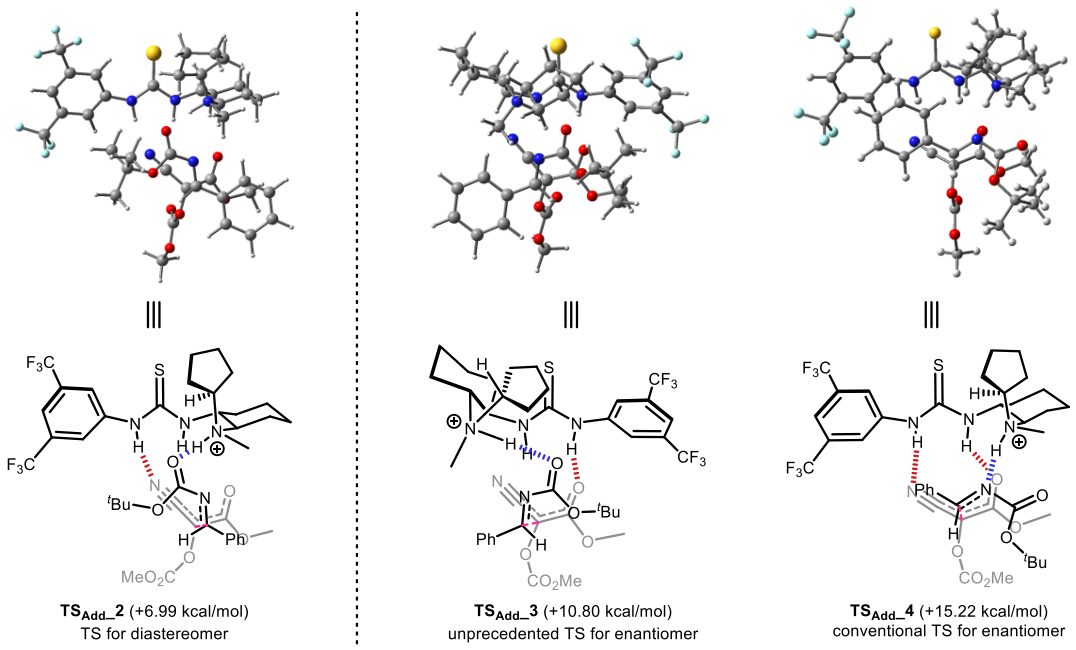


Figure 8. Transition states leading to diastereomer **255′** and enantiomer ***ent*-255**

竹本らのチオ尿素を用いたニトロオレフィンへの 1,4-付加反応について、2006 年 Liu らは、触媒から生成物のアニオンへのプロトン移動が律速段階であると提案している [59]。その他の先行研究では炭素–炭素結合形成が律速段階であることを支持しているが、今回著者の開発した Mannich 反応におけるプロトン移動過程のエネルギーが律速段階となる可能性を検討することとした。**IM3** ではイミンに含まれていたカルバマート上に負電荷が存在するが、カルバマートアニオンの窒素原子はチオ尿素の酸性プロトンと、酸素原子はアンモニウム部位のプロトンと水素結合を形成している。また、アンモニウムプロトンは窒素原子へのプロトン供与も構造的に可能である。そのため、主立体異性体 **255** を与える経路について、プロトン移動にかかるエネルギーを調査した。

まず、チオ尿素がプロトン源となる経路について検討した (Figure 9)。**IM3** からのチオ尿素上のプロトンの移動は+3.09 kcal/mol の遷移状態 **TS_{PT}_A** を介して起こり、+0.39 kcal/mol の中間体 **IM4_A** を与えた。この過程は炭素–炭素結合形成 (+5.18 kcal/mol)より低いエネルギーで進行するが、イオン対型の触媒 **53_C** とアミド型の生成物 **255_A** の解離後のエネルギーは+7.37 kcal/mol であり、原料系に比べ高いことからこの経路は熱力学的に不利であると考えられる。

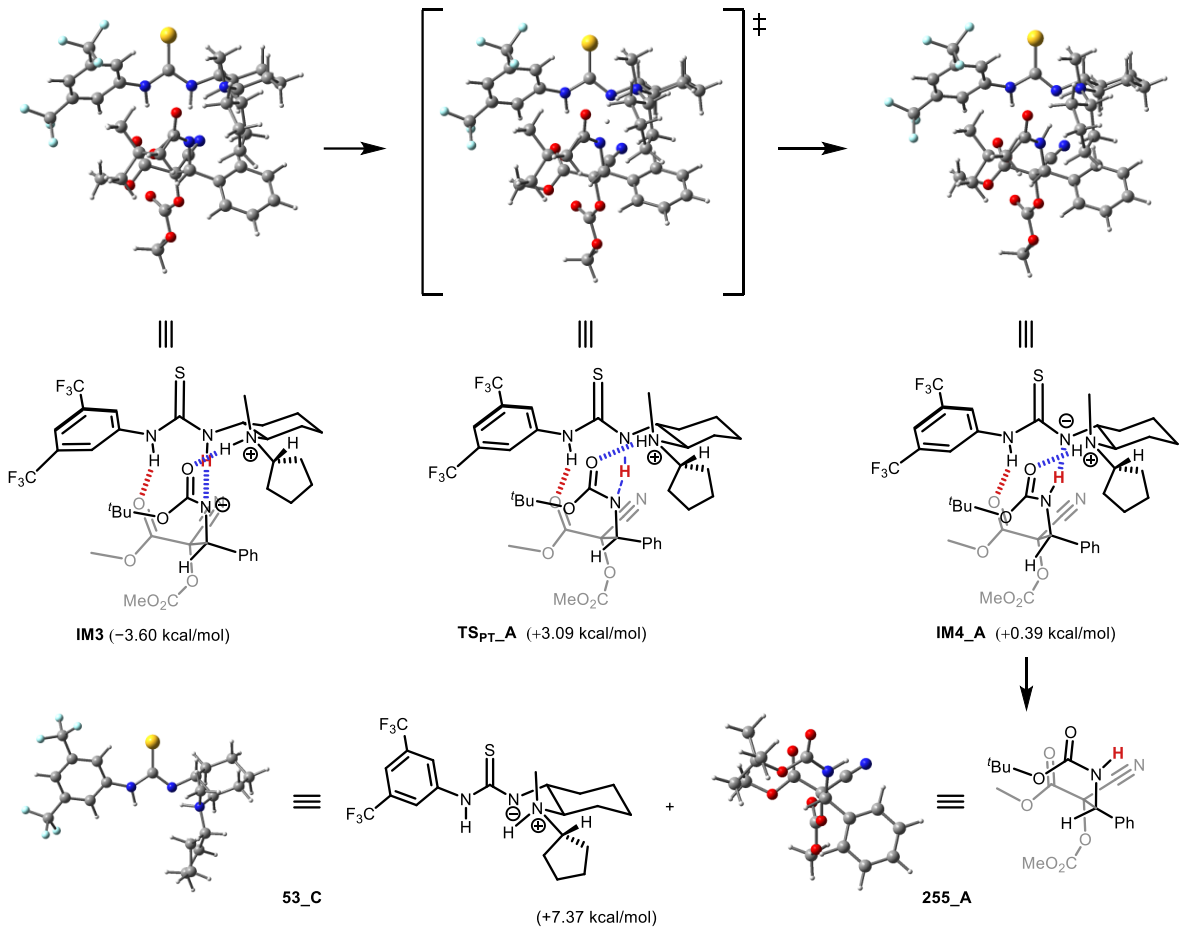


Figure 9. Proton transfer from the thiourea moiety to the nitrogen atom of the carbamate anion

次に、アンモニウム部位がプロトン源となる経路について調査した。**IM3** の時点でこのプロトンはカルバマートアニオンの酸素原子と相互作用しているため、まずこの点でのプロトン移動を検討した (Figure 10)。**IM3** からプロトン移動後の **IM4_B** の間に遷移状態はなく、エネルギーの推移は単調増加であった。また触媒 **53_A′**とイミデート構造の生成物 **255_B** が解離した際のエネルギーは+16.28 kcal/mol と原料系よりも非常に高く、この経路も熱力学的に不利であると考えられる。

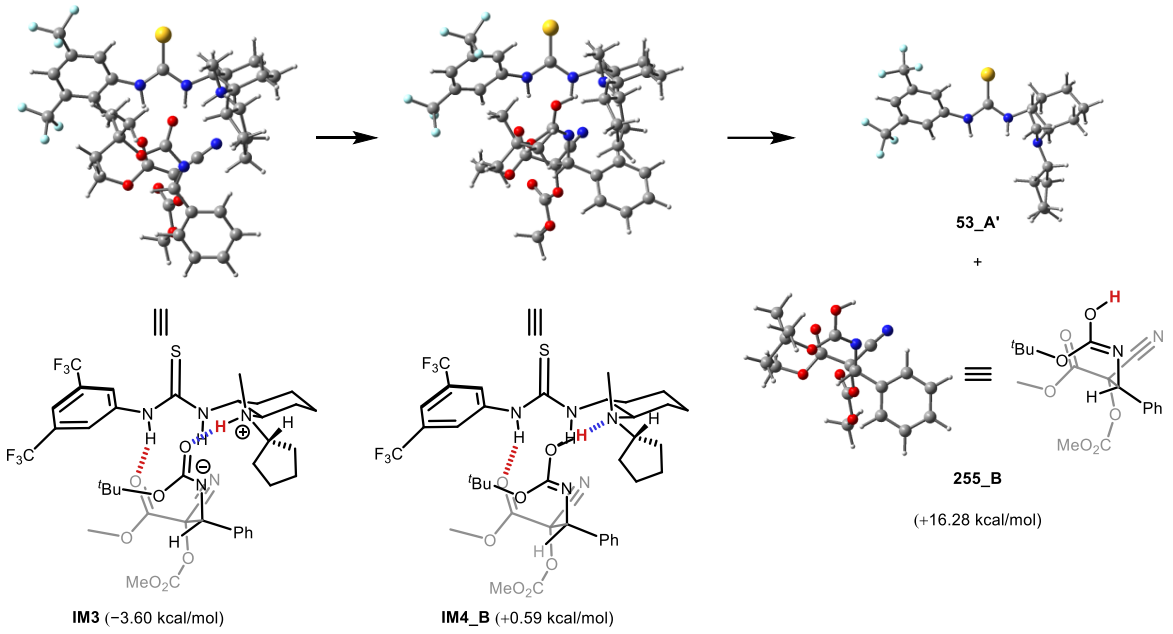


Figure 10. Proton transfer from the ammonium moiety to the oxygen atom of the carbamate anion

さらに、アンモニウムがプロトン源となる経路の内、カルバマートの窒素原子にプロトンが移動する経路を探索した (Figure 11)。−3.60 kcal/mol の中間体 **IM3** から遷移状態 **TS$_{PT}$_C** を経て起こるプロトン移動は−3.39 kcal/mol の中間体 **IM4_C** を与え、また生成物 **255_A** を解離し **53_A′**が再生することで触媒サイクルが完結した際のエネルギーも−3.33 kcal/mol と系全体として発熱的であった。そのため、アンモニウムからカルバマートの窒素原子にプロトンを供与するこの経路はエネルギー的に妥当なプロトン移動過程といえる。

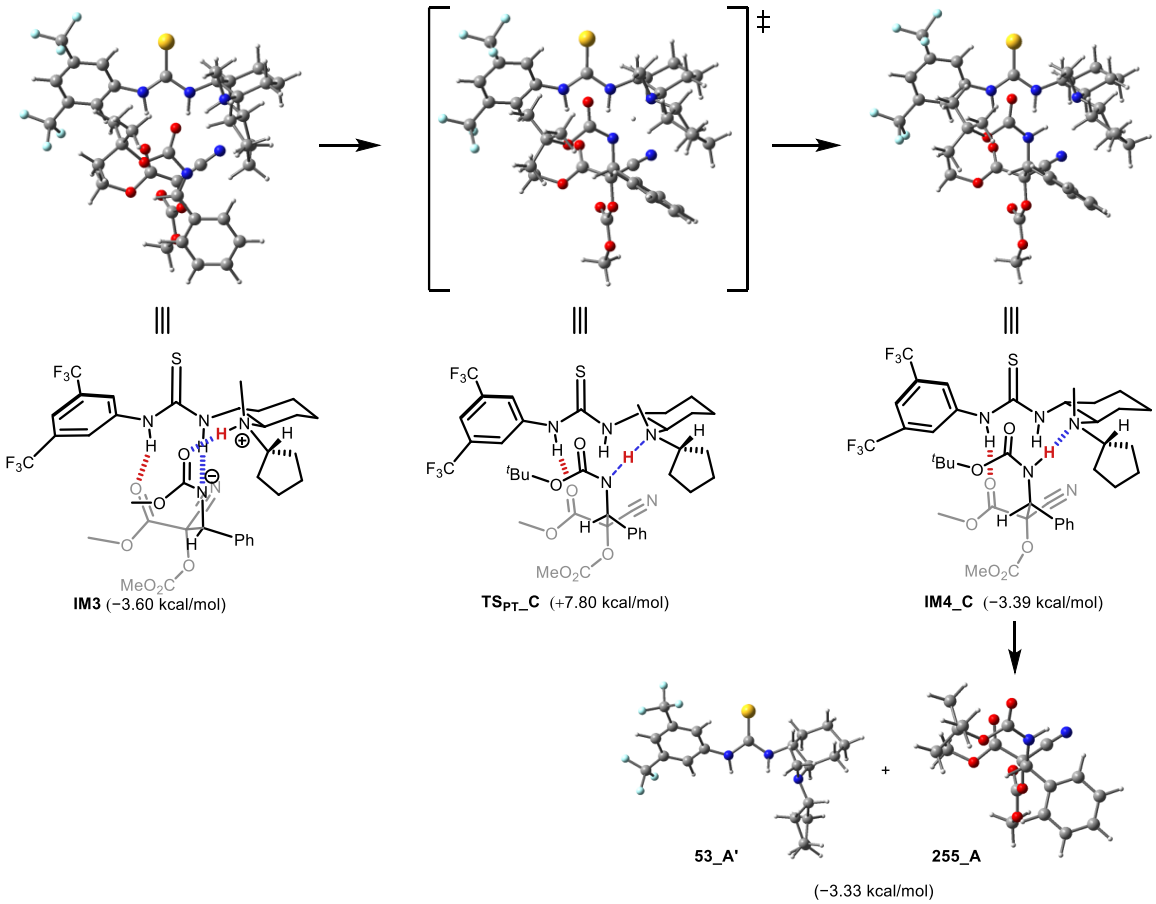


Figure 11. Proton transfer from the ammonium to the nitrogen atom of the carbamate anion

しかし **TS$_{PT}$_C** のエネルギーは+7.80 kcal/mol と炭素–炭素結合形成の+5.18 kcal/mol よりも高く、これは嵩高いアミン上のシクロペンチル基とイミン由来の置換基との間に働く立体反発のためと考えられる。このシクロペンチル基は根本の炭素–窒素結合を軸に自由回転できるため、より立体障害の小さい遷移状態が存在し得ると考え、反応経路を探索した (Figure 12)。シクロペンチル基を 120°回転させる際に経由する遷移状態 **TS$_{Rot}$** のエネルギーは+3.72 kcal/mol と十分低く、準安定な中間体 **IM3-2** に至ることが可能である。この構造から Figure 11 と同様の経路を探索すると、遷移状態 **TS$_{PT}$_D** を経て安定な中間体 **IM4_D** を与え、また触媒 **53_D** と生成物 **255_A** を解離した後のエネルギーも−1.91 kcal/mol であり系として発熱的であったため、本経路も妥当なプロトン移動過程である。さらに、**TS$_{PT}$_D** のエネルギーは+4.22 kcal/mol と **TS$_{Add}$_1** よりも低いことから、炭素–炭素結合形成過程が反応の律速段階であることが示された。

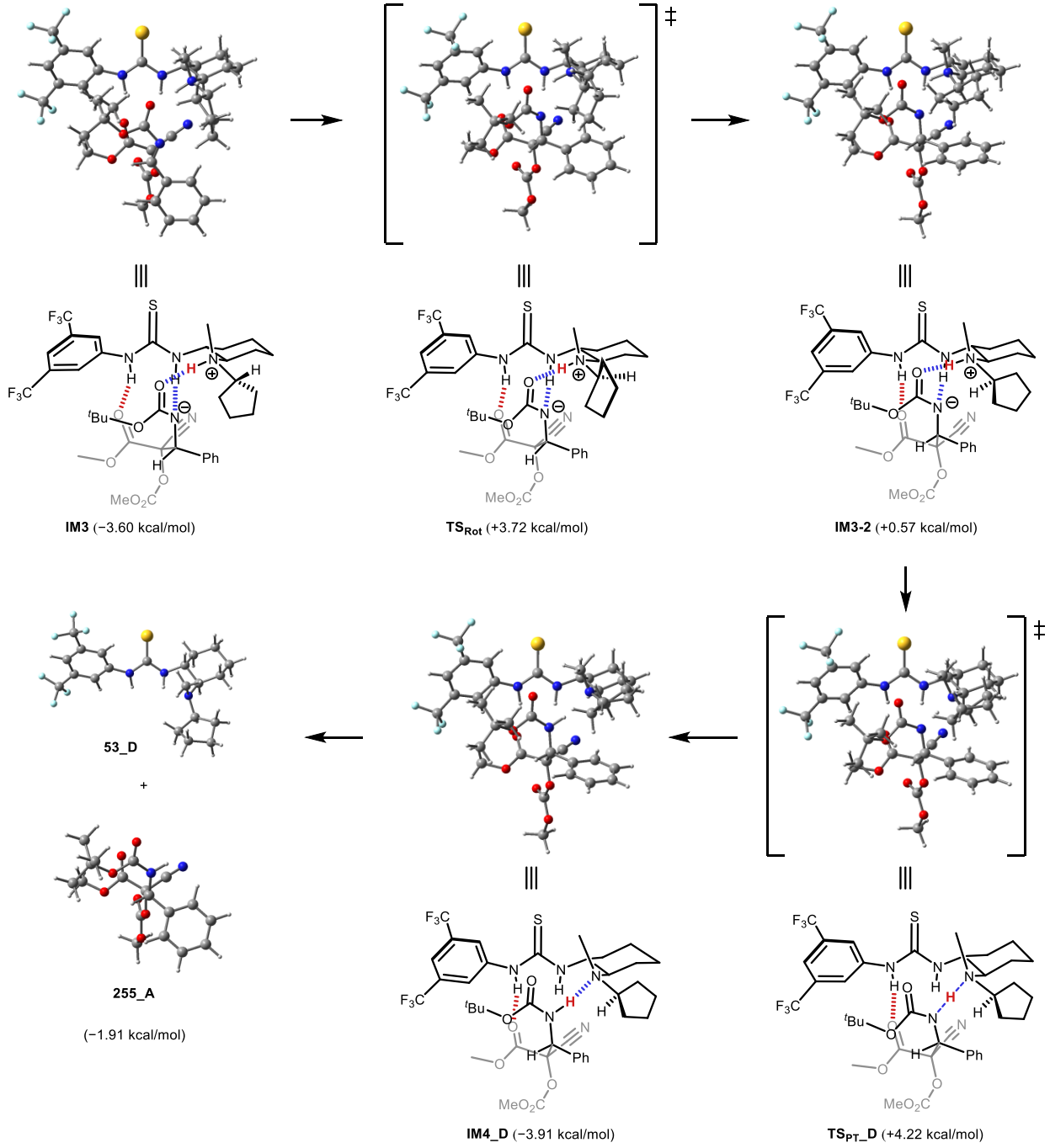


Figure 12. Proton transfer from the ammonium moiety to the nitrogen atom of the carbamate anion after rotation of the cyclopentyl group on the amine moiety of thiourea catalyst

以上の結果によって得られた触媒サイクルのエネルギーダイアグラムを以下にまとめた (Figure 13)。シクロペンチル基がエクアトリアル配向したチオ尿素 **53_A** がグリオキシル酸シアノヒドリン **254** を脱プロトン化し、resting state である **IM1** を与える。続けてイミン **67** を認識することで複合体 **IM2** を形成し、律速段階である $\mathbf{TS_{Add}\_1}$ を経て **IM3** を与える。その後触媒のシクロペンチル基が回転して立体障害を緩和し、$\mathbf{TS_{PT}\_D}$ を経て生成物にプロトンが移動することで生成物 **254_A** と触媒

53_D を与える。触媒 **53_D** はシクロペンチル基を回転させて **53_A′**へと異性化し、触媒サイクルが完結する。

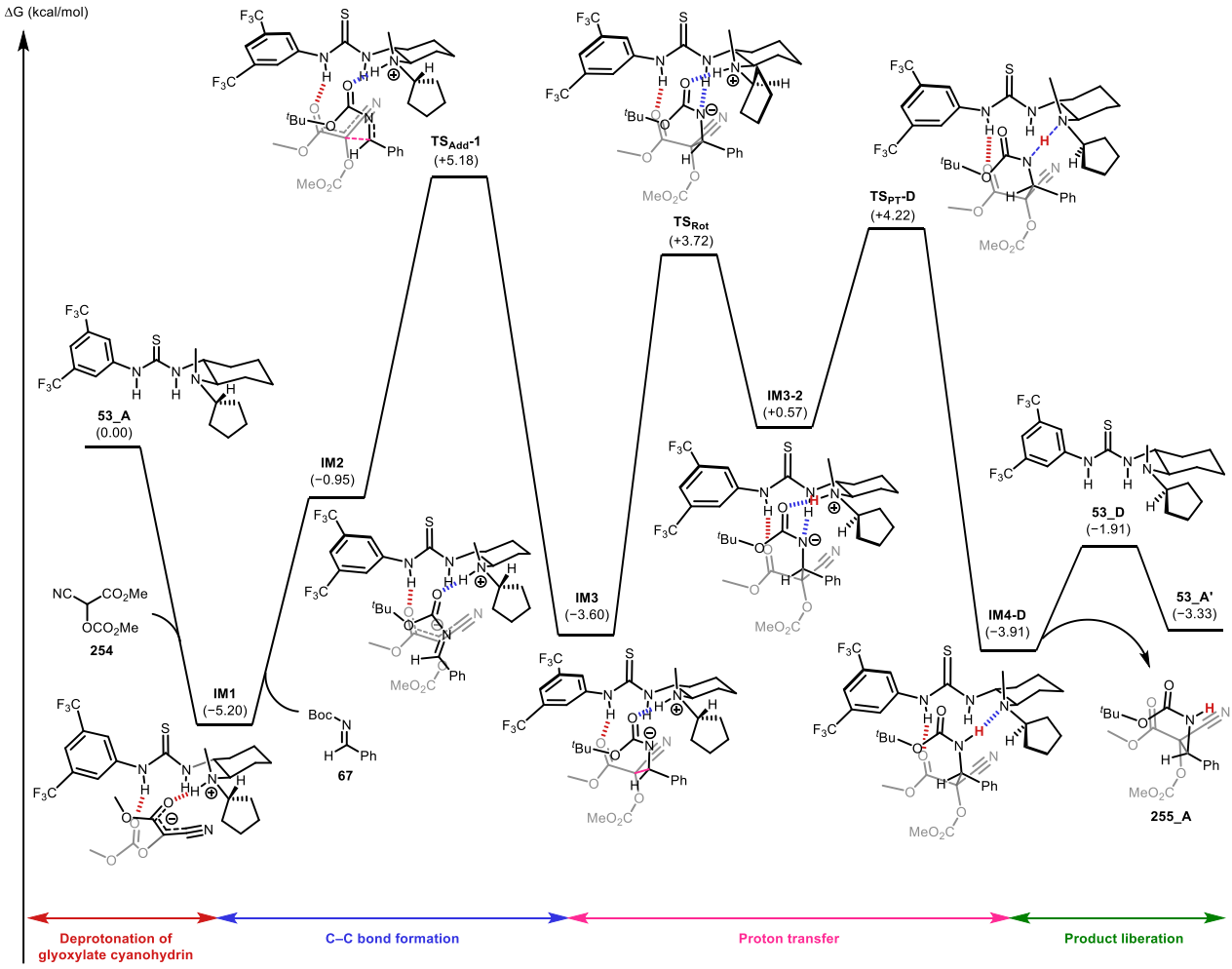


Figure 13. Energy diagram of Mannich-type addition of glyoxylate cyanohydrin **254** to *N*-Boc imine **67** with sterically-tuned amino-thiourea catalyst ***ent*-53** to afford major stereoisomer **255**

炭素–炭素結合形成過程が律速段階であることが確認できたため、3 つの異性体を与える遷移状態のエネルギーを用いて立体選択性の計算値を求め、遷移状態の妥当性を評価した。異性体比は気体定数 R = 0.001987 kcal•K^{-1}•mol^{-1}、温度 T = 233.15 K、相対ギブス自由エネルギーG_i を用いて得られる各遷移状態の存在確率 p_i の和から計算した。

$$p_i = \frac{e^{\frac{-G_i}{RT}}}{\sum(e^{\frac{-G_i}{RT}})}$$

計算によって得られた主立体異性体 **255** とジアステレオマー**255′**の生成比は 30:1 であり、また主異性体 **255** とエナンチオマー***ent*-255** の生成比は>99:1 であった。これらの値は実験値 (**255**:**255′** = 34:1、

255:***ent*-255** = 34:1)と良い一致を示した (Figure 14)。

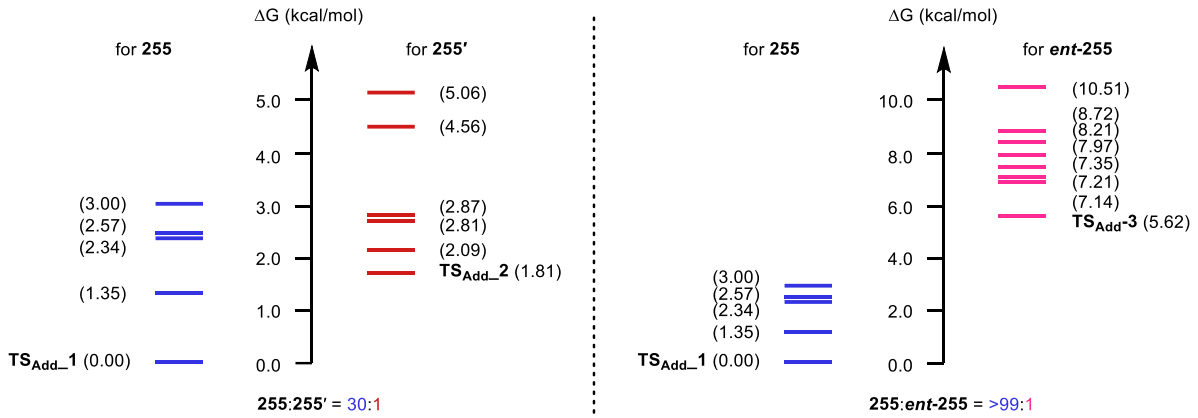


Figure 14. Energy distribution representing the relative stabilities of transition states. Each value of Gibbs free energy is relative to that of **TS$_{Add}$_1**.

第三節 立体選択性の発現機構の解析

チオ尿素触媒を用いた反応経路の探索により律速段階である炭素–炭素結合形成過程の遷移状態をそれぞれの立体異性体に対して得られたため、最も安定なものを用いて立体選択性の発現に関する

① チオ尿素骨格がベンゾチアジアジンに比べ高いエナンチオ選択性を発現した要因

② アミン上の置換基の遷移状態構造に及ぼす影響

③ アミン上にシクロペンチル基、芳香環上に 3,5-ビストリフルオロメチル基の両方がジアステレオ選択性の制御に必要である理由

の 3 つの課題について考察した。なお、本節において構造式下部の括弧内に示した遷移状態のギブス自由エネルギーは、各触媒に対して最も安定な遷移状態のものと比較した値である。

まず、エナンチオ選択性の差について検討した。エナンチオ選択性の発現において、触媒のアミン上の置換基はほとんど影響しないことが分かっている。そこで、考慮すべき触媒の配座異性体の数が最小限であるチオ尿素 **107** とベンゾチアジアジン **114** を用いて、遷移状態の比較を行った (Figure 15)。

主異性体を与える **TS$_{Add}$_5** では、求核剤であるグリオキシル酸シアノヒドリン **254** がエステルのカルボニル酸素を介してチオ尿素の 2 つのプロトンと水素結合を形成し、一方求電子剤であるイミン **67** は Boc 保護基のカルボニル酸素を介してアンモニウムプロトンによる活性化を受けている。エナンチオマーを与える **TS$_{Add}$_6** はシクロヘキサン環がチオ尿素に対して紙面裏側に 180°回転した構造をしており、シクロヘキサン環の下側を向くアミン上のメチル基が立体障害となるため、不利な遷移状態

であると考えられる。また相互作用様式は **TS$_{Add}$_5** と同様であるが、**TS$_{Add}$_6** にはアンモニウム α 位のプロトンとチオ尿素の硫黄原子との間に特徴的な分子内水素結合が見られた。ベンゾチアジアジン **114** からも類似の遷移状態構造 **TS$_{Add}$_7**, **TS$_{Add}$_8** が得られたが、興味深いことにアンモニウム α 位とベンゾチアジアジンの窒素原子の分子内水素結合距離はチオ尿素の C–H···S 相互作用の距離に比べて顕著に短くなっていた (2.56 Å vs 2.27 Å)。この違いによって基質を認識する空間の大きさが制御され、立体障害の影響に差が生じていると考察した。

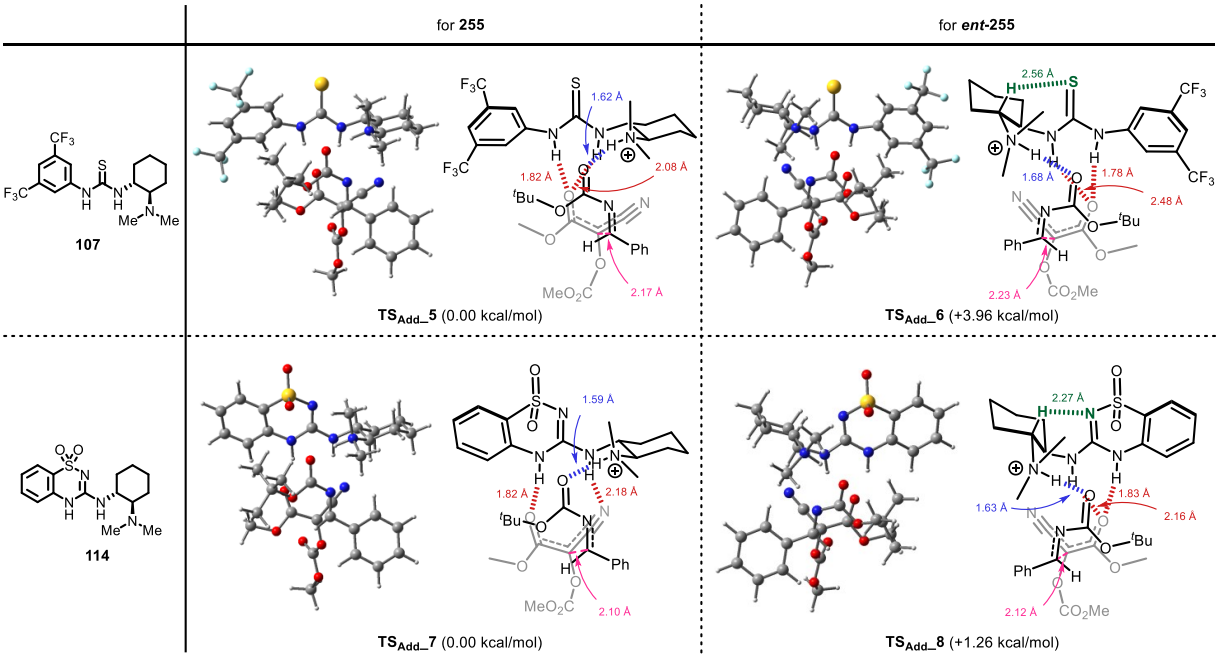


Figure 15. Theoretical investigation into the origin of enantioselectivity

すなわち、エナンチオマーを与える遷移状態について、Figure 16 に示すようにシクロヘキサンジアミン部分の 2 つの二面角 $\varphi_{H1\text{-}C2\text{-}N3\text{-}C4}$ と $\varphi_{H5\text{-}C6\text{-}N7\text{-}C8}$ の和として φ_{total} を定義すると、この値が大きいほど上述の分子内水素結合の距離が短くなり、広い触媒空間を形成することになると想定した。実際に **TS$_{Add}$_6** と **TS$_{Add}$_8** についてこの値を計算すると、**TS$_{Add}$_6** では 31.2°、**TS$_{Add}$_8** では 35.5°と両遷移状態間で 4.3°の差が見られ、チオ尿素 **107** がより狭い触媒空間を形成し、より大きな立体反発を生じさせていることが示唆された。

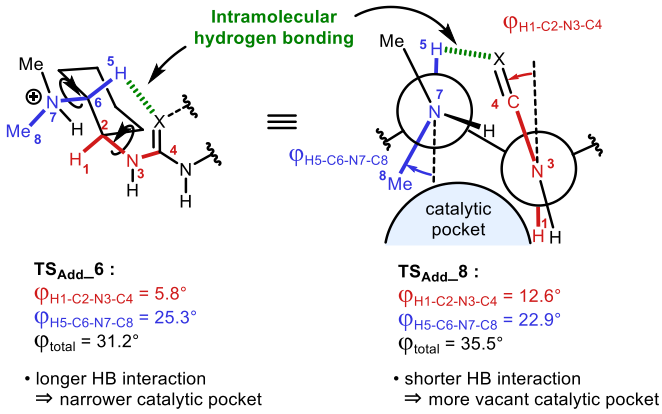


Figure 16. Comparison of the size of catalytic pockets

次に、ジアステレオ選択性の発現する要因について考察した (Figure 17)。ジメチルアミノ基を持つ触媒 **107** がジアステレオマーを与える遷移状態においては求核剤の面選択性が逆転しており、ニトリルを介した水素結合を形成している。グリオキシル酸シアノヒドリン **254** の構造は非対称であり、水素結合に関与する官能基が変わることで反応点の位置がよりシクロヘキサン環側に移動し、触媒の置換基、求核剤のエステル、イミンの芳香環の集まる領域に立体反発が生じていると考えられる。

第二章第二節で述べたようにシクロペンチル基をアミン上の置換基とする触媒 ***ent*-53** は窒素原子上に不斉点をもつため、2 つのジアステレオマーを生じる。この内シクロペンチル基がシクロヘキサン環のエクアトリアル方向に位置する構造が 1,3-ジアキシアル相互作用が小さいためより安定であり、主異性体を与える **TS$_{Add}$_1** と **TS$_{Add}$_11** では前者が 1.35 kcal/mol 安定な遷移状態である。対してジアステレオマーを与える **TS$_{Add}$_10** と **TS$_{Add}$_2** では求核剤 **254** のエステル部位とイミン **67** の芳香環がエクアトリアル方向の置換基の近傍に位置するため、その込み合った環境を避けるために **TS$_{Add}$_2** が 1.00 kcal/mol 安定な遷移状態となり、相互作用に **TS$_{Add}$_9** との大きな差は見られない。

一方、最も有利な遷移状態である **TS$_{Add}$_1** では嵩高いシクロペンチル基がイミン **67** を介して求核剤 **254** を触媒の芳香環側に押し込み、反応点が紙面左側に移動している。この置換基効果によって他の遷移状態にはみられない非共有結合性相互作用が形成され、**TS$_{Add}$_1** が安定化されていることが示唆された。Schreiner らは、3,5-ビストリフルオロメチル基のオルト位 C-H 結合は十分に酸性度が高く、カルボニル基と非古典的な水素結合を形成することを報告している [60]。著者らの **TS$_{Add}$_1** でも求核剤中のエステルのカルボニル酸素が 2.39 Å の距離にあり、そのような二次的な相互作用が生じると考えらえる。この相互作用の強度はトリフルオロメチル基の電子求引性に由来するためにトリフルオロメチル基の導入された数と置換位置に大きく依存し、芳香環パラ位に 1 つのみトリフルオロメチル基を持つチオ尿素触媒 **177** や 3,5-位にジメチル基を持つ触媒 **178** がジアステレオ選択性を向上させなかった第一章第三節の触媒スクリーニングの結果と矛盾しない。また、同報告において Schreiner らは、

触媒中のトリフルオロメチル基と基質のエステル α 位の C–H 結合の間の bond critical point から結合性相互作用が存在することを提唱しており、**TS$_{Add}$_1** も同様の相互作用を含む可能性も考えられる [60,61]。

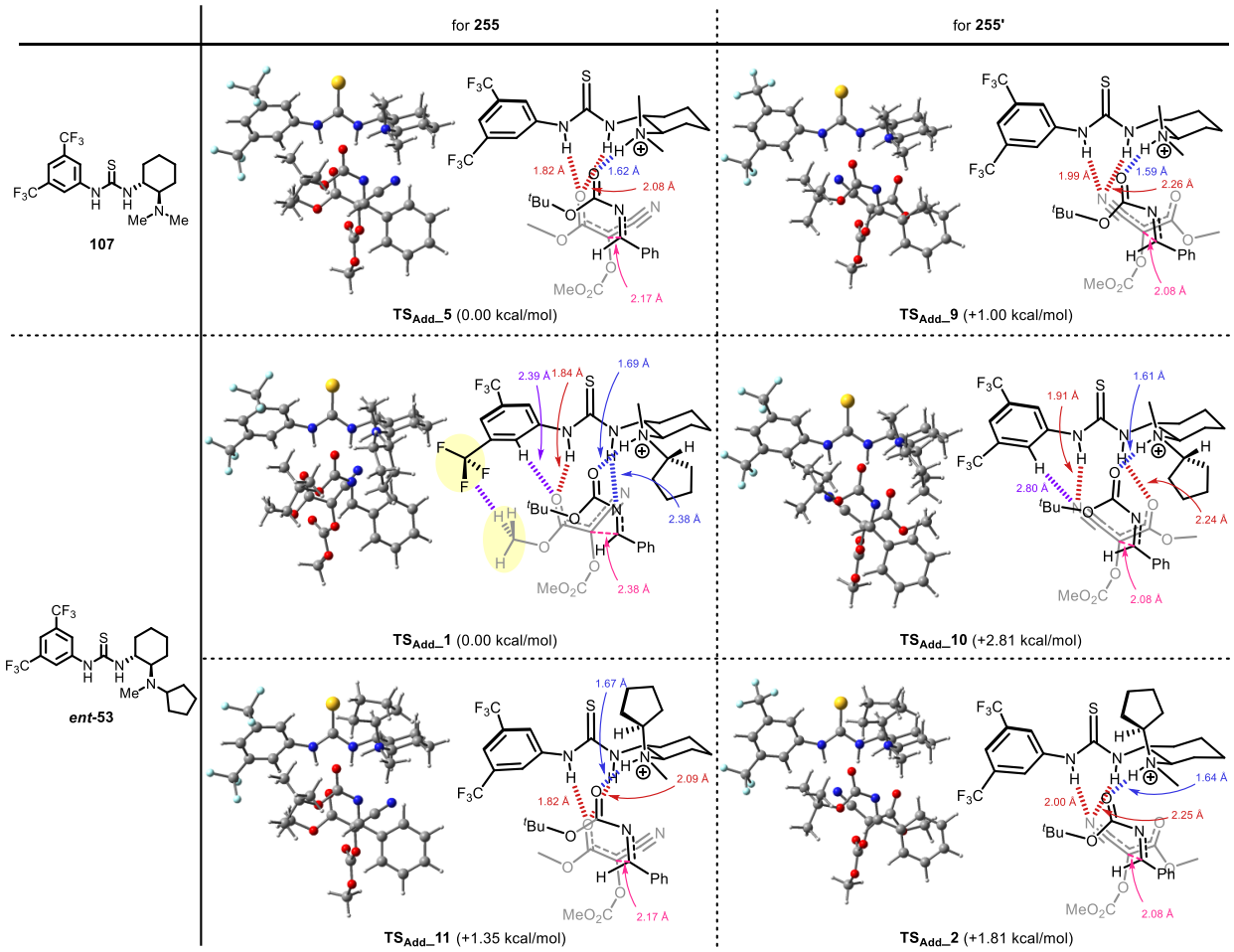


Figure 17. Theoretical insights into the origin of diastereoselectivity

以上の DFT 計算に基づく考察を以下に要約した。

① エナンチオマーを与える遷移状態ではアンモニウム α 位のプロトンと水素結合供与部位のヘテロ原子との間に水素結合が存在し、その距離によって触媒空間の大きさが決定される。より狭い空間をもつチオ尿素は、その置換基に依らず高いエナンチオ選択性を与えた。

② アミン部位に導入したシクロペンチル基は **TS$_{Add}$_1** のようにエクアトリアル方向に位置する方が熱力学的に安定であり、またその嵩高さによって求核剤の位置の制御にも寄与していた。一方でジアステレオマーを与える遷移状態では込み合った環境を避ける構造をとっており相互作用へは影響を及ぼさないが、より大きな 1,3-ジアキシアル相互作用を生むことで、遷移状態の不安定化に寄与していると考えられる。

③ 嵩高いシクロペンチル基によって求核剤の位置が移動した結果、トリフルオロメチル基の置換し

た電子不足な芳香環との間に新たな水素結合性相互作用が形成された。この相互作用が最適触媒の高いジアステレオ選択性の発現を決定づける要因である。

最後に、ここまでに得た遷移状態構造をもとに、ベンゾチアジアジンの 5 位に置換基を導入した際のジアステレオ選択性の逆転現象について考察を行った (Figure 18)。触媒 **174** を用いた場合の炭素–炭素結合形成過程の遷移状態 **TS$_{Add}$_13** と **TS$_{Add}$_14** を示したが、5 位に導入した置換基 (Figure 18 ではフェニル基)は紙面左側の空間を効果的に遮蔽している。ビフェニル構造の二面角 $\varphi_{C1\text{-}C2\text{-}C3\text{-}C4}$ をそれぞれ比べると、**TS$_{Add}$_14** では触媒の安定構造の 59.3°とほぼ同値の 62.7°であるのに対し、**TS$_{Add}$_13** では 45.0°と顕著な差が見られ、**TS$_{Add}$_13** において求核剤 **254** のエステル部位とイミン **67** の Boc 基の末端がフェニル基の近傍に位置するために大きな立体反発が生じていることが示唆された。そのために **TS$_{Add}$_13** が大きく不安定化され、ジアステレオ選択性が逆転する結果となったと考察できる。

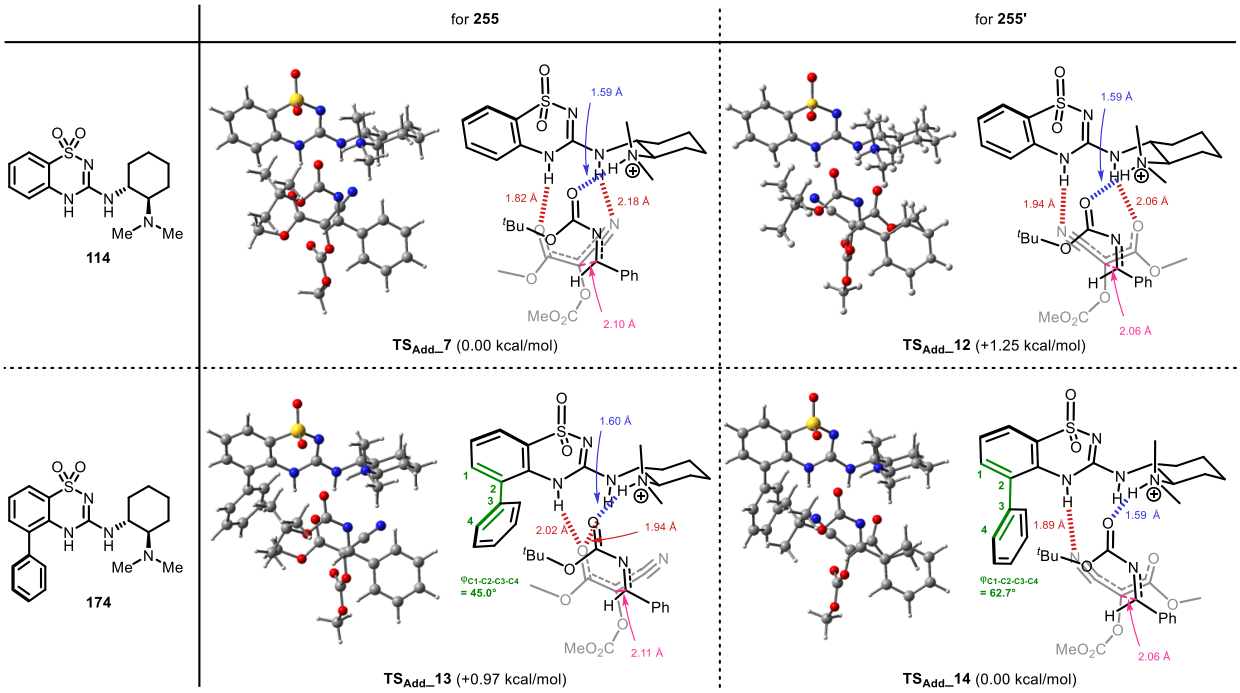
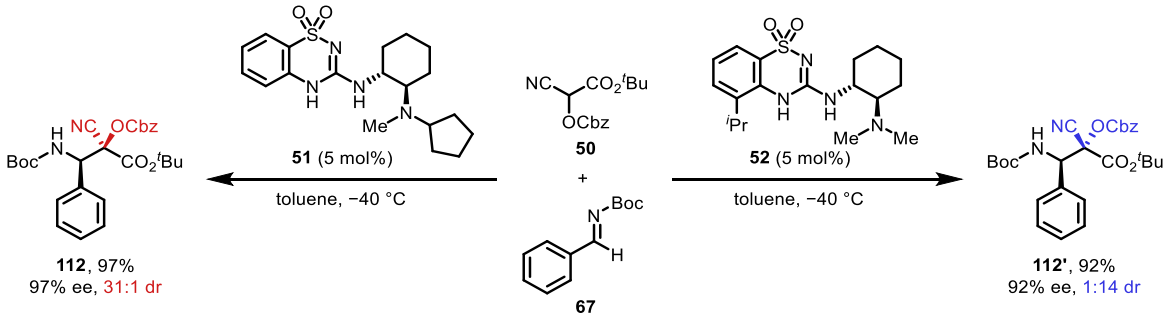


Figure 18. Theoretical insights into the reversal of diastereoselectivity

結論

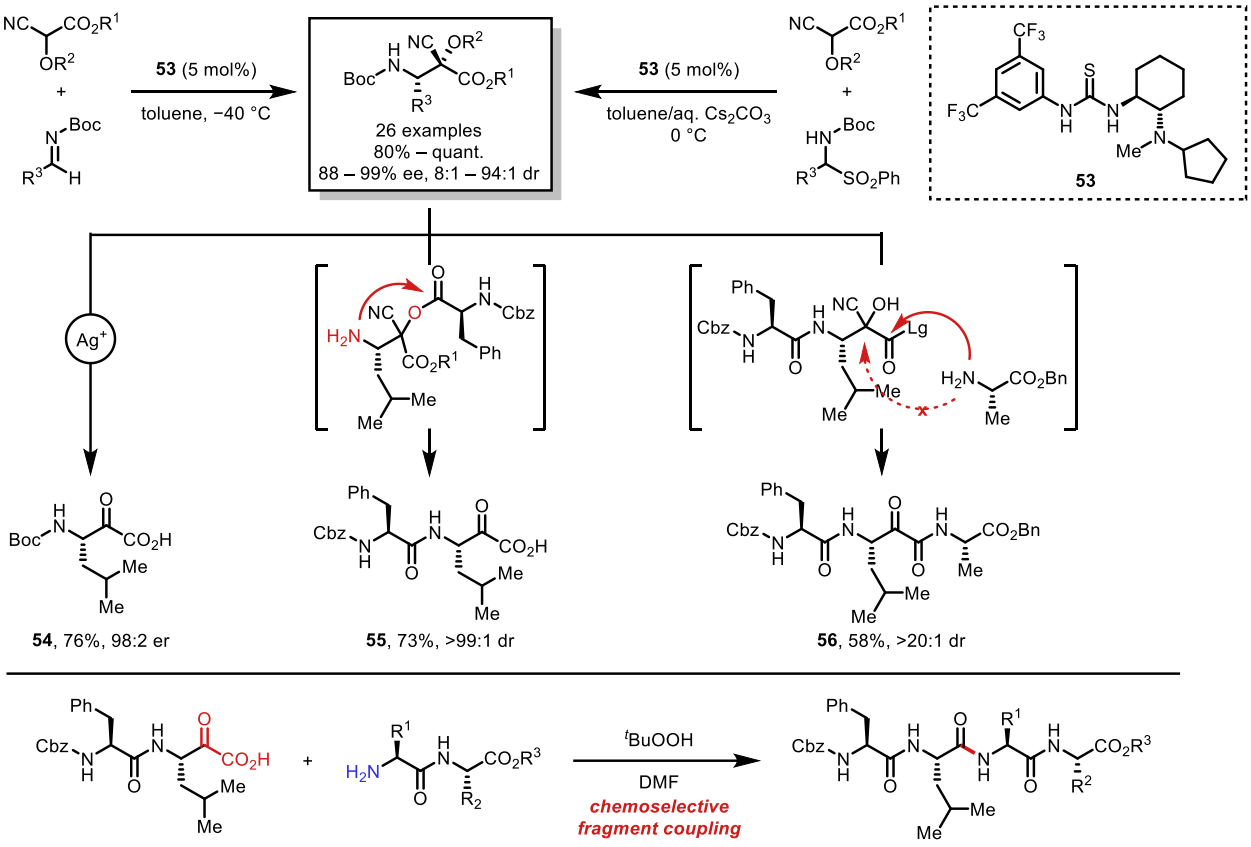
著者は、極性転換によってα-ケトカルボニル構造と等価な求核剤として振る舞うグリオキシル酸シアノヒドリン **50** を用いた触媒的不斉 Mannich 反応を検討した。所属研究室で得られていた Mannich 反応の遷移状態モデルに着想を得て、ベンゾチアジアジンやシクロヘキサンジアミンのような剛直性の高い骨格を利用し置換基効果を最大限に活用する新たな触媒設計戦略を提示し、嵩高い置換基を有するアミノベンゾチアジアジン触媒 **51** が様々な芳香族イミンへの付加反応を高いエナンチオ選択性、ジアステレオ選択性で触媒することを見出した。本戦略は置換基の導入位置を変えることで基質の配座を逆転させることも可能であり、ベンゾチアジアジン触媒の 5 位にイソプロピル基を導入した触媒 **52** を用いることでジアステレオ選択性の逆転した **112′**を立体選択的に得ることにも成功し、同一原料から全ての立体異性体にアクセスできる立体制御法を確立した。有機触媒の置換基効果のみでジアステレオ選択性の逆転する例はほとんど例がなく、特に速度論的に不利な生成物へのアクセスできる触媒設計を示した重要な知見である。

Scheme 23. Summary of Chapter 1, Section 2



また著者は、立体選択性の制御がより困難な脂肪族イミンへの付加反応について詳細に検討し、嵩高い第三級アミンと電子不足な芳香環を兼ね備えたチオ尿素触媒 **53** が非常に高い立体選択性の発現を可能とすることを見出した。エンカルバマートへの異性化が問題となるイミンの場合には前駆体である α-アミドスルホンを直接用いることで良好な結果を与えることも見出し、様々な立体要因、官能基を持つ多彩な β-アミノ-α-ケト酸誘導体の不斉合成を可能とした。また、銀塩による合成した付加体の脱保護によって β-アミノ-α-ケト酸に変換可能であった他、シアノヒドリンを保護基とする新たな合成戦略によってペプチド-α-ケト酸への誘導や、エピメリ化を抑制しつつペプチド-α-ケト酸とアミンを縮合することに成功した。さらに、合成したペプチド-α-ケト酸が、無保護の極性官能基を持つ種々のオリゴペプチドとの脱炭酸型フラグメントカップリングに適用可能であることを示した。

Scheme 24. Summary of Chapter 1, Sections 3 and 4



さらに著者は、最適なチオ尿素を用いた際の触媒サイクルを DFT 計算によって探索し、炭素–炭素結合形成過程が Mannich 反応の律速段階であること、また非対称なアミン置換基が素過程ごとにその配座を変化させ、反応基質の位置や立体障害を調整していることを明らかとした。また、第一章で見られた特徴的な立体制御要因の解明に向け炭素–炭素結合形成過程の遷移状態解析を行い、水素結合供与体の構造によって分子内水素結合の距離が変化し、反応場の大きさが制限されることがエナンチオ選択性の制御に重要であることを提案した。一方でジアステレオ選択性の発現においては、嵩高いアミン部位の導入により特定の遷移状態でのみ触媒との新たな水素結合相互作用が形成され、遷移状態が大きく安定化されることを見出した。加えて、この遷移状態と同様に考えることで、ベンゾチアジアジンによるジアステレオ選択性の逆転が、5 位に導入した置換基と求核剤のエステルとの立体反発による遷移状態の不安定化によることを証明した。本研究で得られた知見は触媒の骨格、置換基を精密に設計することで特定の遷移状態の安定化、不安定化によって生成物の立体を自在にコントロールできることを実証しており、更なる複雑系への適用に向けた有機分子触媒の新たな設計指針となることを期待している。

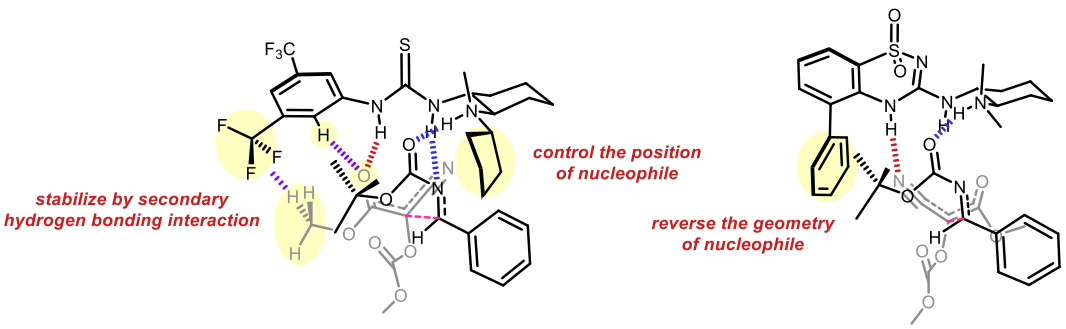


Figure 19. Summary of Chapter 2

実験項

General Information

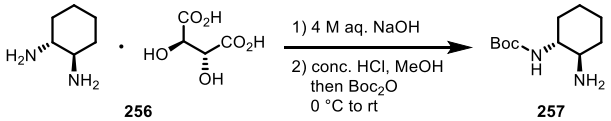
All reactions were carried out under air with no precautions taken to exclude moisture unless otherwise noted. Commercially available reagents that were used as received are noted in the individual reaction procedures. Analytical thin-layer chromatography was performed with Merck TLC Silica gel 60 and Fuji Silysia CHROMATOREX TLC Plates (NH, DIOL, and COOH). Preparative thin-layer chromatography was performed with Merck PLC Silica gel 60. Column chromatography was performed on Fuji Silysia CHROMATOREX (BW-820H, BW-300, NH-DM1020, DIOL MB 100-75/200, and COOH MB 100-75/200). Medium pressure preparative liquid chromatography was performed on Fuji Silysia CHROMATOREX Q-PACK SI 50. ^{1}H NMR spectra were recorded on a JEOL JNM-ECA 500 (500 MHz) and are reported in ppm relative to Me_4Si (δ 0.00) in $CDCl_3$ and internal residual solvents (acetone-d_6 δ 2.04, dimethylsulfoxide-d_6 δ 2.49, and CD_3OD δ 3.31). Data reported as: integration; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz. Protondecoupled ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 500 (126 MHz) and JNM-ECZ 600 (151 MHz) and are reported in ppm relative to ($CDCl_3$ δ 77.0, acetone-d_6 δ 29.8, dimethylsulfoxide-d_6 δ 39.5, and CD_3OD δ 49.0). ^{19}F NMR spectra were recorded on JEOL JNM-ECA 500 (471 MHz). Infrared spectra were recorded on a JASCO FT/IR-4100 Fourier-transform infrared spectrometer ATR (attenuated total reflectance). High-resolution mass spectra were obtained on a SHIMADZU LCMS-IT-TOF fitted with an ESI-MS, Thermo Scientific Exactive Plus and JEOL JMS-700 double-focusing mass spectrometer. High performance liquid chromatography (HPLC) analysis was performed on SHIMADZU Prominence Series instrument equipped with a UV detector. Supercritical fluid chromatography (SFC) analysis was performed on Waters ACQUITY UPC2 equipped with a UV detector. Optical rotations were determined with a JASCO P-2200KDT polarimeter and are the average of five measurements and reported as follows: $[\alpha]^{T\,^{\circ}C}_{\lambda}$ concentration (c = g / 100 mL, solvent). All melting points were measured on BÜCHI M-565 melting point apparatus and are uncorrected. Reactions under microwave irradiation were performed using Biotage Initiator+.

Materials

Anhydrous solvents were purchased from KANTO Chemical Co., Sigma-Aldrich LLC., and Wako chemicals. Materials were obtained from Tokyo Chemical Industry Co., Ltd., Sigma-Aldrich Co., LLC., and other commercial suppliers, and used without further purification.

第一章　Mannich反応を基盤とするβ-アミノ-α-ケト酸の合成と利用

第二節　グリオキシル酸シアノヒドリンを用いたジアステレオ分岐型Mannich反応の開発

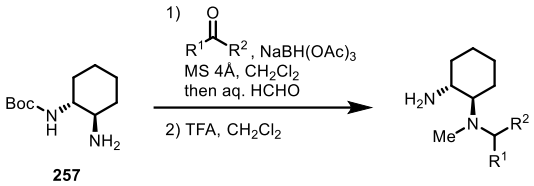


256　　**257**

(1*R*,2*R*)-1,2-Cyclohexanediamine *L*-tartrate **256** (13.2 g, 50.0 mmol, 1.0 equiv.) was dissolved in aqueous NaOH (4 M, 50 mL) and extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over K_2CO_3, filtered, and concentrated under reduced pressure to afford the neutralized diamine as a colorless oil. A 500 mL round bottom flask was charged with a stir bar, diamine, and MeOH (60 mL) and cooled to 0 °C. To the solution were added concentrated HCl (4.16 mL, 50.0 mmol, 1.0 equiv.) and Boc_2O (10.9 g, 50.0 mmol, 1.0 equiv.) in MeOH (60 mL) dropwise. After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure. The resulting white solid was washed with Et_2O (3 x

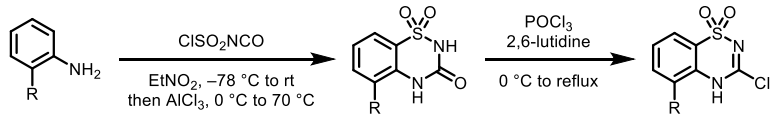
50 mL), dissolved in aqueous NaOH (2 M, 50 mL), and extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (100 mL), dried over K_2CO_3, filtered, and concentrated under reduced pressure to afford mono-protected diamine **257** (7.54 g, 35.2 mmol, 70% yield) as a white solid. This compound was used without further purification.

General Procedure for the Preparation of Chiral Diaminocyclohexane Fragments (GP1):



A 50 mL round bottom flask was charged with a stir bar, a corresponding aldehyde or ketone (1.0 equiv.), CH_2Cl_2 (0.1 M) under Ar atmosphere. To the solution were added amine **257** (1.0 equiv.) and MS 4Å (1.00 g/mmol). After stirring overnight at room temperature, $NaBH(OA)_3$ (3.0 equiv.) was added and the mixture was stirred for appropriate time. Then formalin (37%, 2.0 equiv.) was added to the mixture. After stirring for appropriate time, to the mixture was added saturated aqueous $NaHCO_3$ and filtered through a short celite pad. The filtrate was concentrated under reduced pressure to remove CH_2Cl_2 then the resulting aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over K_2CO_3, filtered, and concentrated under reduced pressure to afford a crude dialkylated *N*-Boc-diaminocyclohexane as a colorless oil, which was used immediately used in a next reaction without further purification. A round bottom flask was charged with a stir bar, *N*-Boc-diaminocyclohexane (1.0 equiv.), and CH_2Cl_2 (0.1 M). To the stirred solution was added TFA (15 equiv.). After stirring for appropriate time at room temperature, the mixture was concentrated under reduced pressure to afford a crude TFA salt of N^1,N^1-dialkyldiaminocyclohexane. This salt was used without further purification.

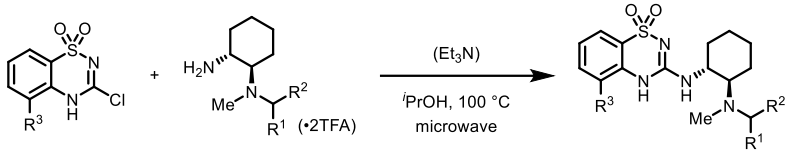
General Procedure for the Synthesis of Benzothiadiazine Fragments (GP2):



A round bottom flask was charged with a stir bar and $EtNO_2$ (1.5 M), which was dehydrated by the treatment with molecular sieve 4Å, under Ar atmosphere and cooled to −78 °C. To the mixture were added $ClSO_2NCO$ (1.2 equiv.) and corresponding aniline (1.0 equiv.) dropwise. After the completion of the addition, the mixture was warmed to room temperature and stirred for 1 hour. The mixture was cooled to 0 °C and $AlCl_3$ (1.2 equiv.) was added. The mixture was stirred overnight at 70 °C and cooled to room temperature. The reaction mixture was poured into ice and the precipitate was collected by filtration. The obtained solid was washed with water (3 times) and hexane (3 times) and dried under reduced pressure.

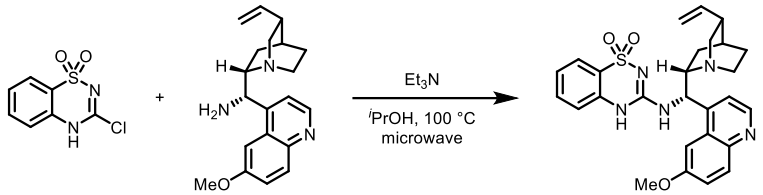
A two-necked round bottom flask equipped with reflux condenser was charged with a stir bar and the obtained solid (1.0 equiv.) under Ar atmosphere and cooled to 0 °C. To the solid was added $POCl_3$ (15 equiv.) and 2,6-lutidine (1.2 equiv.) and the mixture was refluxed at 130 °C. After stirring overnight, the mixture was cooled to room temperature and poured into ice. The precipitate was collected by filtration, washed with water (3 times) and hexane (3 times), and dried under reduced pressure to afford 3-chlorobenzothiadizine which was used without further purification.

General Procedure for the Preparation of Amino-benzothiadiazine Catalysts (GP3):



A sealed vial was charged with a stir bar, 3-chlorobenzothiadiazine (1.0 equiv.), diamine (1.0 equiv.), Et_3N (1.0 equiv. for free diamine, or excess amount for diamine TFA salt) and *i*-PrOH. The mixture was stirred at 100 °C under microwave irradiation for appropriate time. Then the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding catalyst.

3-(((6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (115):

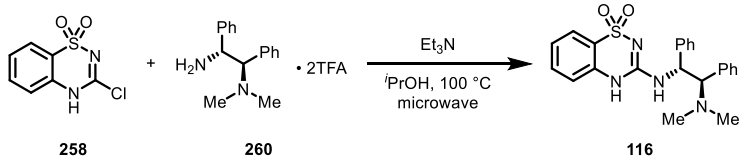


258 **259** **115**

According to **GP3**, benzothiadiazine **258** (217 mg, 1.00 mmol, 1.0 equiv.) reacted with amine **259** (323 mg, 1.00 mmol, 1.0 equiv.) and Et_3N (0.139 mL, 1.00 mmol, 1.0 equiv.) in *i*-PrOH (3.3 mL) at 100 °C under microwave irradiation for 6 hours. The crude residue was purified by silica gel column chromatography (NH SiO_2, eluted with EtOAc/MeOH = 5:1) to afford **115** (373 mg, 0.740 mmol, 74% yield) as a pale yellow solid.

^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ 10.66 (1H, br), 8.74 (1H, d, J = 4.6 Hz), 7.94 (1H, d, J = 9.2 Hz), 7.82 (1H, s), 7.61 (1H, d, J = 4.6 Hz), 7.59 (1H, d, J = 8.0 Hz), 7.50 (1H, t, J = 7.7 Hz), 7.42 (1H, dd, J = 9.2, 2.9 Hz), 7.19 (1H, t, J = 7.4 Hz), 7.07 (1H, d, J = 8.6 Hz), 5.91–5.84 (1H, m), 5.50 (1H, br), 5.01 (1H, d, J = 17.2 Hz), 4.94 (1H, d, J = 10.3 Hz), 3.97 (3H, s), 3.38–3.14 (4H, m), 2.75–2.62 (2H, m), 2.26 (1H, s), 1.65–1.45 (3H, m), 1.35 (1H, t, J = 13.7 Hz), 0.75 (1H, s); **^{13}C-NMR (126 MHz, DMSO-*d*$_6$):** δ 157.3, 150.6, 147.6, 144.2, 144.1, 142.0, 135.5, 132.3, 131.3, 127.8, 123.7, 122.9, 122.4, 121.5, 120.4, 116.5, 114.3, 102.3, 58.5, 55.7, 55.3, 51.5, 40.7, 27.2, 27.1, 25.9, 11.9; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{27}H_{30}N_5O_3S$ 504.2064; Found 504.2061; **IR (ATR):** 3283, 2931, 1622, 1257, 1156 cm^{-1}; **Melting Point:** 203.3–206.2 °C; **Optical Rotation:** $[\alpha]^{18}_D$ −41.6 (c 1.00, DMSO).

3-(((1*R*,2*R*)-2-(Dimethylamino)-1,2-diphenylethyl)amino)-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (116):



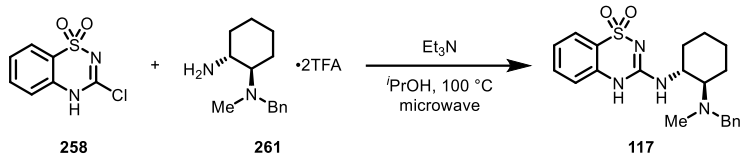
258 **260** **116**

According to **GP3**, benzothiadiazine **258** (407 mg, 1.88 mmol, 1.0 equiv.) reacted with amine TFA salt **260** (881 mg, 1.88 mmol, 1.0 equiv.) and Et_3N (2.62 mmol, 18.8 mmol, 10 equiv.) in *i*-PrOH (6.3 mL) at 100 °C under microwave irradiation for 6 hours. The crude residue was purified by silica gel column chromatography (NH SiO_2, eluted with EtOAc/MeOH = 20:1) to afford **116** (705 mg, 1.68 mmol, 89% yield) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.84 (1H, dd, J = 8.0, 1.1 Hz), 7.26 (2H, t, J = 7.4 Hz), 7.19–7.16 (6H, m), 7.06 (2H, t, J = 7.2 Hz),

7.03−6.97 (3H, m), 6.66 (1H, br), 5.26 (1H, d, J = 10.9 Hz), 3.80 (1H, d, J = 10.9 Hz), 2.19 (6H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 151.0, 139.9, 136.0, 132.8, 132.1, 129.9, 128.3, 128.0, 127.8, 127.7, 127.4, 124.2, 123.7, 121.8, 116.8, 73.5, 56.1, 40.8; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{23}H_{25}N_4O_2S$ 421.1693; Found 421.1693; **IR (ATR):** 3329, 1624, 1259, 1150 cm^{-1}; **Melting Point:** 247.2–249.0 °C; **Optical Rotation:** $[\alpha]^{22}_D$ +60.4 (c 1.00, $CHCl_3$).

3-(((1*R*,2*R*)-2-(Benzyl(methyl)amino)cyclohexyl)amino)-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (117):

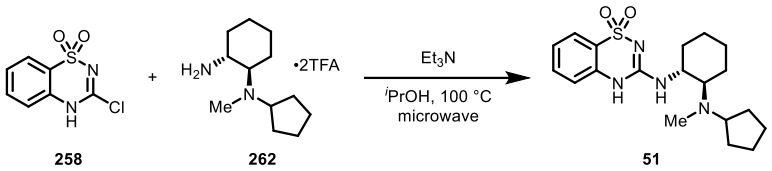


258 261 117

According to **GP3**, benzothiadiazine **258** (217 mg, 1.00 mmol, 1.0 equiv.) reacted with amine TFA salt **261** (446 mg, 1.00 mmol, 1.0 equiv.) and Et_3N (0.836 mL, 6.00 mmol, 6.0 equiv.) in *i*-PrOH (3.3 mL) at 100 °C under microwave irradiation for 9 hours. The crude residue was purified by column chromatography (NH SiO_2, eluted with EtOAc/MeOH = 20:1) to afford **117** (225 mg, 0.564 mmol, 56% yield) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.71 (1H, d, J = 8.0 Hz), 7.29–7.25 (4H, m), 7.20–7.15 (3H, m), 7.03 (1H, t, J = 7.4 Hz), 6.84 (1H, br), 3.70–3.58 (2H, m), 3.49 (1H, d, J = 12.0 Hz), 2.47 (1H, t, J = 9.7 Hz), 2.29 (1H, s), 2.14 (3H, s), 1.88 (1H, d, J = 12.0 Hz), 1.75 (1H, d, J = 10.3 Hz), 1.59 (1H, d, J = 9.7 Hz), 1.29–1.20 (1H, m), 1.18–1.08 (3H, m); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 151.3, 139.6, 136.1, 132.6, 128.8, 128.2, 126.8, 123.8, 123.3, 121.4, 116.6, 66.3, 57.9, 52.4, 36.4, 32.8, 25.0, 24.5, 23.3; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{21}H_{27}N_4O_2S$ 399.1849; Found 399.1849; **IR (ATR):** 3291, 2930, 1624, 1255, 1151 cm^{-1}; **Melting Point:** 113.8–116.8 °C; **Optical Rotation:** $[\alpha]^{23}_D$ +85.2 (c 1.00, $CHCl_3$).

3-(((1*R*,2*R*)-2-(Cyclopentyl(methyl)amino)cyclohexyl)amino)-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (51):

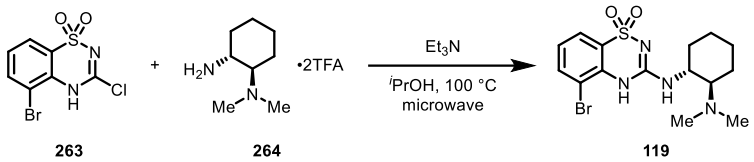


258 262 51

According to **GP3**, benzothiadiazine **258** (203 mg, 0.936 mmol, 1.0 equiv.) reacted with amine TFA salt **262** (397 mg, 0.936 mmol, 1.0 equiv.) and Et_3N (0.783 mL, 5.62 mmol, 6.0 equiv.) in *i*-PrOH (3.1 mL) at 100 °C under microwave irradiation for 12 hours. The crude residue was purified by column chromatography (NH SiO_2, eluted with EtOAc/MeOH = 20:1) to afford **51** (169 mg, 0.449 mmol, 48% yield) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.91 (1H, d, J = 7.4 Hz), 7.43 (1H, t, J = 7.4 Hz), 7.24 (1H, t, J = 7.7 Hz), 6.89 (1H, d, J = 8.0 Hz), 5.01 (1H, br), 3.39 (1H, s), 3.01 (1H, t, J = 7.2 Hz), 2.68 (1H, t, J = 9.2 Hz), 2.39 (3H, s), 2.26 (1H, s), 1.90–1.82 (4H, m), 1.74 (1H, s), 1.63 (2H, s), 1.55–1.47 (2H, m), 1.41– 1.35 (3H, m), 1.25–1.17 (3H, m); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 152.2, 136.3, 132.4, 123.8, 123.5, 122.3, 116.9, 64.5, 63.7, 52.8, 33.4, 32.9, 31.1, 30.5, 25.0, 24.4, 23.42, 23.35 (One aliphatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{19}H_{29}N_4O_2S$ 377.2006; Found 377.2006; **IR (ATR):** 3289, 2939, 1631, 1235, 1153 cm^{-1}; **Melting Point:** 217.7–220.8 °C; **Optical Rotation:** $[\alpha]^{24}_D$ +97.3 (c 1.00, $CHCl_3$).

5-Bromo-3-(((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)amino)-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (119):

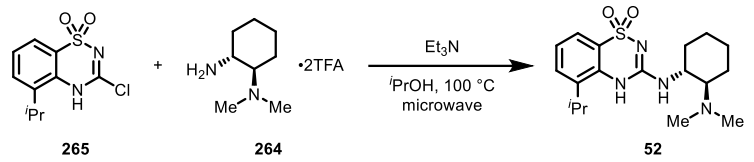


263 264 119

According to **GP3**, benzothiadiazine **263** (148 mg, 0.500 mmol, 1.0 equiv.) reacted with amine TFA salt **264** (71.1 mg, 0.500 mmol, 1.0 equiv.) and Et_3N (209 μL, 1.50 mmol, 3.0 equiv.) in *i*-PrOH (1.7 mL) at 100 °C under microwave irradiation for 3 hours. The crude residue was purified by column chromatography (NH SiO_2, eluted with $CHCl_3$/MeOH = 40:1) to afford **119** (125 mg, 0.311 mmol, 62% yield) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.85 (1H, d, J = 8.0 Hz), 7.64 (1H, d, J = 7.4 Hz), 7.10 (1H, t, J = 8.0 Hz), 6.99 (1H, br), 3.68 (1H, s), 2.49 (1H, t, J = 10.0 Hz), 2.41–2.30 (7H, m), 1.94 (1H, d, J = 9.7 Hz), 1.83 (1H, d, J = 9.2 Hz), 1.69 (1H, d, J = 6.3 Hz), 1.30–1.19 (4H, m); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 152.2, 135.4, 135.2, 124.8, 124.4, 123.0, 110.7, 67.5, 53.8, 41.1, 32.7, 24.8, 24.6, 23.0; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{15}H_{22}N_4O_2SBr$ 401.0641; Found 401.0644; **IR (ATR):** 3295, 2932, 1618, 1283, 1157 cm^{-1}; **Melting Point:** 157.0–160.6 °C; **Optical Rotation:** $[\alpha]^{24}_D$ −24.8 (c 1.00, $CHCl_3$).

3-(((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)amino)-5-isopropyl-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (52):

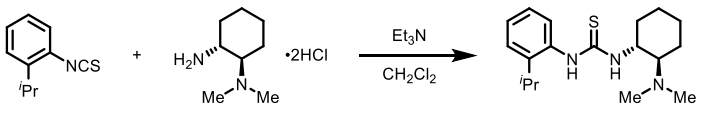


265 264 52

According to **GP3**, benzothiadiazine **265** (259 mg, 1.00 mmol, 1.0 equiv.) reacted with amine TFA salt **264** (142 mg, 1.00 mmol, 1.0 equiv.) in *i*-PrOH (10 mL) at 100 °C under microwave irradiation for 1 hour. The crude residue was purified by column chromatography (NH SiO_2, EtOAc/MeOH = 1:0 → 10:1) and (SiO_2, eluted with EtOAc/MeOH/Et_3N = 80:20:1) to afford **52** (254 mg, 0.698 mmol, 70% yield) as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.76 (1H, dd, J = 8.0, 1.1 Hz), 7.38 (1H, d, J = 7.4 Hz), 7.22 (1H, t, J = 7.7 Hz), 6.50 (1H, br), 3.61 (1H, s), 3.04–2.99 (1H, m), 2.37 (2H, t, J = 10.6 Hz), 2.30 (6H, s), 1.91 (1H, d, J = 10.3 Hz), 1.81 (1H, d, J = 9.7 Hz), 1.68 (1H, d, J = 12.0 Hz), 1.32–1.14 (10H, m); **^{13}C-NMR (126 MHz, DMSO-d_6):** δ 151.3, 134.4, 132.6, 128.6, 123.3, 122.8, 120.5, 65.4, 51.7, 32.6, 26.3, 24.5, 24.3, 22.9, 22.5, 21.2; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{18}H_{29}N_4O_2S$ 365.2006; Found 365.2009; **IR (ATR):** 3328, 2931, 1619, 1271, 1153 cm^{-1}; **Melting Point:** 149.3–152.3 °C; **Optical Rotation:** $[\alpha]^{24}_D$ −24.5 (c 1.00, $CHCl_3$).

1-((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)-3-(2-isopropylphenyl)thiourea (120):



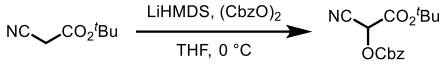
266 267 120

A 50 mL round bottom flask was charged with a stir bar, amine HCl salt **267** (611.1 mg, 2.84 mmol, 1.0 equiv.), Et_3N (1.19 mL, 8.52 mmol, 3.0 equiv.), and CH_2Cl_2 (10 mL). To the suspension was added isothiocyanate **266** (503.4 mg, 2.84 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL), and the mixture was stirred at room temperature for 11 hours. The solution was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with

hexane/EtOAc = 100:0 → 30:70 → 50:50 → 30:70) to afford **120** (480.2 mg, 1.50 mmol, 53% yield) as a yellow solid.

^{1}H-NMR (500 MHz, CD_3OD): δ 7.29 (1H, dd, J = 7.7, 1.4 Hz), 7.21 (1H, td, J = 7.3, 1.7 Hz), 7.14–7.08 (2H, m), 4.00 (1H, t, J = 8.9 Hz), 3.11–3.03 (1H, m), 2.32–2.27 (2H, m), 2.14 (6H, s), 1.76–1.73 (1H, m), 1.70–1.66 (1H, m), 1.59–1.55 (1H, m), 1.23–1.09 (9H, m), 0.98 (1H, ddd, J = 23.7, 12.7, 2.9 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 180.9, 146.1, 133.4, 128.5, 128.1, 1268, 126.7, 66.7, 56.2, 39.7, 32.6, 23.2, 25.1, 24.5, 23.4, 23.1, 12.5; **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{18}H_{30}N_3S$ 320.2160; Found 320.2165; **IR (ATR):** 3177, 2932, 2862, 2785, 1718, 1676, 1453, 1350, 1257, 1200 cm^{-1}; **Melting Point:** 86.4–88.5 °C; **Optical Rotation:** $[\alpha]^{19}_D$ −59.6 (c 0.51, $CHCl_3$).

***tert*-Butyl 2-(((benzyloxy)carbonyl)oxy)-2-cyanoacetate (50):**



183 **50**

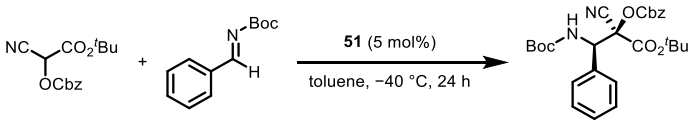
A 50 mL round bottom flask was charged with a stir bar, *tert*-butyl cyanoacetate **183** (472 µL, 3.31 mmol, 1.0 equiv.) in THF (7.0 mL) under Ar atmosphere and cooled to 0 °C. To the mixture was added LiHMDS (1.3 M in THF, 2.54 mL, 3.31 mmol, 1.0 equiv.) dropwise and the mixture was stirred at 0 °C for 30 minutes. The solution of dibenzyl peroxydicarbonate ($(CbzO)_2$, 1.00 g, 3.31 mmol, 1.0 equiv.) in THF (7.0 mL) was added dropwise to the reaction mixture. After stirring overnight, the reaction was quenched by AcOH (379 µL, 6.60 mmol) and the mixture was stirred for a while. H_2O (20 mL) was added, and the mixture was extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) to afford cyanohydrin **50** (444 mg, 1.52 mmol, 46% yield) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.35 (5H, m), 5.56 (1H, s), 5.27 (1H, d, J = 13.2 Hz), 5.25 (1H, d, J = 12.9 Hz), 1.52 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 159.7, 153.0, 134.0, 129.0, 128.7, 128.6, 112.3, 86.7, 71.4, 62.5, 27.8; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{15}H_{17}NO_5Na$ 314.0999; Found 314.0997; **IR (ATR):** 1755, 1234, 1150, 1134 cm^{-1}.

General Procedure for Mannich-type Addition (GP4):

A 10 mL tube equipped with a Teflon-coated screw cap was charged with a stir bar, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) and toluene (0.50 mL). *N*-Boc imine (0.150 mmol, 1.5 equiv.) in toluene (0.50 mL) was added to the mixture and the tube was cooled to −40 °C. To the stirred solution was added catalyst **51** or **52** (0.005 mmol, 5 mol%) and the mixture was stirred for 24 hours. The solution was filtered through a short silica gel plug, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc) to afford the mixture of diastereomers. The values of ee and dr of the products were determined by chiral HPLC analysis.

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-phenylpropanoate (112):**



50 **67** **112**

According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography

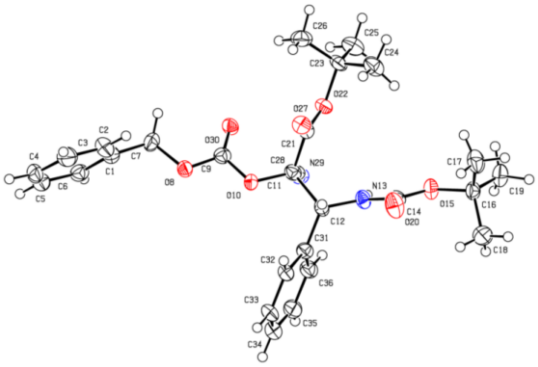
(SiO_2, eluted with hexane/EtOAc = 9:1) afforded **112** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(112')}$ = 10.1 min, $t_{R(ent\text{-}112')}$ = 11.7 min, $t_{R(112)}$ = 19.0 min, $t_{R(ent\text{-}112)}$ = 24.5 min.

Yield: 48.1 mg, 0.0969 mmol, 97% yield

Ratio of Stereoisomers: 112:***ent*-**112**:**112′**:***ent*-**112′** = 95.5:1.4:1.6:1.5, dr = 31:1, **112**: 97% ee, **112′**: 2% ee

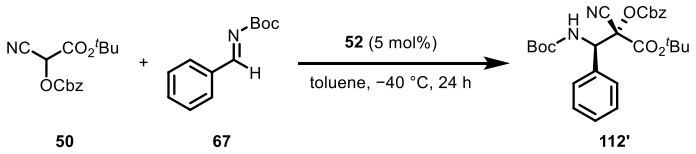
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.32 (10H, m), 5.51 (1H, d, J = 10.3 Hz), 5.42 (1H, d, J = 10.0 Hz), 5.22 (1H, d, J = 11.8 Hz), 5.17 (1H, d, J = 12.1 Hz), 1.42 (9H, s), 1.34 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.1, 154.2, 152.5, 134.4, 133.9, 129.2, 129.1, 128.9, 128.7, 128.6, 128.3, 114.1, 86.4, 80.9, 78.2, 71.3, 58.1, 28.2, 27.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{32}N_2O_7Na$ 519.2102; Found 519.2101. **IR (ATR):** 2978, 1760, 1718, 1247, 1156 cm^{-1}; **Melting Point:** 142.3–143.4 °C; **Optical Rotation:** $[\alpha]^{18}_D$ −0.7 (c 1.03, $CHCl_3$).

ORTEP Diagram of 112:



CCDC 1913488 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data request/cif.

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-phenylpropanoate (112′):**



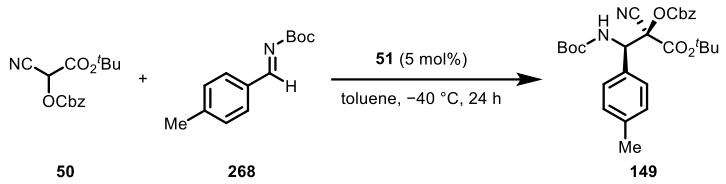
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **112′** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis.

Yield: 45.6 mg, 0.0918 mmol, 92% yield

Ratio of Stereoisomers: 112:***ent*-**112**:**112′**:***ent*-**112′** = 6.2:0.7:89.2:3.9, dr = 1:14, **112**: 81% ee, **112′**: 92% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.65 (2H, dd, J = 7.7, 1.4 Hz), 7.50–7.30 (9H, m), 5.47 (1H, d, J = 10.3 Hz), 5.33 (1H, d, J = 12.0 Hz), 5.24 (1H, d, J = 12.0 Hz), 1.45 (9H, s), 1.35 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.0, 155.5, 153.6, 136.2, 135.6, 129.9, 129.8, 129.5, 129.2, S18 114.9, 86.6, 80.0, 79.2, 71.8, 60.0, 28.4, 27.6 (Two aromatic carbon peaks are missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{32}N_2O_7Na$ 519.2102; Found 519.2077; **IR (ATR):** 3373, 2980, 1756, 1712, 1244, 1158 cm^{-1}; **Melting Point:** 56.9–58.0 °C; **Optical Rotation:** $[\alpha]^{26}_D$ −23.4 (c 1.00, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(*p*-tolyl)propanoate (149):**



50 **268** **149**

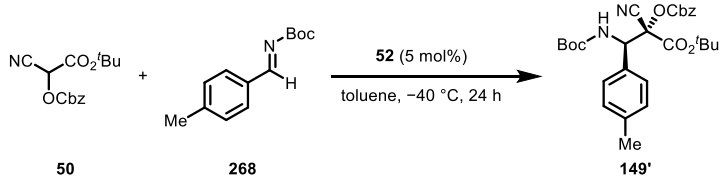
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **268** (32.9 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **149** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{149'})}$ = 10.2 min, $t_{R(\textit{ent}\text{-}\mathbf{149'})}$ = 11.7 min, $t_{R(\mathbf{149})}$ = 20.6 min, $t_{R(\textit{ent}\text{-}\mathbf{149})}$ = 25.9 min.

Yield: 49.9 mg, 0.0977 mmol, 98% yield

Ratio of Stereoisomers: 149:***ent*-149**:**149′**:***ent*-149′** = 97.2:0.8:1.3:0.7, dr = 48:1, **149**: 98% ee, **149′**: 30% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.38 (5H, m), 7.29–7.27 (2H, m), 7.16 (2H, d, J = 7.5 Hz), 5.47 (1H, d, J = 10.3 Hz), 5.38 (1H, d, J = 10.3 Hz), 5.21 (1H, d, J = 12.0 Hz), 5.16 (1H, d, J = 12.0 Hz), 2.34 (3H, s), 1.41 (9H, s), 1.36 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.2, 154.2, 152.5, 139.1, 133.9, 131.4, 129.2, 129.0, 128.9, 128.7, 128.1, 114.2, 86.3, 80.8, 78.2, 71.2, 57.8, 28.2, 27.4, 21.2; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_7Na$ 533.2258; Found 533.2260; **IR (ATR):** 2980, 1757, 1706, 1245, 1158 cm^{-1}; **Melting Point:** 127.7–132.1 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −4.7 (c 0.65, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(*p*-tolyl)propanoate (149′):**



50 **268** **149'**

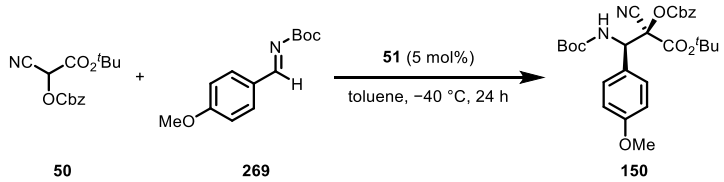
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **268** (32.9 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **149′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{149'})}$ = 9.8 min, $t_{R(\textit{ent}\text{-}\mathbf{149'})}$ = 11.1 min, $t_{R(\mathbf{149})}$ = 19.0 min, $t_{R(\textit{ent}\text{-}\mathbf{149})}$ = 22.8 min.

Yield: 51.2 mg, 0.100 mmol, 100% yield

Ratio of Stereoisomers: 149:***ent*-149**:**149′**:***ent*-149′** = 8.3:0.7:86.0:5.1, dr = 1:10, **149**: 85% ee, **149′**: 89% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.52–7.38 (7H, m), 7.27 (1H, d, J = 8.6 Hz), 7.20 (2H, d, J = 8.0 Hz), 5.41 (1H, d, J = 10.3 Hz), 5.30 (1H, d, J = 12.0 Hz), 5.21 (1H, d, J = 12.0 Hz), 2.31 (3H, s), 1.43 (9H, s), 1.33 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.0, 155.5, 153.6, 139.5, 135.6, 133.2, 129.8, 129.7, 129.5, 114.9, 86.5, 80.0, 79.3, 71.7, 59.8, 28.4, 27.6, 21.1 (Two aromatic carbon peaks are missing due to overlapping); **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_7Na$ 533.2264; Found 533.2266; **IR (ATR):** 2979, 1756, 1714, 1246, 1159 cm^{-1}; **Optical Rotation:** $[\alpha]^{27}_D$ −28.8 (c 0.79, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(4-methoxyphenyl)propanoate (150):**



50 **269** **150**

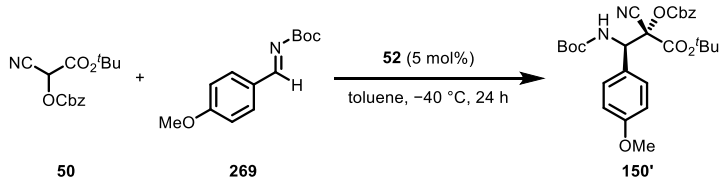
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **269** (35.3 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 7:1) afforded **150** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 238 nm, $t_{R(\mathbf{150'})}$ = 21.2 min, $t_{R(\mathbf{\textit{ent}\text{-}150'})}$ = 26.1 min, $t_{R(\mathbf{150})}$ = 49.7 min, $t_{R(\mathbf{\textit{ent}\text{-}150})}$ = 60.8 min.

Yield: 44.5 mg, 0.0845 mmol, 85% yield

Ratio of Stereoisomers: 150:***ent*-150**:**150′**:***ent*-150′** = 98.8:0.7:0.2:0.2, dr = >99:1, **150**: 99% ee, **150′**: 8% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.26 (7H, m), 6.87 (2H, d, J = 9.0 Hz), 5.45 (1H, d, J = 9.7 Hz), 5.37 (1H, d, J = 9.7 Hz), 5.22 (1H, d, J = 12.0 Hz), 5.17 (1H, d, J = 12.0 Hz), 3.80 (3H, s), 1.41 (9H, s), 1.35 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.2, 160.1, 154.2, 152.5, 133.9, 129.5, 129.0, 128.9, 128.7, 126.5, 114.2, 113.9, 86.3, 80.8, 78.3, 71.3, 57.6, 55.2, 28.2, 27.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_8Na$ 549.2207; Found 549.2208; **IR (ATR):** 2978, 1758, 1718, 1246, 1159 cm^{-1}; **Melting Point:** 110.5–112.7 °C; **Optical Rotation:** $[\alpha]^{20}_D$ −4.4 (c 1.10, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(4-methoxyphenyl)propanoate (150′):**



50 **269** **150'**

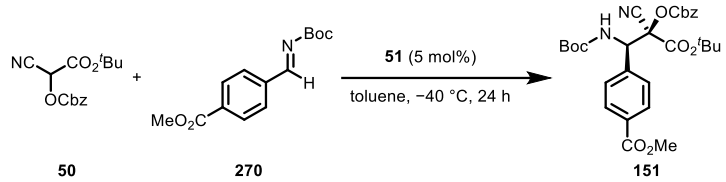
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **269** (35.3 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 7:1) afforded **150′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{150'})}$ = 20.6 min, $t_{R(\mathbf{\textit{ent}\text{-}150'})}$ = 25.4 min, $t_{R(\mathbf{150})}$ = 47.9 min, $t_{R(\mathbf{\textit{ent}\text{-}150})}$ = 55.5 min.

Yield: 39.1 mg, 0.0743 mmol, 74% yield

Ratio of Stereoisomers: 150:***ent*-150**:**150′**:***ent*-150′** = 4.5:0.7:88.5:6.2, dr = 1:18, **150**: 73% ee, **150′**: 87% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.55 (2H, d, J = 8.6 Hz), 7.50–7.39 (5H, m), 7.26 (1H, d, J = 6.9 Hz), 6.95 (2H, d, J = 8.6 Hz), 5.41 (1H, d, J = 10.3 Hz), 5.32 (1H, d, J = 12.0 Hz), 5.23 (1H, d, J = 12.0 Hz), 3.81 (3H, s), 1.44 (9H, s), 1.35 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.0, 161.0, 155.4, 153.6, 135.6, 131.1, 129.7, 129.5, 128.2, 115.0, 114.5, 86.5, 79.9, 79.4, 71.7, 59.5, 55.5, 28.4, 27.7 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_8Na$ 549.2207; Found 549.2180; **IR (ATR):** 2979, 1757, 1714, 1249, 1161 cm^{-1}; **Optical Rotation:** $[\alpha]^{27}_D$ −32.1 (c 0.87, MeOH).

Methyl 4-((5*S*,6*R*)-5-(*tert*-butoxycarbonyl)-5-cyano-10,10-dimethyl-3,8-dioxo-1-phenyl-2,4,9-trioxa-7-azaundecan-6-yl)benzoate (151):



50 **270** **151**

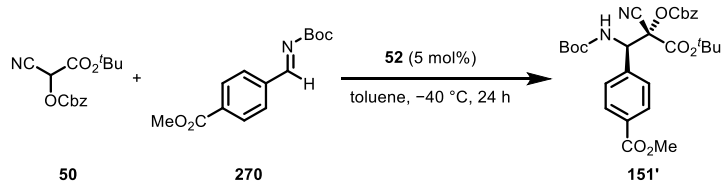
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **270** (39.5 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 8:1) afforded **151** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 7% 2-propanol/hexane, λ = 238 nm, $t_{R(\mathbf{151'})}$ = 14.5 min, $t_{R(\textit{ent}\text{-}\mathbf{151'})}$ = 15.9 min, $t_{R(\textit{ent}\text{-}\mathbf{151})}$ = 21.7 min, $t_{R(\mathbf{151})}$ = 24.3 min.

Yield: 50.5 mg, 0.0911 mmol, 91% yield

Ratio of Stereoisomers: 151:***ent*-151**:**151′**:***ent*-151′** = 97.0:2.6:0.2:0.2, dr = >99:1, **151**: 95% ee, ***ent*-151′**: 5% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.03 (2H, d, J = 8.0 Hz), 7.48 (2H, d, J = 8.0 Hz), 7.39 (5H, s), 5.53 (1H, d, J = 9.7 Hz), 5.46 (1H, d, J = 10.6 Hz), 5.22 (1H, d, J = 11.7 Hz), 5.17 (1H, d, J = 12.0 Hz), 3.92 (3H, s), 1.41 (9H, s), 1.35 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 166.4, 160.9, 154.1, 152.3, 139.2, 133.8, 130.9, 129.8, 129.1, 128.9, 128.7, 128.4, 113.8, 86.7, 81.2, 77.8, 71.4, 57.8, 52.3, 28.2, 27.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{29}H_{34}N_2O_9Na$ 577.2157; Found 577.2165; **IR (ATR):** 2980, 1759, 1719, 1243, 1155 cm^{-1}; **Melting Point:** 150.3–153.0 °C; **Optical Rotation:** $[\alpha]^{24}_D$ −2.8 (c 1.00, $CHCl_3$).

Methyl 4-((5*R*,6*R*)-5-(*tert*-butoxycarbonyl)-5-cyano-10,10-dimethyl-3,8-dioxo-1-phenyl-2,4,9-trioxa-7-azaundecan-6-yl)benzoate (151′):



50 **270** **151'**

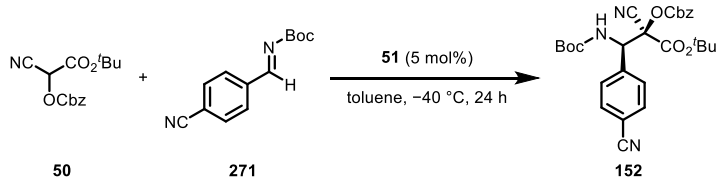
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **270** (39.5 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 8:1) afforded **151′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 254 nm, min, $t_{R(\mathbf{151'})}$ = 20.7 min, $t_{R(\textit{ent}\text{-}\mathbf{151'})}$ = 23.2, $t_{R(\textit{ent}\text{-}\mathbf{151})}$ = 33.0 min, $t_{R(\mathbf{151})}$ = 36.2 min.

Yield: 51.3 mg, 0.0925 mmol, 93% yield

Ratio of Stereoisomers: 151:***ent*-151**:**151′**:***ent*-151′** = 7.9:1.2:87.4:3.6, dr = 1:10, **151**: 75% ee, **151′**: 92% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 8.04 (2H, d, J = 8.6 Hz), 7.79 (2H, d, J = 8.3 Hz), 7.50–7.38 (6H, m), 5.55 (1H, d, J = 9.7 Hz), 5.33 (1H, d, J = 12.0 Hz), 5.23 (1H, d, J = 11.7 Hz), 3.89 (3H, s), 1.46 (9H, s), 1.35 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 166.7, 161.7, 155.5, 153.5, 141.0, 135.5, 131.6, 130.2, 130.2, 129.8, 129.5, 114.8, 86.9, 80.3, 78.7, 71.9, 59.7, 52.5, 28.4, 27.7 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{29}H_{34}N_2O_9Na$ 577.2157; Found 577.2130; **IR (ATR):** 2978, 1763, 1709, 1245, 1163 cm^{-1}; **Optical Rotation:** $[\alpha]^{27}_D$ −30.9 (c 0.92, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(4-cyanophenyl)propanoate (152):**



50 **271** **152**

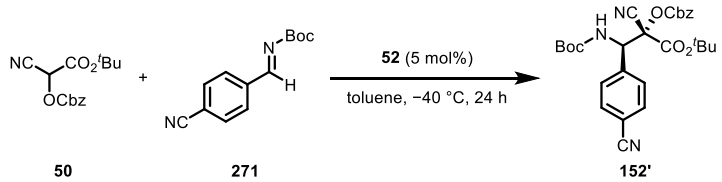
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **271** (34.5 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 7:1) afforded **152** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 238 nm, $t_{R(\mathbf{152'})}$ = 28.0 min, $t_{R(\textit{ent}\text{-}\mathbf{152'})}$ = 40.2 min, $t_{R(\textit{ent}\text{-}\mathbf{152})}$ = 44.3 min, $t_{R(\mathbf{152})}$ = 50.5 min.

Yield: 52.0 mg, 0.0997 mmol, 100% yield

Ratio of Stereoisomers: 152:***ent*-152**:**152′**:***ent*-152′** = 91.9:2.7:2.9:2.5, dr = 18:1, **152**: 94% ee, **152′**: 7% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (2H, d, J = 8.0 Hz), 7.53 (2H, d, J = 8.0 Hz), 7.40 (5H, m), 5.52 (1H, d, J = 10.0 Hz), 5.44 (1H, d, J = 10.0 Hz), 5.23 (1H, d, J = 12.0 Hz), 5.18 (1H, t, J = 12.0 Hz), 1.41 (9H, s), 1.37 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 160.8, 154.0, 152.1, 139.6, 133.6, 132.3, 129.21, 129.15, 129.0, 128.8, 118.2, 113.6, 113.2, 87.0, 81.5, 77.5, 71.6, 57.6, 28.1, 27.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{31}N_3O_7Na$ 544.2054; Found 544.2057; **IR (ATR):** 2980, 2231, 1759, 1719, 1245, 1157 cm^{-1}; **Melting Point:** 120.7–123.3 °C; **Optical Rotation:** $[\alpha]^{25}_D$ +0.2 (c 1.00, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(4-cyanophenyl)propanoate (152′):**



50 **271** **152'**

According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **271** (34.5 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 7:1) afforded **152′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 238 nm, $t_{R(\mathbf{152'})}$ = 28.1 min, $t_{R(\textit{ent}\text{-}\mathbf{152'})}$ = 40.6 min, $t_{R(\textit{ent}\text{-}\mathbf{152})}$ = 44.6 min, $t_{R(\mathbf{152})}$ = 51.9 min.

Yield: 52.3 mg, 0.100 mmol, 100% yield

Ratio of Stereoisomers: 152:***ent*-152**:**152′**:***ent*-152′** = 9.8:1.4:85.8:2.9, dr = 1:7.9, **152**: 75% ee, **152′**: 93% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.79–7.73 (4H, m), 7.44 (1H, d, J = 9.2 Hz), 7.36–7.27 (5H, m), 5.45 (1H, d, J = 10.3 Hz), 5.21 (1H, d, J = 11.5 Hz), 5.11 (1H, d, J = 12.0 Hz), 1.35 (9H, s), 1.23 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 161.6, 155.4, 153.4, 141.2, 135.5, 133.1, 131.0, 130.8, 129.8, 129.5, 118.8, 114.7, 113.7, 87.1, 80.4, 78.4, 72.0, 59.6, 28.4, 27.7; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{31}N_3O_7Na$ 544.2054; Found 544.2030; **IR (ATR):** 2979, 2232, 1758, 1716, 1247, 1159 cm^{-1}; **Optical Rotation:** $[\alpha]^{26}_D$ −33.0 (c 0.94, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(*m*-tolyl)propanoate (153):**

50 272 153

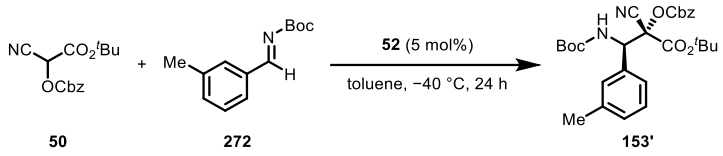
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **272** (32.9 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **153** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 238 nm, $t_{R(\mathbf{153'})}$ = 10.1 min, $t_{R(\textit{ent}\text{-}\mathbf{153'})}$ = 12.0 min, $t_{R(\mathbf{153})}$ = 19.3 min, $t_{R(\textit{ent}\text{-}\mathbf{153})}$ = 25.7 min.

Yield: 50.1 mg, 0.0981 mmol, 98% yield

Ratio of Stereoisomers: 153:***ent*-153**:**153′**:***ent*-153′** = 86.3:5.6:5.0:3.1, dr = 11:1, **153**: 88% ee, **153′**: 23% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39 (5H, m), 7.27–7.15 (4H, m), 5.50 (1H, d, J = 9.0 Hz), 5.38 (1H, d, J = 10.5 Hz), 5.22 (1H, d, J = 12.0 Hz), 5.17 (1H, t, J = 11.5 Hz), 2.34 (3H, s), 1.42 (9H, s), 1.34 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.1, 154.2, 152.5, 138.2, 134.3, 133.9, 129.9, 129.0, 128.9, 128.7, 128.5, 125.3, 114.2, 86.3, 80.8, 78.1, 71.2, 58.1, 28.2, 27.4, 21.4 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_7Na$ 533.2258; Found 533.2260; **IR (ATR):** 2980, 1756, 1705, 1243, 1158 cm^{-1}; **Melting Point:** 147.9–149.3 °C; **Optical Rotation:** $[\alpha]^{25}_D$ −2.8 (c 1.00, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(*m*-tolyl)propanoate (153′):**



50 272 153'

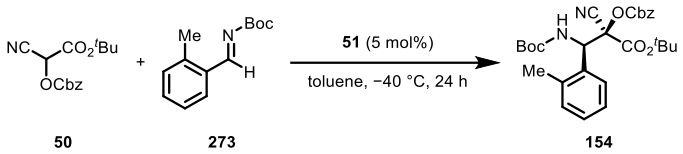
According to **GP4**, cyanohydrin **50** (28.4 mg, 0.0975 mmol, 1.0 equiv.) reacted with *N*-Boc imine **272** (32.1 mg, 0.146 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.00485 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **153′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 238 nm, $t_{R(\mathbf{153'})}$ = 9.6 min, $t_{R(\textit{ent}\text{-}\mathbf{153'})}$ = 11.5 min, $t_{R(\mathbf{153})}$ = 18.5 min, $t_{R(\textit{ent}\text{-}\mathbf{153})}$ = 25.8 min.

Yield: 41.6 mg, 0.0815 mmol, 84% yield

Ratio of Stereoisomers: 153:***ent*-153**:**153′**:***ent*-153′** = 3.4:0.8:93.4:2.4, dr = 1:23, **153**: 63% ee, **153′**: 95% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.51–7.38 (7H, m), 7.33–7.25 (2H, m), 7.22 (1H, d, J = 7.4 Hz), 5.42 (1H, d, J = 10.3 Hz), 5.33 (1H, d, J = 12.0 Hz), 5.25 (1H, d, J = 12.0 Hz), 2.35 (3H, s), 1.44 (9H, s), 1.36 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.0, 155.4, 153.6, 138.7, 136.0, 135.6, 130.5, 130.4, 129.69, 129.67, 129.5, 129.1, 126.8, 114.9, 86.5, 80.0, 79.3, 71.7, 60.0, 28.4, 27.6, 21.3; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_7Na$ 533.2258; Found 533.2241; **IR (ATR):** 2979, 1756, 1713, 1245, 1159 cm^{-1}; **Optical Rotation:** $[\alpha]^{26}_D$ −22.0 (c 1.17, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(*o*-tolyl)propanoate (154):**



50 **273** **154**

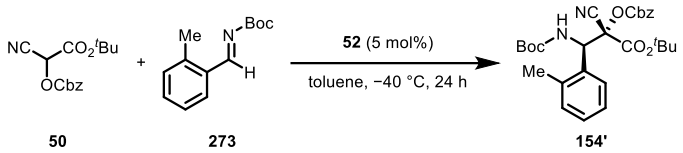
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **273** (32.9 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **153** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{153'})}$ = 9.0 min, $t_{R(\textit{ent}\text{-}\mathbf{153'})}$ = 13.8 min, $t_{R(\mathbf{153})}$ = 17.2 min, $t_{R(\textit{ent}\text{-}\mathbf{153})}$ = 29.5 min.

Yield: 51.0 mg, 0.0999 mmol, 100% yield

Ratio of Stereoisomers: 153:***ent*-153**:**153′**:***ent*-153′** = 87.8:2.8:4.8:4.6, dr = 9.7:1, **153**: 94% ee, **153′**: 3% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.47–7.36 (6H, m), 7.27–7,18 (3H, m), 5.81 (1H, d, J = 10.5 Hz), 5.43 (1H, d, J = 9.0 Hz), 5.22 (1H, d, J = 11.5Hz), 5.14 (1H, d, J = 12.5 Hz), 2.47 (3H, s), 1.41 (9H, s), 1.31 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.5, 154.2, 152.5, 137.4, 134.0, 133.8, 130.7, 129.0, 128.8, 128.7, 126.8, 126.4, 114.2, 86.2, 80.8, 78.7, 71.2, 53.0, 28.2, 27.2, 19.9 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_7Na$ 533.2258; Found 533.2257; **IR (ATR):** 2980, 1759, 1706, 1245, 1156 cm^{-1}; **Optical Rotation:** $[\alpha]^{22}_D$ −10.5 (c 1.00, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(*o*-tolyl)propanoate (154′):**



50 **273** **154'**

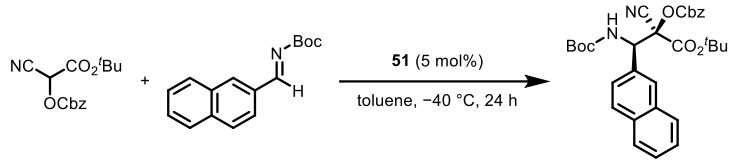
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **273** (32.9 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **154′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{154'})}$ = 9.2 min, $t_{R(\textit{ent}\text{-}\mathbf{154'})}$ = 13.8 min, $t_{R(\mathbf{154})}$ = 17.3 min, $t_{R(\textit{ent}\text{-}\mathbf{154})}$ = 28.0 min.

Yield: 48.0 mg, 0.0940 mmol, 94% yield

Ratio of Stereoisomers: 154:***ent*-154**:**154′**:***ent*-154′** = 2.9:0.7:91.3:5.1, dr = 1:27, **154**: 60% ee, **154′**: 89% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.74 (1H, dd, J = 5.7, 2.3 Hz), 7.46 (2H, d, J = 6.9 Hz), 7.39 (3H, q, J = 7.4 Hz), 7.27–7.20 (4H, m), 5.89 (1H, d, J = 9.7 Hz), 5.30 (1H, d, J = 12.0 Hz), 5.22 (1H, d, J = 12.0 Hz), 2.49 (3H, s), 1.39 (9H, s), 1.30 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.1, 155.7, 153.6, 137.2, 135.6, 131.3, 129.7, 129.54, 129.46, 129.4, 127.2, 114.8, 86.5, 80.0, 78.7, 71.8, 54.7, 28.4, 27.6, 20.0 (Two aromatic carbon peaks are missing due to overlapping); **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_7Na$ 533.2264; Found 533.2260; **IR (ATR):** 2979, 1756, 1714, 1247, 1158 cm^{-1}; **Optical Rotation:** $[\alpha]^{25}_D$ −41.5 (c 0.88, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(naphthalen-2-yl)propanoate (155):**



50 **274** **155**

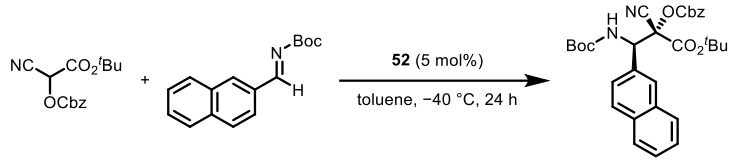
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **274** (38.3 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **155** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 238 nm, $t_{R(\mathbf{155'})}$ = 27.9 min, $t_{R(\mathbf{\textit{ent}\text{-}155'})}$ = 33.1 min, $t_{R(\mathbf{155})}$ = 63.0 min, $t_{R(\mathbf{\textit{ent}\text{-}155})}$ = 78.0 min.

Yield: 45.7 mg, 0.0836 mmol, 84% yield

Ratio of Stereoisomers: 155:***ent*-155**:**155′**:***ent*-155′** = 90.4:3.8:2.9:3.0, dr = 16:1, **155**: 92% ee, **155′**: 2% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.87–7.82 (4H, m), 7.53–7.48 (3H, m), 7.41–7.36 (5H, m), 5.63 (1H, d, J = 10.9 Hz), 5.59 (1H, d, J = 10.4 Hz), 5.22 (1H, d, J = 11.5Hz), 5.17 (1H, d, J = 12.6 Hz), 1.42 (9H, s), 1.31 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.1, 154.2, 152.5, 133.9, 133.4, 132.8, 131.8, 129.0, 128.9, 128.7, 128.5, 128.2, 128.1, 127.6, 126.8, 126.5, 125.2, 114.2, 86.4, 81.0, 78.2, 71.3, 58.3, 28.2, 27.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{31}H_{34}N_2O_7Na$ 569.2258; Found 569.2259; **IR (ATR):** 2980, 1761, 1706, 1245, 1159 cm^{-1}; **Melting Point:** 157.4–158.3 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −10.8 (c 1.00, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(naphthalen-2-yl)propanoate (155′):**



50 **274** **155'**

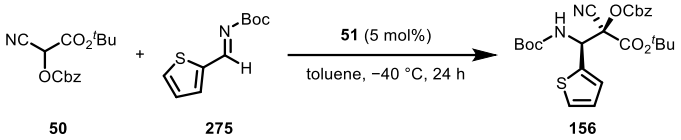
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **274** (38.3 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **155′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{155'})}$ = 26.6 min, $t_{R(\mathbf{\textit{ent}\text{-}155'})}$ = 32.0 min, $t_{R(\mathbf{155})}$ = 60.9 min, $t_{R(\mathbf{\textit{ent}\text{-}155})}$ = 71.8 min.

Yield: 45.9 mg, 0.0839 mmol, 84% yield

Ratio of Stereoisomers: 155:***ent*-155**:**155′**:***ent*-155′** = 1.5:0.4:94.8:3.3, dr = 1:52, **155**: 60% ee, **155′**: 93% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 8.02 (1H, s), 7.85–7.78 (3H, m), 7.69 (1H, dd, J = 8.6, 1.7 Hz), 7.43–7.26 (8H, m), 5.53 (1H, d, J = 9.7 Hz), 5.21 (1H, d, J = 12.0 Hz), 5.11 (1H, d, J = 12.0 Hz), 1.31 (9H, s), 1.23 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162,0, 155.5, 153.6, 135.6, 134.3, 133.8, 133.6, 129.7, 129.51, 129.48, 129.04, 128.98, 128.4, 127.6, 127.3, 127.0, 115.0, 86.7, 80.1, 79.4, 71.8, 60.2, 28.4, 27.6 (One aromatic carbon peak is missing due to overlapping); **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{31}H_{34}N_2O_7Na$ 569.2264; Found 569.2267; **IR (ATR):** 2980, 1757, 1714, 1247, 1159 cm^{-1}; **Optical Rotation:** $[\alpha]^{25}_D$ −40.2 (c 0.79, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(thiophen-2-yl)propanoate (156):**



50 **275** **156**

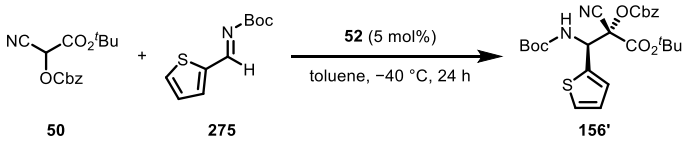
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **275** (31.7 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **156** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{156'})}$ = 18.0 min, $t_{R(\textit{ent}\text{-}\mathbf{156'})}$ = 20.2 min, $t_{R(\mathbf{156})}$ = 30.9 min, $t_{R(\textit{ent}\text{-}\mathbf{156})}$ = 41.1 min.

Yield: 50.0 mg, 0.0995 mmol, 100% yield

Ratio of Stereoisomers: 156:***ent*-156**:**156′**:***ent*-156′** = 84.3:6.2:4.2:5.2, dr = 9.6:1, **156**: 86% ee, **156′**: 11% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.37 (5H, m), 7.32 (1H, d, J = 5.2 Hz), 7.17–7.14 (1H, m), 7.00– 6.96 (1H, m), 5.75 (1H, d, J = 10.3 Hz), 5.36 (1H, d, J = 10.3 Hz), 5.26 (1H, d, J = 12.0 Hz), 5.22 (1H, d, J = 12.6 Hz), 1.43 (9H, s), 1.35 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 160.6, 154.0, 152.3, 136.6, 133.9, 129.0, 128.8, 128.7, 127.7, 126.7, 126.6, 113.9, 86.5, 81.1, 78.0, 71.4, 54.4, 28.2, 27.3; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{25}H_{30}N_2O_7SNa$ 525.1666; Found 525.1677; **IR (ATR):** 2980, 1760, 1718, 1243, 1158 cm^{-1}; **Melting Point:** 105.4–108.3 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −10.6 (c 0.65, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(thiophen-2-yl)propanoate (156′):**



50 **275** **156'**

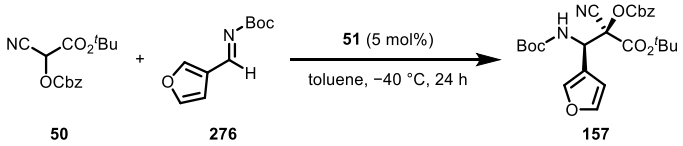
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **275** (31.7 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **156′** as a yellow oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 254 nm, $t_{R(\mathbf{156'})}$ = 17.6 min, $t_{R(\textit{ent}\text{-}\mathbf{156'})}$ = 19.9 min, $t_{R(\mathbf{156})}$ = 31.0 min, $t_{R(\textit{ent}\text{-}\mathbf{156})}$ = 40.4 min.

Yield: 49.7 mg, 0.0989 mmol, 99% yield

Ratio of Stereoisomers: 156:***ent*-156**:**156′**:***ent*-156′** = 3.6:1.0:88.6:6.8, dr = 1:21, **156**: 55% ee, **156′**: 86% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.52–7.37 (7H, m), 7.23 (1H, d, J = 8.6 Hz), 7.06 (1H, dd, J = 5.2, 3.4 Hz), 5.76 (1H, d, J = 10.3 Hz), 5.35 (1H, d, J = 12.0 Hz), 5.28 (1H, d, J = 12.0 Hz), 1.45 (9H, s), 1.36 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 161.6, 155.3, 153.4, 137.8, 135.5, 129.71, 129.67, 129.5, 129.2, 127.6, 127.4, 114.8, 86.8, 80.3, 78.9, 71.8, 55.7, 28.4, 27.6; **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{25}H_{30}N_2O_7SNa$ 525.1671; Found 525.1677; **IR (ATR):** 2980, 1158, 1715, 1244, 1157 cm^{-1}; **Optical Rotation:** $[\alpha]^{26}_D$ −27.0 (c 0.94, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(furan-3-yl)propanoate (157):**



50 **276** **157**

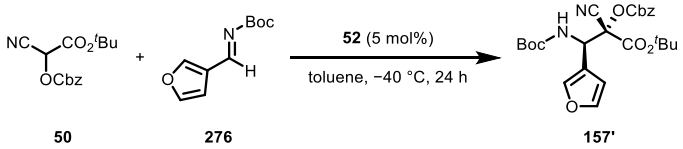
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **276** (29.3 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **157** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{157'})}$ = 24.4 min, $t_{R(\textit{ent}\text{-}\mathbf{157'})}$ = 29.0 min, $t_{R(\mathbf{157})}$ = 42.2 min, $t_{R(\textit{ent}\text{-}\mathbf{157})}$ = 48.8 min.

Yield: 48.6 mg, 0.0999 mmol, 100% yield

Ratio of Stereoisomers: 157:***ent*-157**:**157′**:***ent*-157′** = 95.8:1.7:1.5:1.1, dr = 39:1, **157**: 97% ee, **157′**: 15% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50 (1H, s), 7.43–7.36 (6H, m), 6.51 (1H, s), 5.45 (1H, d, J = 9.7 Hz), 5.26–5.21 (3H, m), 1.43 (9H, s), 1.37 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.0, 154.2, 152.4, 143.5, 141.3, 133.9, 129.1, 128.9, 128.7, 119.6, 114.1, 109.5, 86.4, 81.0, 78.0, 71.3, 51.2, 28.2, 27.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{25}H_{30}N_2O_8Na$ 509.1894; Found 509.1902; **IR (ATR):** 2980, 1758, 1719, 1246, 1158 cm^{-1}; **Melting Point:** 109.8–112.4 °C; **Optical Rotation:** $[\alpha]^{24}_D$ −8.0 (c 1.00, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-(furan-3-yl)propanoate (157′):**



50 **276** **157'**

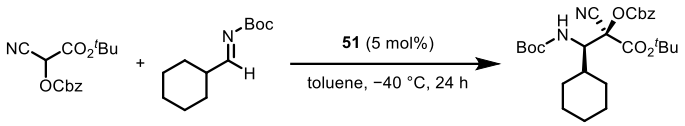
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **276** (29.3 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **157′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{157'})}$ = 22.1 min, $t_{R(\textit{ent}\text{-}\mathbf{157'})}$ = 27.4 min, $t_{R(\mathbf{157})}$ = 39.2 min, $t_{R(\textit{ent}\text{-}\mathbf{157})}$ = 43.7 min.

Yield: 45.9 mg, 0.0943 mmol, 94% yield

Ratio of Stereoisomers: 157:***ent*-157**:**157′**:***ent*-157′** = 5.0:0.7:89.9:4.3, dr = 1:16, **157**: 75% ee, **157′**: 91% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.83 (1H, s), 7.57 (1H, s), 7.48 (2H, d, J = 6.3 Hz), 7.45–7.40 (3H, m), 7.15 (1H, d, J = 8.0 Hz), 6.78 (1H, s), 5.49 (1H, d, J = 10.3 Hz), 5.33 (1H, d, J = 11.5 Hz), 5.25 (1H, d, J = 12.0 Hz), 1.45 (9H, s), 1.36 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 161.8, 155.4, 153.6, 144.3, 142.8, 135.6, 129.7, 129.5, 121.1, 115.1, 111.3, 86.6, 80.0, 79.2, 71.8, 52.6, 28.5, 27.7 (One aromatic carbon peak is missing due to overlapping); **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{25}H_{30}N_2O_8Na$ 509.1900; Found 509.1895; **IR (ATR):** 2980, 1756, 1712, 1246, 1156 cm^{-1}; **Optical Rotation:** $[\alpha]^{26}_D$ −6.4 (c 1.09, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-cyclohexylpropanoate (158):**



50 **277** **158**

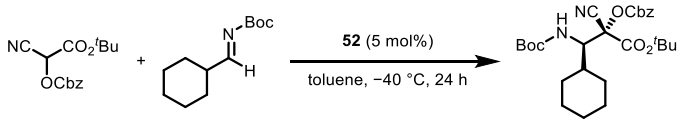
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **277** (31.7 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **158** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{158'})}$ = 15.3 min, $t_{R(\mathbf{\textit{ent}\text{-}158'})}$ = 18.6 min, $t_{R(\mathbf{158})}$ = 35.9 min, $t_{R(\mathbf{\textit{ent}\text{-}158})}$ = 54.7 min.

Yield: 50.2 mg, 0.0999 mmol, 100% yield

Ratio of Stereoisomers: 158:***ent*-158**:**158′**:***ent*-158′** = 82.7:2.9:6.1:8.3, dr = 5.9:1, **158**: 93% ee, **158′**: 15% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45–7.37 (5H, m), 5.30–5.19 (2H, m), 4.86 (1H, d, J = 10.9 Hz), 4.24 (1H, dd, J = 11.5, 3.4 Hz), 1.99–1.62 (6H, m), 1.44 (9H, s), 1.43 (9H, s), 1.35–0.99 (5H, m); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.9, 155.0, 152.6, 134.0, 129.0, 128.9, 128.7, 114.6, 86.1, 80.4, 77.7, 71.3, 58.0, 38.8, 31.1, 28.2, 27.4, 26.6, 26.1, 25.80, 25.78; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{38}N_2O_7Na$ 525.2571; Found 525.2570; **IR (ATR):** 2930, 1756, 1720, 1243, 1156 cm^{-1}; **Melting Point:** 119.2–129.2 °C; **Optical Rotation:** $[\alpha]^{23}_D$ +2.6 (c 0.65, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-cyclohexylpropanoate (158′):**



50 **277** **158'**

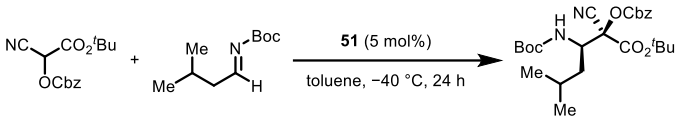
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **277** (31.7 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **158′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{158'})}$ = 13.8 min, $t_{R(\mathbf{\textit{ent}\text{-}158'})}$ = 17.5 min.

Yield: 26.1 mg, 0.0519 mmol, 52% yield

Ratio of Stereoisomers: 158′:***ent*-158′** = 70.7:29.3, dr = >1:99, **158′**: 41% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.50–7.37 (5H, m), 6.34 (1H, d, J = 10.3 Hz), 5.32 (1H, d, J = 12.0 Hz), 5.24 (1H, d, J = 12.0 Hz), 4.27 (1H, dd, J = 10.6, 3.7 Hz), 2.00 (1H, t, J = 5.4 Hz), 1.90 (1H, d, J = 7.4 Hz), 1.74 (3H, s), 1.63 (1H, d, J = 12.6 Hz), 1.46 (9H, s), 1.37 (9H, s), 1.30–1.20 (4H, m), 1.19–1.09 (1H, m); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.3, 156.3, 153.6, 135.7, 129.7, 129.5, 115.6, 86.3, 79.6, 78.8, 71.7, 59.6, 41.2, 32.0, 28.5, 27.9, 27.7, 26.8, 26.7, 26.5 (One aromatic carbon peak is missing due to overlapping); **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{38}N_2O_7Na$ 525.2577; Found 525.2582; **IR (ATR):** 2930, 1758, 1720, 1249, 1159 cm^{-1}; **Optical Rotation:** $[\alpha]^{25}_D$ +8.7 (c 0.81, MeOH).

***tert*-Butyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-methylhexanoate (159):**



50 **172** **159**

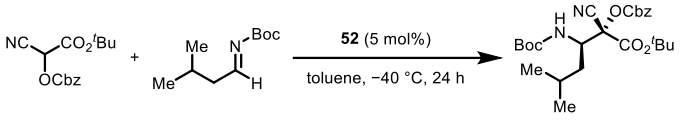
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **172** (27.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **159** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 254 nm, $t_{R(\mathbf{159'})}$ = 10.3 min, $t_{R(\mathbf{159})}$ = 15.9 min, $t_{R(\textit{ent}\text{-}\mathbf{159'})}$ = 18.6 min, $t_{R(\textit{ent}\text{-}\mathbf{159})}$ = 46.4 min.

Yield: 50.1 mg, quant.

Ratio of Stereoisomers: 159:***ent*-159**:**159′**:***ent*-159′** = 83.6:8.5:6.1:1.8, dr = 12:1, **159**: 82% ee, **159′**: 55% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.44–7.36 (5H, m), 5.26 (1H, d, J = 11.5 Hz), 5.21 (1H, d, J = 12.0 Hz), 4.63 (1H, d, J = 10.9 Hz), 4.39 (1H, td, J = 9.6, 5.0 Hz), 1.75–1.60 (1H, m), 1.52–1.40 (20H, m), 0.94 (6H, t, J = 7.7 Hz); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.6, 154.7, 152.6, 134.0, 129.1, 128.9, 128.8, 114.2, 86.1, 80.4, 78.8, 71.3, 53.0, 38.9, 28.2, 27.5, 24.5, 23.5, 21.2; **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{25}H_{37}N_2O_7$ 477.2601; Found 477.2597; **IR (ATR):** 2967, 1757, 1715, 1246, 1159 cm^{-1}; **Melting Point:** 115.2–117.3 °C; **Optical Rotation:** $[\alpha]^{26}_D$ +15.6 (c 1.00, MeOH).

***tert*-Butyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-methylhexanoate (159′):**



59 **172** **159'**

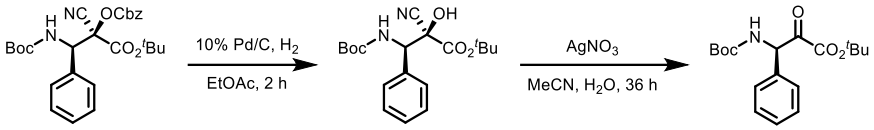
According to **GP4**, cyanohydrin **50** (29.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **172** (27.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **159′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{159'})}$ = 10.2 min, $t_{R(\mathbf{159})}$ = 19.1 min.

Yield: 47.9 mg, 0.100 mmol, 100% yield

Ratio of Stereoisomers: 159′:***ent*-159′** = 86.9:13.1, dr = >1:99, **159′**: 74% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.51–7.36 (5H, m), 6.42 (1H, d, J = 9.7 Hz), 5.31 (1H, d, J = 12.0 Hz), 5.26 (1H, d, J = 12.0 Hz), 4.41 (1H, td, J = 10.9, 2.3 Hz), 1.81–1.68 (2H, m), 1.55–1.47 (1H, S59 m), 1.47 (9H, s), 1.37 (9H, s), 0.95 (6H, t, J = 7.2 Hz); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.1, 156.1, 153.7, 135.6, 129.72, 129.70, 129.5, 115.6, 86.3, 79.6, 79.4, 71.7, 54.6, 39.5, 28.5, 27.7, 25.4, 23.7, 21.2; **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{25}H_{37}N_2O_7$ 477.2601; Found 477.2596; **IR (ATR):** 2967, 1757, 1715, 1506, 1253, 1161 cm^{-1}; **Optical Rotation:** $[\alpha]^{27}_D$ +32.4 (c 0.65, MeOH).

***tert*-Butyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-2-oxo-3-phenylpropanoate (162):**



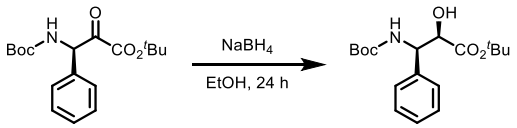
112 **160** **162**

A 20 mL round bottom flask was charged with a stir bar, Mannich adduct **112** (49.7 mg, 0.100 mmol, 1.0 equiv.), and 10% Pd/C (2.1 mg, 0.0020 mmol, 2 mol%) under Ar atmosphere and purged with H_2 gas. To the mixture was added EtOAc (2.0 mL) and the suspension was stirred for 2 hours at room temperature. The mixture was filtered through a short Celite pad and concentrated under reduced pressure. The obtained crude cyanohydrin **160** was used for the next reaction without further purification.

A 20 mL round bottom flask was charged with a stir bar, the crude cyanohydrin **160**, and MeCN (1.5 mL). To the solution was added aqueous $AgNO_3$ (2 M, 0.50 mL, 1.0 mmol, 10 equiv.) and the mixture was stirred for 36 hours at room temperature in the dark. Then the mixture was diluted with EtOAc (10 mL) and distilled H_2O (5 mL), and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (diol SiO_2, eluted with hexane/EtOAc = 10:0 → 9:1) to afford α-ketoester **162** (18.7 mg, 0.0558 mmol, 56% over 2 steps) as a colorless oil.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 7.31–7.21 (5H, m), 6.68 (1H, d, J = 7.4 Hz), 5.78 (1H, d, J = 8.0 Hz), 1.27 (9H, s), 1.25 (9H, s); **^{13}C-NMR (126 MHz, acetone-*d*$_6$):** δ 191.8, 160.9, 155.9, 135.6, 129.8, 129.7, 129.4, 84.7, 79.7, 62.3, 28.5, 27.7; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{18}H_{25}NO_5Na$ 358.1625; Found 358.1626; **IR (ATR):** 3412, 2979, 2932, 1721, 1483 cm^{-1}; **Optical Rotation:** $[\alpha]^{24}_D$ −28.8 (c 1.23, acetone).

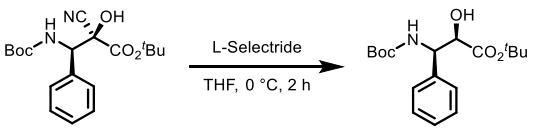
Separation of enantiomers of **162** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of ee of **162** was determined after the reduction of a carbonyl group as a following procedure:



162 **163**

A 10 mL round bottom flask was charged with a stir bar, α-ketoester **162** (5.1 mg, 0.015 mmol, 1.0 equiv.), and EtOH (0.30 mL). To the mixture was added $NaBH_4$ (2.9 mg, 0.0760 mmol, 5.0 equiv.) and the mixture was stirred for 24 hours at room temperature. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1 → 5:1) to afford β-amino-α-hydroxyester **163** (3.5 mg, 0.010 mmol, 68% yield, 94% ee). The value of ee of the product was determined by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 2% methanol/CO_2, λ = 210–400 nm, $t_{R(ent\text{-}163)}$ = 7.0 min, $t_{R(163)}$ = 8.4 min.

***tert*-Butyl (2*R*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoate (163):**



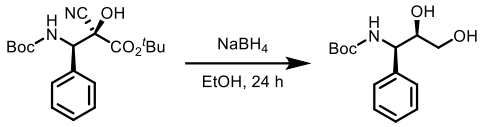
160 **163**

A 20 mL round bottom flask was charged with a stir bar, the crude cyanohydrin **160**, and THF (2.0 mL) under Ar atmosphere and

cooled to 0 °C. To the solution was added L-Selectride (1 M in THF, 0.30 mL, 0.300 mmol, 3.0 equiv.), and the mixture was stirred for 2 hours. The reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1 → 5:1) to afford β-amino-α-hydroxyester **163** (22.1 mg, 0.0655 mmol, 66% yield over 2 steps, 95% ee) as a colorless oil. The value of ee of the product was determined by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 2% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{ent}\text{-}\mathbf{163})}$ = 7.0 min, $t_{R(\mathbf{163})}$ = 8.5 min.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36–7.24 (5H, m), 5.62 (1H, d, J = 8.0 Hz), 5.06 (1H, dd, J = 9.2, 2.9 Hz), 4.48 (1H, s), 3.03 (1H, s), 1.42 (9H, s), 1.35 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 170.9, 155.0, 137.2, 128.2, 128.0, 127.9, 83.5, 79.8, 73.0, 56.3, 28.4, 27.9; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{18}H_{27}NO_5Na$ 360.1781; Found 360.1781; **IR (ATR):** 3392, 2978, 1713, 1495 cm^{-1}; **Optical Rotation:** $[\alpha]^{24}_D$ −20.4 (c 1.75, $CHCl_3$).

***tert*-Butyl (2*R*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoate (164):**

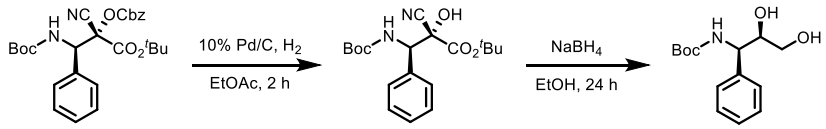


160 **164**

A 20 mL round bottom flask was charged with a stir bar, the crude cyanohydrin **160**, and EtOH (2.0 mL). To the solution was added $NaBH_4$ (18.9 mg, 0.500 mmol, 5.0 equiv.), and the mixture was stirred for 24 hours at room temperature. The mixture was diluted with EtOAc (15 mL) and H_2O (15 mL), and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 4:1 → 1:1) to afford aminodiol **164** (18.1 mg, 0.0677 mmol, 68% yield over 2 steps, 92% ee) as a white solid. The value of ee of the product was determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 10% 2-propanol/hexane, λ = 254 nm, $t_{R(\mathbf{164})}$ = 15.0 min, $t_{R(\textit{ent}\text{-}\mathbf{164})}$ = 18.1 min.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.27 (5H, m), 5.32 (1H, s), 4.69 (1H, t, J = 7.4 Hz), 3.83 (1H, s), 3.65 (2H, s), 3.28 (1H, br), 2.79 (1H, br), 1.43 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 156.4, 139.0, 128.9, 128.1, 127.4, 80.5, 74.2, 63.0, 56.7, 28.3; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{14}H_{21}NO_4Na$ 290.1363; Found 290.1366; **IR (ATR):** 3378, 2978, 1685, 1496 cm^{-1}; **Melting Point:** 108.6–109.6 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −42.9 (c 1.06, $CHCl_3$).

Determination of Absolute Configuration of Mannich Adduct 112′:



112' **160'** **164**

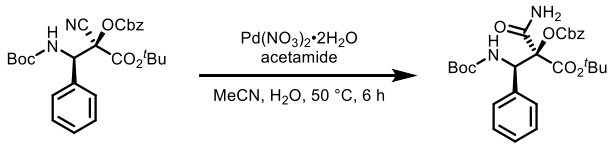
A 20 mL round bottom flask was charged with a stir bar, Mannich adduct **112′** prepared in Table 1, entry 12 (24.8 mg, 0.0500 mmol, 1.0 equiv.), and 10% Pd/C (1.1 mg, 0.0010 mmol, 2 mol%) under Ar atmosphere and purged with H_2 gas. To the mixture was added EtOAc (2.0 mL) and the suspension was stirred for 2 hours at room temperature. The mixture was filtered through a short Celite pad and concentrated under reduced pressure to afford a crude cyanohydrin.

A 20 mL round bottom flask was charged with a stir bar, the crude cyanohydrin, and EtOH (1.0 mL). To the stirred solution was added $NaBH_4$ (9.5 mg, 0.25 mmol, 5.0 equiv.), and the mixture was stirred for 24 hours at room temperature. The mixture was

diluted with EtOAc (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 4:1 → 1:1) to afford aminodiol **164** (18.1 mg, 0.0677 mmol, 68% yield over 2 steps, 93% ee) as a white solid. The values of ee of the product was determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 10% 2-propanol/hexane, λ = 254 nm, $t_{R(\mathbf{164})}$ = 15.0 min, $t_{R(\textit{ent}\text{-}\mathbf{164})}$ = 18.1 min.

The optical rotation for obtained aminodiol **164** was $[\alpha]^{23}_D$ −42.7 (c 0.67, $CHCl_3$), thus the absolute configuration of aminodiol **164** was determined as (1*R*, 2*R*). This result also indicates that the absolute and relative configuration of the Mannich adduct **112′** was (2*R*, 3*R*).

***tert*-Butyl (*S*)-3-amino-2-(((benzyloxy)carbonyl)oxy)-2-((*R*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-3-oxopropanoate (165):**



112 **165**

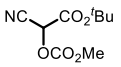
A 10 mL test tube equipped with a Teflon-coated screw cap was charged with a stir bar, the adduct **112** (49.7 mmol, 0.100 mmol, 1.0 equiv.), acetamide (23.6 mmol, 0.400 mmol, 4.0 equiv.), MeCN (0.15 mL), and H_2O (0.05 mL). To the mixture was added $Pd(NO_3)_2$•$2H_2O$ (1.3 mg, 0.005 mmol, 5 mol%) in MeCN (0.15 mL) and the mixture was stirred at 50 °C. After stirring for 6 hours, the solution was cooled to room temperature. To the resulting solution was added QuadraSil™ AP (20.0 mg), and the suspension was stirred for 1 hour at room temperature. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 3:1 → 2:1) to afford the amide **165** as a colorless oil. The values of ee and dr of the product was determined by chiral HPLC analysis: CHIRALPAK IA, 1.0 mL/min, 15% 2-propanol/hexane, λ = 254 nm, $t_{R(\textit{ent}\text{-}\mathbf{165})}$ = 6.7 min, $t_{R(\mathbf{165'})}$ = 8.2 min, $t_{R(\mathbf{165})}$ = 10.6 min, $t_{R(\textit{ent}\text{-}\mathbf{165'})}$ = 12.7 min.

Yield: 42.8 mg, 0.0831 mmol, 83% yield

Ratio of Stereoisomers: 165: ***ent*-165**: **165′**: ***ent*-165′** = 96.4:1.0:1.2:1.3, dr = 39:1, **165**: 98% ee, **165′**: 2% ee

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.86 (1H, s), 7.44–7.26 (10H, m), 5.72 (2H, d, *J* = 8.0 Hz), 5.27 (1H, d, *J* = 8.6 Hz), 5.23 (1H, d, *J* = 12.0 Hz), 5.13 (1H, d, *J* = 12.0 Hz), 1.38 (9H, s), 0.97 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** *δ* 167.0, 166.2, 154.7, 153.5, 136.5, 134.8, 128.8, 128.7, 128.6, 128.4, 128.2, 84.8, 84.6, 80.1, 70.4, 59.8, 28.2, 27.0 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{34}N_2O_8Na$ 537.2207; Found 537.2181; **IR (ATR):** 3426, 2977, 1722, 1255, 1162 cm^{-1}; **Optical Rotation:** $[\alpha]^{26}_D$ −19.7 (c 1.11, MeOH).

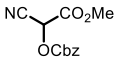
***tert*-Butyl 2-cyano-2-((methoxycarbonyl)oxy)acetate (167):**



167

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 5.58 (1H, s), 3.91 (3H, s), 1.55 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** *δ* 159.6, 153.6, 112.3, 86.6, 62.4, 56.2, 27.7; **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_9H_{14}NO_5$ 216.0872; Found 216.0875; **IR (ATR):** 2984, 1759, 1444, 1256, 1138 cm^{-1}.

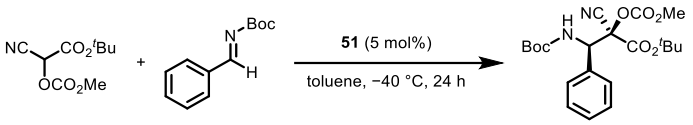
Methyl 2-(((benzyloxy)carbonyl)oxy)-2-cyanoacetate (169):



169

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.36 (5H, m), 5.72 (1H, s), 5.27 (2H, s), 3.92 (3H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.5, 152.9, 133. 8, 129.1, 128.7, 128.5, 111.8, 71.6, 61.9, 54.4; **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{12}H_{12}NO_5$ 250.0715; Found 250.0710; **IR (ATR):** 2983, 2937, 1758, 1243, 1151 cm^{-1}.

***tert*-Butyl (2*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-2-((methoxycarbonyl)oxy)-3-phenylpropanoate (168):**



167 **67** **168**

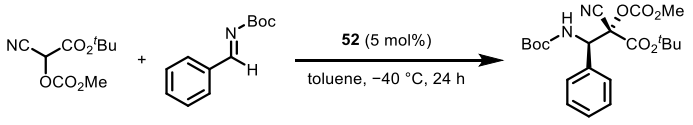
According to **GP4**, cyanohydrin **167** (21.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **168** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, hexane/2-propanol/dichloromethane = 96.5:3.0:0.5, λ = 220 nm, $t_{R(\mathbf{168'})}$ = 11.0 min, $t_{R(\mathbf{\textit{ent}\text{-}168'})}$ = 15.3 min, $t_{R(\mathbf{168})}$ = 22.7 min, $t_{R(\mathbf{\textit{ent}\text{-}168})}$ = 39.5 min.

Yield: 32.3 mg, 0.0768 mmol, 77% yield

Ratio of Stereoisomers: 168:***ent*-168**: **168′**:***ent*-168′** = 92.0:2.1:2.5:3.4, dr = 16:1, **168**: 95% ee, **168′**: 15% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.59 (2H, d, J = 5.7 Hz), 7.45–7.37 (4H, m), 5.45 (1H, d, J = 10.3 Hz), 3.86 (3H, s), 1.42 (9H, s), 1.39 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 162.2, 155.6, 153.9, 136.1, 129.74, 129.72, 129.1, 114.9, 86.4, 80.1, 79.4, 59.6, 56.5, 28.4, 27.6; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{21}H_{29}N_2O_7$ 421.1969; Found 421.1952; **IR (ATR):** 2979, 1762, 1708, 1265, 1158 cm^{-1}; **Optical Rotation:** $[\alpha]^{26}_D$ +2.8 (c 0.93, MeOH).

***tert*-Butyl (2*R*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-2-((methoxycarbonyl)oxy)-3-phenylpropanoate (168′):**



167 **67** **168'**

According to **GP4**, cyanohydrin **167** (21.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **168′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, hexane/2-propanol/dichloromethane = 96.5:3.0:0.5, λ = 220 nm, $t_{R(\mathbf{168'})}$ = 12.3 min, $t_{R(\mathbf{\textit{ent}\text{-}168'})}$ = 17.0 min, $t_{R(\mathbf{168})}$ = 27.3 min, $t_{R(\mathbf{\textit{ent}\text{-}168})}$ = 46.1 min.

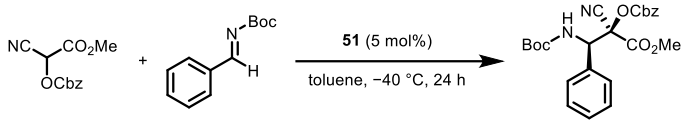
Yield: 37.8 mg, 0.0899 mmol, 90% yield

Ratio of Stereoisomers: 168:***ent*-168**: **168′**:***ent*-168′** = 4.6:1.0:90.5:3.9, dr = 1:17, **168**: 92% ee, **168′**: 64% ee

^{1}H-NMR (500 MHz, acetone-d_6): δ 7.63 (2H, d, J = 6.9 Hz), 7.45–7.38 (3H, m), 7.28 (1H, d, J = 7.4 Hz), 5.45 (1H, d, J = 9.7 Hz), 3.87 (3H, s), 1.47 (9H, s), 1.36 (9H, s); **^{13}C-NMR (126 MHz, acetone-d_6):** δ 161.9, 155.5, 154.1, 136.1, 129.9, 129.8, 129.2, 114.9, 86.6, 80.1, 79.0, 60.0, 56.5, 28.4, 27.7; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{21}H_{29}N_2O_7$ 421.1969; Found 421.1956; **IR (ATR):**

2979, 1760, 1714, 1259, 1162 cm^{-1}; **Optical Rotation:** $[\alpha]^{26}_D$ −25.4 (c 0.95, MeOH).

Methyl (2*S*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-phenylpropanoate (170):



169 **67** **170**

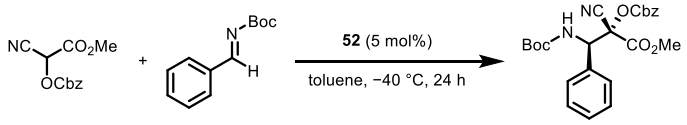
According to **GP4**, cyanohydrin **169** (24.9 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **51** (1.9 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **170** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 254 nm, $t_{R(\mathbf{170'})}$ = 15.6 min, $t_{R(\textit{ent}\text{-}\mathbf{170'})}$ = 26.8 min, $t_{R(\textit{ent}\text{-}\mathbf{170})}$ = 32.2 min, $t_{R(\mathbf{170})}$ = 38.4 min.

Yield: 35.0 mg, 0.0771 mmol, 77% yield

Ratio of Stereoisomers: 170:***ent*-170**: **170′**:***ent*-170′** = 93.7:1.8:3.7:0.9, dr = 21:1, **170**: 96% ee, **170′**: 66% ee

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 7.59 (2H, d, *J* = 5.7 Hz), 7.49 (1H, d, *J* = 9.7 Hz), 7.45–7.35 (8H, m), 5.45 (1H, d, *J* = 9.7 Hz), 5.24 (2H, s), 3.78 (3H, s), 1.38 (9H, s); **^{13}C-NMR (126 MHz, acetone-*d*$_6$):** δ 164.2, 155.7, 153.4, 135.4, 129.9, 129.7, 129.6, 129.52, 129.46, 129.3, 114.6, 80.3, 78.9, 71.9, 59.7, 54.7, 28.4 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{24}H_{27}N_2O_7$ 455.1813; Found 455.1804; **IR (ATR):** 2978, 1763, 1708, 1245, 1161 cm^{-1}; **Melting Point:** 58.7–60.1 °C; **Optical Rotation:** $[\alpha]^{27}_D$ −2.8 (c 1.30, MeOH).

Methyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-phenylpropanoate (170′):



169 **67** **170'**

According to **GP4**, cyanohydrin **169** (24.9 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **52** (1.8 mg, 0.005 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 9:1) afforded **170′** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(\mathbf{170'})}$ = 15.6 min, $t_{R(\textit{ent}\text{-}\mathbf{170'})}$ = 26.9 min, $t_{R(\textit{ent}\text{-}\mathbf{170})}$ = 32.3 min, $t_{R(\mathbf{170})}$ = 39.0 min.

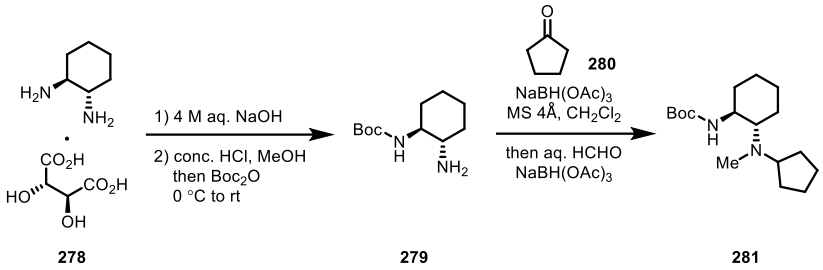
Yield: 44.3 mg, 0.0974 mmol, 97 % yield

Ratio of Stereoisomers: 170:***ent*-170**: **170′**:***ent*-170′** = 14.1:1.3:76.7:7.9, dr = 1:5.5, **170**: 83% ee, **170′**: 81% ee

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 7.65 (2H, dd, *J* = 7.3, 1.6 Hz), 7.48–7.36 (9H, m), 5.47 (1H, d, *J* = 10.0 Hz), 5.32 (1H, d, *J* = 11.7 Hz), 5.25 (1H, d, *J* = 11.7 Hz), 3.83 (3H, s), 1.36 (9H, s); **^{13}C-NMR (126 MHz, acetone-*d*$_6$):** δ 164.0, 155.7, 153.6, 135.5, 135.4, 129.9, 129.8, 129.7, 129.5, 129.3, 114.5, 80.2, 78.4, 72.0, 60.3, 54.8, 28.4 (One aromatic carbon peak is missing due to overlapping); **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{24}H_{26}N_2O_7Na$ 472.1638; Found 477.1640; **IR (ATR):** 2977, 1761, 1709, 1241, 1161 cm^{-1}; **Optical Rotation:** $[\alpha]^{28}_D$ −7.2 (c 0.94, MeOH).

第三節　脂肪族イミンへの高立体選択的Mannich型付加反応の開発

***tert*-Butyl ((1*S*,2*S*)-2-(cyclopentyl(methyl)amino)cyclohexyl)carbamate (281):**



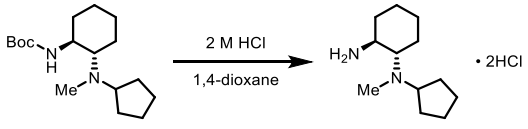
278 **279** **281**

(1*S*,2*S*)-1,2-Cyclohexanediamine *D*-tartrate **278** (13.2 g, 49.9 mmol, 1.0 equiv.) was dissolved in aqueous NaOH (4 M, 50 mL) and extracted with CH_2Cl_2 (5 x 50 mL). The combined organic layers were dried over K_2CO_3, filtered, and concentrated under reduced pressure to afford the neutralized diamine as a colorless oil. A 300 mL round bottom flask was charged with a stir bar, diamine, and MeOH (60 mL) and cooled to 0 °C. To the solution were added concentrated HCl (4.46 mL, 50.0 mmol, 1.0 equiv.) and Boc_2O (10.9 g, 50.0 mmol, 1.0 equiv.) in MeOH (60 mL) dropwise over 1.5 hours at same temperature. After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure. The resulting white solid was washed with Et_2O (3 x 50 mL), dissolved in aqueous NaOH (2 M, 50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (100 mL), dried over K_2CO_3, filtered, and concentrated under reduced pressure to afford Boc-protected diamine **279** (8.90 g, 41.5 mmol, 83% yield) as a white solid, which is storable in refrigerator under Ar atmosphere. This compound was used for next reaction without further purification.

A 200 mL round bottom flask was charged with a stir bar, amine **279** (2.14 g, 9.99 mmol, 1.0 equiv.), molecular sieve 4Å (10 g), and CH_2Cl_2 (50 mL) under Ar atmosphere. To the suspension was added cyclopentanone **280** (974 μL, 11.0 mmol, 1.1 equiv.). After stirring at room temperature for 1.5 hours, to the mixture was added $NaBH(OAc)_3$ (4.24 g, 20.0 mmol, 2.0 equiv.) portionwise under maintaining the temperature with water bath. After stirring overnight, to the reaction mixture were added formalin (37%, 2.23 mL, 29.9 mmol, 3.0 equiv.) and $NaBH(OAc)_3$ (6.36 g, 30.0 mmol, 3.0 equiv.). After stirring for 7 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), filtered through a Celite pad, and separated, and the aqueous layer was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (NH SiO_2, eluted with hexane) to afford **281** (2.62 g, 8.84 mmol, 88% yield) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.35 (1H, s), 3.17 (1H, t, J = 10.6 Hz), 2.87–2.79 (1H, m), 2.50 (1H, d, J = 12.0 Hz), 2.39 (1H, td, J = 10.7, 3.2 Hz), 2.10 (3H, s), 1.83–1.70 (4H, m), 1.70–1.60 (3H, m), 1.56–1.48 (3H, m), 1.45 (9H, s), 1.41–1.34 (1H, m), 1.34–1.12 (4H, m), 1.08–0.99 (1H, m); **^{13}C-NMR (151 MHz, DMSO-d_6):** δ 156.6, 78.7, 63.7, 62.7, 51.8, 33.2, 33.1, 31.9, 31.0, 28.5, 25.7, 24.6, 23.7, 23.5, 22.6; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{17}H_{33}N_2O_2$ 297.2537; Found 297.2536; **IR (ATR):** 3374, 2933, 1710, 1478, 1361, 1238, 1022 cm^{-1}; **Optical Rotation:** $[\alpha]^{20}_D$ +40.8 (c 1.15, $CHCl_3$).

(1*S*,2*S*)-N^1-Cyclopentyl-N^1-methylcyclohexane-1,2-diaminium dichloride (282):

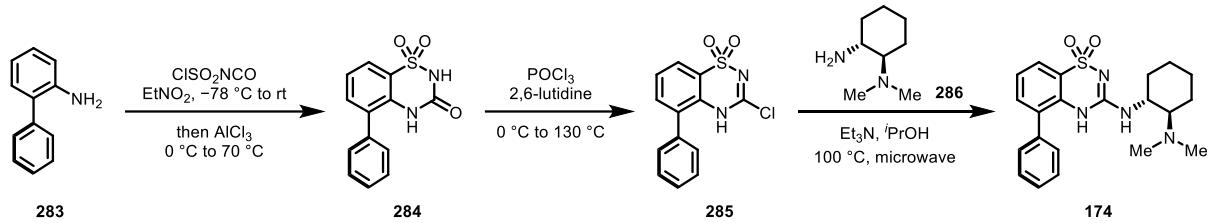


281 **282**

A 50 mL round bottom flask was charged with a stir bar, amine **281** (2.57 g, 8.67 mmol, 1.0 equiv.), and 1,4-dioxane (12 mL). To

the solution was added HCl solution (4 M in 1,4-dioxane, 12 mL, 48 mmol, 5.6 equiv.), and the mixture was stirred at room temperature for 3 hours. Then the suspension was concentrated under reduced pressure, and the residue was washed with Et_2O to afford ammonium salt **282** (2.31 g, 8.58 mmol, 99% yield) as a white solid, which was used for next reactions without further purification.

3-(((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)amino)-5-phenyl-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (174):

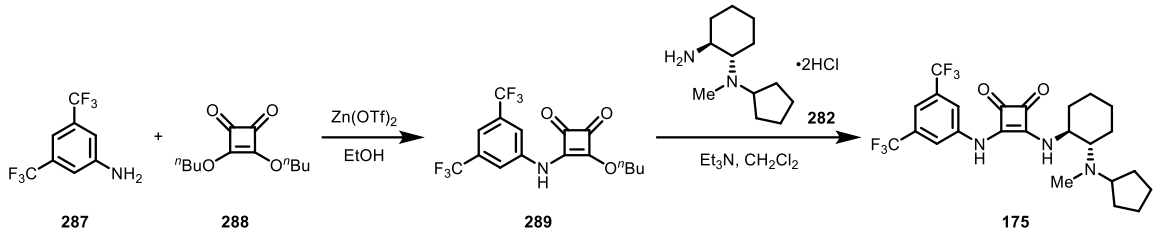


According to **GP2**, a 50 mL round bottom flask was charged with a stir bar and $EtNO_2$ (6.7 mL), which was dehydrated by the treatment with molecular sieve 4Å, under Ar atmosphere, and cooled to −78 °C. To the mixture were added chlorosulfonyl isocyanate (1.04 mL, 12.1 mmol, 1.2 equiv.) and aniline **283** (1.69 g, 9.99 mmol, 1.0 equiv.). After the completion of the addition, the mixture was warmed to room temperature and stirred for 1 hour. Then the mixture was cooled to 0 °C and $AlCl_3$ (1.60 g, 12.0 mmol, 1.2 equiv.) was added to the solution. After stirring at 70 °C overnight, the reaction mixture was cooled to room temperature, and was poured into ice. The precipitate was washed with water and hexane and dried under reduced pressure to afford **284** (2.05 g, 7.47 mmol, 75% yield) as a brown solid.

A 20 mL two-necked round bottom flask equipped with reflux condenser was charged with a stir bar and **284** (1.00 g, 3.65 mmol, 1.0 equiv.) under Ar atmosphere and cooled to 0 °C. To the solid were added $POCl_3$ (5.11 mL, 54.8 mmol, 15 equiv.) and 2,6-lutidine (0.51 mL, 4.4 mmol, 1.2 equiv.). After stirring at 110 °C for 24 hours, the mixture was cooled to room temperature, and was poured into ice. The precipitate was washed with water and hexane and dried under reduced pressure to afford **285** (998 mg, 3.41 mmol, 93% yield) as a brown solid.

According to **GP3**, a 10 mL sealed vial was charged with a stir bar, **285** (146 mg, 0.500 mmol, 1.0 equiv.), diamine **286** (71.1 mg, 0.500 mmol, 1.0 equiv.), Et_3N (139 μL, 0.998 mmol, 2.0 equiv.), and *i*-PrOH (5.0 mL). The mixture was stirred at 100 °C for 3 hours under microwave irradiation and concentrated under reduced pressure. The residue was purified by column chromatography (NH SiO_2, eluted with EtOAc/MeOH = 100:0 → 30:1) to afford catalyst **174** (117 mg, 0.293 mmol, 59% yield) as a yellow solid. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 7.92 (1H, dd, J = 7.7, 1.4 Hz), 7.50 (2H, t, J = 7.7 Hz), 7.44–7.36 (4H, m), 7.31 (1H, t, J = 7.7 Hz), 5.98 (1H, br s), 3.41 (1H, t, J = 8.3 Hz), 2.39–2.30 (1H, m), 2.26 (1H, td, J = 10.9, 2.9 Hz), 2.05 (6H, s), 1.86–1.77 (2H, m), 1.72–1.66 (1H, m), 1.30–1.04 (4H, m) (One NH peak is missing); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 151.6, 136.3, 133.4, 132.9, 129.7, 129.3, 129.1, 128.4, 123.9, 123.8, 123.2, 69.0, 54.5, 40.6, 32.7, 24.9, 24.6, 23.1; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{21}H_{27}N_4O_2S$ 399.1849; Found 399.1838; **IR (ATR):** 3299, 2931, 1614, 1564, 1430, 1263, 1154 cm^{-1}; **Melting Point:** 231.0 °C (decomposition); **Optical Rotation:** $[\alpha]^{26}_D$ −44.6 (c 1.03, $CHCl_3$).

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*S*,2*S*)-2-(cyclopentyl(methyl)amino)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (175):

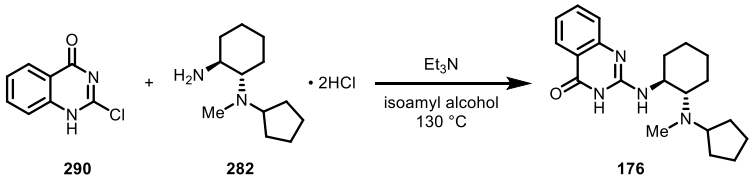


A 50 mL round bottom flask was charged with a stir bar, squarate **288** (1.36 g, 6.01 mmol, 1.2 equiv.), and EtOH (20 mL) under Ar atmosphere. To the solution were added $Zn(OTf)_2$ (90.9 mg, 0.250 mmol, 5 mol%) and aniline **287** (774 μL, 5.00 mmol, 1.0 equiv.), and the mixture was stirred at room temperature for 8 hours. Then the precipitate was collected by filtration and dried under reduced pressure to afford squarate **289** (970 mg, 2.54 mmol, 51% yield) as a yellow solid.

A 20 mL round bottom flask was charged with a stir bar, squarate **289** (73.6 mg, 0.193 mmol, 1.0 equiv.), ammonium salt **282** (51.9 mg, 0.193 mmol, 1.0 equiv.), Et_3N (80.7 μL, 0.579 mmol, 3.0 equiv.), and CH_2Cl_2 (1.9 mL). After stirring at room temperature for 24 hours, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc/Et_3N = 50:50:0 → 0:100:1) to afford catalyst **175** (79.5 mg, 0.158 mmol, 82% yield) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.94 (2H, s), 7.43 (1H, s), 4.03 (1H, d, J = 1.7 Hz), 2.83 (1H, t, J = 6.9 Hz), 2.58 (1H, t, J = 10.0 Hz), 2.21–2.05 (4H, m), 1.88–1.74 (2H, m), 1.74–1.60 (3H, m), 1.57–1.36 (5H, m), 1.35–1.08 (5H, m) (Two NH peaks are missing); **^{13}C-NMR (151 MHz, DMSO-d_6):** δ 184.5, 178.0, 170.0, 161.6, 141.2, 131.3 (q, J = 32.8 Hz), 123.2 (q, J = 273.1 Hz), 117.9, 114.5, 64.2, 62.7, 54.7, 34.2, 33.4, 31.1, 30.2, 24.7, 24.5, 23.4, 23.2, 23.1; **^{19}F-NMR (471 MHz, $CDCl_3$):** δ −63.1; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{24}H_{28}N_3O_2F_6$ 504.2080; Found 504.2077; **IR (ATR):** 3204, 2943, 1794, 1669, 1552, 1445, 1372, 1274, 1127 cm^{-1}; **Melting Point:** 165.7 °C (decomposition); **Optical Rotation:** $[\alpha]^{26}_D$ +108.2 (c 0.21, $CHCl_3$).

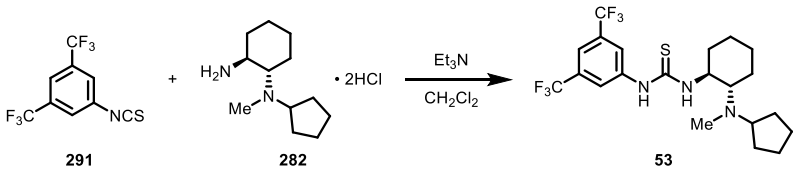
2-(((1*S*,2*S*)-2-(Cyclopentyl(methyl)amino)cyclohexyl)amino)quinazolin-4(3*H*)-one (176):



A 20 mL round bottom flask was charged with a stir bar, quinazoline **290** (99.3 mg, 0.550 mmol, 1.1 equiv.), ammonium salt **282** (135 mg, 0.500 mmol, 1.0 equiv.), Et_3N (244 μL, 1.75 mmol, 3.5 equiv.), and isoamyl alcohol (1.0 mL) under Ar atmosphere. After stirring at 130 °C for 19 hours, the mixture was cooled to room temperature, diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 90:10 → 50:50 → 0:100) to afford catalyst **176** (115 mg, 0.338 mmol, 68% yield) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.11 (1H, dd, J = 8.0, 1.7 Hz), 7.58–7.53 (1H, m), 7.30 (1H, d, J = 8.0 Hz), 7.14 (1H, t, J = 7.2 Hz), 5.98 (1H, br s), 3.49 (1H, t, J = 10.3 Hz), 3.03–2.97 (1H, m), 2.73 (1H, td, J = 10.9, 3.1 Hz), 2.46 (1H, d, J = 9.7 Hz), 2.32 (3H, s), 1.91–1.80 (4H, m), 1.78–1.74 (1H, m), 1.67–1.58 (2H, m), 1.56–1.42 (4H, m), 1.40–1.20 (4H, m) (One NH peak is missing); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 147.9, 138.0, 135.8, 122,6, 116,7, 114.3, 113.2, 109.9, 67.4, 66.7, 58.2, 42.1, 42.0, 40.2, 40.1, 35.4, 35.2, 34.4, 34.3, 34.1; **HRMS (ESI) *m/z*:** $[M+H]^+$ Caclcd for $C_{20}H_{29}N_4O$ 341.2336; Found 341.2342; **IR (ATR):** 3284, 1635, 1541, 1470, 1421, 1341 cm^{-1}; **Melting Point:** 122.3–124.4 °C; **Optical Rotation:** $[\alpha]^{26}_D$ −21.0 (c 0.88, $CHCl_3$).

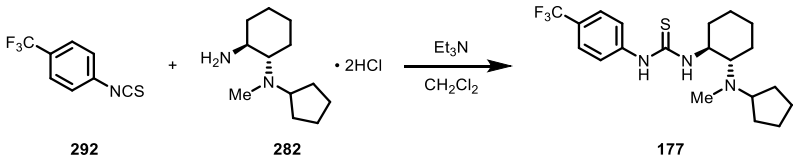
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(cyclopentyl(methyl)amino)cyclohexyl)thiourea (53):



A 100 mL round bottom flask was charged with a stir bar, isothiocyanate **291** (2.09 mL, 11.4 mmol, 1.2 equiv.), ammonium salt **282** (2.56 g, 9.51 mmol, 1.0 equiv.), Et_3N (2.91 mL, 20.9 mmol, 2.2 equiv.), and CH_2Cl_2 (50 mL) under Ar atmosphere. After stirring at room temperature for 21 hours, the mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc/Et_3N = 100:0:0 → 90:10:0 → 50:50:0.5). Fractions containing impurities were purified by column chromatography again to fully remove yellow color. The combined fractions were concentrated under reduced pressure. The residue was dissolved in Et_2O (50 mL), washed with saturated aqueous NH_4Cl (3 x 30 mL) and saturated aqueous $NaHCO_3$ (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Azeotropic drying with hexane three times afforded catalyst **53** (3.71 g, 7.94 mmol, 83% yield) as a white solid.

^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ 10.10 (1H, s), 8.20 (2H, s), 7.88 (1H, d, J = 6.3 Hz), 7.70 (1H, s), 4.10 (1H, s), 2.91–2.84 (1H, m), 2.66 (1H, t, J = 10.0 Hz), 2.23 (1H, s), 2.11 (3H, s), 1.85–1.80 (1H, m), 1.79–1.66 (3H, m), 1.65–1.55 (3H, m), 1.54–1.40 (2H, m), 1.41–1.26 (2H, m), 1.25–1.04 (4H, m); **^{13}C-NMR (151 MHz, DMSO-*d*$_6$):** δ 178.8, 141.7, 130.3 (q, J = 32.8 Hz), 123.3 (q, J = 271.7 Hz), 121.4, 115.7, 63.1, 61.9, 54.9, 33.4, 31.9, 31.4, 29.8, 25.0, 24.6, 23.4, 23.1, 22.8; **^{19}F-NMR (471 MHz, $CDCl_3$):** δ −61.4; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{21}H_{28}N_3F_6S$ 468.1903; Found 468.1883; **Anal.** Calcd for $C_{21}H_{27}N_3F_6S$: C, 53.95; H, 5.82; O, 8.99. Found: C, 53.80; H, 5.80; O, 8.89; **IR (ATR):** 3266, 2943, 1503, 1468, 1381, 1270, 1173, 1128 cm^{-1}; **Melting Point:** 87.5–88.1 °C; **Optical Rotation:** $[\alpha]^{27}_D$ −49.4 (c 0.90, $CHCl_3$).

1-((1*S*,2*S*)-2-(Cyclopentyl(methyl)amino)cyclohexyl)-3-(4-(trifluoromethyl)phenyl)thiourea (177):

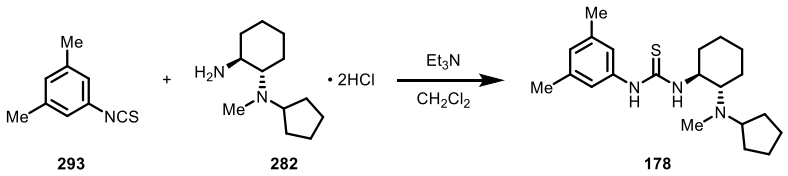


A 20 mL round bottom flask was charged with a stir bar, isothiocyanate **292** (112 mg, 0.550 mmol, 1.1 equiv.), ammonium salt **282** (135 mg, 0.500 mmol, 1.0 equiv.), Et_3N (139 µL, 0.998 mmol, 2.0 equiv.), and CH_2Cl_2 (5.0 mL) under Ar atmosphere. After stirring at room temperature for 3 hours, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc/Et_3N = 100:0:0 → 90:10:0 → 80:20:0 → 50:50:0.5). The fractions were concentrated under reduced pressure, and the residue was dissolved in Et_2O (5 mL), washed with saturated aqueous NH_4Cl (3 x 5 mL) and saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Azeotropic drying with hexane three times afforded catalyst **177** (113 mg, 0.284 mmol, 57% yield) as a white solid.

^{1}H-NMR (500 MHz, CD_3OD): δ 7.64 (2H, d, J = 8.6 Hz), 7.58 (2H, d, J = 8.6 Hz), 4.10 (1H, t, J = 9.2 Hz), 2.95–2.89 (1H, m), 2.72 (1H, td, J = 11.0, 3.1 Hz), 2.49 (1H, d, J = 11.5 Hz), 2.20 (3H, s), 1.92–1.85 (2H, m), 1.84–1.77 (2H, m), 1.72–1.63 (3H, m),

1.63–1.53 (2H, m), 1.40–1.21 (5H, m), 1.20–1.09 (1H, m); **^{13}C-NMR (151 MHz, CD_3OD):** δ 180.9, 143.9, 127.1 (d, J = 4.3 Hz), 126.8 (q, J = 33.2 Hz), 125.7 (q, J = 270.7 Hz), 123.7, 64.8, 64.3, 57.0, 34.0, 33.5, 33.1, 32.0, 26.5, 25.9, 24.8, 24.6, 23.8; **^{19}F-NMR (471 MHz, CD_3OD):** δ −63.5; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{20}H_{29}N_3F_3S$ 400.2029; Found 400.2037; **IR (ATR):** 3206, 2938, 1611, 1518, 1322, 1165, 1119 cm^{-1}; **Melting Point:** 127.3–127.6 °C; **Optical Rotation:** $[\alpha]^{20}_D$ +37.6 (c 0.77, $CHCl_3$).

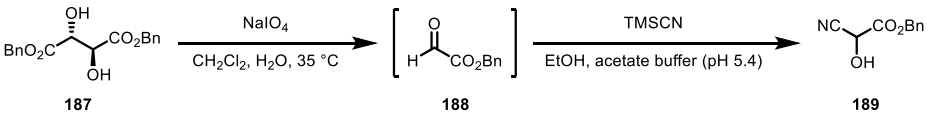
1-((1*S*,2*S*)-2-(Cyclopentyl(methyl)amino)cyclohexyl)-3-(3,5-dimethylphenyl)thiourea (178):



A 20 mL round bottom flask was charged with a stir bar, isothiocyanate **293** (54.9 µL, 0.350 mmol, 1.2 equiv.), ammonium salt **282** (80.8 mg, 0.300 mmol, 1.0 equiv.), Et_3N (125 µL, 8.97 mmol, 3.0 equiv.), and CH_2Cl_2 (3.0 mL) under Ar atmosphere. After stirring at room temperature for 14 hours, the mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL). The aqueous layer was separated and extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc/Et_3N = 100:0:0 → 90:10:0 → 50:50:1). The fractions were concentrated under reduced pressure, and the residue was dissolved in Et_2O (5 mL), washed with saturated aqueous NH_4Cl (3 x 5 mL) and saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Azeotropic drying with hexane three times afforded catalyst **178** (56.9 mg, 0.158 mmol, 53% yield) as a white amorphous solid.

^{1}H-NMR (500 MHz, CD_3OD): δ 6.90 (3H, s), 3.92 (1H, td, J = 10.7, 3.6 Hz), 2.86–2.80 (1H, m), 2.68–2.57 (2H, m), 2.30 (6H, s), 2.13 (3H, s), 1.86–1.72 (4H, m), 1.70–1.64 (1H, m), 1.62–1.49 (4H, m), 1.36–1.17 (4H, m), 1.11–1.02 (2H, m); **^{13}C-NMR (151 MHz, CD_3OD):** δ 180.8, 140.6, 138.6, 128.9, 123.6, 64.8, 64.0, 57.0, 33.9, 33.8, 33.1, 32.2, 26.5, 25.8, 24.6, 24.3, 23.9, 21.4; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{21}H_{34}N_3S$ 360.2468; Found 360.2474; **IR (ATR):** 3185, 2931, 1601, 1521, 1466, 1362, 1225 cm^{-1}; **Melting Point:** 52.0–55.7 °C; **Optical Rotation:** $[\alpha]^{20}_D$ +55.9 (c 0.84, $CHCl_3$).

Benzyl 2-cyano-2-hydroxyacetate (189):



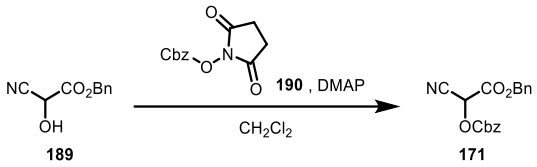
A 200 mL round bottom flask was charged with a stir bar, dibenzyl *L*-tartrate **187** (16.5 g, 49.9 mmol, 1.0 equiv.), CH_2Cl_2 (80 mL), and H_2O (6.0 mL). To the solution was added $NaIO_4$ (16.0 g, 74.8 mmol, 1.5 equiv.), and the suspension was vigorously stirred at 35 °C for 16 hours in the dark. The precipitate was removed by filtration through a Celite pad, and the filtrate was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The residue containing glyoxylate **188** was dissolved in EtOH (150 mL) and acetate buffer solution (pH 5.4, 0.2 M, 150 mL), and stirred at room temperature for 1 hour. To the solution was added TMSCN (18.6 mL, 150 mmol, 1.5 equiv.) dropwise, and the mixture was stirred at same temperature for 4 hours. The mixture was diluted with $CHCl_3$ (200 mL) and saturated aqueous $NaHCO_3$ (100 mL), and the aqueous layer was extracted with $CHCl_3$ (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 80:20) to afford cyanohydrin **189** (14.7 g, 76.9 mmol, 77% yield over

2 steps) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45–7.32 (5H, m), 5.37 (1H, d, J = 12.0 Hz), 5.32 (1H, d, J = 12.0 Hz), 4.95 (1H, s), 3.73 (1H, br s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 165.9, 133.5, 129.2, 128.8, 128.6, 114.8, 69.8, 60.0; **HRMS (ESI) *m/z*:** $[M-H]^-$ Calcd for $C_{10}H_8NO_3$ 190.0499; Found 190.0497; **IR (ATR):** 3423, 1758, 1281, 1215, 1112 cm^{-1}.

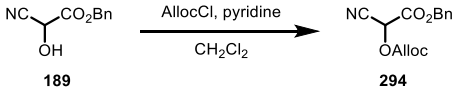
Benzyl 2-(((benzyloxy)carbonyl)oxy)-2-cyanoacetate (171):



A 200 mL round bottom flask was charged with a stir bar, cyanohydrin **189** (5.74 g, 30.0 mmol, 1.0 equiv.), *O*-Cbz-succinimide **190** (11.2 g, 44.9 mmol, 1.5 equiv.), DMAP (733 mg, 6.00 mmol, 20 mol%), and CH_2Cl_2 (100 mL) under Ar atmosphere. After stirring at room temperature for 24 hours, the mixture was washed with aqueous HCl (1 M, 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 85:15) to afford cyanohydrin **171** (8.86 g, 27.2 mmol, 91% yield) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.35 (10H, m), 5.72 (1H, s), 5.33 (1H, d, J = 12.0 Hz), 5.30 (1H, d, J = 12.0 Hz), 5.25 (2H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 160.9, 152.9, 133.8, 133.6, 129.1, 129.0, 128.8, 128.7, 128.51, 128.48, 111.8, 71.6, 69.5, 62.1; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{18}H_{15}NO_5Na$ 348.0842; Found 348.0831; **IR (ATR):** 3036, 2952, 1758, 1249, 1217 cm^{-1}; **Melting Point:** 32.1–33.8 °C.

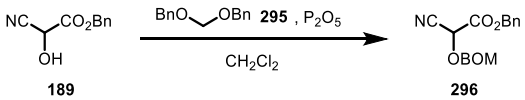
Benzyl 2-(((allyloxy)carbonyl)oxy)-2-cyanoacetate (294):



A 50 mL round bottom flask was charged with a stir bar, cyanohydrin **189** (574 mg, 3.00 mmol, 1.0 equiv.), and CH_2Cl_2 (15 mL) under Ar atmosphere, and was cooled to 0 °C. To the mixture was added pyridine (728 μL, 9.00 mmol, 3.0 equiv.) and AllocCl (384 μL, 3.60 mmol, 1.2 equiv.). After stirring at same temperature for 3.5 hours, the mixture was quenched with water (10 mL). The aqueous layer was separated and extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) to afford cyanohydrin **294** (633 mg, 2.30 mmol, 77% yield) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.36 (5H, m), 5.96–5.88 (1H, m), 5.72 (1H, s), 5.41 (1H, d, J = 17.2 Hz), 5.35–5.30 (3H, m), 4.72 (2H, d, J = 5.7 Hz); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 160.9, 152.7, 133.6, 130.2, 129.1, 128.8, 128.6, 120.2, 111.8, 70.3, 69.6, 62.0; **HRMS (FAB) *m/z*:** [M+H]+ Calcd for $C_{14}H_{14}NO_5$ 276.0872; Found 276.0870; **IR (ATR):** 2929, 1764, 1254 cm^{-1}.

Benzyl 2-((benzyloxy)methoxy)-2-cyanoacetate (296):

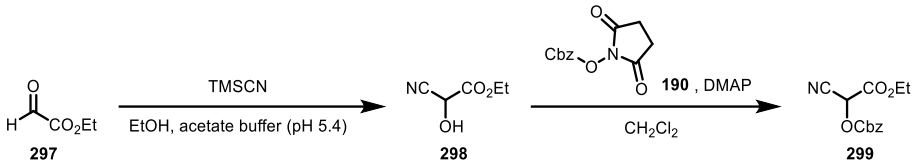


A 50 mL round bottom flask was charged with a stir bar, cyanohydrin **189** (140 mg, 0.732 mmol, 1.0 equiv.), dibenzylacetal **295** (835 mg, 3.66 mmol, 5.0 equiv.), and CH_2Cl_2 (7.3 mL) under Ar atmosphere. To the solution was added P_2O_5 (519.5 mg, 3.66 mmol,

5.0 equiv.). After stirring at room temperature for 6 hours, the mixture was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 95:5 → 90:10) to afford cyanohydrin **296** (186 mg, 0.596 mmol, 81% yield) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39–7.30 (10H, m), 5.32–5.26 (2H, m), 5.07 (1H, s), 4.97 (1H, d, J = 7.4 Hz), 4.94 (1H, d, J = 6.9 Hz), 4.69 (1H, d, J = 11.5 Hz), 4.66 (1H, d, J = 11.5 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.1, 136.3, 134.0, 129.0, 128.8, 128.6, 128.5, 128.2, 128.1, 113.7, 94.0, 70.8, 68.9, 63.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{18}H_{17}NO_4Na$ 334.1050; Found 334.1051; **IR (ATR):** 3034, 2898, 1762, 1212, 1060 cm^{-1}.

Ethyl 2-(((benzyloxy)carbonyl)oxy)-2-cyanoacetate (299):

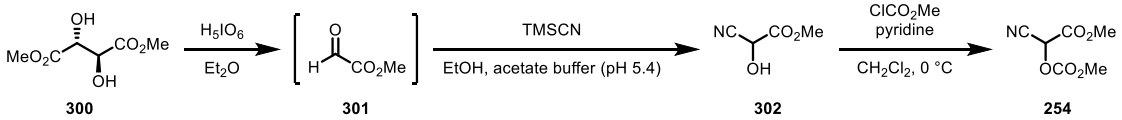


A 200 mL round bottom flask was charged with a stir bar, glyoxylate **297** (polymer form, 47% in toluene, 4.21 mL, 20.0 mmol, 1.0 equiv.), EtOH (30 mL) and acetate buffer solution (pH 5.4, 0.2 M, 30 mL), and stirred at room temperature for 2 hours. To the mixture was added TMSCN (3.72 mL, 30.0 mmol, 1.5 equiv.) dropwise. After stirring at room temperature for 5 hours, the mixture was diluted with $CHCl_3$ (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was separated and extracted with $CHCl_3$ (4 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10 → 75:25) to afford cyanohydrin **298** (1.95 g, 15.1 mmol, 76% yield) as a colorless oil.

A 200 mL round bottom flask was charged with a stir bar, cyanohydrin **298** (1.95 g, 15.1 mmol, 1.0 equiv.), *O*-Cbz-succinimide **190** (5.66 g, 22.7 mmol, 1.5 equiv.), DMAP (185 mg, 1.51 mmol, 10 mol%), and CH_2Cl_2 (76 mL) under Ar atmosphere. After stirring at room temperature for 24 hours, the mixture was washed with aqueous HCl (1 M, 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) to afford cyanohydrin **299** (2.77 g, 10.5 mmol, 70% yield) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50–7.25 (5H, m), 5.69 (1H, s), 5.27 (2H, s), 4.37 (2H, q, J = 7.2 Hz), 1.34 (3H, t, J = 7.2 Hz); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.0, 152.9, 133.8, 129.1, 128.7, 128.5, 111.9, 71.6, 64.3, 62.1, 13.8; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{13}H_{13}NO_5Na$ 286.0686; Found 286.0684; **IR (ATR):** 2984, 1761, 1457, 1382, 1259 cm^{-1}.

Methyl 2-cyano-2-((methoxycarbonyl)oxy)acetate (254):



A 20 mL round bottom flask was charged with a stir bar, dimethyl *L*-tartrate **300** (891 mg, 5.00 mmol, 1.0 equiv.), H_5IO_4 (1.25 g, 5.48 mmol, 1.1 equiv.), and Et_2O (10 mL), After stirring at room temperature for 3 hours, the mixture was filtered through a Celite pad. The filtrate was concentrated at 30 °C under 300 Torr to remove only Et_2O to afford the crude material of **301**.

A 200 mL round bottom flask was charged with a stir bar, glyoxylate **301**, EtOH (50 mL), and acetate buffer solution (pH 5.4, 0.2 M, 50 mL). After stirring at room temperature for 1 hour, to the mixture was added TMSCN (1.88 mL, 15.0 mmol, 1.5 equiv.).

After stirring at same temperature for 7 hours, the mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 75:25) to afford cyanohydrin **302** (414 mg, 3.60 mmol, 36% yield over 2 steps) as a colorless oil.

A 100 mL round bottom flask was charged with a stir bar, cyanohydrin **302** (414 mg, 3.60 mmol, 1.0 equiv.), and CH_2Cl_2 (36 mL) under Ar atmosphere, and was cooled to 0 °C. To the solution was added pyridine (870 μL, 10.8 mmol, 3.0 equiv.) and $ClCO_2Me$ (415 μL, 5.40 mmol, 1.5 equiv.). After stirring at same temperature for 12 hours, the mixture was washed with aqueous HCl (1 M, 15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 80:20) to afford cyanohydrin **254** (459 mg, 2.65 mmol, 74% yield) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, s), 3.94 (3H, s), 3.93 (3H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 161.5, 153.5, 111.8, 61.9, 56.5, 54.5; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_6H_7NO_5Na$ 196.0216; Found 196.0216; **IR (ATR):** 2961, 1764, 1444, 1265 cm^{-1}.

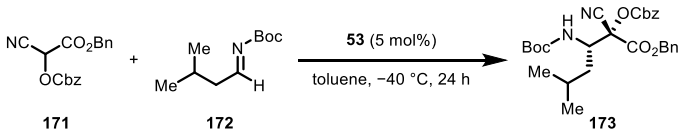
General Procedure for Conditions A in Table 5 (GP5):

A 10 mL test tube was charged with a stir bar, cyanohydrin (1.0 equiv.) and toluene (0.50 mL/mmol) under Ar atmosphere. To the solution was added *N*-Boc imine (1.5 equiv.) in toluene (0.50 mL/mmol) and the mixture was cooled to −40 °C. To the solution was added catalyst **53** (5 mol%) and the mixture was stirred for 24 hours. The solution was filtered through a short silica gel plug, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the Mannich adduct. The values of ee and dr of the products were determined by chiral HPLC analysis. A racemic sample was prepared by the Mannich-type addition using ***rac*-114** as a catalyst.

General Procedure for Conditions B in Table 5 (GP6):

A 10 mL test tube equipped with a Teflon-coated screw cap was charged with a stir bar, cyanohydrin (1.0 equiv.), α-amido sulfone (1.5 equiv.) and toluene (1.0 mL/mmol), and was cooled to 0 °C. To the solution was added catalyst **53** (5 mol%) and Cs_2CO_3 (4.5 equiv.) dissolved in H_2O (1.0 mL/mmol). After stirring at 0 °C for appropriate time, the aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the Mannich adduct. The values of ee and dr of the products were determined by chiral HPLC analysis. A racemic sample was prepared by the Mannich-type addition using ***rac*-114** as a catalyst.

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-methylhexanoate (173):



According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **172** (27.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **173** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm,

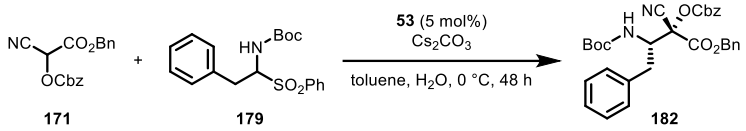
$t_{R(ent\text{-}173')}$ = 12.5 min, $t_{R(ent\text{-}173)}$ = 26.2 min, $t_{R(173')}$ = 30.7 min, $t_{R(173)}$ = 49.3 min.

Yield: 49.1 mg, 0.0962 mmol, 96% yield

Ratio of Stereoisomers: 173:***ent*-**173**: **173′**:***ent*-**173′** = 96.9:1.1:1.3:0.7, dr = 49:1, **173**: 98% ee, **173′**: 33% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.31 (10H, m), 5.27 (1H, d, J = 12.0 Hz), 5.22–5.14 (3H, m), 4.67 (1H, d, J = 10.3 Hz), 4.39 (0.9H, td, J = 10.7, 2.9 Hz), 4.28 (0.1H, t, J = 10.9 Hz), 1.71–1.62 (1H, m), 1.52–1.44 (2H, m), 1.41 (9H, s), 0.89 (2.7H, d, J = 6.3 Hz), 0.84 (0.3H, d, J = 6.3 Hz), 0.82 (2.7H, d, J = 6.3 Hz), 0.75 (0.3H, d, J = 5.7 Hz) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 163.0, 154.8, 152.5, 134.1, 133.7, 129.0, 128.71, 128.69, 128.66, 128.6, 128.5, 113.8, 80.6, 78.2, 71.4, 69.3, 53.4, 38.2, 28.1, 24.4, 23.4, 20.9; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{28}H_{35}N_2O_7$ 511.2439; Found 511.2434; **IR (ATR):** 3381, 2963, 2255, 1761, 1712, 1502, 1455, 1369, 1237, 1160 cm^{-1}; **Melting Point:** 41.2–43.5 °C; **Optical Rotation:** $[\alpha]^{19}_D$ −23.3 (c 1.32, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-4-phenylbutanoate (182):



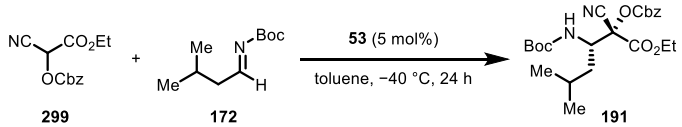
According to **GP6**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with α-amido sulfone **179** (54.2 mg, 0.150 mmol, 1.5 equiv.), catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%), and Cs_2CO_3 (146.6 mg, 0.450 mmol, 4.5 equiv.) in toluene (1.0 mL) and H_2O (1.0 mL) at 0 °C for 48 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **182** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}182')}$ = 27.4 min, $t_{R(ent\text{-}182)}$ = 33.5 min, $t_{R(182')}$ = 57.0 min, $t_{R(182)}$ = 65.7 min.

Yield: 41.6 mg, 0.0764 mmol, 76% yield

Ratio of Stereoisomers: 182:***ent*-**182**:**182′**:***ent*-**182′** = 92.6:3.2:2.2:1.9, dr = 23:1, **182**: 93% ee, **182′**: 8% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50–7.32 (10H, m), 7.32–7.15 (3H, m), 7.13–6.95 (2H, m), 5.25 (1H, d, J = 12.3 Hz), 5.21 (2H, s), 5.18 (1H, d, J = 12.0 Hz), 4.68 (1H, d, J = 10.3 Hz), 4.61 (1H, td, J = 10.6, 3.4 Hz), 3.16 (0.9H, dd, J = 14.2, 3.3 Hz), 2.96 (0.1H, d, J = 12.6 Hz), 2.69 (0.9H, dd, J = 14.3, 11.2 Hz), 2.58 (0.1H, d, J = 10.6 Hz), 1.25 (8H, s), 1.15 (1H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 162.8, 154.5, 152,4, 135,3, 134.0, 133.7, 129.13, 129.07, 128.8, 128.72, 128.67, 128.6, 128.5, 127.0, 113.6, 80.6, 77.9, 71.6, 69.5, 55.6, 35.9, 28.0 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{31}H_{33}N_2O_7$ 545.2282; Found 545.2263; **IR (ATR):** 3385, 2976, 2922, 1759, 1719, 1514, 1455, 1378, 1257, 1163, 1093 cm^{-1}; **Melting Point:** 135.9–136.5 °C; **Optical Rotation:** $[\alpha]^{25}_D$ −12.0 (c 0.88, $CHCl_3$).

Ethyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-methylhexanoate (191):



According to **GP5**, cyanohydrin **299** (263 mg, 1.00 mmol, 1.0 equiv.) reacted with *N*-Boc imine **172** (278 mg, 1.50 mmol, 1.5 equiv.) and catalyst **53** (23.4 mg, 0.0501 mmol, 5 mol%) in toluene (5.0 + 5.0 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **191** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% ethanol/hexane, λ = 220 nm, $t_{R(ent\text{-}191')}$ = 8.8 min, $t_{R(191')}$ =

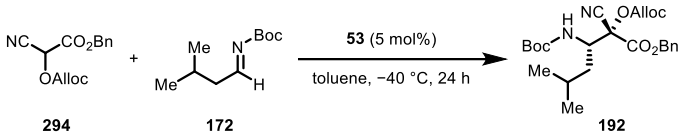
11.6 min, $t_{R(ent\text{-}191)}$ = 16.6 min, $t_{R(191)}$ = 22.1 min.

Yield: 454 mg, 1.01 mmol, quant.

Ratio of Stereoisomers: 191:***ent*-**191**:**191′**:***ent*-**191′** = 95.9:0.8:2.5:0.7, dr = 30:1, **191**: 98% ee, **191′**: 54% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.37 (5H, m), 5.26 (1H, d, J = 12.0 Hz), 5.22 (1H, d, J = 12.0 Hz), 4.63 (1H, d, J = 10.3 Hz), 4.37 (1H, td, J = 10.2, 4.4 Hz), 4.30–4.23 (2H, m), 1.75–1.67 (1H, m), 1.55–1.52 (2H, m), 1.43 (9H, s), 1.27 (3H, t, J = 7.2 Hz), 0.95 (3H, d, J = 6.3 Hz), 0.91 (3H, d, J = 6.9 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.1, 154.7, 152.6, 133.8, 129.1, 128.7, 113.9, 80.5, 78.2, 71.4, 64.0, 53.2, 38.5, 28.1, 24.5, 23.4, 21.0, 13.8 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI)** ***m/z*:** $[M+Na]^+$ Calcd for $C_{23}H_{32}N_2O_7Na$ 471.2102; Found 471.2106; **IR (ATR):** 3376, 2964, 1763, 1714, 1515, 1456, 1370, 1249, 1164 cm^{-1}; **Melting Point:** 95.5–96.2 °C; **Optical Rotation:** $[\alpha]^{17}_D$ −27.0 (c 0.86, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((allyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-methylhexanoate (192):



294 **172** **192**

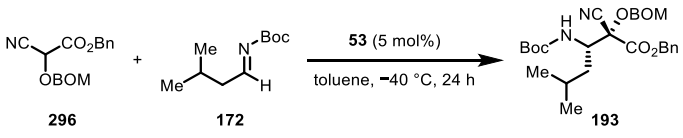
According to **GP5**, cyanohydrin **294** (27.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **172** (27.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **192** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}192')}$ = 10.1 min, $t_{R(ent\text{-}192)}$ = 20.9 min, $t_{R(192')}$ = 24.8 min, $t_{R(192)}$ = 39.6 min.

Yield: 45.8 mg, 0.0995 mmol, 100% yield

Ratio of Stereoisomers: 192:***ent*-**192**:**192′**:***ent*-**192′** = 95.8:1.4:1.9:0.9, dr = 35:1, **192**: 97% ee, **192′**: 36% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45–7.30 (5H, m), 5.93–5.80 (1H, m), 5.37 (1H, d, J = 17.2 Hz), 5.31 (1H, d, J = 12.0 Hz), 5.30 (1H, d, J = 10.3 Hz), 5.19 (1H, d, J = 12.0 Hz), 4.75–4.59 (3H, m), 4.39 (0.9H, td, J = 10.6, 3.2 Hz), 4.31 (0.1H, t, J = 12.9 Hz), 1.73–1.63 (1H, m), 1.52–1.44 (2H, m), 1.42 (9H, s), 0.91 (2.7H, d, J = 6.3 Hz), 0.84 (3H, d, J = 6.3 Hz), 0.76 (0.3H, d, J = 5.7 Hz) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.0, 154.8, 152.3, 134.1, 130.2, 128.7, 128.6, 128.5, 120.4, 113.8, 80.6, 78.1, 70.2, 69.3, 53.4, 38.3, 28.1, 24.5, 23.4, 20.9; **HRMS (ESI)** ***m/z*:** $[M+H]^+$ Calcd for $C_{24}H_{33}N_2O_7$ 461.2282; Found 461.2271; **IR (ATR):** 3362, 2961, 1756, 1713, 1527, 1456, 1371, 1255, 1163 cm^{-1}; **Melting Point:** 91.7–93.0 °C; **Optical Rotation:** $[\alpha]^{25}_D$ −26.4 (c 1.12, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-((benzyloxy)methoxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-methylhexanoate (193):



296 **172** **193**

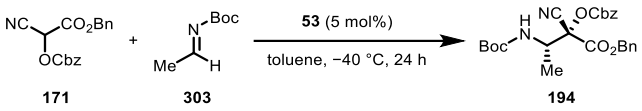
According to **GP5**, cyanohydrin **296** (31.1 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **172** (27.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, hexane/EtOAc = 100:0 → 90:10) afforded **193** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 1% ethanol/hexane, λ = 220 nm, $t_{R(ent\text{-}193')}$ = 8.2 min, $t_{R(ent\text{-}193)}$ = 11.1 min, $t_{R(193')}$ = 13.1 min, $t_{R(193)}$ = 30.0 min.

Yield: 40.2 mg, 0.0809 mmol, 81% yield

Ratio of Stereoisomers: 193:***ent*-**193**:**193′**:***ent*-**193′** = 94.3:2.9:1.7:1.1, dr = 34:1, **193**: 94% ee, **193′**: 21% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.25 (10H, m), 5.16 (1H, d, J = 12.3 Hz), 5.11 (1H, d, J = 7.2 Hz), 5.06 (1H, d, J = 12.3 Hz), 4.93 (1H, d, J = 7.2 Hz), 4.65 (1H, d, J = 10.0 Hz), 4.58 (2H, s), 4.39 (0.9H, td, J = 10.9, 2.6 Hz), 4.27 (0.1H, t, J = 9.6 Hz), 1.72–1.62 (1H, m), 1.50-1.34 (11H, m), 0.91 (3H, d, J = 6.6 Hz), 0.88–0.83 (3H, m) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 165.5, 154.9, 136.8, 134.3, 128.7, 128.61, 128.59, 128.4, 127.9, 127.8, 114.6, 93.5, 80.20, 80.16, 71.2, 68.9, 54.4, 38.7, 28.2, 24.5, 23.5, 21.2; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{36}N_2O_6Na$ 519.2466; Found 519.2470; **IR (ATR):** 2963, 1753, 1712, 1505 cm^{-1}; **Optical Rotation:** $[\alpha]^{13}_D$ −8.6 (c 1.14, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyanobutanoate (194):



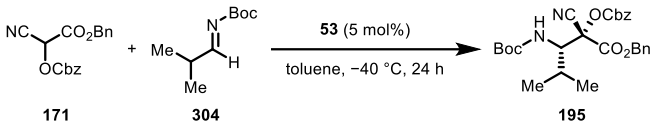
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **303** (21.5 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **194** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}194')}$ = 11.4 min, $t_{R(194')}$ = 13.6 min, $t_{R(ent\text{-}194)}$ = 17.1 min, $t_{R(194)}$ = 26.1 min.

Yield: 47.8 mg, 0.102 mmol, quant.

Ratio of Stereoisomers: 194:***ent*-**194**:**194′**:***ent*-**194′** = 91.3:1.6:6.2:0.9, dr = 13:1, **194**: 97% ee, **194′**: 74% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.58–7.15 (10H, m), 5.24 (1H, d, J = 12.0 Hz), 5.20 (1H, d, J = 12.0 Hz), 5.17 (2H, s), 4.81 (1H, d, J = 9.7 Hz), 4.56 (0.1H, dt, J = 16.6, 6.7 Hz), 4.45 (0.9H, dt, J = 16.0, 6.9 Hz), 1.41 (9H, s), 1.33 (3H, d, J = 6.9 Hz) (Peaks of rotamer are observed in the ratio of 9:1); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 163.0, 154.4, 152.5, 134.1, 133.7, 129.0, 128.7, 128.6, 128.3, 128.2, 113.6, 80.7, 78.4, 71.5, 69.3, 50.8, 28.1, 16.2 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{25}H_{28}N_2O_7Na$ 491.1789; Found 491.1771; **IR (ATR):** 3389, 2980, 1763, 1713, 1509, 1455, 1377, 1248, 1161 cm^{-1}; **Optical Rotation:** $[\alpha]^{23}_D$ −12.3 (c 1.51, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-4-methylpentanoate (195):



According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **304** (25.7 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **195** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(195')}$ = 10.6 min, $t_{R(ent\text{-}195')}$ = 15.0 min, $t_{R(ent\text{-}195)}$ = 25.0 min, $t_{R(195)}$ = 29.6 min.

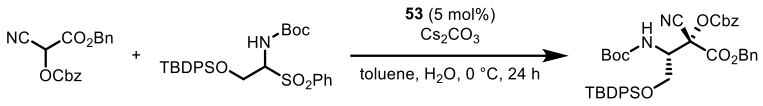
Yield: 50.6 mg, 0.102 mmol, quant.

Ratio of Stereoisomers: 195:***ent*-**195**:**195′**:***ent*-**195′** = 97.4:0.6:1.1:0.7, dr = 53:1, **195**: 99% ee, **195′**: 22% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41–7.32 (10H, m), 5.29 (0.2H, s), 5.24 (1.8H, s), 5.20 (0.2H, s), 5.18 (1.8H, s), 4.87 (0.9H, d, J = 10.9 Hz), 4.61 (0.1H, d, J = 12.0 Hz), 4.30 (0.9H, dd, J = 10.9, 3.4 Hz), 4.17 (0.1H, d, J = 10.3 Hz), 2.13–2.07 (0.9H, m), 1.89

(0.1H, s), 1.46 (0.9H, s), 1.42 (8.1H, s), 0.98 (2.7H, d, J = 6.9 Hz), 0.92 (2.7H, d, J = 6.9 Hz), 0.90–0.87 (0.6H, m) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.3, 155.2, 152.5, 134.0, 133.7, 129.1, 128.73, 128.71, 128.67, 128.6, 128.3, 114.1, 80.7, 71.4, 69.4, 58.2, 28.5, 28.1, 21.1, 16.2 (One aliphatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{32}N_2O_7Na$ 519.2102; Found 519.2107; **IR (ATR):** 3377, 2971, 1752, 1710, 1519, 1461, 1377, 1253, 1161 cm^{-1}; **Melting Point:** 79.8–80.7 °C; **Optical Rotation:** $[\alpha]^{21}_D$ −12.1 (c 0.93, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldiphenylsilyl)oxy)-2-cyanobutanoate (196):



171 **305** **196**

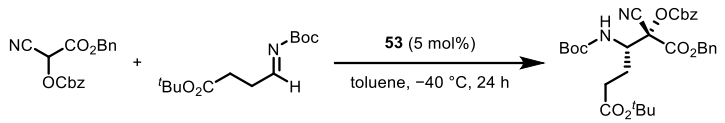
According to **GP6**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with α-amido sulfone **305** (81.0 mg, 0.150 mmol, 1.5 equiv.), catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%), and Cs_2CO_3 (147 mg, 0.450 mmol, 4.5 equiv.) in toluene (1.0 mL) and H_2O (1.0 mL) at 0 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **196** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(\textit{ent}\text{-}196')}$ = 6.7 min, $t_{R(196')}$ = 8.4 min, $t_{R(\textit{ent}\text{-}196)}$ = 8.9 min, $t_{R(196)}$ = 11.3 min.

Yield: 67.8 mg, 0.0938 mmol, 94% yield

Ratio of Stereoisomers: 196:***ent*-196**:**196′**:***ent*-196′** = 88.4:4.9:3.9:2.8, dr = 14:1, **196**: 90% ee, **196′**: 17% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.63 (4H, d, J = 6.9 Hz), 7.43–7.30 (16H, m), 5.27 (1H, d, J = 12.6 Hz), 5.21–5.15 (3H, m), 5.11 (1H, d, J = 12.0 Hz), 4.40–4.37 (1H, m), 4.00 (1H, dd, J = 10.9, 4.0 Hz), 3.78 (1H, dd, J = 11.2, 3.7 Hz), 1.41 (9H, s), 1.07 (9H, s); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.2, 154.8, 152.3, 135.6, 134.1, 133.8, 132.3, 132.2, 129.99, 129.96, 129.0, 128.7, 128.64, 128.55, 128.5, 128.0, 127.9, 127.8, 113.6, 80.7, 75.4, 71.4, 69.4, 61.6, 55.3, 28.1, 26.7, 19.2 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{41}H_{46}N_2O_8SiNa$ 745.2916; Found 745.2923; **IR (ATR):** 3438, 2940, 1765, 1719, 1496, 1375, 1250, 1110 cm^{-1}; **Optical Rotation:** $[\alpha]^{23}_D$ +1.4 (c 1.89, $CHCl_3$).

1-Benzyl 6-(*tert*-butyl) (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyanohexanedioate (197):



171 **306** **197**

According to **GP5**, cyanohydrin **171** (325 mg, 1.00 mmol, 1.0 equiv.) reacted with *N*-Boc imine **306** (386 mg, 1.50 mmol, 1.5 equiv.) and catalyst **53** (23.4 mg, 0.0501 mmol, 5 mol%) in toluene (5.0 + 5.0 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **197** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IE, 1.0 mL/min, 5% ethanol/hexane, λ = 220 nm, $t_{R(\textit{ent}\text{-}197')}$ = 14.0 min, $t_{R(197')}$ = 15.1 min, $t_{R(\textit{ent}\text{-}197)}$ = 16.2 min, $t_{R(197)}$ = 18.9 min.

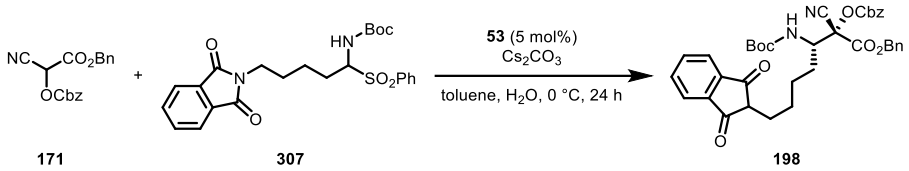
Yield: 594 mg, 1.02 mmol, quant.

Ratio of Stereoisomers: 197:***ent*-197**:**197′**:***ent*-197′** = 92.0:4.2:3.0:0.8, dr = 25:1, **197**: 91% ee, **197′**: 57% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.30 (10H, m), 5.31–5.26 (0.2H, m), 5.24 (1H, d, J = 12.6 Hz), 5.20 (1H, d, J = 12.0 Hz), 5.17 (1.8H, s), 4.89 (1H, d, J = 10.3 Hz), 4.48–4.40 (0.1H, m), 4.33 (0.9H, dt, J = 15.1, 5.9 Hz), 2.31 (2H, t, J = 7.4 Hz), 2.11–2.05

(0.9H, m), 1.98–1.91 (0.1H, m), 1.89–1.81 (1H, m), 1.43 (9H, s), 1.41 (9H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 171.7, 162.8, 154.8, 152.4, 134.0, 133.7, 129.0, 128.7, 128.60, 128.57, 128.3, 113.5, 81.0, 80.7, 77.9, 71.5, 69.4, 54.7, 31.4, 28.1, 28.0, 24.4 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{31}H_{38}N_2O_9Na$ 605.2470; Found 605.2476; **IR (ATR):** 3270, 2979, 1758, 1706, 1540, 1455, 1375, 1244, 1157 cm^{-1}; **Melting Point:** 118.1–119.3 °C; **Optical Rotation:** $[\alpha]^{21}_D$ −7.9 (c 0.83, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-7-(1,3-dioxoisoindolin-2-yl)heptanoate (198):



171 307 198

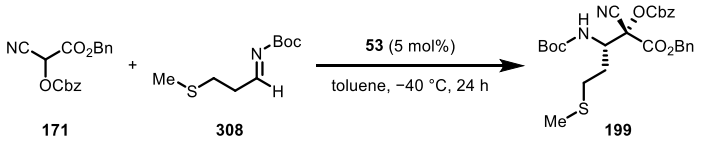
According to **GP6**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with α-amido sulfone **307** (70.9 mg, 0.150 mmol, 1.5 equiv.), catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%), and Cs_2CO_3 (147 mg, 0.450 mmol, 4.5 equiv.) in toluene (1.0 mL) and H_2O (1.0 mL) at 0 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10 → 80:20) afforded **198** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 10% 2-propanol/hexane, λ = 220 nm, $t_{R(\textit{ent}\text{-}198')}$ = 27.1 min, $t_{R(\textit{ent}\text{-}198)}$ = 29.1 min, $t_{R(198')}$ = 32.7 min, $t_{R(198)}$ = 39.1 min.

Yield: 58.6 mg, 0.0894 mmol, 89% yield

Ratio of Stereoisomers: 198:***ent*-198**:**198′**:***ent*-198′** = 87.5:4.7:5.3:2.4, dr = 12:1, **198**: 90% ee, **198′**: 38% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.83 (2H, dd, *J* = 5.4, 3.2 Hz), 7.71 (2H, dd, *J* = 5.4, 3.2 Hz), 7.43–7.31 (10H, m), 5.26 (1H, d, *J* = 12.0 Hz), 5.21 (1H, d, *J* = 12.0 Hz), 5.17 (2H, s), 4.80 (1H, d, *J* = 9.7 Hz), 4.27 (1H, td, *J* = 10.9, 2.1 Hz), 3.69–3.60 (2H, m), 1.79–1.64 (2H, m), 1.61–1.50 (2H, m), 1.48–1.25 (11H, m); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 168.4, 162.9, 154.9, 152.4, 134.1, 133.9, 133.7, 132.0, 129.0, 128.7, 128.63, 128.61, 128.4, 123.2, 113.6, 80.6, 78.0, 71.4, 69.3, 54.9, 37.1, 28.8, 28.1, 27.8, 22.5 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{36}H_{37}N_3O_9Na$ 678.2422; Found 678.2419; **IR (ATR):** 3357, 2938, 1762, 1706, 1510, 1449, 1390, 1371, 1239, 1161 cm^{-1}; **Melting Point:** 47.6–49.5 °C; **Optical Rotation:** $[\alpha]^{21}_D$ −11.8 (c 0.89, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-(methylthio)pentanoate (199):



171 308 199

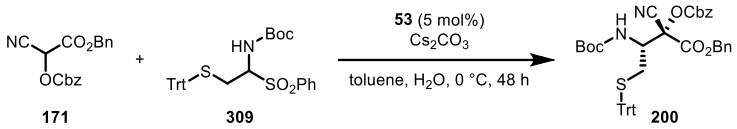
According to **GP5**, cyanohydrin **171** (325 mg, 1.00 mmol, 1.0 equiv.) reacted with *N*-Boc imine **308** (305 mg, 1.50 mmol, 1.5 equiv.) and catalyst **53** (23.4 mg, 0.0501 mmol, 5 mol%) in toluene (5.0 + 5.0 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **199** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(\textit{ent}\text{-}199')}$ = 16.2 min, $t_{R(\textit{ent}\text{-}199)}$ = 19.6 min, $t_{R(199')}$ = 23.3 min, $t_{R(199)}$ = 32.5 min.

Yield: 323.2 mg, 0.611 mmol, 61% yield

Ratio of Stereoisomers: 199:***ent*-199**:**199′**:***ent*-199′** = 96.5:1.5:1.6:0.4, dr = 49:1, **199**: 97% ee, **1919**: 59% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.32 (10H, m), 5.31 (0.2H, d, J = 12.3 Hz), 5.25 (1H, d, J = 12.0 Hz), 5.21 (1H, d, J = 12.0 Hz), 5.18 (1.8H, s), 4.75 (1H, d, J = 10.3 Hz), 4.47 (0.9H, td, J = 10.7, 2.5 Hz), 4.40 (0.1H, s), 2.62–2.56 (1H, m), 2.47–2.40 (1H, m), 2.11–1.99 (4H, m), 1.80–1.70 (1H, m), 1.46 (0.9H, s), 1.42 (8.1H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 162.8, 154.8, 152.4, 134.0, 133.6, 129.1, 128.8, 128.68, 128.66, 128.4, 113.6, 81.0, 77.9, 71.6, 69.4, 54.1, 29.9, 29.7, 28.1, 15.6 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{32}N_2O_7NaS$ 551.1822; Found 551.1829; **IR (ATR):** 3371, 2978, 1762, 1712, 1510, 1450, 1375, 1248, 1164 cm^{-1}; **Melting Point:** 104.3–105. 3 °C; **Optical Rotation:** $[\alpha]^{22}_D$ −26.2 (c 0.78, $CHCl_3$).

Benzyl (2*R*,3*R*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-4-(tritylthio)butanoate (200):



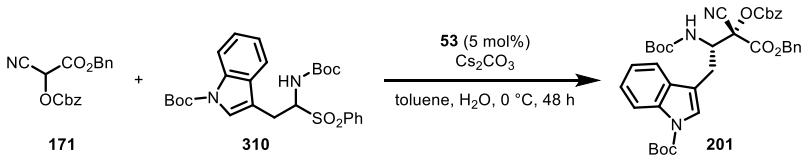
According to **GP6**, cyanohydrin **171** (12.2 mg, 0.0375 mmol, 1.0 equiv.) reacted with α-amido sulfone **309** (31.4 mg, 0.0561 mmol, 1.5 equiv.), catalyst **53** (0.87 mg, 0.0019 mmol, 5 mol%), and Cs_2CO_3 (54.8 mg, 0.168 mmol, 4.5 equiv.) in toluene (0.38 mL) and H_2O (0.38 mL) at 0 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 94:6 → 90:10) to afforded **200** as a white solid. The values of ee and dr of the products were estimated by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 254 nm, $t_{R(ent\text{-}200')}$ = 15.4 min, $t_{R(200')}$ = 28.4 min, $t_{R(ent\text{-}200)}$ = 34.9 min, $t_{R(200)}$ = 50.5 min.

Yield: 23.6 mg, 0.0318 mmol, 85% yield

Ratio of Stereoisomers: 200:***ent*-200**:**200′**:***ent*-200′** = 84.9:3.9:8.1:3.2, dr = 7.9:1, **200**: 91% ee, **200′**: 43% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41–7.33 (13H, m), 7.32–7.24 (9H, m), 7.21–7.15 (3H, m), 5.16–5.11 (2H, m), 5.08 (1H, d, J = 12.0 Hz), 5.05 (1H, d, J = 12.6 Hz), 4.47 (0.1H, d, J = 10.3 Hz), 4.29 (0.9H, d, J = 9.7 Hz), 4.05 (1H, td, J = 10.5, 3.1 Hz), 2.72 (0.9H, dd, J = 13.5, 3.2 Hz), 2.62 (0.1H, d, J = 10.3 Hz), 2.44 (0.9H, dd, J = 13.2, 10.9 Hz), 2.36 (0.1H, t, J = 7.2 Hz), 1.40 (8.1H, s), 1.38 (0.9H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 162.4, 154.5, 152.2, 144.1, 134.1, 133.7, 130.0, 129.5, 129.1, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.1, 126.9, 113.2, 80.7, 77.5, 71.4, 69.3, 68.0, 54.4, 31.6, 28.1 (Three aromatic carbon peaks of rotamers are observed); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{44}H_{42}N_2O_7NaS$ 765.2605; Found 765.2591; **IR (ATR):** 3425, 3021, 2926, 1764, 1723, 1497, 1451, 1375, 1221, 1163 cm^{-1}; **Melting Point:** 73.0–76.4 °C; **Optical Rotation:** $[\alpha]^{22}_D$ −4.6 (c 1.04, $CHCl_3$).

***tert*-Butyl 3-((2*S*,3*R*)-4-(benzyloxy)-3-(((benzyloxy)carbonyl)oxy)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-4-oxobutyl)-1*H*-indole-1-carboxylate (201):**



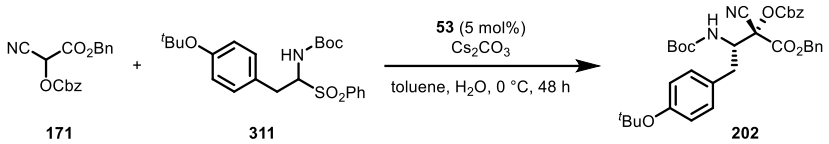
According to **GP6**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with α-amido sulfone **310** (75.1 mg, 0.150 mmol, 1.5 equiv.), catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%), and Cs_2CO_3 (147 mg, 0.450 mmol, 4.5 equiv.) in toluene (1.0 mL) and H_2O (1.0 mL) at 0 °C for 48 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **201** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}201')}$ = 64.8 min, $t_{R(ent\text{-}201)}$ = 110.2 min, $t_{R(201')}$ = 123.8 min, $t_{R(201)}$ = 172.7 min.

Yield: 56.2 mg, 0.0822 mmol, 82% yield

Ratio of Stereoisomers: 201:***ent*-**201**:**201′**:***ent*-**201′** = 87.2:5.3:4.4:3.1, dr = 12:1, **201**: 88% ee, **201′**: 17% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.13 (1H, s), 7.45–7.33 (12H, m), 7.30 (1H, t, J = 7.6 Hz), 7.21 (1H, t, J = 7.4 Hz), 5.37–5.14 (4H, m), 4.78–4.70 (1.8H, m), 4.65 (0.1H, t, J = 9.3 Hz), 4.45 (0.1H, s), 3.19 (0.9H, d, J = 14.9 Hz), 3.06 (0.1H, d, J = 14.6 Hz), 2.89 (0.9H, dd, J = 15.2, 10.6 Hz), 2.74 (0.1H, t, J = 13.3 Hz), 1.64 (9H, s), 1.27 (8.1H, s), 1.01 (0.9H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 162.9, 154.6, 152.4, 149.4, 135.4, 134.0, 133.7, 130.0, 129.1, 128.8, 128.70, 128.65, 128.4, 124.6, 123.7, 122.7, 118.5, 115.2, 114.4, 113.6, 83.6, 80.6, 77.9, 71.6, 69.5, 54.3, 28.1, 27.9, 25.8; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{38}H_{41}N_3O_9Na$ 706.2735; Found 706.2711; **IR (ATR):** 3363, 2978, 1762, 1721, 1507, 1451, 1373, 1249, 1157 cm^{-1}; **Melting Point:** 64.5–68.7 °C; **Optical Rotation:** $[\alpha]^{22}_D$ −3.6 (c 0.86, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-4-(4-(*tert*-butoxy)phenyl)-3-((*tert*-butoxycarbonyl)amino)-2-cyanobutanoate (202):



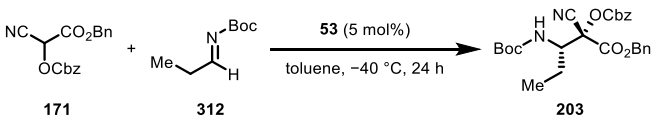
According to **GP6**, cyanohydrin **171** (163 mg, 0. 500 mmol, 1.0 equiv.) reacted with α-amido sulfone **311** (325 mg, 0.750 mmol, 1.5 equiv.), catalyst **53** (11.7 mg, 0.0250 mmol, 5 mol%), and Cs_2CO_3 (733 mg, 2.25 mmol, 4.5 equiv.) in toluene (5.0 mL) and H_2O (5.0 mL) at 0 °C for 48 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **202** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}202')}$ = 32.3 min, $t_{R(ent\text{-}202)}$ = 37.0 min, $t_{R(202')}$ = 69.2 min, $t_{R(202)}$ = 77.5 min.

Yield: 285 mg, 0.461 mmol, 92% yield

Ratio of Stereoisomers: 202:***ent*-**202**:**202′**:***ent*-**202′** = 93.7:2.7:2.2:1.4, dr = 27:1, **202**: 94% ee, **202′**: 24% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.33 (10H, m), 6.99 (2H, d, J = 8.0 Hz), 6.88 (2H, d, J = 8.0 Hz), 5.35–5.30 (0.2H, m), 5.25 (1H, d, J = 12.0 Hz), 5.21–5.16 (2.8H, m), 4.69 (0.9H, d, J = 10.3 Hz), 4.58 (0.9H, td, J = 10.6, 3.2 Hz), 4.48 (0.1H, d, J = 10.3 Hz), 4.40 (0.1H, t, J = 9.5 Hz), 3.12 (0.9H, dd, J = 14.3, 3.4 Hz), 2.92 (0.1H, d, J = 13.7 Hz), 2.65 (0.9H, dd, J = 14.3, 10.9 Hz), 2.54 (0.1H, t, J = 12.9 Hz), 1.30 (9H, s), 1.27 (8.1H, s), 1.21 (0.9H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 162.8, 154.5, 154.3, 152.4, 134.0, 133.7, 130.1, 129.5, 129.1, 128.8, 128.72, 128.67, 128.6, 128.4, 124.3, 113.6, 80.5, 78.4, 77.9, 71.5, 69.4, 55.6, 35.3, 28.7, 28.0; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{35}H_{41}N_2O_8$ 617.2857; Found 617.2873; **IR (ATR):** 3385, 2979, 1762, 1712, 1514, 1454, 1373, 1265, 1241, 1161 cm^{-1}; **Melting Point:** 112.2–115.5 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −9.3 (c 0.90, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyanopentanoate (203):



According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **312** (23.6 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **203** as a white solid. The values of ee and dr of the

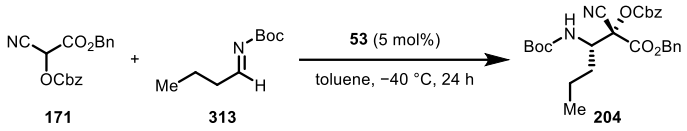
products were determined by chiral HPLC analysis: CHIRALPAK IA, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}203')}$ = 19.6 min, $t_{R(ent\text{-}203)}$ = 28.1 min, $t_{R(203')}$ = 30.3 min, $t_{R(203)}$ = 43.8 min.

Yield: 38.4 mg, 0.0796 mmol, 80% yield

Ratio of Stereoisomers: 203:***ent*-**203**:**203′**:***ent*-**203′** = 96.8:0.6:2.3:0.4, dr = 37:1, **203**: 99% ee, **203′**: 72% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45–7.30 (10H, m), 5.22 (2H, s), 5.17 (2H, s), 4.65 (1H, d, J = 10.0 Hz), 4.22 (1H, td, J = 10.7, 2.6 Hz), 1.90–1.80 (1H, m), 1.50–1.38 (10H, m), 0.96 (3H, t, J = 7.4 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.0, 155.0, 152.5, 134.1, 133.7, 129.1, 128.73, 128.65, 128.6, 128.3, 113.7, 80.6, 78.1, 71.5, 69.3, 56.3, 28.1, 23.0, 10.0 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{26}H_{30}N_2O_7Na$ 505.1945; Found 505.1935; **IR (ATR):** 3359, 2973, 1756, 1712, 1530, 1458, 1388, 1374, 1285, 1247, 1160 cm^{-1}; **Melting Point:** 99.7–100.6 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −16.1 (c 1.52, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyanohexanoate (204):



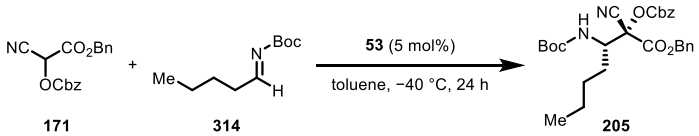
According to **GP5**, cyanohydrin **171** (163 mg, 0.500 mmol, 1.0 equiv.) reacted with *N*-Boc imine **313** (128 mg, 0.750 mmol, 1.5 equiv.) and catalyst **53** (11.7 mg, 0.0250 mmol, 5 mol%) in toluene (2.5 + 2.5 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **204** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% ethanol/hexane, λ = 220 nm, $t_{R(ent\text{-}204')}$ = 8.2 min, $t_{R(204')}$ = 9.9 min, $t_{R(ent\text{-}204)}$ = 11.0 min, $t_{R(204)}$ = 13.9 min.

Yield: 243 mg, 0.490 mmol, 98% yield

Ratio of Stereoisomers: 204:***ent*-**204**:**204′**:***ent*-**204′** = 96.1:0.8:2.4:0.6, dr = 32:1, **204**: 98% ee, **204′**: 59% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.31 (10H, m), 5.25 (1H, d, J = 12.3 Hz), 5.20 (1H, d, J = 12.0 Hz), 5.17 (2H, s), 4.66 (1H, d, J = 10.0 Hz), 4.31 (1H, td, J = 10.6, 2.3 Hz), 1.73–1.67 (1H, m), 1.49–1.39 (11H, m), 1.32–1.26 (1H, m), 0.87 (3H, t, J = 7.0 Hz) (Small peaks of rotamers are observed); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.0, 154.9, 152.5, 134.1, 133.7, 129.0, 128.7, 128.63, 128.57, 128.4, 113.7, 80.6, 78.1, 71.4, 69.3, 54.7, 31.6, 28.1, 18.8, 13.5 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{32}N_2O_7Na$ 519.2102; Found 519.2108; **IR (ATR):** 3384, 2971, 1763, 1713, 1509, 1457, 1376, 1254, 1163 cm^{-1}; **Melting Point:** 93.9–95.5 °C; **Optical Rotation:** $[\alpha]^{21}_D$ −23.1 (c 0.96, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyanoheptanoate (205):



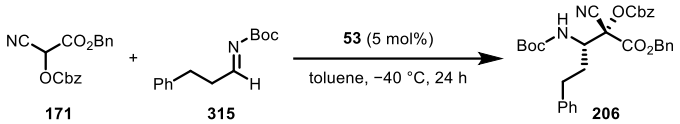
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **314** (27.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **205** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}205')}$ = 10.7 min, $t_{R(205')}$ = 18.2 min, $t_{R(ent\text{-}205)}$ = 19.9 min, $t_{R(205)}$ = 26.3 min.

Yield: 50.3 mg, 0.0985 mmol, 99% yield

Ratio of Stereoisomers: 205:***ent*-**205**:**205′**:***ent*-**205′** = 96.3:1.1:1.9:0.7, dr = 37:1, **205**: 98% ee, **205′**: 49% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.32 (10H, m), 5.25 (1H, d, J = 12.6 Hz), 5.20 (1H, d, J = 12.0 Hz), 5.17 (2H, s), 4.65 (1H, d, J = 10.3 Hz), 4.29 (1H, td, J = 10.7, 2.3 Hz), 1.77–1.69 (1H, m), 1.48–1.34 (11H, m), 1.33–1.18 (3H, m), 0.86 (3H, t, J = 6.9 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.0, 154.9, 152.5, 134.1, 133.7, 129.1, 128.73, 128.68, 128.6, 128.4, 113.8, 80.6, 78.1, 71.5, 69.3, 55.0, 29.4, 28.1, 27.5, 22.1, 13.8 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{28}H_{34}N_2O_7Na$ 533.2258; Found 533.2264; **IR (ATR):** 3381, 2964, 1764, 1714, 1510, 1458, 1376, 1252, 1166 cm^{-1}; **Melting Point:** 97.2–98.4 °C; **Optical Rotation:** $[\alpha]^{21}_D$ −20.6 (c 0.97, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-5-phenylpentanoate (206):



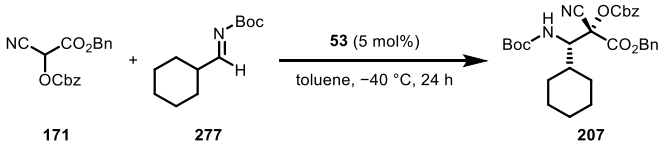
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **315** (35.0 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **206** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}206')}$ = 22.6 min, $t_{R(206')}$ = 29.5 min, $t_{R(ent\text{-}206)}$ = 37.1 min, $t_{R(206)}$ = 54.0 min.

Yield: 53.7 mg, 0.0962 mmol, 96% yield

Ratio of Stereoisomers: 206:***ent*-**206**:**206′**:***ent*-**206′** = 95.9:1.1:2.4:0.7, dr = 32:1, **206**: 98% ee, **206′**: 54% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38–7.29 (10H, m), 7.26 (2H, t, J = 7.4 Hz), 7.18 (1H, t, J = 7.2 Hz), 7.09 (2H, d, J = 6.9 Hz), 5.19 (2H, s), 5.15 (2H, s), 4.78 (0.9H, d, J = 10.3 Hz), 4.55 (0.1H, d, J = 10.3 Hz), 4.36 (0.9H, td, J = 10.9, 2.5 Hz), 4.18 (0.1H, t, J = 10.3 Hz), 2.78–2.70 (1H, m), 2.62–2.54 (1H, m), 2.11–2.02 (0.9H, m), 1.93–1.87 (0.1H, m), 1.83–1.73 (1H, m), 1.44 (9H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 162.8, 154.8, 152.4, 140.1, 134.0, 133.6, 129.0, 128.70, 128.67, 128.58, 128.5, 128.34, 128.31, 126.3, 113.6, 80.8, 78.0, 71.5, 69.3, 54.7, 31.7, 31.5, 28.1; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{32}H_{34}N_2O_7Na$ 581.2258; Found 581.2254; **IR (ATR):** 3378, 2977, 2923, 1763, 1715. 1507, 1457, 1376, 1240, 1164, 1092 cm^{-1}; **Optical Rotation:** $[\alpha]^{23}_D$ −10.4 (c 1.17, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-cyclohexylpropanoate (207):



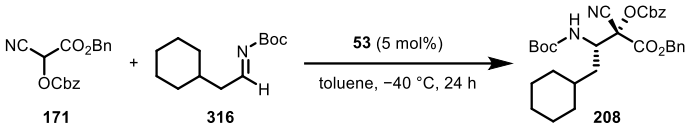
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **277** (31.7 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **207** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}207')}$ = 12.8 min, $t_{R(207')}$ = 18.1 min, $t_{R(ent\text{-}207)}$ = 20.8 min, $t_{R(207)}$ = 30.8 min.

Yield: 49.9 mg, 0.0930 mmol, 93% yield

Ratio of Stereoisomers: 207:***ent*-**207**:**207′**:***ent*-**207′** = 98.5:0.4:0.6:0.5, dr = 94:1, **207**: 99% ee, **207′**: 8% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.32 (10H, m), 5.26 (1H, d, J = 12.0 Hz), 5.21 (1H, d, J = 12.0 Hz), 5.19 (2H, s), 4.89 (0.9H, d, J = 10.9 Hz), 4.61 (0.1H, d, J = 10.9 Hz), 4.25 (0.9H, dd, J = 10.9, 3.4 Hz), 4.12 (0.1H, d, J = 7.4 Hz), 1.92 (0.9H, d, J = 12.6 Hz), 1.82 (0.1H, d, J = 12.0 Hz), 1.74–1.48 (5H, m), 1.46 (0.9H, s), 1.42 (8.1H, s), 1.17–0.93 (5H, m) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 163.3, 155.1, 152.5, 134.0, 133.7, 129.0, 128.73, 128.70, 128.6, 128.5, 114.2, 80.6, 77.1, 71.4, 69.3, 58.4, 38.3, 31.0, 28.1, 26.6, 25.9, 25.68, 25.65 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{30}H_{37}N_2O_7$ 537.2595; Found 537.2596; **IR (ATR):** 3374, 2930, 2858, 1762, 1718, 1504, 1455, 1375, 1242, 1162 cm^{-1}; **Melting Point:** 99.0–101.2 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −13.9 (c 1.02, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-4-cyclohexylbutanoate (208):



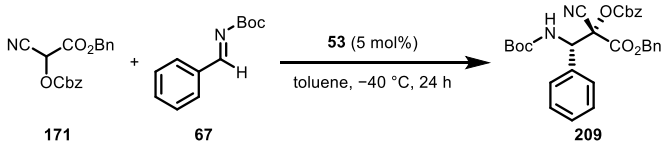
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **316** (33.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **208** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 2% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}208')}$ = 20.6 min, $t_{R(ent\text{-}208)}$ = 48.3 min, $t_{R(208')}$ = 56.8 min, $t_{R(208)}$ = 101.7 min.

Yield: 52.6 mg, 0.0955 mmol, 96% yield

Ratio of Stereoisomers: 208:***ent*-208**:**208′**:***ent*-208′** = 97.9:0.8:0.9:0.3, dr = 76:1, **208**: 98% ee, **208′**: 46% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50–7.31 (10H, m), 5.32 (0.1H, d, J = 11.5 Hz), 5.27 (0.9H, d, J = 12.0 Hz), 5.21–5.16 (3H, m), 4.63 (0.9H, d, J = 10.0 Hz), 4.41 (0.9H, td, J = 10.7, 2.8 Hz), 4.33 (0.2H, s), 1.73–1.53 (5H, m), 1.52–1.37 (11H, m), 1.37–1.02 (5H, m), 0.97–0.85 (1H, m), 0.72–0.62 (0.9H, m), 0.56 (0.1H, t, J = 11.2 Hz) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.0, 154.8, 152.5, 134.1, 133.7, 129.1, 128.72, 128.69, 128.62, 128.56, 113.8, 80.6, 78.2, 71.4, 69.3, 52.7, 37.0, 33.9, 33.7, 31.6, 28.1, 26.24, 26.20, 25.8 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{31}H_{38}N_2O_7Na$ 573.2571; Found 573.2562; **IR (ATR):** 3363, 2925, 2851, 1756, 1718, 1526, 1456, 1378, 1282, 1251, 1164 cm^{-1}; **Melting Point:** 118.2–119.3 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −19.5 (c 1.47, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-phenylpropanoate (209):



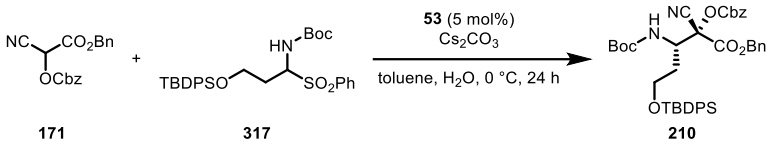
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **209** as a white amorphous solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}209')}$ = 15.9 min, $t_{R(209')}$ = 23.5 min, $t_{R(ent\text{-}209)}$ = 30.1 min, $t_{R(209)}$ = 33.3 min.

Yield: 52.4 mg, 0.0988 mmol, 99% yield

Ratio of Stereoisomers: 209:***ent*-209**:**209′**:***ent*-209′** = 97.5:0.4:1.5:0.6, dr = 46:1, **209**: 99% ee, **209′**: 44% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38–7.26 (15H, m), 5.50 (1H, d, J = 9.7 Hz), 5.43 (1H, d, J = 9.7 Hz), 5.18 (1H, d, J = 12.0 Hz), 5.15–5.14 (3H, m), 1.41 (9H, s) (Small peaks of rotamers are observed); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 162.6, 154.3, 152.3, 133.74, 133.71, 133.65, 129.2, 129.0, 128.74, 128.67, 128.6, 128.5, 128.0, 113.7, 81.0, 77.8, 71.4, 69.4, 58.3, 28.1 (Two aromatic carbon peaks are missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{30}H_{31}N_2O_7$ 531.2126; Found 531.2125; **IR (ATR):** 3322, 2979, 1761, 1713, 1504, 1456, 1374, 1240, 1161 cm^{-1}; **Melting Point:** 111.2–113.9 °C; **Optical Rotation:** $[\alpha]^{24}_D$ −4.8 (c 1.03, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-5-((*tert*-butyldiphenylsilyl)oxy)-2-cyanopentanoate (210):



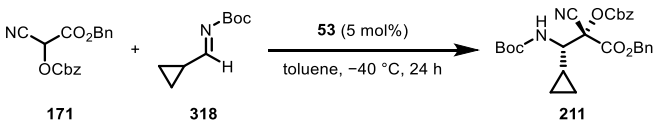
According to **GP6**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with α-amido sulfone **317** (83.1 mg, 0.150 mmol, 1.5 equiv.), catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%), and Cs_2CO_3 (147 mg, 0.450 mmol, 4.5 equiv.) in toluene (1.0 mL) and H_2O (1.0 mL) at 0 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **210** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}210')}$ = 17.9 min, $t_{R(ent\text{-}210)}$ = 23.1 min, $t_{R(210')}$ = 26.5 min, $t_{R(210)}$ = 33.8 min.

Yield: 67.4 mg, 0.0915 mmol, 92% yield

Ratio of Stereoisomers: 210:***ent*-210**:**210′**:***ent*-210′** = 88.9:2.6:6.8:1.7, dr = 11:1, **210**: 94% ee, **210′**: 60% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.65–7.62 (4H, m), 7.45–7.30 (16H, m), 5.30 (1H, d, J = 12.6 Hz), 5.18–5.14 (3H, m), 5.09 (0.9H, d, J = 9.2 Hz), 4.84 (0.1H, d, J = 10.3 Hz), 4.78 (0.1H, td, J = 10.2, 2.1 Hz), 4.62 (0.9H, td, J = 9.9, 2.9 Hz), 3.78 (1H, td, J = 9.6, 3.6 Hz), 3.69–3.65 (1H, m), 2.32–2.25 (0.1H, m), 2.18–2.10 (0.9H, m), 1.92 (0.1H, s), 1.75–1.67 (0.9H, m), 1.41 (9H, s), 1.03 (9H, s); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 163.1, 154.9, 152.5, 135.6, 135.5, 134.2, 133.8, 133.1, 132.9, 129.7, 129.0, 128.7, 128.61, 128.56, 128.5, 128.1, 127.7, 113.8, 80.5, 78.1, 71.4, 69.3, 59.9, 53.0, 32.1, 28.1, 26.7, 19.0 (Two aromatic carbon peaks are missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{42}H_{48}N_2O_8SiNa$ 759.3072; Found 759.3042; **IR (ATR):** 3398, 2938, 1763, 1717, 1504, 1463, 1376, 1248, 1162, 1105 cm^{-1}; **Optical Rotation:** $[\alpha]^{25}_D$ −8.8 (c 0.66, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-3-cyclopropylpropanoate (211):



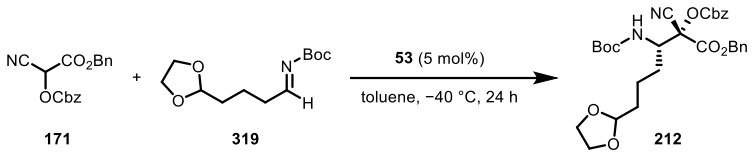
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **318** (25.4 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, hexane/EtOAc = 100:0 → 90:10) afforded **211** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}211')}$ = 15.5 min, $t_{R(ent\text{-}211)}$ = 21.2 min, $t_{R(211')}$ = 23.6 min, $t_{R(211)}$ = 27.4 min.

Yield: 44.3 mg, 0.0896 mmol, 90% yield

Ratio of Stereoisomers: 211:***ent*-211**:**211′**:***ent*-211′** = 96.8:0.5:2.2:0.5, dr = 36:1, **211**: 99% ee, **211′**: 63% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.35 (10H, m), 5.28–5.24 (2H, m), 5.21 (2H, s), 4.95 (1H, d, J = 10.3 Hz), 3.83 (1H, t, J = 10.0 Hz), 1.42 (9H, s), 1.15–1.04 (1H, m), 0.51–0.47 (2H, m), 0.38–0.34 (1H, m), 0.27–0.24 (1H, m); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 162.6, 154.8, 152.6, 133.8, 129.1, 128.9, 128.74, 128.69, 128.6, 113.9, 80.7, 78.0, 71.4, 69.3, 58.8, 28.1, 11.7, 5.1, 2.0 (Two aromatic carbon peaks are missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{30}N_2O_7Na$ 517.1945; Found 517.1943; **IR (ATR):** 3391, 2976, 2929, 1763, 1714, 1505, 1459, 1376, 1248, 1164 cm^{-1}; **Optical Rotation:** $[\alpha]^{22}_D$ −10.6 (c 0.99, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-6-(1,3-dioxolan-2-yl)hexanoate (212):



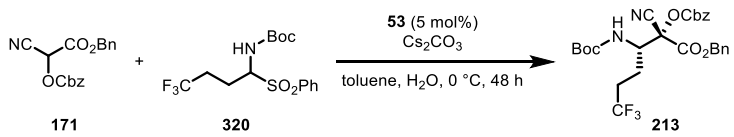
According to **GP5**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **319** (36.5 mg, 0.150 mmol, 1.5 equiv.) and catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10 → 80:20) afforded **212** as a white solid. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IC, 1.0 mL/min, 5% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}212')}$ = 33.9 min, $t_{R(212')}$ = 41.2 min, $t_{R(ent\text{-}212)}$ = 44.8 min, $t_{R(212)}$ = 67.5 min.

Yield: 54.6 mg, 0.0960 mmol, 96% yield

Ratio of Stereoisomers: 212:***ent*-212**:**212′**:***ent*-212′** = 96.9:0.8:1.6:0.7, dr = 43:1, **212**: 98% ee, **212′**: 41% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45–7.30 (10H, m), 5.32–5.27 (0.2H, m), 5.23 (1H, d, J = 12.0 Hz), 5.20 (1H, d, J = 12.0 Hz), 5.17 (1.8H, s), 4.82 (1H, t, J = 4.4 Hz), 4.73 (0.9H, d, J = 10.0 Hz), 4.38 (0.1H, d, J = 10.9 Hz), 4.30 (0.9H, td, J = 10.7, 2.5 Hz), 4.21 (0.1H, t, J = 10.6 Hz), 3.95–3.91 (2H, m), 3.84–3.80 (2H, m), 1.85–1.75 (1H, m), 1.75–1.44 (5H, m), 1.42 (9H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 162.9, 154.9, 152.4, 134.1, 133.7, 129.1, 128.72, 128.65, 128.6, 128.3, 113.7, 103.9, 80.7, 78.0, 71.5, 69.3, 64.84, 64.81, 55.0, 33.0, 29.4, 28.1, 20.0 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{30}H_{36}N_2O_9Na$ 591.2313; Found 591.2316; **IR (ATR):** 3285, 2963, 1758, 1719, 1528, 1453, 1373, 1241, 1156, 1008 cm^{-1}; **Melting Point:** 117.4–118.4 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −13.3 (c 2.33, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-6,6,6-trifluorohexanoate (213):



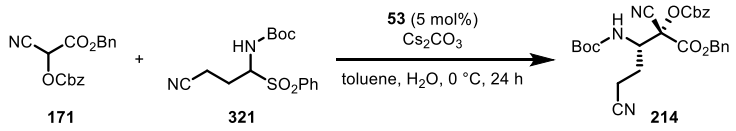
According to **GP6**, cyanohydrin **163** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with α-amido sulfone **320** (55.1 mg, 0.150 mmol, 1.5 equiv.), catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%), and Cs_2CO_3 (147 mg, 0.450 mmol, 4.5 equiv.) in toluene (1.0 mL) and H_2O (1.0 mL) at 0 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **213** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 3% 2-propanol/hexane, λ = 220 nm, $t_{R(ent\text{-}213')}$ = 11.5 min, $t_{R(ent\text{-}213)}$ = 14.0 min, $t_{R(213')}$ = 17.3 min, $t_{R(213)}$ = 26.1 min.

Yield: 51.8 mg, 0.0941 mmol, 94% yield

Ratio of Stereoisomers: 213:***ent*-213**:**213′**:***ent*-213′** = 93.4:2.5:2.9:1.3, dr = 23:1, **213**: 95% ee, **213′**: 38% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.42–7.32 (10H, m), 5.27 (1H, d, J = 12.0 Hz), 5.23–5.16 (3H, m), 4.74 (1H, d, J = 10.3 Hz), 4.43 (0.1H, t, J = 11.7 Hz), 4.35 (0.9H, td, J = 11.1, 2.5 Hz), 2.26–2.13 (1H, m), 2.13–1.95 (2H, m), 1.85 (0.1H, br s), 1.74–1.64 (0.9H, m), 1.43 (9H, s) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 162.5, 154.7, 152.2, 133.8, 133.5, 129.2, 128.9, 128.8, 128.7, 128.5, 126.3 (q, J = 276.0 Hz), 113.3, 81.3, 77.6, 71.7, 69.6, 53.9, 30.3 (q, J = 29.9 Hz), 28.1, 22.7 (One aromatic carbon peak is missing due to overlapping); **^{19}F-NMR (471 MHz, $CDCl_3$):** δ −66.2 (t, J = 10.1 Hz); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{27}H_{30}N_2O_7F_3$ 551.2000; Found 551.1982; **IR (ATR):** 3376, 2979, 1765, 1716, 1510, 1454, 1376, 1261, 1158 cm^{-1}; **Optical Rotation:** $[\alpha]^{25}_D$ −16.8 (c 1.04, $CHCl_3$).

Benzyl (2*R*,3*S*)-2-(((benzyloxy)carbonyl)oxy)-3-((*tert*-butoxycarbonyl)amino)-2,5-dicyanopentanoate (214):



According to **GP6**, cyanohydrin **171** (32.5 mg, 0.0999 mmol, 1.0 equiv.) reacted with α-amido sulfone **321** (48.7 mg, 0.150 mmol, 1.5 equiv.), catalyst **53** (2.3 mg, 0.0049 mmol, 5 mol%), and Cs_2CO_3 (147 mg, 0.450 mmol, 4.5 equiv.) in toluene (1.0 mL) and H_2O (1.0 mL) at 0 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10 → 80:20) afforded **214** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 10% 2-propanol/hexane, λ = 220 nm, $t_{R(\textit{ent}\text{-}214')}$ = 14.2 min, $t_{R(\textit{ent}\text{-}214)}$ = 15.5 min, $t_{R(214')}$ = 16.3 min, $t_{R(214)}$ = 21.4 min.

Yield: 37.1 mg, 0.0731 mmol, 73% yield

Ratio of Stereoisomers: 214:***ent*-214**:**214′**:***ent*-214′** = 82.1:6.8:8.1:3.0, dr = 8.0:1, **214**: 85% ee, **214′**: 46% ee

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.34 (10H, m), 5.35–5.15 (4H, m), 4.82 (0.81H, d, J = 10.6 Hz), 4.76 (0.081H, d, J = 11.2 Hz), 4.71 (0.099H, d, J = 6.3 Hz), 4.47 (0.099H, td, J = 11.5, 2.4 Hz), 4.39 (0.89H, td, J = 11.0, 2.7 Hz), 2.48–2.31 (2H, m), 2.11–2.05 (0.81H, m), 1.97–1.88 (0.18H, m), 1.86–1.78 (0.81H, m), 1.77–1.65 (0.18H, m), 1.43 (9H, s) (Peaks of rotamers and diastereomers are observed in the ratio of 9:1 and 8:1, respectively); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 162.3, 154.6, 152.1, 133.7, 133.4, 129.2, 129.0, 128.8, 128.74, 128.68, 128.6, 118.1, 113.1, 81.6, 77.3, 71.8, 69.8, 54.2, 28.1, 26.0, 14.0; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{29}N_3O_7Na$ $[M+Na]^+$ 530.1898; Found 530.1902; **IR (ATR):** 3370, 2978, 2252, 1762, 1713, 1510, 1453, 1376, 1245, 1160 cm^{-1}; **Optical Rotation:** $[\alpha]^{21}_D$ −15.1 (c 0.93, $CHCl_3$).

第四節 β-アミノ-α-ケト酸および関連するペプチドの合成と利用

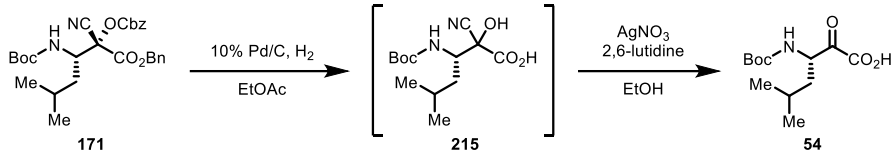
General Procedure for Conversion to β-Amino-α-ketoacids (GP7):

A round bottom flask was charged with a stir bar, Mannich adduct (1.0 equiv.) and EtOAc (10 mL/mmol) under Ar atmosphere. To the mixture was added 10% Pd/C (2 or 5 mol%), and the flask was evacuated and refilled with H_2 gas. After stirring at room temperature for appropriate time, the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was used for next reaction without further purification.

A round bottom flask was charged with a stir bar, crude carboxylic acid (1.0 equiv.), and EtOH (20 mL/mmol). To the stirred solution were added $AgNO_3$ (2.0 equiv.) and 2,6-lutidine (2.0 equiv.), and the mixture was stirred in the dark at room temperature for 12 hours. The resulting suspension was diluted with EtOAc and aqueous HCl (1 M) and filtered through a Celite pad. The filtrate was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. In the presence of alcohol solvent, a part of β-amino-α-ketoacids form hemiacetal at α-position, thus the fractions were dissolved in $CHCl_3$

and concentrated again to remove the hemiacetal, which afford corresponding β-amino-α-ketoacid.

Boc-Leu-CO_2H (54):

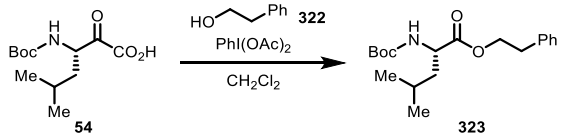


171 215 54

According to **GP7**, adduct **171** (153 mg, 0.300 mmol, 1.0 equiv.) was subsequently treated with 10% Pd/C (6.4 mg, 0.0060 mmol, 2 mol%) under H_2 atmosphere (1 atm) and $AgNO_3$ (102 mg, 0.600 mmol, 2.0 equiv.) with 2,6-lutidine (69.5 μL, 0.600 mmol, 2.0 equiv.). Column chromatography (COOH SiO_2, eluted with hexane/EtOAc/MeOH = 100:0:0 → 50:50:0 → 0:100:0 → 0:70:30) afforded Boc-Leu-CO_2H **54** (59.3 mg, 0.229 mmol, 76% yield) as a brown oil.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 6.41 (1H, d, J = 6.9 Hz), 4.83–4.77 (1H, m), 1.86–1.76 (1H, m), 1.65–1.58 (1H, m), 1.56–1.51 (1H, m), 1.39 (9H, s), 0.97 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.3 Hz) (Small peaks of rotamers are observed); **^{13}C-NMR (151 MHz, acetone-*d*$_6$):** δ 196.4, 163.2, 156.5, 79.4, 56.1, 39.4, 28.4, 25.6, 23.4, 21.4; **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{12}H_{21}NO_5Na$ 282.1317; Found 282.1313; **Optical Rotation:** $[\alpha]^{21}_D$ +7.3 (c 1.24, $CHCl_3$).

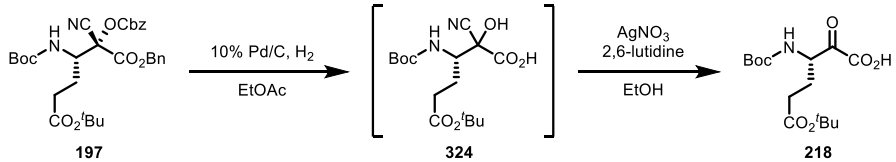
Separation of enantiomers of **54** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of ee of **54** was determined after transformation to known ester **323** as a following procedure:



54 323

A 4 mL screw vial was charged with a stir bar, Boc-Leu-CO_2H **54** (5.2 mg, 0.020 mmol, 1.0 equiv.), alcohol **322** (2.35 μL, 0.0196 mmol, 1.0 equiv.), and CH_2Cl_2 (0.20 mL). To the solution was added $PhI(OAc)_2$ (6.4 mg, 0.020 mmol, 1.0 equiv.), and the mixture was stirred at room temperature for 24 hours in the dark. The solution was directly purified by preparative TLC (eluted with hexane/EtOAc = 90:10) to afford **323** (4.7 mg, 0.014 mmol, 70% yield, L/D = 98:2 from 99:1). The values of ee of the product was determined by chiral SFC analysis: Trefoil CEL1, 1.0 mL/min, 2% methanol/CO_2, λ = 210–400 nm, $t_{R(\mathbf{323})}$ = 2.9 min, $t_{R(\textit{ent}\text{-}\mathbf{323})}$ = 4.1 min.

Boc-Glu(O^{t}Bu)-CO_2H (218):



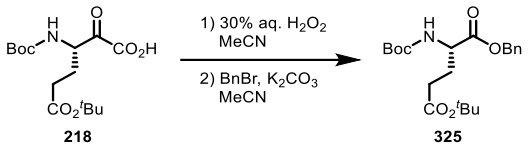
197 324 218

According to **GP7**, adduct **197** (175 mg, 0.300 mmol, 1.0 equiv.) was subsequently treated with 10% Pd/C (6.4 mg, 0.0060 mmol, 2 mol%) under H_2 atmosphere (1 atm) and $AgNO_3$ (102 mg, 0.600 mmol, 2.0 equiv.) with 2,6-lutidine (69.5 μL, 0.600 mmol, 2.0 equiv.). Column chromatography (COOH SiO_2, eluted with hexane/EtOAc/MeOH = 50:50:0 → 0:100:0 → 0.70:30) afforded Boc-Glu(O^{t}Bu)-CO_2H **218** (77.2 mg, 0.233 mmol, 78% yield) as a brown oil.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 6.48 (1H, d, J = 6.3 Hz), 4.75 (1H, dd, J = 12.3, 8.3 Hz), 2.39 (2H, t, J = 7.2 Hz), 2.22–2.14 (1H, m), 1.94–1.86 (1H, m), 1.43 (9H, s), 1.39 (9H, s) (Small peaks of rotamers are observed); **^{13}C-NMR (151 MHz, acetone-*d*$_6$):** δ 195.5, 172.5, 163.1, 156.5, 80.7, 79.7, 56.9, 31.9, 28.5, 28.2, 26.1; **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{15}H_{25}NO_7Na$ 354.1529;

Found 354.1533; **Optical Rotation:** $[\alpha]^{21}_D$ +7.3 (c 1.32, $CHCl_3$).

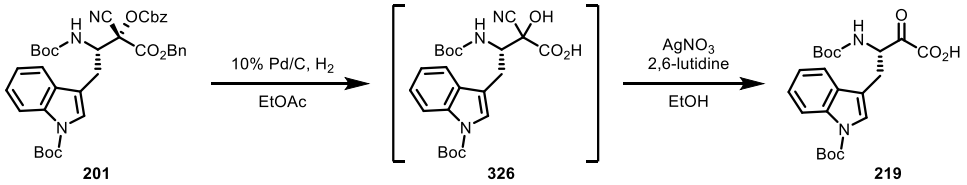
Separation of enantiomers of **218** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of ee of **218** was determined after transformation to known ester **325** as a following procedure:



218 **325**

A 4 mL screw vial was charged with a stir bar, Boc-Glu(O^{t}Bu)-CO_2H **218** (6.6 mg, 0.020 mmol, 1.0 equiv.), H_2O_2 (30% in H_2O, 6.13 µL, 0.0600 mmol, 3.0 equiv.), and MeCN (0.20 mL). After stirring at room temperature for 2.5 hours in the dark, the mixture was concentrated under reduced pressure. The residue was dissolved in MeCN (0.20 mL). To the solution were added BnBr (3.56 µL, 0.0300 mmol, 1.5 equiv.) and K_2CO_3 (5.5 mg, 0.040 mmol, 2.0 equiv.), and the suspension was stirred at room temperature for 24 hours. The mixture was directly purified by preparative TLC (eluted with hexane/EtOAc = 90:10) to afford ester **325** (11.7 mg, quant., *L/D* = 95:5 from 95:5). The values of ee of the product was determined by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 3% methanol/CO_2, λ = 210–400 nm, $t_{R(\mathbf{325})}$ = 3.5 min, $t_{R(\textit{ent}\text{-}\mathbf{325})}$ = 4.3 min.

Boc-Trp(Boc)-CO_2H (219):

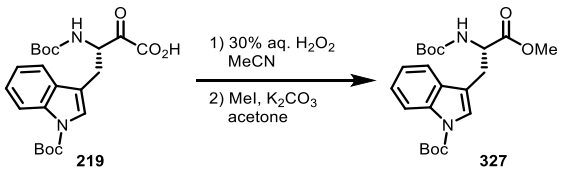


201 **326** **219**

According to **GP7**, adduct **201** (205 mg, 0.300 mmol, 1.0 equiv.) was subsequently treated with 10% Pd/C (16.0 mg, 0.0150 mmol, 5 mol%) under H_2 atmosphere (4 atm) and $AgNO_3$ (102 mg, 0.600 mmol, 2.0 equiv.) with 2,6-lutidine (69.5 µL, 0.600 mmol, 2.0 equiv.). Column chromatography (COOH SiO_2, eluted with hexane/EtOAc/MeOH = 50:50:0 →0:100:0 → 0:70:30) afforded Boc-Trp(Boc)-CO_2H **219** (91.3 mg, 0.211 mmol, 70% yield) as a yellow amorphous solid.

^{1}H-NMR (500 MHz, acetone-d_6): δ 8.11 (1H, d, *J* = 7.2 Hz), 7.74 (1H, d, *J* = 7.7 Hz), 7.58 (1H, s), 7.30 (1H, t, *J* = 7.4 Hz), 7.24 (1H, t, *J* = 7.3 Hz), 6.44 (1H, d, *J* = 8.3 Hz), 5.13–5.08 (1H, m), 3.41 (1H, dd, *J* = 14.6, 3.7 Hz), 3.02 (1H, dd, *J* = 15.0, 9.6 Hz), 1.65 (9H, s), 1.32 (9H, s) (Small peaks of rotamers are observed); **^{13}C-NMR (151 MHz, acetone-d_6):** δ 196.9, 173.7, 164.5, 156.3, 150.2, 136.3, 131.5, 125.1, 123.3, 120.1, 117.1, 115.8, 84.1, 79.5, 57.4, 28.4, 28.2, 26.3; **HRMS (ESI) *m/z*:** $[M-H]^-$ Calcd for $C_{22}H_{27}N_2O_7$ 431.1813; Found 431.1828; **Melting Point:** 121.6–125.2 °C; **Optical Rotation:** $[\alpha]^{19}_D$ −4.8 (c 1.52, $CHCl_3$).

Separation of enantiomers of **219** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of ee of **219** was determined after transformation to known ester **327** as a following procedure:



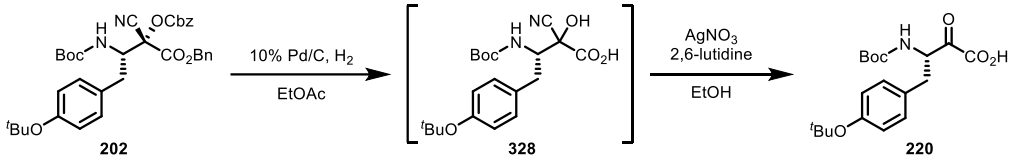
219 **327**

A 4 mL screw vial was charged with a stir bar, Boc-Trp(Boc)-CO_2H **219** (8.6 mg, 0.020 mmol, 1.0 equiv.), H_2O_2 (30% in H_2O, 6.12 µL, 0.0599 mmol, 3.0 equiv.), and MeCN (0.20 mL). After stirring at room temperature for 3 hours in the dark, the mixture was concentrated under reduced pressure.

The residue was dissolved in MeCN (0.20 mL). To the solution were added MeI (4.98 µL, 0.0800 mmol, 4.0 equiv.) and K_2CO_3

(4.1 mg, 0.030 mmmol, 2.0 equiv.), and the suspension was stirred at room temperature for 17 hours. The mixture was directly purified by preparative TLC (eluted with hexane/EtOAc = 80:20) to afford ester **327** (5.5 mg, 0.013 mmol, 66% yield, *L*/*D* = 88:12 from 91:9). The values of ee of the product was determined by chiral SFC analysis: Trefoil CEL1, 1.0 mL/min, 3% methanol/CO_2, λ = 210–400 nm, $t_{R(\mathbf{327})}$ = 4.2 min, $t_{R(\textit{ent}\text{-}\mathbf{327})}$ = 4.6 min.

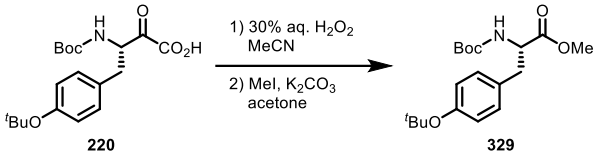
Boc-Tyr(ᵗBu)-CO_2H (220):



According to **GP7**, adduct **202** (185 mg, 0.300 mmol, 1.0 equiv.) was subsequently treated with 10% Pd/C (16.0 mg, 0.0150 mmol, 5 mol%) under H_2 atmosphere (4 atm) and $AgNO_3$ (102 mg, 0.600 mmol, 2.0 equiv.) with 2,6-lutidine (69.5 μL, 0.600 mmol, 2.0 equiv.). Column chromatography (COOH SiO_2, eluted with hexane/EtOAc/MeOH = 100:0:0 → 90:10:0 → 0:50:50 → 0:100:0 → 0:70:30) afforded Boc-Tyr(ᵗBu)-CO_2H **220** (73.1 mg, 0.200 mmol, 67% yield) as a brown oil.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 7.20 (2H, d, *J* = 8.6 Hz), 6.92 (2H, d, *J* = 8.0 Hz), 6.41 (1H, d, *J* = 8.0 Hz), 5.00–4.94 (1H, m), 3.22 (1H, dd, *J* = 14.0, 4.9 Hz), 2.88 (1H, dd, *J* = 14.0, 9.5 Hz), 1.34 (9H, s), 1.30 (9H, s) (Small peaks of rotamers are observed); **^{13}C-NMR (151 MHz, acetone-*d*$_6$):** δ 195.4, 163.1, 156.2, 155.2, 132.7, 130.6, 124.7, 79.5, 78.4, 59.0, 35.8, 29.1, 28.4; **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{19}H_{27}NO_6Na$ 388.1736; Found 388.1732; **Optical Rotation:** $[\alpha]^{19}_D$ +8.8 (c 0.93, $CHCl_3$).

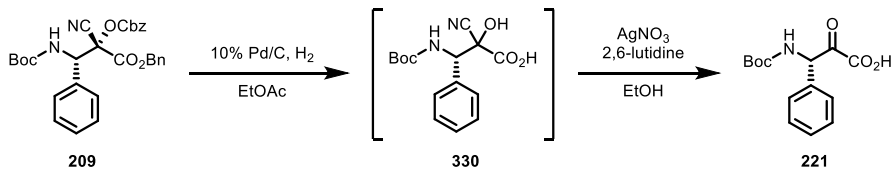
Separation of enantiomers of **220** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of ee of **220** was determined after transformation to known ester **329** as a following procedure:



A 4 mL screw vial was charged with a stir bar, Boc-Tyr(ᵗBu)-CO_2H **220** (11.0 mg, 0.0301 mmol, 1.0 equiv.), H_2O_2 (30% in H_2O, 9.19 μL, 0.0900 mmol, 3.0 equiv.), and MeCN (0.30 mL). After stirring at room temperature for 5 hours in the dark, the mixture was concentrated under reduced pressure.

The residue was dissolved in acetone (0.30 mL). To the solution were added MeI (3.73 μL, 0.0599 mmol, 2.0 equiv.) and K_2CO_3 (6.2 mg, 0.045 mmmol, 1.5 equiv.), and the suspension was stirred at room temperature for 17 hours. The mixture was directly purified by preparative TLC (eluted with hexane/EtOAc = 80:20) to afford ester **329** (9.0 mg, 0.026 mmol, 85% yield, *L*/*D* = 95:5 from 95:5). The values of ee of the product was determined by chiral SFC analysis: CHIRALPAK IC-3/SFC, 1.0 mL/min, 3% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{ent}\text{-}\mathbf{329})}$ = 4.8 min, $t_{R(\mathbf{329})}$ = 5.3 min.

Boc-Phg-CO_2H (221):

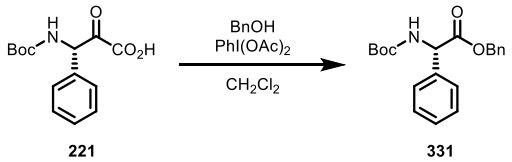


According to **GP7**, adduct **209** (159 mg, 0.300 mmol, 1.0 equiv.) was subsequently treated with 10% Pd/C (6.4 mg, 0.0060 mmol,

2 mol%) under H_2 atmosphere (1 atm) and $AgNO_3$ (102 mg, 0.600 mmol, 2.0 equiv.) with 2,6-lutidine (69.5 μL, 0.600 mmol, 2.0 equiv.). Column chromatography (COOH SiO_2, eluted with hexane/EtOAc/MeOH = 50:50:0 → 0:100:0 → 0:90:10 → 0:70:30) afforded Boc-Phg-CO_2H **221** (55.2 mg, 0.198 mmol, 66% yield) as a white amorphous solid.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 7.42–7.32 (5H, m), 6.82 (1H, d, J = 5.4 Hz), 6.03 (1H, d, J = 6.9 Hz), 1.38 (9H, s) (Small peaks of rotamers are observed); **^{13}C-NMR (151 MHz, acetone-*d*$_6$):** δ 192.6, 162.4, 156.0, 135.5, 129.7, 129.6, 129.4, 79.7, 61.5, 28.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{14}H_{17}NO_5Na$ 302.0999; Found 302.0996; **Melting Point:** 53.4–56.8 °C; **Optical Rotation:** $[\alpha]^{19}_D$ +14.2 (c 1.46, $CHCl_3$).

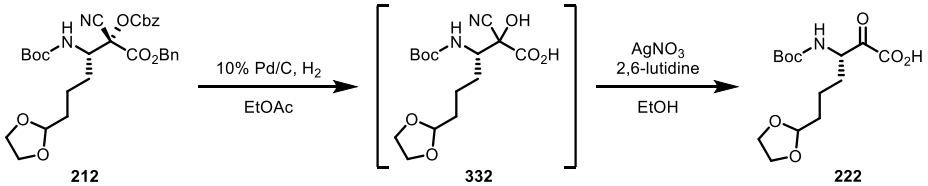
Separation of enantiomers of **221**was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of ee of **221** was determined after transformation to known ester **331** as a following procedure:



221 **331**

A 4 mL screw vial was charged with a stir bar, Boc-Phg-CO_2H **221** (5.6 mg, 0.020 mmol, 1.0 equiv.), BnOH (4.13 μL, 0.00400 mmol, 2.0 equiv.), $PhI(OAc)_2$ (6.4 mg, 0.020 mmol, 1.0 equiv.), and CH_2Cl_2 (0.20 mL). After stirring at room temperature for 22 hours in the dark, the mixture was directly purified by preparative TLC (eluted with hexane/EtOAc = 90:10) to afford ester **331** (3.9 mg, 0.011 mmol, 57% yield, L/D = 93:7 from 99:1). The values of ee of the product was determined by chiral SFC analysis: Trefoil CEL1, 1.0 mL/min, 10% methanol/CO_2, λ = 210–400 nm, $t_{R(ent\text{-}331)}$ = 1.4 min, $t_{R(331)}$ = 1.5 min.

Boc-Aea-CO_2H (222):

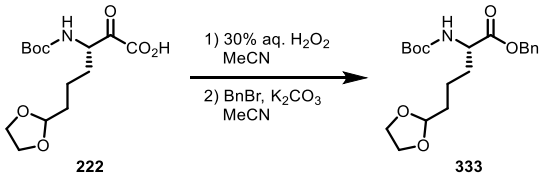


212 **332** **222**

According to **GP7**, adduct **212** (284 mg, 0.500 mmol, 1.0 equiv.) was subsequently treated with 10% Pd/C (10.6 mg, 0.0100 mmol, 2 mol%) under H_2 atmosphere (1 atm) and $AgNO_3$ (170 mg, 1.00 mmol, 2.0 equiv.) with 2,6-lutidine (116 μL, 1.00 mmol, 2.0 equiv.). Column chromatography (COOH SiO_2, eluted with EtOAc/MeOH = 100:0 → 90:10 → 70:30) afforded Boc-Aea-CO_2H **222** (93.9 mg, 0.296 mmol, 59% yield) as a brown oil.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 6.42 (1H, d, J = 7.4 Hz), 4.79 (1H, t, J = 4.3 Hz), 4.71 (1H, s), 3.92–3.85 (2H, m), 3.81–3.73 (2H, m), 1.95–1.87 (1H, m), 1.70–1.50 (5H, m), 1.38 (9H, s); **^{13}C-NMR (151 MHz, acetone-*d*$_6$):** δ 196.5, 163.6, 156.5, 104.7, 79.5, 65.3, 57.4, 34.1, 30.6, 28.5, 21.2; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{14}H_{23}NO_7Na$ 340.1367; Found 340.1368; **Optical Rotation:** $[\alpha]^{19}_D$ +9.9 (c 1.68, $CHCl_3$).

Separation of enantiomers of **222** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of ee of **222** was determined after transformation to ester **333** as a following procedure:



222 **333**

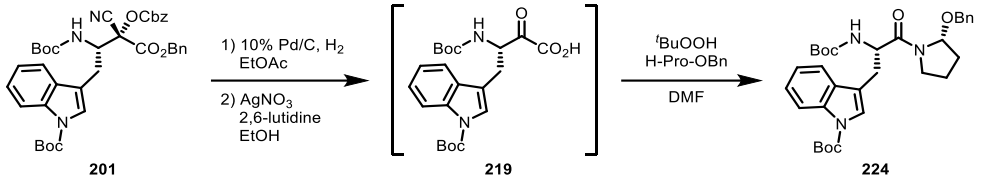
A 4 mL screw vial was charged with a stir bar, Boc-Aea-CO_2H **222** (15.9 mg, 0.0501 mmol, 1.0 equiv.), H_2O_2 (30% in H_2O, 15.3

μL, 0.150 mmol, 3.0 equiv.), and MeCN (0.50 mL). After stirring at room temperature for 5 hours in the dark, the mixture was concentrated under reduced pressure.

The residue was dissolved in MeCN (0.50 mL). To the solution were added BnBr (8.91 μL, 0.0750 mmol, 1.5 equiv.) and K_2CO_3 (13.8 mg, 0.0998 mmmol, 2.0 equiv.), and the suspension was stirred at room temperature for 20 hours. The mixture was directly purified by preparative TLC (eluted with hexane/EtOAc = 75:25) to afford ester **333** (15.8 mg, 0.0416 mmol, 83% yield, *L*/*D* = 93:7 from 96:4) as a colorless oil. The values of ee of the product was determined by chiral SFC analysis: CHIRALPAK IC-3/SFC, 1.0 mL/min, 5% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{ent}\text{-}333)}$ = 4.7 min, $t_{R(333)}$ = 5.4 min.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39–7.31 (5H, m), 5.20 (1H, d, *J* = 12.0 Hz), 5.14 (1H, d, *J* = 12.6 Hz), 5.02 (1H, d, *J* = 8.6 Hz), 4.80 (1H, t, *J* = 4.6 Hz), 4.35 (1H, q, *J* = 6.9 Hz), 3.97–3.90 (2H, m), 3.86–3.79 (2H, m), 1.90–1.83 (1H, m), 1.72–1.56 (3H, m), 1.52–1.45 (2H, m), 1.43 (9H, s); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 172.7, 155.3, 135.4, 128.6, 128.4, 128.2, 104.1, 79.8, 67.0, 64.9, 53.5, 33.3, 32.5, 28.3, 19.7; **HRMS (ESI) *m/z*:** [M+Na]+ Calcd for $C_{20}H_{29}NO_6Na$ 402.1887; Found 402.1893; **IR (ATR):** 3353, 2931, 1712, 1510, 1454, 1361, 1250, 1165, 1037 cm^{-1}; **Optical Rotation:** $[\alpha]^{19}_D$ −3.1 (c 0.98, $CHCl_3$).

Direct Use of Crude β-Amino-α-ketoacid for Decarboxylative Condensation:



A 20 mL round bottom flask was charged with a stir bar, adduct **201** (103 mg, 0.150 mmol, 1.0 equiv.), 10% Pd/C (16.0 mg, 0.0150 mmol, 10 mol%), and EtOAc (1.5 mL) and the mixture was purged with H_2 gas (4 atm). After stirring at room temperature for 24 hours, the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was used for next reaction without further purification.

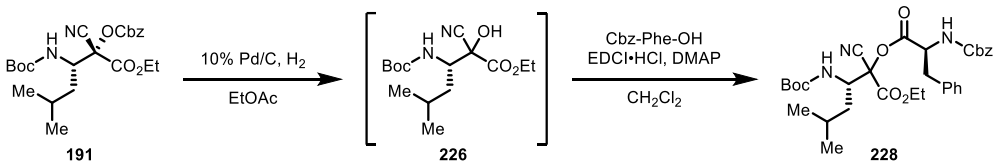
A 20 mL round bottom flask was charged with a stir bar, the crude carboxylic acid (1.0 equiv.), and EtOH (3.0 mL). To the stirred solution were added $AgNO_3$ (51.0 mg, 0.300 mmol, 2.0 equiv.) and 2,6-lutidine (34.7 μL, 0.300 mmol, 2.0 equiv.), and the mixture was stirred in the dark at room temperature for 12 hours. The suspension was diluted with EtOAc and 1 M HCl and filtered through a Celite pad. The filtrate was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ to remove acetal at α-position, and concentrated again to afford crude product of Boc-Trp(Boc)-CO_2H **219**.

A 10 mL test tube equipped with a Teflon-coated cap was charged with a stir bar, H-Pro-OBn (20.5 mg, 0.100 mmol, 1.0 equiv.), and DMF (0.50 mL). To the solution was added *t*-BuOOH (70% in H_2O, 20.5 μL, 0.150 mmol, 1.5 equiv.) and crude α-ketoacid **219** (1.5 equiv.) in DMF (0.50 mL). After stirring at room temperature for 12 hours, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10 → 80:20) to afford Boc-Trp(Boc)-Pro-OBn **224** (24.4 mg, 0.0219 mmol, 73% yield, 99:1 dr) as a colorless oil. The values of dr of the products was determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 15% 2-propanol/hexane, λ = 220 nm, $t_{R(\textit{epi}\text{-}224)}$ = 8.5 min, $t_{R(224)}$ = 10.4 min.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.13 (1H, s), 7.59–7.46 (2H, m), 7.37–7.18 (7H, m), 5.49 (0.25H, d, *J* = 8.0 Hz), 5.31 (0.75H, d, *J* = 8.6 Hz), 5.22–5.05 (2H, m), 4.88–4.83 (0.25H, m), 4.79 (0.75H, dd, *J* = 15.5, 6.9 Hz), 4.58 (1H, dd, *J* = 8.6, 4.0 Hz), 3.70–3.62 (1H, m), 3.53–3.48 (0.25H, m), 3.38–3.22 (0.75H, m), 3.13 (1H, dd, *J* = 14.9, 5.7 Hz), 3.10–3.05 (0.25H, m), 2.97 (0.75H, dd, *J* = 14.9, 7.4 Hz), 2.22–2.13 (1H, m), 1.98–1.88 (2H, m), 1.78–1.72 (0.25H, m), 1.68–1.60 (9.75H, m), 1.43 (2.3H, s), 1.38 (6.7H, s)

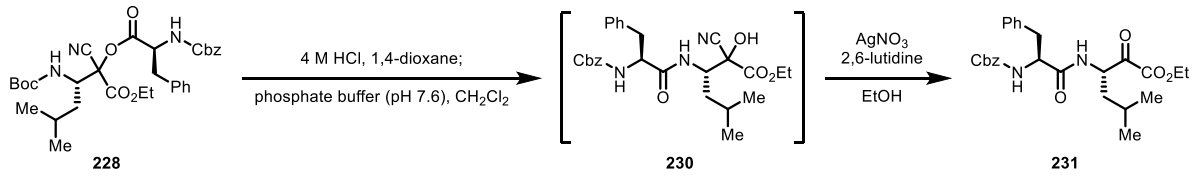
(Peaks of rotamers are observed in the ratio of 3:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 171.5, 170.7, 155.2, 149.7, 135.7, 135.3, 130.7, 128.6, 128.3, 128.1, 124.6, 124.3, 122.5, 118.8, 115.2, 115.1, 83.2, 79.6, 66.8, 64.8, 58.9, 51.6, 47.0, 29.0, 28.3, 28.2, 24.8 (Small peaks of rotamers are observed); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{33}H_{41}N_3O_7Na$ 614.2837; Found 614.2842; **IR (ATR):** 3307, 2976, 2931, 1723, 1646, 1501, 1447, 1371, 1254, 1162 cm^{-1}; **Optical Rotation:** $[\alpha]^{19}_D$ −22.9 (c 0.95, $CHCl_3$).

Cbz-Phe-Leu-CO_2H (55):



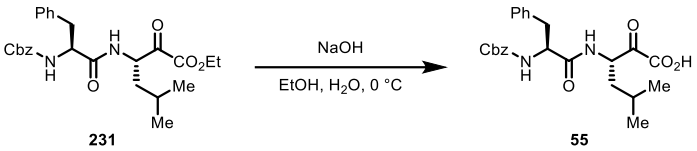
A 50 mL round bottom flask was charged with a stir bar, Mannich adduct **191** (1.70 g, 3.79 mmol, 1.0 equiv.), and 10% Pd/C (404 mg, 0.380 mmol, 10 mol%) under Ar atmosphere. Then the flask was evacuated and refilled with H_2 gas (1 atm). To the flask was added EtOAc (19 mL), and the suspension was vigorously stirred at room temperature for 5 hours. The mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure to afford the crude product of **226**.

A 100 mL round bottom flask was charged with a stir bar, the crude product of **226**, and CH_2Cl_2 (19 mL) under Ar atmosphere. To the stirred solution was added Cbz-Phe-OH (1.37 g, 4.57 mmol, 1.2 equiv.), DMAP (46.4 mg, 0.380 mmol, 10 mol%), and EDCI•HCl (1.09 g, 5.69 mmol, 1.5 equiv.), and the mixture was stirred at room temperature for 12 hours. The mixture was washed with aqueous citric acid (10%, 2 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10 → 85:15 → 80:20) to afford **228** (2.13 g, 3.58 mmol, 94% yield) as a white amorphous solid as a mixture of diastereomers.



A 100 mL round bottom flask was charged with a stir bar and **228** (1.79 g, 3.00 mmol, 1.0 equiv.), and cooled to 0 °C. To the flask was added HCl solution (4 M in 1,4-dioxane, 60 mmol, 15 mL), and the mixture was stirred at room temperature for 4 hours. Then the mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (30 mL). After cooling to 0 °C, to the solution was added phosphate buffer solution (pH 7.6, 0.1 M, 30 mL), and the mixture was stirred at same temperature for 1 hour. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated reduced pressure to afford the crude product of **230**.

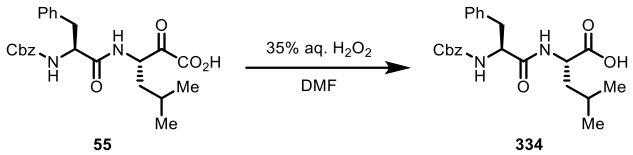
A 100 mL round bottom flask was charged with a stir bar, the crude product of **230**, and EtOH (30 mL). To the solution was added $AgNO_3$ (1.02 g, 6.00 mmol, 2.0 equiv.) and 2,6-lutidine (695 μL, 6.00 mmol, 2.0 equiv.), and the suspension was stirred at room temperature for 12 hours in the dark. The mixture was diluted with EtOAc (20 mL) and aqueous HCl (1 M, 20 mL), and filtered through a Celite pad. The aqueous layer was separated and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by Column chromatography (SiO_2, eluted with hexane/EtOAc = 70:30 → 60:40) to afford **231** (1.28 g, 2.73 mmol, 91% yield) as a yellow oil. Compound **231** was immediately used for next reaction to avoid the epimerization.



A 100 mL round bottom flask was charged with a stir bar, **231** (1.27 g, 2.71 mmol, 1.0 equiv.), and EtOH (24 mL), and cooled to 0 °C. To the solution was added aqueous NaOH (1 M, 3.5 mL, 1.3 equiv.) dropwise for 3 min, and stirred at same temperature for 1 hour. To the mixture was added EtOAc (30 mL), and the bilayer solution was acidified with aqueous HCl (1 M). The aqueous layer was separated and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization from Et_2O to afford Cbz-Phe-Leu-CO_2H **55** (1.01 g, 2.29 mmol, 85% yield) as a white solid.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 7.77 (1H, d, J = 6.9 Hz), 7.34–7.22 (9H, m), 7.22–7.16 (1H, m), 6.49 (0.9H, d, J = 8.6 Hz), 6.07 (0.1H, s), 5.10–5.06 (1H, m), 5.00 (1H, d, J = 12.6 Hz), 4.97 (1H, d, J = 12.6 Hz), 4.49 (1H, td, J = 9.0, 4.8 Hz), 3.18 (1H, dd, J = 14.3, 4.6 Hz), 2.90 (1H, dd, J = 14.0, 9.5 Hz), 1.76–1.72 (1H, m), 1.69–1.63 (1H, m), 1.56–1.51 (1H, m), 0.94 (3H, d, J = 6.3 Hz), 0.91 (3H, d, J = 6.3 Hz) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, acetone-*d*$_6$):** δ 194.9, 172.5, 162.6, 156.8, 138.5, 138.1, 130.2, 129.1, 129.0, 128.5, 128.4, 127.3, 66.6, 56.8, 54.6, 39.6, 38.7, 25.5, 23.4, 21.6; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{24}H_{28}N_2O_6Na$ 463.1840; Found 463.1840; **Melting Point:** 143.4–144.9 °C; **Optical Rotation:** $[\alpha]^{17}_D$ −3.4 (c 1.00, $CHCl_3$).

Separation of diastereomer of **55** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of dr of **55** was determined after the transformation to carboxylic acid **334** as a following procedure:



A 4 mL screw vial was charged with a stir bar, Cbz-Phe-Leu-CO_2H **55** (4.4 mg, 0.010 mmol, 1.0 equiv.), and DMF (0.10 mL). To the mixture was added H_2O_2 (35% in H_2O, 2.58 μL, 0.0300 mmol, 3.0 equiv.). After stirring at room temperature for 1 hour, the mixture was concentrated under reduced pressure to afford carboxylic acid **334** (>99:1 dr). The values of dr of the product **334** was determined by chiral SFC analysis: Trefoil CEL1, 1.0 mL/min, 15% methanol/CO_2, λ = 210–400 nm, $t_{R(334)}$ = 5.0 min, $t_{R(epi\text{-}334)}$ = 6.1 min.

General Procedure for Deprotection of *N*-Boc Protected Dipeptides (GP8):

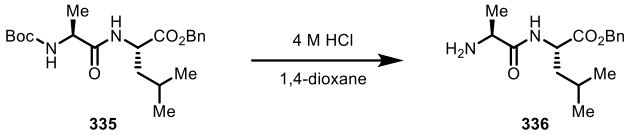
A 10 mL test tube equipped with a Teflon-coated screw cap was charged with a stir bar and dipeptide, and cooled to 0 °C. To the dipeptide was added HCl solution (4 M in 1,4-dioxane), and the mixture was stirred at room temperature until starting material was fully consumed. Then the mixture was concentrated under reduced pressure and washed with Et_2O (3 x). To the residue was added saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used for the decarboxylative peptide coupling without further purification.

General Procedure for Deprotection of *N*-Cbz Protected Dipeptides (GP9):

A 10 mL test tube equipped with a Teflon-coated screw cap was charged with a stir bar, dipeptide, and MeOH under Ar atmosphere.

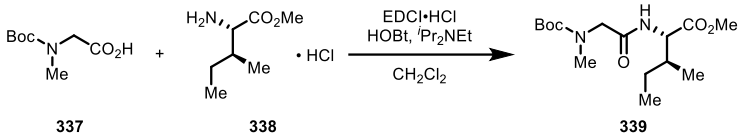
To the solution was added 10% Pd/C, and the flask was evacuated and refilled with H_2 gas (1 atm). After vigorous stirring at room temperature until starting material was fully consumed, the suspension was filtered through a Celite pad. The filtrate was concentrated under reduced pressure and used for the decarboxylative peptide coupling without further purification.

H-Ala-Leu-OBn (336):



According to GP8, Boc-Ala-Leu-OBn **335** (78.5 mg, 0.200 mmol) was treated with HCl solution (4 M in 1,4-dioxane, 1.0 mL) to afford H-Ala-Leu-OBn **336**, which was used for the decarboxylative peptide coupling without further purification.

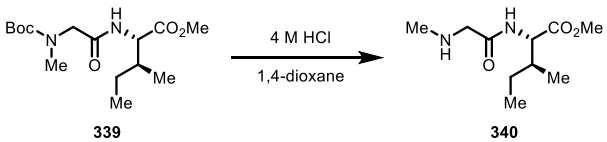
Boc-Sar-Ile-OMe (339):



A 50 mL round bottom flask was charged with a stir bar, Boc-Sar-OH **337** (284 mg, 1.50 mmol, 1.0 equiv.), H-Ile-OBn•HCl **338** (273 mg, 1.50 mmol, 1.0 equiv.), and CH_2Cl_2 (7.5 mL). To the mixture were added *i*-Pr_2NEt (784 µL, 4.50 mmol, 3.0 equiv.), HOBt (304 mg, 2.25 mmol, 1.5 equiv.), and EDCI•HCl (345 mg, 1.80 mmol, 1.2 equiv.), and the mixture was stirred at room temperature for 12 hours. The mixture was washed with saturated aqueous $NaHCO_3$ (3 x 5 mL), aqueous citric acid (10%, 3 x 5 mL), and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 70:30 → 65:35) to afford Boc-Sar-Ile-OBn **339** (408 mg, 1.29 mmol, 86% yield) as a colorless oil.

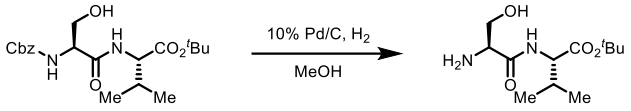
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.75 (0.5H, br s), 6.42 (0.5H, br s), 4.60 (1H, s), 3.95 (1H, d, J = 16.6 Hz), 3.82 (1H, d, J = 16.6 Hz), 3.74 (3H, s), 2.96 (3H, s), 1.95–1.87 (1H, m), 1.48 (9H, s), 1.45–1.36 (1H, m), 1.19–1.10 (1H, m), 0.93–0.90 (6H, m) (Peaks of rotamers are observed in the ratio of 1:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 172.1, 169.4, 168.9, 156.4, 155.2, 80.99, 80.7, 56.1, 53.3, 53.1, 52.1, 37.9, 37.7, 35.7, 35.6, 28.2, 24.9, 15.4, 11.5 (Peaks of rotamers are observed); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{15}H_{28}N_2O_5Na$ 339.1890; Found 339.1893; **IR (ATR):** 3315, 2969, 1743, 1697, 1536, 1455, 1392, 1249, 1154 cm^{-1}; **Optical Rotation:** $[\alpha]^{18}_D$ +23.4 (c 0.99, $CHCl_3$).

H-Sal-Ile-OMe (340):



According to **GP8**, Boc-Sar-Ile-OMe **339** (63.3 mg, 0.200 mmol) was treated with HCl solution (4 M in 1,4-dioxane, 1.0 mL) to afford H-Sar-Ile-OMe **340**, which was used for the decarboxylative peptide coupling without further purification.

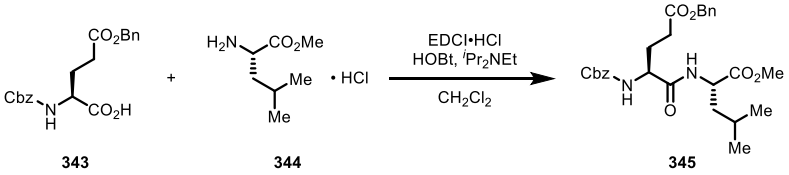
H-Ser-Val-O^{t}Bu (342):



341 342

According to **GP9**, Cbz-Ser-Val-O^{t}Bu **341** (39.5 mg, 0.100 mmol, 1.0 equiv.) was treated with 10% Pd/C (10.6 mg, 0.00996 mmol, 10 mol%) in MeOH (1.0 mL) under H_2 atmosphere (1 atm) to afford H-Ser-Val-O^{t}Bu **342**, which was used for the decarboxylative peptide coupling without further purification.

Cbz-Glu(OBn)-Leu-OMe (345):

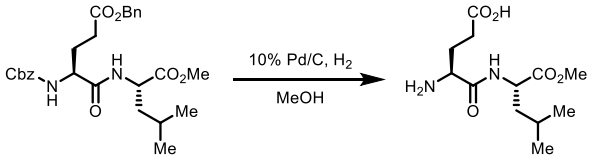


343 344 345

A 50 mL round bottom flask was charged with a stir bar, Cbz-Glu(OBn)-OH **343** (557 mg, 1.50 mmol, 1.0 equiv.), H-Leu-OMe•HCl **344** (273 mg, 1.50 mmol, 1.0 equiv.), and CH_2Cl_2 (7.5 mL). To the mixture were added *i*-Pr$_2$NEt (784 µL, 4.50 mmol, 3.0 equiv.), HOBt (304 mg, 2.25 mmol, 1.5 equiv.), and EDCI•HCl (345 mg, 1.80 mmol, 1.2 equiv.), and the mixture was stirred at room temperature for 12 hours. The mixture was washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), aqueous citric acid (10%, 3 x 10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 70:30 → 60:40 as gradient) to afford Cbz-Glu(OBn)-Leu-OMe **345** (621 mg, 1.24 mmol, 83% yield) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39–7.29 (10H, m), 6.56 (1H, d, J = 7.4 Hz), 5.57 (1H, d, J = 7.4 Hz), 5.16–5.07 (4H, m), 4.57 (1H, td, J = 8.7, 5.0 Hz), 4.31 (1H, dd, J = 13.0, 6.7 Hz), 3.71 (3H, s), 2.63–2.50 (2H, m), 2.20–2.12 (1H, m), 2.01–1.93 (1H, m), 1.67–1.61 (2H, m), 1.56–1.50 (1H, m), 0.94–0.90 (6H, m); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 173.4, 173.0, 171.0, 156.1, 136.1, 135.6, 128.6, 128.5, 128.32, 128.26, 128.2, 128.0, 67.0, 66.7, 53.7, 52.3, 50.8, 41.0, 30.2, 28.4, 24.8, 22.8, 21.7; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{27}H_{34}N_2O_7Na$ 521.2258; Found 521.2259; **IR (ATR):** 3315, 2955, 1668, 1536, 1452, 1398, 1256, 1165 cm^{-1}; **Melting Point:** 100.8–101.2 °C; **Optical Rotation:** $[\alpha]^{17}_D$ −7.4 (c 1.00, $CHCl_3$).

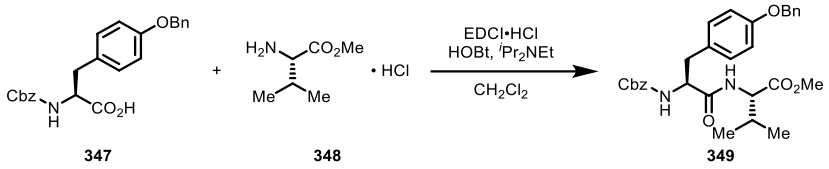
H-Glu-Leu-OMe (346):



345 346

According to **GP9**, Cbz-Glu(Bn)-Leu-OMe **345** (49.9 mg, 0.100 mmol) was treated with 10% Pd/C (10.6 mg, 0.00996 mmol, 10 mol%) in MeOH (1.0 mL) under H_2 atmosphere (1 atm) to afford H-Glu-Leu-OMe **346**, which was used for the decarboxylative peptide coupling without further purification.

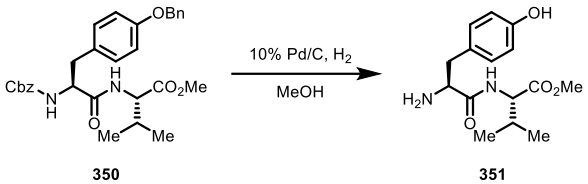
Cbz-Tyr(Bn)-Val-OMe (349):



A 50 mL round bottom flask was charged with a stir bar, Cbz-Tyr(Bn)-OH **347** (1.22 g, 3.01 mmol, 1.0 equiv.), H-Val-OMe•HCl **348** (503 mg, 3.00 mmol, 1.0 equiv.), and CH_2Cl_2 (15 mL). To the mixture were added *i*-Pr_2NEt (1.57 mL, 9.01 mmol, 3.0 equiv.), HOBt (608 mg, 4.50 mmol, 1.5 equiv.), and EDCI•HCl (690 mg, 3.60 mmol, 1.2 equiv.), and the mixture was stirred at room temperature for 12 hours. The mixture was washed with aqueous citric acid (10%, 3 x 10 mL), saturated aqueous $NaHCO_3$ (3 x 10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 75:25 → 70:30) to afford Cbz-Tyr(Bn)-Val-OMe **349** (1.12 g, 2.16 mmol, 72% yield) as a white solid.

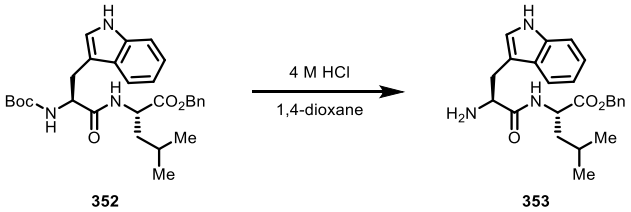
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.44–7.30 (10H, m), 7.11 (2H, d, J = 8.0 Hz), 6.89 (2H, d, J = 8.6 Hz), 6.23 (1H, d, J = 8.0 Hz), 5.30 (1H, d, J = 8.0 Hz), 5.12 (1H, d, J = 12.0 Hz), 5.08 (1H, d, J = 12.6 Hz), 5.03 (2H, s), 4.44 (1H, dd, J = 8.6, 4.6 Hz), 4.39 (1H, dd, J = 13.2, 6.3 Hz), 3.69 (3H, s), 3.07 (1H, dd, J = 14.3, 6.3 Hz), 2.99 (1H, dd, J = 13.7, 6.9 Hz), 2.12–2.04 (1H, m), 0.84 (3H, d, J = 6.9 Hz), 0.81 (3H, d, J = 6.9 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 171.7, 170.8, 157.9, 155.9, 136.9, 136.1, 130.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.4, 115.0, 70.0, 67.1, 57.3, 56.3, 52.1, 37.4, 31.2, 18.8, 17.7; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{30}H_{34}N_2O_6Na$ 541.2309; Found 541.2311; **IR (ATR):** 3309, 3065, 2956, 1662, 1519, 1458, 1395, 1250 cm^{-1}; **Melting Point:** 136.3–136.6 °C; **Optical Rotation:** $[\alpha]^{18}_D$ +11.7 (c 1.00, $CHCl_3$).

H-Tyr-Val-OMe (350):



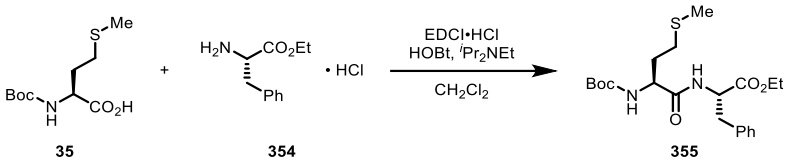
According to **GP9**, Cbz-Tyr(Bn)-Val-OMe **349** (104 mg, 0.200 mmol) was treated with 10% Pd/C (21.3 mg, 0.0200 mmol, 10 mol%) in MeOH (2.0 mL) under H_2 atmosphere (1 atm) to afford H-Tyr-Val-OMe **350**, which was used for the decarboxylative peptide coupling without further purification.

H-Trp-Leu-OBn (352):



According to **GP8**, Boc-Trp-Leu-OBn **351** (103.5 mg, 0.204 mmol) was treated with HCl solution (4 M in 1,4-dioxane, 1.0 mL) to afford H-Trp-Leu-OBn **352**, which was used for the decarboxylative peptide coupling without further purification.

Boc-Met-Phe-OEt (355):

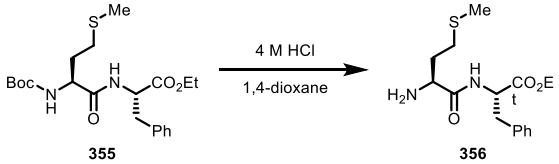


35 354 355

A 50 mL round bottom flask was charged with a stir bar, Cbz-Met-OH **353** (748 mg, 3.00 mmol, 1.0 equiv.), H-Phe-OEt•HCl **354** (689 mg, 3.00 mmol, 1.0 equiv.), and CH_2Cl_2 (15 mL). To the mixture were added *i*-Pr_2NEt (1.57 mL, 9.01 mmol, 3.0 equiv.), HOBt (608 mg, 4.50 mmol, 1.5 equiv.), and EDCI•HCl (690 mg, 3.60 mmol, 1.2 equiv.), and the mixture was stirred at room temperature for 12 hours. The mixture was washed with aqueous citric acid (10%, 3 x 10 mL), saturated aqueous $NaHCO_3$ (3 x 10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 78:20 → 75:25) to afford Cbz-Met-Phe-OEt **355** (1.17 g, 2.76 mmol, 92% yield) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31–7.28 (2H, m), 7.25–7.23 (1H, m), 7.13 (2H, d, J = 6.9 Hz), 6.58 (1H, d, J = 8.0 Hz), 5.14 (1H, d, J = 6.9 Hz), 4.83 (1H, dd, J = 13.7, 5.7 Hz), 4.26 (1H, dd, J = 12.6, 5.7 Hz), 4.17 (2H, q, J = 7.1 Hz), 3.16-3.08 (2H, m), 2.54 (2H, t, J = 6.9 Hz), 2.06 (3H, s), 2.05-1.99 (1H, m), 1.94–1.86 (1H, m), 1.44 (9H, s), 1.24 (3H, t, J = 7.2 Hz); **^{13}C-NMR (151 MHz, CD_3OD):** δ 174.5, 172.7, 157.7, 137.9, 130.4, 129.5, 127.9, 80.7, 62.4, 55.1, 55.0, 38.4, 33.0, 31.0, 28.7, 15.2, 14.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{21}H_{32}N_2O_5NaS$ 447.1924; Found 447.1929; **IR (ATR):** 3308, 2977, 2926, 1665, 1523, 1447, 1375, 1173 cm^{-1}; **Melting Point:** 116.4–116.5 °C; **Optical Rotation:** $[\alpha]^{17}_D$ +26.4 (c 1.00, $CHCl_3$).

H-Met-Phe-OEt (356):



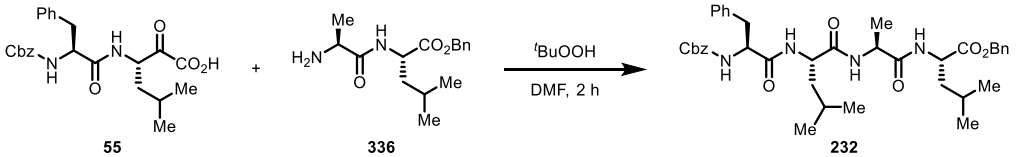
355 356

According to **GP8**, Boc-Met-Phe-OEt **355** (84.9 mg, 0.200 mmol) was treated with HCl solution (4 M in 1,4-dioxane, 1.0 mL) to afford H-Met-Phe-OEt **356**, which was used for the decarboxylative peptide coupling without further purification.

General Procedure for the Decarboxylative Peptide Coupling (GP10):

A 10 mL test tube equipped with a Teflon-coated screw cap was charged with a stir bar, dipeptide (1.0 equiv.), and DMF (5.0 mL/mmol). To the solution was added *t*-BuOOH (70% in H_2O, 1.5 equiv.), and peptide-α-ketoacid (1.2 equiv.) in DMF (5.0 mL/mmol). After stirring at room temperature for appropriate time, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography to afford corresponding tetrapeptide if otherwise noted. The value of dr was determined by chiral SFC analysis.

Cbz-Phe-Leu-Ala-Leu-OBn (232):

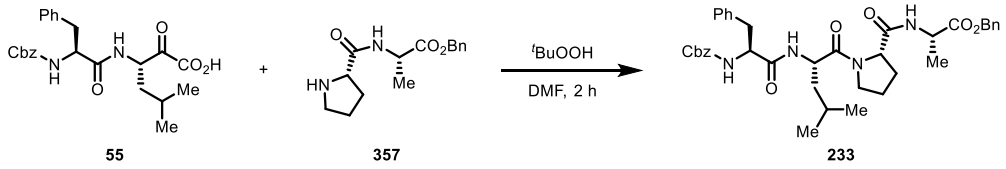


55 336 232

According to **GP10**, H-Ala-Leu-OBn **336** (14.6 mg, 0.0499 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (26.4 mg, 0.0599 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 10.3 μL, 0.0752 mmol, 1.5 equiv.) in DMF (0.25 + 0.25 mL) at room temperature for 2 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 60:40 → 50:50) afforded Cbz-Phe-Leu-Ala-Leu-OBn **232** (31.3 mg, 0.0456 mmol, 91% yield, >99:1 dr (the value of dr of the crude product was 99:1)) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IB-3/SFC, 1.0 mL/min, 8% methanol/CO_2, λ = 210–400 nm, $t_{R(epi\text{-}232)}$ =8.0 min, $t_{R(232)}$ = 9.2 min.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36–7.29 (8H, m), 7.28–7.24 (2H, m), 7.24–7.17 (5H, m), 7.13–7.06 (3H, m), 5.65 (1H, br s), 5.17 (1H, d, *J* = 12.0 Hz), 5.10 (1H, d, *J* = 12.6 Hz), 5.05 (1H, d, *J* = 12.6 Hz), 5.01 (1H, d, *J* = 12.0 Hz), 4.71–4.61 (3H, m), 4.55 (1H, q, *J* = 5.7 Hz), 3.07 (1H, dd, *J* = 14.3, 5.7 Hz), 3.00 (1H, dd, *J* = 13.7, 6.9 Hz), 1.65–1.42 (6H, m), 1.36 (3H, d, *J* = 6.9 Hz), 0.88–0.84 (12H, m); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 172.5, 172.0, 171.5, 171.0, 156.2, 136.03, 135.99, 135.4, 129.3, 128.6, 128.5, 128.3, 128.22, 128.16, 128.0, 127.0, 67.1, 66.9, 56.0, 51.6, 50.8, 48.6, 41.7, 41.0, 38.7, 24.73, 24.65, 22.82, 22.79, 22.1, 21.7, 18.3 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{39}H_{51}N_4O_7$ 687.3755; Found 687.3752; **IR (ATR):** 3267, 2948, 1740, 1675, 1628, 1538, 1391, 1254, 1160 cm^{-1}; **Melting Point:** 185.3–186.5 °C; **Optical Rotation:** $[\alpha]^{17}_D$ −42.3 (c 0.96, $CHCl_3$).

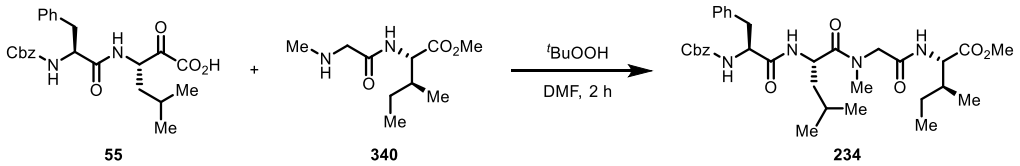
Cbz-Phe-Leu-Pro-Ala-OBn (233):



According to **GP10**, H-Pro-Ala-OBn **357** (13.8 mg, 0.0499 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (26.4 mg, 0.0599 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 10.3 μL, 0.0752 mmol, 1.5 equiv.) in DMF (0.25 + 0.25 mL) at room temperature for 2 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 50:50 → 35:65) afforded Cbz-Phe-Leu-Pro-Ala-OBn **233** (27.8 mg, 0.0414 mmol, 83% yield, >99:1 dr (The dr value of the crude product was >99:1)) as a colorless oil. The value of dr was determined by chiral SFC analysis: Trefoil CEL1, 1.0 mL/min, 10% methanol/CO_2, λ = 210–400 nm, $t_{R(epi\text{-}233)}$ = 7.3 min, $t_{R(233)}$ = 8.3 min.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.58 (1H, s), 7.37–7.25 (11H, m), 7.21–7.15 (3H, m), 7.08–7.03 (2H, m), 5.39 (1H, d, *J* = 8.6 Hz), 5.17 (1H, d, *J* = 12.6 Hz), 5.09 (1H, d, *J* = 12.0 Hz), 5.04 (1H, d, *J* = 12.0 Hz), 4.98 (1H, d, *J* = 12.6 Hz), 4.86 (1H, q, *J* = 6.9 Hz), 4.72 (1H, q, *J* = 4.6 Hz), 4.55–4.49 (2H, m), 3.77–3.71 (1H, m), 3.65–3.58 (1H, m), 3.02 (1H, dd, *J* = 13.7, 4.6 Hz), 2.90 (1H, dd, *J* = 13.2, 6.6 Hz), 2.20–2.11 (2H, m), 1.99 (2H, s), 1.60–1.52 (1H, m), 1.50 (2H, t, *J* = 6.6 Hz), 1.27 (3H, d, *J* = 6.9 Hz), 0.96 (2.7H, d, *J* = 6.3 Hz), 0.90–0.83 (3.3H, m) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 172.5, 171.8, 170.9, 170.7, 155.9, 136.3, 136.1, 135.4, 129.3, 128.6, 128.5, 128.3, 128.1, 128.0, 126.9, 66.9, 59.7, 55.5, 50.9, 48.9, 48.0, 47.4, 42.0, 39.3, 31.6, 28.1, 25.0, 24.6, 23.3, 22.6, 21.8, 17.7, 14.1 (Peaks of rotamers are observed); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{38}H_{47}N_4O_7$ 671.3439; Found 671.3436; **IR (ATR):** 3291, 3065, 2956, 1673, 1629, 1540, 1450, 1258 cm^{-1}; **Optical Rotation:** $[\alpha]^{19}_D$ −61.6 (c 0.84, $CHCl_3$).

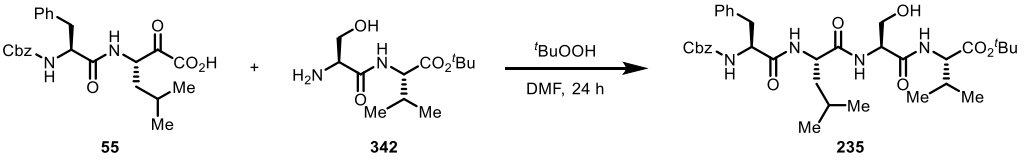
Cbz-Phe-Leu-Sar-Ile-OMe (234):



According to **GP10**, H-Sar-Ile-OMe **340** (21.6 mg, 0.0999 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (52.9 mg, 0.120 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 20.5 µL, 0.150 mmol, 1.5 equiv.) in DMF (0.50 + 0.50 mL) at room temperature for 2 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 70:30 → 65:35) to afford Cbz-Phe-Leu-Sar-Ile-OMe **234** (44.4 mg, 0.0727 mmol, 73% yield, 99:1 dr (The value of dr of the crude product was 99:1)) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IB-3/SFC, 1.0 mL/min, 10% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{epi}\text{-}234)}$ = 3.0 min, $t_{R(234)}$ = 3.4 min.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.37–7.29 (5H, m), 7.29–7.20 (3H, m), 7.19–7.15 (2H, m), 7.06 (0.1H, d, *J* = 6.9 Hz), 6.81 (0.9H, d, *J* = 8.0 Hz), 6.63 (0.9H, d, *J* = 6.3 Hz), 6.40 (0.1H, d, *J* = 6.9 Hz), 5.32 (0.9H, d, *J* = 8.0 Hz), 5.25 (0.1H, d, *J* = 7.4 Hz), 5.10-5.04 (2H, m), 4.88 (0.9H, dd, *J* = 13.7, 8.0 Hz), 4.67 (0.1H, s), 4.54 (2H, dd, *J* = 8.6, 4.6 Hz), 4.18–4.00 (2H, m), 3.70 (3H, s), 3.18 (2.7H, s), 3.05 (2H, d, *J* = 6.3 Hz), 2.98 (0.3H, s), 1.95 (0.1H, s), 1.90-1.85 (0.9H, m), 1.57–1.50 (1H, m), 1.48–1.44 (2H, m), 1.42–1.34 (1H, m), 1.18–1.11 (1H, m), 0.96–0.83 (12H, m); **^{13}C-NMR (151 MHz, $CDCl_3$):** *δ* 172.8, 172.2, 170.8, 168.2, 155.8, 136.2, 129.4, 128.6, 128.5, 128.2, 128.1, 127.0, 67.0, 56.5, 55.7, 52.2, 52.1, 47.7, 41.5, 38.4, 37.5, 36.6, 25.1, 24.6, 23.2, 21.7, 15.4, 11.5 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{33}H_{47}N_4O_7$ 611.3439; Found 611.3435; IR (ATR): 3299, 3065, 2958, 1635, 1537, 1254 cm^{-1}; **Melting Point:** 97.7–98.5 °C; **Optical Rotation:** $[\alpha]^{19}_D$ +2.9 (c 0.52, $CHCl_3$).

Cbz-Phe-Leu-Ser-Val-O^{t}Bu (235):

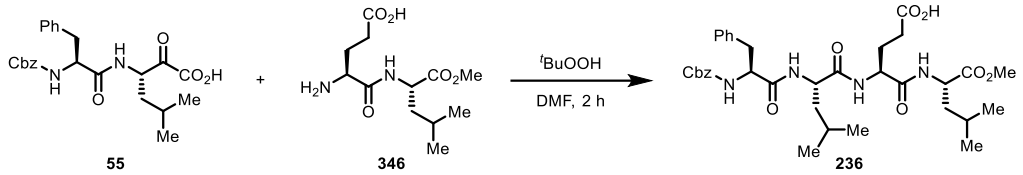


According to **GP10**, H-Ser-Val-O^{t}Bu **342** (13.0 mg, 0.0499 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (26.4 mg, 0.0599 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 10.3 µL, 0.0752 mmol, 1.5 equiv.) in DMF (0.25 + 0.25 mL) at room temperature for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 50:50 → 40:60) afforded Cbz-Phe-Leu-Ser-O^{t}Bu **235** (18.7 mg, 0.0286 mmol, 57% yield, >99:1 dr (The value of dr of the crude product was >99:1)) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IC-3/SFC, 1.0 mL/min, 15% methanol/CO_2, λ = 210–400 nm, $t_{R(235)}$ = 3.7 min, $t_{R(\textit{epi}\text{-}235)}$ = 4.2 min.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.42–7.25 (7H, m), 7.24–7.15 (4H, m), 7.14–7.08 (2H, m), 5.72 (1H, br s), 5.08 (1H, d, *J* = 12.6 Hz), 5.02 (1H, d, *J* = 12.0 Hz), 4.68–4.59 (3H, m), 4.41 (1H, dd, *J* = 8.6, 4.6 Hz), 4.01–3.94 (1H, m), 3.89–3.81 (1H, m), 3.69–3.62 (1H, m), 3.06 (1H, dd, *J* = 13.7, 5.7 Hz), 2.99 (1H, dd, *J* = 13.7, 7.4 Hz), 2.22–2.14 (1H, m), 1.63–1.42 (12H, m), 0.92 (3H, d, *J* = 7.4 Hz), 0.90 (3H, d, *J* = 6.9 Hz), 0.87 (6H, d, *J* = 6.3 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** *δ* 172.4, 171.0, 170.7, 170.6, 156.1, 136.0, 129.3, 128.5, 128.2, 128.1, 128.0, 127.0, 82.2, 67.1, 62.7, 57.9, 55.9, 54.1, 51.6, 41.7, 38.6, 31.0, 28.0, 24.6, 22.8, 22.0, 19.0, 18.6 (One aromatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{35}H_{50}N_4O_8Na$ 677.3521; Found 677.3526; **IR (ATR):** 3288, 3071, 2964, 1641, 1535, 1254, 1151 cm^{-1}; **Melting Point:** 80.4–84.2 °C; **Optical Rotation:**

$[\alpha]^{19}_D$ −17.3 (c 1.00, $CHCl_3$).

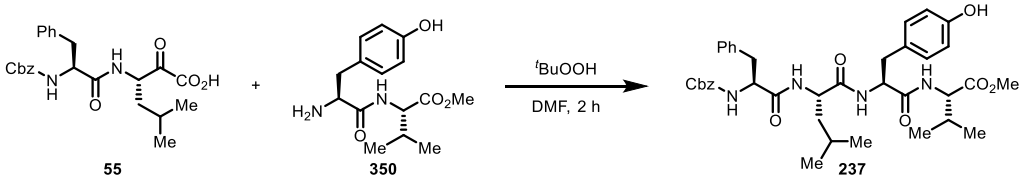
Cbz-Phe-Leu-Glu-Leu-OMe (236):



According to **GP10**, H-Glu-Leu-OMe **346** (13.7 mg, 0.0499 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (26.4 mg, 0.0599 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 10.3 µL, 0.0752 mmol, 1.5 equiv.) in DMF (0.25 + 0.25 mL) at room temperature for 2 hours. The crude was subsequently washed with Et_2O three times and aqueous HCl (1 M) three times to afford Cbz-Phe-Leu-Glu-Leu-OMe **236** (26.8 mg, 0.0401 mmol, 80% yield, >99:1 dr (The value of dr of the crude product was 98:2)) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IC-3/SFC, 1.0 mL/min, 15% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{epi}\text{-}236)}$ = 3.6 min, $t_{R(236)}$ = 4.3 min.

^{1}H-NMR (500 MHz, CD_3OD): δ 8.28 (1H, d, J = 8.0 Hz), 8.20–8.14 (2H, m), 7.32–7.18 (10H, m), 5.04 (1H, d, J = 12.6 Hz), 4.99 (1H, d, J = 12.6 Hz), 4.46–4.41 (1H, m), 4.41–4.36 (3H, m), 3.69 (3H, s), 3.12 (1H, dd, J = 14.0, 4.9 Hz), 2.86 (1H, dd, J = 14.0, 9.5 Hz), 2.41 (2H, t, J = 8.0 Hz), 2.14–2.07 (1H, m), 1.99–1.91 (1H, m), 1.72–1.65 (1H, m), 1.65–1.55 (5H, m), 0.94–0.91 (6H, m), 0.89 (6H, d, J = 6.3 Hz) (One NH peak and CO_2H peak is missing); **^{13}C-NMR (151 MHz, CD_3OD):** δ 176.6, 175.1, 174.4, 174.3, 173.6, 158.4, 138.4, 138.1, 130.4, 129.5, 129.0, 128.7, 127.8, 67.7, 57.8, 53.7, 53.6, 53.3, 52.7, 52.3, 52.2, 49.6, 41.6, 41.2, 38.8, 31.04, 30.92, 28.3, 28.2, 25.8, 25.7, 23.5, 23.4, 22.0, 21.8 (One aromatic carbon peak is missing due to overlapping, and peaks of rotamers are observed); **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{35}H_{49}N_4O_9$ 669.3500; Found: 669.3504; **IR (ATR):** 3290, 3068, 2956, 1732, 1695, 1631, 1533, 1444, 1255, 1218 cm^{-1}; **Melting Point:** 194.8 °C (decomposition); **Optical Rotation:** $[\alpha]^{22}_D$ −10.8 (c 0.72, DMSO).

Cbz-Phe-Leu-Tyr-Val-OMe (237):

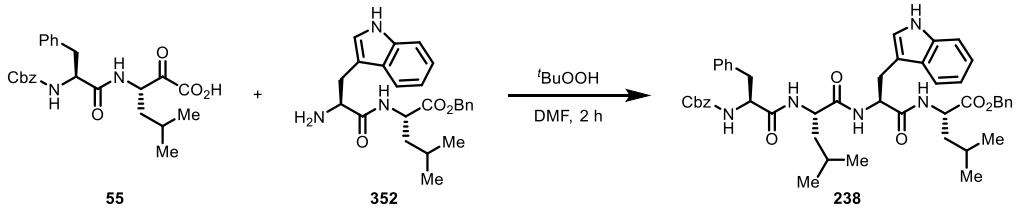


According to **GP10**, H-Tyr-Val-OMe **350** (14.7 mg, 0.0499 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (26.4 mg, 0.0599 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 10.3 µL, 0.0752 mmol, 1.5 equiv.) in DMF (0.25 + 0.25 mL) at room temperature for 2 hours. The crude product was washed with Et_2O three times to afford Cbz-Phe-Leu-Tyr-Val-OMe **237** (29.3 mg, 0.0425 mmol, 85% yield, >99:1 dr (The value of dr of the crude product was 98:2)) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IB-3/SFC, 1.0 mL/min, 7% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{epi}\text{-}237)}$ = 18.7 min, $t_{R(237)}$ = 20.2 min.

^{1}H-NMR (500 MHz, CD_3OD): δ 7.32–7.17 (10H, m), 7.00 (2H, d, J = 8.6 Hz), 6.66 (2H, dt, J = 9.0, 2.3 Hz), 5.01 (1H, d, J = 12.6 Hz), 4.97 (1H, d, J = 12.6 Hz), 4.58 (1H, t, J = 7.4 Hz), 4.42–4.38 (2H, m), 4.28–4.25 (1H, m), 3.65 (3H, s), 3.09–2.97 (2H, m), 2.86–2.77 (2H, m), 2.10–2.03 (1H, m), 1.60–1.51 (1H, m), 1.51–1.45 (2H, m), 0.90–0.85 (12H, m); **^{13}C-NMR (151 MHz, CD_3OD):** δ 174.2, 174.1, 173.5, 173.1, 158.3, 157.3, 138.6, 138.1, 131.4, 130.4, 129.4, 128.9, 128.7, 128.71, 127.68, 116.2, 67.6, 59.2, 57.7, 56.1, 53.1, 52.5, 42.1, 39.0, 38.0, 32.0, 25.7, 23.4, 22.1, 19.5, 18.6 (One aromatic carbon peak is missing due to overlapping);

HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{38}H_{49}N_4O_8$ 689.3550; Found 689.3544; **IR (ATR):** 3285, 2958, 1636, 1523, 1444, 1226 cm^{-1}; **Melting Point:** 207.7–207.9 °C; **Optical Rotation:** $[\alpha]^{19}_D$ −2.5 (c 0.96, DMSO).

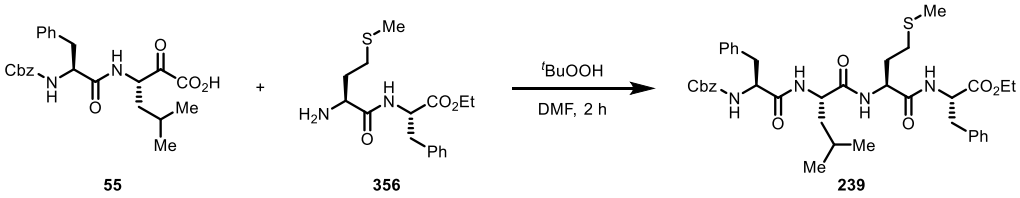
Cbz-Phe-Leu-Trp-Leu-OBn (238):



According to **GP10**, H-Trp-Leu-OBn **352** (20.4 mg, 0.0501 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (26.4 mg, 0.0599 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 10.3 μL, 0.0752 mmol, 1.5 equiv.) in DMF (0.25 + 0.25 mL) at room temperature for 2 hours. The crude product was washed with Et_2O three times to afford Cbz-Phe-Leu-Trp-Leu-OBn **238** (29.4 mg, 0.0367 mmol, 73% yield, >99:1 dr (The value of dr of the crude product was 98:2)) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IB-3/SFC, 1.0 mL/min, 15% methanol/CO_2, λ = 210–400 nm, $t_{R(\mathbf{238})}$ = 9.4 min, $t_{R(\textit{epi}\text{-}\mathbf{238})}$ = 10.3 min.

^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ 10.80 (1H, s), 8.38 (1H, d, *J* = 8.0 Hz), 8.06–8.02 (2H, m), 7.52 (1H, d, *J* = 7.4 Hz), 7.43 (1H, d, *J* = 8.6 Hz), 7.35–7.19 (15H, m), 7.15 (1H, t, *J* = 6.9 Hz), 7.11 (1H, d, *J* = 1.8 Hz), 7.03 (1H, t, *J* = 7.4 Hz), 6.95 (1H, t, *J* = 7.2 Hz), 5.09 (2H, s), 4.91 (1.8H, s), 4.86 (0.2H, s), 4.59 (1H, dd, *J* = 13.5, 7.7 Hz), 4.37–4.28 (2H, m), 4.27–4.20 (1H, m), 3.09 (1H, dd, *J* = 14.9, 5.2 Hz), 2.93–2.88 (2H, m), 2.66 (1H, dd, *J* = 13.7, 10.9 Hz), 1.61–1.45 (4H, m), 1.39 (2H, t, *J* = 7.4 Hz), 0.86–0.73 (12H, m) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, DMSO-*d*$_6$):** δ 172.1, 171.7, 171.5, 171.3, 155.8, 138.2, 137.0, 135.9, 129.2, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.43, 127.37, 126.7, 126.2, 123.4, 120.8, 118.4, 118.2, 111.2, 109.8, 65.9, 65.2, 55.9, 52.9, 51.1, 50.3, 41.0, 40.0, 37.2, 27.5, 24.08, 24.06, 23.1, 22.8, 21.7, 21.2; **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{47}H_{56}N_5O_7$ 802.4180; Found: 802.4185; **IR (ATR):** 3281, 2955, 1737, 1692, 1634, 1535, 1445, 1251 cm^{-1}; **Melting Point:** 198.2–199.6 °C; **Optical Rotation:** $[\alpha]^{23}_D$ −15.9 (c 1.00, DMSO).

Cbz-Phe-Leu-Met-Phe-OEt (239):

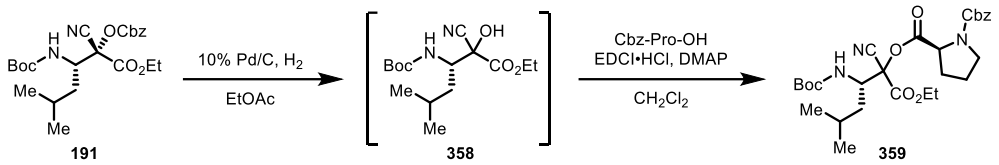


According to **GP10**, H-Met-Phe-OEt **356** (16.2 mg, 0.0499 mmol, 1.0 equiv.) reacted with Cbz-Phe-Leu-CO_2H **55** (26.4 mg, 0.0599 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 10.3 μL, 0.0752 mmol, 1.5 equiv.) in DMF (0.25 + 0.25 mL) at room temperature for 2 hours. The crude was suspended in EtOAc and filtered through a Celite pad. The filter cake was washed with EtOAc three times, and suspended in DMF. After vigorous stirring for 1 hour, the suspension was filtered through glass filter. The filtrate was concentrated under reduced pressure to afford Cbz-Phe-Leu-Met-Phe-OEt **239** (34.5 mg, 0.0480 mmol, 96% yield, >99:1 dr (The value of dr of the crude product was 98:2)) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IB-3/SFC, 1.0 mL/min, 10% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{epi}\text{-}\mathbf{239})}$ = 5.8 min, $t_{R(\mathbf{239})}$ = 6.5 min.

^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ 8.34 (1H, d, *J* = 7.4 Hz), 8.18 (0.1H, d, *J* = 9.2 Hz), 8.11 (0.9H, d, *J* = 8.0 Hz), 7.97 (1H, d, *J*

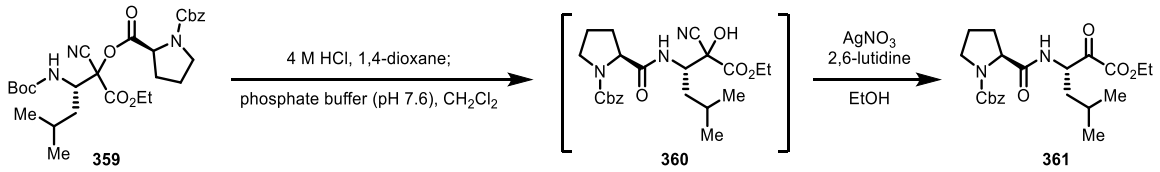
= 8.0 Hz), 7.48 (0.9H, d, *J* = 8.6 Hz), 7.32–7.16 (15H, m), 7.08 (0.1H, d, *J* = 9.7 Hz), 4.95–4.88 (2H, m), 4.42 (1H, dd, *J* = 14.9, 8.0 Hz), 4.38–4.28 (2H, m), 4.27–4.23 (1H, m), 4.00 (2H, q, *J* = 7.1 Hz), 3.02–2.90 (3H, m), 2.70 (1H, dd, *J* = 13.7, 10.9 Hz), 2.44–2.35 (2H, m), 2.01 (3H, s), 1.90–1.81 (1H, m), 1.79–1.71 (1H, m), 1.61–1.54 (1H, m), 1.48–1.36 (2H, m), 1.07 (3H, t, *J* = 6.9 Hz), 0.87 (2.7H, d, *J* = 6.3 Hz), 0.83–0.76 (3.3H, m) (Peaks of rotamers are observed in the ratio of 9:1); **^{13}C-NMR (151 MHz, DMSO-*d*$_6$):** δ 171.8, 171.5, 171.3, 171.0, 155.8, 138.2, 137.04, 136.99, 129.2, 129.1, 128.3, 128.2, 128.0, 127.7, 127.4, 126.8, 126.6, 126.2, 65.2, 60.5, 56.0, 53.6, 51.5, 51.0, 48.6, 40.7, 40.0, 37.3, 36.5, 32.3, 29.3, 24.1, 23.1, 21.6 (Peaks of rotamers are observed); **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{39}H_{51}N_4O_7S$ 719.3478; Found: 719.3483; **IR (ATR):** 3278, 2958, 1726, 1690, 1634, 1539, 1445, 1255 cm^{-1}; **Melting Point:** 200.9–202.1 °C; **Optical Rotation:** $[\alpha]^{24}_D$ −1.9 (c 0.99, DMSO).

Cbz-Pro-Leu-CO$_2$H (240):



A 50 mL round bottom flask was charged with a stir bar, Mannich adduct **191** (314 mg, 0.700 mmol, 1.0 equiv.), and 10% Pd/C (74.5 mg, 0.0700 mmol, 10 mol%) under Ar atmosphere. Then the flask was evacuated and refilled with H_2 gas (1 atm). To the flask was added EtOAc (3.5 mL), and the suspension was vigorously stirred at room temperature for 1.5 hours. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to afford the crude product of **358**.

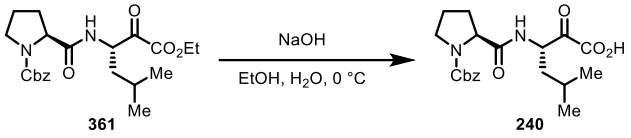
A 100 mL round bottom flask was charged with a stir bar, the crude product of **358**, and CH_2Cl_2 (3.5 mL) under Ar atmosphere. To the stirred solution was added Cbz-Pro-OH (209 mg, 0.840 mmol, 1.2 equiv.), DMAP (8.55 mg, 0.0700 mmol, 10 mol%), and EDCI•HCl (201 mg, 1.05 mmol, 1.5 equiv.), and the mixture was stirred at room temperature for 12 hours. The mixture was washed with aqueous citric acid (10%, 2 x 5 mL), saturated aqueous $NaHCO_3$ (2 x 5 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 85:15 → 80:20) to afford **359** (313 mg, 0.574 mmol, 82% yield) as a white amorphous solid as a mixture of diastereomers.



A 100 mL round bottom flask was charged with a stir bar and **359** (311.0 mg, 0.570 mmol, 1.0 equiv.), and was cooled to 0 °C. To the flask was added HCl solution (4 M in 1,4-dioxane, 2.9 mL), and the mixture was stirred at room temperature for 2.5 hours. Then the mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (5.8 mL). After cooling to 0 °C, to the solution was added phosphate buffer solution (pH 7.6, 0.1 M, 5.8 mL), and the mixture was stirred at same temperature for 1 hour. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated reduced pressure to afford the crude product of **360**.

A 100 mL round bottom flask was charged with a stir bar, the crude product of **360**, and EtOH (5.8 mL). To the solution was added $AgNO_3$ (194 g, 1.14 mmol, 2.0 equiv.) and 2,6-lutidine (132 μL, 1.14 mmol, 2.0 equiv.), and the suspension was stirred at room temperature for 12 hours in the dark. The mixture was diluted with EtOAc (10 mL) and aqueous HCl (1 M, 10 mL), and filtered through a Celite pad. The aqueous layer was separated and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The

residue was purified by column chromatography (SiO_2, eluted with hexane/EtOAc = 60:40 → 50:50) to afford **361** (205 mg, 0.490 mmol, 86% yield) as a yellow oil. This compound was immediately used for next reaction to avoid the epimerization.

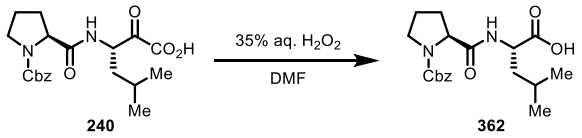


361 **240**

A 100 mL round bottom flask was charged with a stir bar, **361** (205 mg, 0.490 mmol, 1.0 equiv.), and EtOH (4.5 mL), and cooled to 0 °C. To the solution was added NaOH (1 M, 0.56 mL, 1.1 equiv.) dropwise for 30 sec, and stirred at same temperature for 20 min. To the mixture was added EtOAc (30 mL), and the bilayer solution was acidified with aqueous HCl (1 M). The aqueous layer was separated and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization from Et_2O to afford Cbz-Phe-Leu-CO_2H **240** (107 mg, 0.274 mmol, 56% yield) as a white solid.

^{1}H-NMR (500 MHz, acetone-*d*$_6$): δ 7.74 (1H, s), 7.40–7.28 (5H, m), 5.15–4.96 (3H, m), 4.37–4.32 (1H, m), 3.54–3.48 (1H, m), 3.45–3.38 (1H, m), 2.24–1.59 (4H, m), 1.58–1.48 (3H, m), 0.92 (3H, d, J = 6.3 Hz), 0.88–0.83 (3H, m); **^{13}C-NMR (151 MHz, acetone-*d*$_6$):** δ 195.1, 173.5, 173.0, 162.8, 155.7, 155.0, 138.2, 129.2, 129.1, 128.6, 128.5, 128.4, 128.1, 67.1, 66.9, 60.9, 60.5, 54.6, 54.5, 47.9, 47.5, 39.5, 39.2, 32.0, 25.5, 24.9, 23.9, 23.4, 23.4, 21.7, 21.5 (Peaks of rotamers are observed); **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{20}H_{27}N_2O_6$ 391.1864; Found 391.1864; **Melting Point:** 128.1–130.3 °C; **Optical Rotation:** $[\alpha]^{17}_D$ −69.8 (c 1.00, $CHCl_3$).

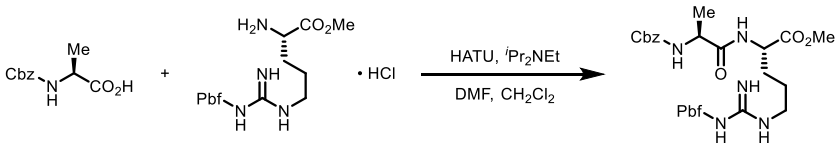
Separation of diastereomer of **240** was hard under any conditions in chiral HPLC or SFC analysis, therefore the value of dr of **231** was determined after the transformation to carboxylic acid **362** as a following procedure:



240 **362**

A 4 mL screw vial was charged with a stir bar, Cbz-Pro-Leu-CO_2H **240** (3.9 mg, 0.010 mmol, 1.0 equiv.), and DMF (0.10 mL). To the mixture was added H_2O_2 (35% in H_2O, 2.58 μL, 0.0300 mmol, 3.0 equiv.). After stirring at room temperature for 1 hour, the mixture was concentrated under reduced pressure to afford carboxylic acid **362** (99:1 dr). The value of dr was determined by chiral SFC analysis: CHIRALPAK IC-3/SFC, 1.0 mL/min, 15% methanol/CO_2, λ = 210–400 nm, $t_{R(\textit{epi}\text{-}362)}$ = 2.9 min, $t_{R(362)}$ = 4.0 min.

Cbz-Ala-Arg(Pbf)-OMe (365):



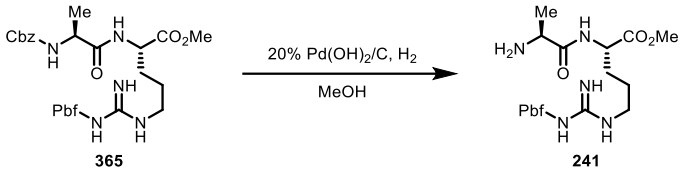
363 **364** **365**

A 20 mL round bottom flask was charged with a stir bar, Cbz-Ala-OH **363** (112 mg, 0.500 mmol, 1.0 equiv.), H-Arg(Pbf)-OMe•HCl **364** (239 mg, 0.500 mmol, 1.0 equiv.), DMF (0.50 mL), and CH_2Cl_2 (2.0 mL). To the solution were added *i*-Pr_2NEt (261 μL, 1.50 mmol, 3.0 equiv.) and HATU (228 mg, 0.600 mmol, 1.2 equiv.), and the mixture was stirred at room temperature for 3 hours. Then the mixture was washed with aqueous HCl (1 M, 2 x 2 mL), saturated aqueous $NaHCO_3$ (2 mL), and brine (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CHCl_3$/MeOH = 98:2 → 96:4) to afford Cbz-Ala-Arg(Pbf)-OMe **365** (304 mg, 0.470 mmol, 94% yield) as a white amorphous solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36 (1H, s), 7.31–7.25 (5H, m), 6.27 (2H, s), 6.09 (1H, s), 5.87 (1H, s), 5.05 (1H, d, J = 12.6 Hz),

4.99 (1H, d, J = 12.6 Hz), 4.47 (1H, s), 4.37–4.30 (1H, m), 3.70 (3H, s), 3.23–3.07 (2H, m), 2.93 (2H, s), 2.56 (3H, s), 2.49 (3H, s), 2.08 (3H, s), 1.87–1.79 (1H, m), 1.75–1.66 (1H, m), 1.56–1.47 (2H, m), 1.45 (6H, s), 1.36 (3H, d, J = 6.9 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 173.3, 172.2, 158.7, 156.3, 156.2, 138.3, 136.1, 132.8, 132.2, 128.5, 128.1, 127.8, 124.6, 117.5, 86.4, 66.9, 52.4, 52.1, 50.4, 43.2, 40.5, 29.7, 29.1, 28.6, 25.2, 19.2, 18.5, 17.9, 12.4; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{31}H_{43}N_5O_8NaS$ 668.2725; Found 668.2723; **IR (ATR):** 3329, 2934, 1667, 1621, 1547, 1450, 1250, 1099 cm^{-1}; **Optical Rotation:** $[\alpha]^{17}_D$ +2.0 (c 0.88, $CHCl_3$).

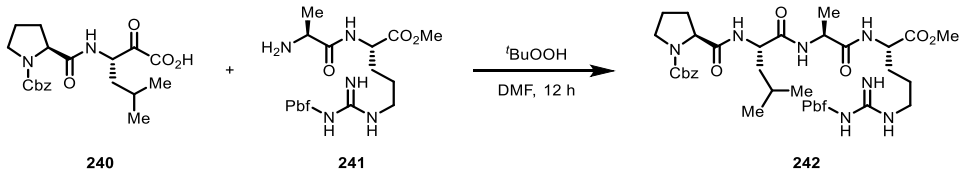
H-Ala-Arg(Pbf)-OMe (241):



365 241

According to **GP9**, Cbz-Ala-Arg(Pbf)-OMe **3656** (64.6 mg, 0.100 mmol) was treated with 20% $Pd(OH)_2/C$ (containing 50 wt% of H_2O, 35.1 mg, 0.0333 mmol, 33 mol%) in MeOH (1.0 mL) under H_2 atmosphere (1 atm) to afford H-Ala-Arg(Pbf)-OMe **241**, which was used for the decarboxylative peptide coupling without further purification.

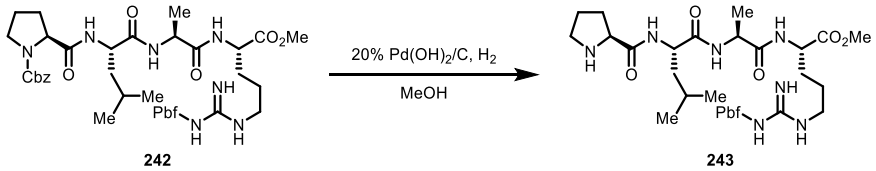
Cbz-Pro-Leu-Ala-Arg(Pbf)-OMe (242):



240 241 242

According to **GP10**, H-Ala-Arg(Pbf)-OMe **241** (30.7 mg, 0.0600 mmol, 1.0 equiv.) was reacted with Cbz-Pro-Leu-CO_2H **240** (28.1 mg, 0.0720 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 12.3 μL, 0.0898 mmol, 1.5 equiv.) in DMF (0.30 + 0.30 mL) at room temperature for 12 hours. Column chromatography (SiO_2, eluted with $CHCl_3$/MeOH = 98:2 → 96:4) afforded Cbz-Pro-Leu-Ala-Arg(Pbf)-OMe **242** (33.9 mg, 0.0396 mmol, 66% yield, >99:1 dr) as a white solid. The value of dr was determined by chiral SFC analysis: CHIRALPAK IB-3/SFC, 1.0 mL/min, 20% methanol/CO_2, λ = 210–400 nm, $t_{R(epi\text{-}242)}$ = 5.4 min, $t_{R(242)}$ = 6.6 min.

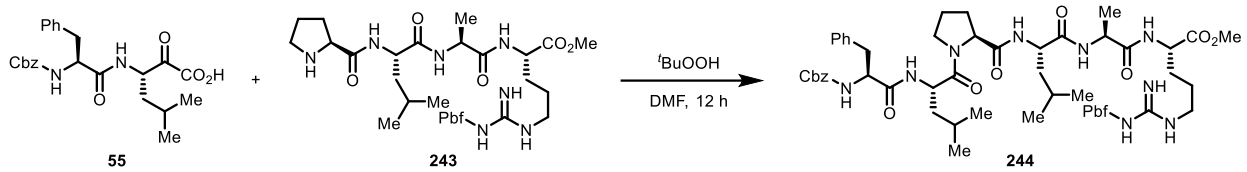
H-Pro-Leu-Ala-Arg(Pbf)-OMe (243):



242 243

A 10 mL test tube was charged with a stir bar, Cbz-Pro-Leu-Ala-Arg(Pbf)-OMe **242** (30.0 mg, 0.0350 mmol, 1.0 equiv.), 20% $Pd(OH)_2/C$ (containing 50 wt% of H_2O, 12.3 mg, 0.0117 mmol, 33 mol%), and MeOH (0.35 mL) under H_2 atmosphere (1 atm). After stirring at room temperature for 1 hour, the suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure to afford H-Pro-Leu-Ala-Arg(Pbf)-OMe **243** (23.0 mg, 0.0319 mmol, 91% yield), which was used for the next reaction without further purification.

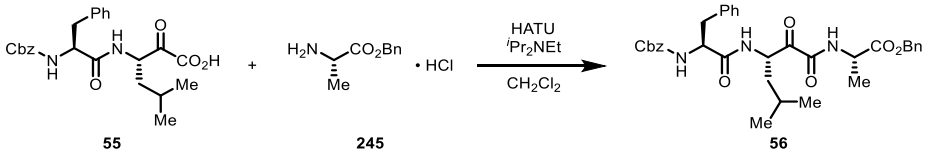
Cbz-Phe-Leu-Pro-Leu-Ala-Arg(Pbf)-OMe (244):



According to **GP10**, H-Pro-Leu-Ala-Arg(Pbf)-OMe **243** (21.7 mg, 0.0301 mmol, 1.0 equiv.) was reacted with Cbz-Phe-Leu-CO_2H **55** (15.9 mg, 0.0361 mmol, 1.2 equiv.) and *t*-BuOOH (70% in H_2O, 6.16 μL, 0.0450 mmol, 1.5 equiv.) in DMF (0.15 + 0.15 mL) at room temperature for 12 hours. Column chromatography (SiO_2, eluted with $CHCl_3$/MeOH = 99:1 → 97:3) afforded Cbz-Phe-Leu-Pro-Leu-Ala-Arg(Pbf)-OMe **244** as a white solid. The value of dr was determined by SFC analysis: CHIRALPAK IB-3/SFC, 0.50 mL/min, 25% 2-propanol/CO_2, λ = 210–400 nm, $t_{R(epi\text{-}244)}$ = 12.5 min, $t_{R(244)}$ = 16.6 min.

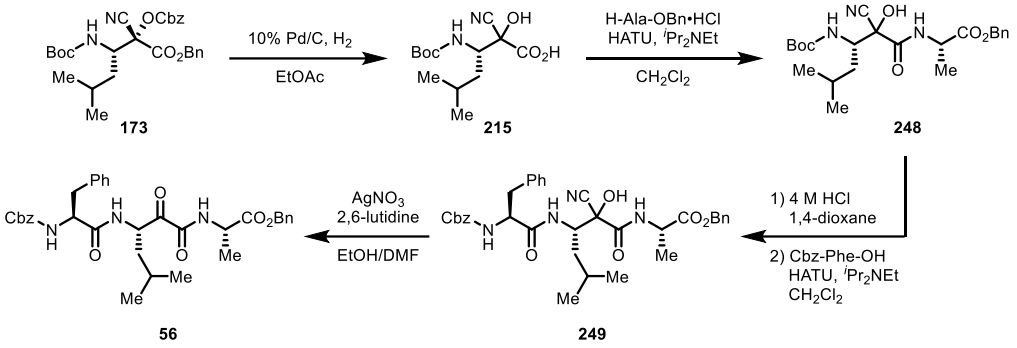
^{1}H-NMR (500 MHz, acetone-d_6): δ 7.78 (1H, s), 7.68 (1H, d, J = 7.4 Hz), 7.47 (1H, d, J = 6.9 Hz), 7.38 (1H, d, J = 7.4 Hz), 7.34–7.16 (10H, m), 6.67 (1H, d, J = 8.6 Hz), 6.57 (1H, s), 5.01 (1H, d, J = 12.6 Hz), 4.97 (1H, d, J = 12.6 Hz), 4.67–4.60 (1H, m), 4.54–4.48 (1H, m), 4.44–4.36 (2H, m), 4.35–4.29 (2H, m), 3.79–3.73 (1H, m), 3.63 (3H, s), 3.60–3.55 (1H, m), 3.19–3.15 (3H, m), 2.97 (2H, s), 2.93 (1H, dd, J = 14.3, 9.7 Hz), 2.57 (3H, s), 2.50 (3H, s), 2.17-2.10 (1H, m), 2.05 (3H, s), 1.99–1.91 (3H, m), 1.85–1.78 (1H, m), 1.73–1.54 (9H, m), 1.43 (6H, s), 1.34 (3H, d, J = 7.4 Hz), 0.93–0.84 (12H, m); **^{13}C-NMR (151 MHz, acetone-d_6):** δ 173.4, 173.2, 172.9, 172.8, 172.7, 172.6, 158.9, 157.3, 156.8, 138.7, 138.4, 138.0, 135.5, 132.8, 130.2, 129.2, 129.1, 128.6, 128.4, 127.3, 125.3, 117.5, 86.9, 66.7, 62.6, 57.2, 53.1, 52.7, 52.3, 51.6, 49.5, 48.1, 43.6, 41.3, 40.9, 40.8, 38.6, 28.7, 26.1, 25.9, 25.4, 25.2, 23.6, 23.5, 21.9, 21.7, 19.5, 18.2, 17.7, 12.5; **HRMS (ESI) *m/z*:** $[M+H]^+$ Calcd for $C_{57}H_{82}N_9O_{12}S$ 1116.5798; Found 1116.5794; **IR (ATR):** 3308, 2956, 1636, 1547, 1447, 1253, 1159, 1100 cm^{-1}; **Melting Point:** 113.8–116.5 °C; **Optical Rotation:** $[\alpha]^{19}_D$ −35.8 (c 1.00, $CHCl_3$).

Direct Condensation of Peptide-α-ketoacid and α-Amino Acid:



A 10 mL test tube equipped with a Teflon-coated screw cap was charged with a stir bar, Cbz-Phe- Leu-CO_2H **55** (22.0 mg, 0.0499 mmol, 1.0 equiv.), H-Ala-OBn•HCl **245** (10.8 mg, 0.0501 mmol, 1.0 equiv.), and CH_2Cl_2 (0.50 mL). To the suspension were added HATU (20.9 mg, 0.0550 mmol, 1.1 equiv.) and *i*-Pr_2NEt (17.4 μL, 0.0999 mmol, 1.0 equiv.), and the mixture was stirred at room temperature for 17 hours. The mixture was diluted with $CHCl_3$ (3.0 mL), quenched with saturated aqueous $NaHCO_3$ (3.0 mL). The aqueous layer was separated and extracted with $CHCl_3$ (2 x 3.0 mL). The combined organic layers were washed with aqueous HCl (1 M, 5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with CH_2Cl_2/EtOAc = 100:0 → 90:10) to afford **56** (22.1 mg, 0.0367 mmol, 74% yield, 10:1 dr) as a white solid. The value of dr of **56** was determined by ^{1}H NMR spectra.

Synthesis of Peptide-α-ketoamide 56 Using Cyanohydrin as a Protecting Group:



A 20 mL round bottom flask was charged with a stir bar, Mannich adduct **173** (51.1 mg, 0.100 mmol, 1.0 equiv.), 10% Pd/C (2.1 mg, 0.0020 mmol, 2 mol%) and EtOAc (1.0 mL) under H_2 atmosphere (1 atm). After vigorous stirring at room temperature for 2 hours, the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to afford the crude product of **215**, which was used for the next reaction without further purification.

A 20 mL round bottom flask was charged with a stir bar, the crude product of **215**, and CH_2Cl_2 (1.0 mL) under Ar atmosphere. To the solution were added H-Ala-OBn•HCl (21.6 mg, 0.100 mmol, 1.0 equiv.), HATU (45.6 mg, 0.120 mmol, 1.2 equiv.), and *i*-Pr_2NEt (34.8 μL, 0.200 mmol, 2.0 equiv.), and the mixture was stirred at room temperature for 15 hours. Then the mixture was quenched with aqueous HCl (1 M, 5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product of **248**, which was used for the next reaction without further purification.

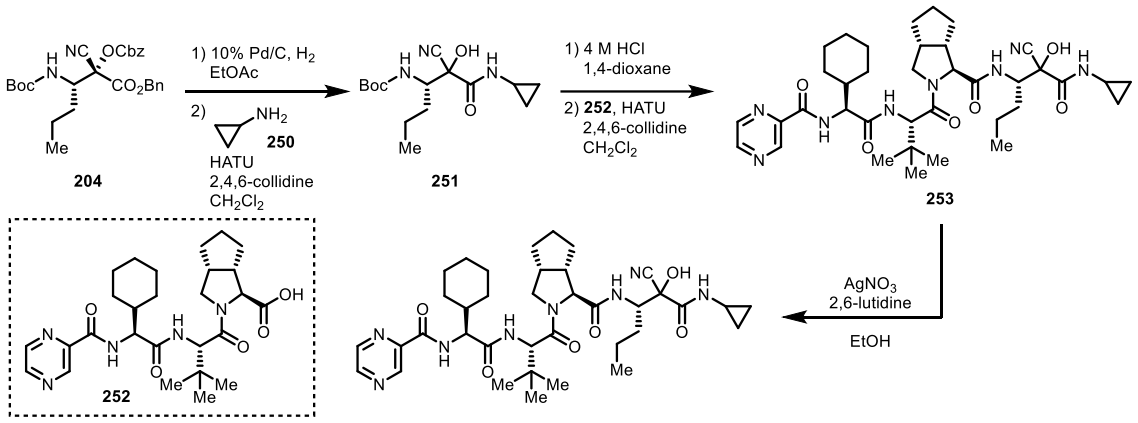
A 20 mL round bottom flask was charged with a stir bar, the crude product of **248**, and HCl solution (4 M in 1,4-dioxane, 2.0 mL). After stirring at room temperature for 2 hours, the mixture was concentrated under reduced pressure. To the residue were added CH_2Cl_2 (1.0 mL), Cbz-Phe-OH (35.9 mg, 0.120 mmol, 1.2 equiv.), HATU (57.0 mg, 0.150 mmol, 1.5 equiv.), and *i*-Pr_2NEt (38.3 μL, 0.220 mmol, 2.2 equiv.), and the mixture was stirred at room temperature for 15 hours. Then the mixture was quenched with aqueous HCl (1 M, 5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product of **249**, which was used for the next reaction without further purification.

A 20 mL round bottom flask was charged with a stir bar, the crude product of **249**, EtOH (2.0 mL), and DMF (1.0 mL). To the mixture was added $AgNO_3$ (34.0 mg, 0.200 mmol, 2.0 equiv.) and 2,6-lutidine (23.2 μL, 0.200 mmol, 2.0 equiv.), and the mixture was stirred at room temperature for 12 hours in the dark. The mixture was diluted with EtOAc (5 mL), quenched with aqueous HCl (1 M, 5 mL), and filtered through a Celite pad. The aqueous layer was separated and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, eluted with CH_2Cl_2/EtOAc = 100:0 → 90:10) to afford Cbz-Phe-Leu-(CO)-Ala-OBn **56** (34.7 mg, 0.0577 mmol, 58% yield, >20:1 dr) as a white solid. The epimer of **56** was not observed in ^1H NMR spectra.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.30 (10H, m), 7.29–7.17 (5H, m), 6.31 (1H, s), 5.32 (1H, d, J = 7.2 Hz), 5.26–5.15 (3H, m), 5.11 (1H, d, J = 12.3 Hz), 5.08 (1H, d, J = 12.3 Hz), 4.59–4.53 (1H, m), 4.43 (1H, dd, J = 13.3, 6.7 Hz), 3.13 (1H, dd, J = 13.7, 6.0 Hz), 3.01 (1H, dd, J = 13.9, 7.3 Hz), 1.65–1.49 (2H, m), 1.47 (3H, d, J = 7.2 Hz), 1.39–1.30 (1H, m), 0.95 (3H, d, J = 6.3 Hz), 0.86 (3H, d, J = 6.6 Hz); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 194.9, 171.5, 170.5, 158.5, 155.9, 136.2, 136.1, 135.0, 129.3, 128.73, 128.68, 128.59, 128.55, 128.3, 128.2, 128.1, 127.1, 67.5, 67.1, 56.1, 53.1, 48.2, 40.5, 38.3, 25.0, 23.1, 21.4, 18.0; **HRMS (FAB) *m/z*:** $[M+H]^+$ Calcd for $C_{34}H_{40}N_3O_7$ 602.2866; Found 602.2863; **IR (ATR):** 3305, 2952, 1735, 1660, 1534, 1456, 1378, 1251, 1156 cm^{-1};

Melting Point: 155.1–155.7 °C; **Optical Rotation:** $[\alpha]^{19}_{D}$ +3.0 (c 0.82, $CHCl_3$).

Telaprevir:



A 20 mL round bottom flask was charged with a stir bar, Mannich adduct **204** (49.7 mg, 0.100 mmol, 1.0 equiv.), and EtOAc (1.0 mL) under Ar atmosphere. To the solution was added 10% Pd/C (2.1 mg, 0.0020 mmol, 2 mol%) and the flask was evacuated and refilled with H_2 gas (1 atm). After vigorous stirring at room temperature for 2 hours, the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. To the residue were added CH_2Cl_2 (1.0 mL), HATU (45.6 mg, 0.120 mmol, 1.2 equiv.), and 2,4,6-collidine (13.2 μL, 0.100 mmol, 1.0 equiv.) under Ar atmosphere, and the mixture was stirred at room temperature for 30 min. Then to the mixture was added cyclopropylamine **250** (8.35 μL, 0.120 mmol, 1.2 equiv.), and the mixture was stirred at room temperature for 17 hours. The mixture was quenched with aqueous HCl (1 M, 5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product of **251** (0.0873 mmol), which was used for the next reaction without further purification.

A 20 mL round bottom flask was charged with a stir bar, the crude product of **251**, and HCl solution (4 M in 1,4-dioxane, 0.90 mL). After stirring at room temperature for 2 hours, the mixture was concentrated under reduced pressure. To the residue were subsequently added CH_2Cl_2 (0.90 mL), known carboxylic acid **252** (53.9 mg, 0.105 mmol, 1.2 equiv.), HATU (39.9 mg, 0.105 mmol, 1.2 equiv.), and 2,4,6-collidine (13.8 μL, 0.105 mmol, 1.2 equiv.), and the mixture was stirred at room temperature for 30 min. Then to the mixture was added 2,4,6-collidine (11.5 μL, 0.873 mmol, 1.0 equiv.), and the mixture was stirred at room temperature for 24 hours. The mixture was quenched with aqueous HCl (1 M, 5 mL). The aqueous layer was separated extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product of **253**, which was used for the next reaction without further purification.

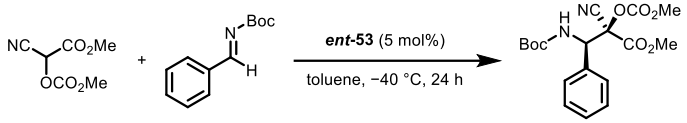
A 20 mL round bottom flask was charged with a stir bar, the crude product of **253**, and EtOH (1.8 mL). To the mixture was added $AgNO_3$ (29.7 mg, 0.175 mmol, 2.0 equiv.) and 2,6-lutidine (20.3 μL, 0.175 mmol, 2.0 equiv.), and the mixture was stirred at room temperature for 12 hours in the dark. The mixture was diluted with EtOAc (5 mL), quenched with aqueous HCl (1 M, 5 mL), and filtered through a Celite pad. The filtrate was separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (eluted with hexane/EtOAc = 20:80) to afford Telaprevir (27.7 mg, 0.0407 mmol, 41% yield, >20:1 dr) as a white solid. The epimer of Telaprevir was not observed in ^{1}H NMR spectra.

^{1}H-NMR (500 MHz, DMSO-*d*$_6$): δ 9.18 (1H, s), 8.90 (1H, d, J = 2.9 Hz), 8.76–8.75 (1H, m), 8.71 (1H, d, J = 5.2 Hz), 8.49 (1H,

d, J = 9.2 Hz), 8.25 (1H, d, J = 6.3 Hz), 8.21 (1H, d, J = 9.2 Hz), 4.95– 4.91 (1H, m), 4.67 (1H, dd, J = 9.2, 6.3 Hz), 4.52 (1H, d, J = 9.2 Hz), 4.26 (1H, d, J = 3.4 Hz), 3.73 (1H, dd, J = 10.0, 7.7 Hz), 3.62 (1H, dd, J = 10.3, 2.9 Hz), 2.76–2.70 (1H, m), 2.64–2.58 (1H, m), 1.82–1.21 (17H, m), 1.18–0.95 (4H, m), 0.92 (9H, s), 0.88–0.84 (4H, m), 0.66–0.62 (2H, m), 0.57–0.54 (2H, m); **^{13}C-NMR (151 MHz, $CDCl_3$):** δ 197.7, 171.1, 170.6, 170.4, 162.8, 162.5, 160.3, 147.4, 144.4, 144.1, 142.8, 65.8, 58.1, 58.0, 56.64, 56.58, 54.9, 54.4, 54.0, 53.5, 45.5, 44.3, 42.9, 41.2, 40.9, 36.5, 36.4, 35.6, 33.5, 33.3, 32.7, 32.4, 32.20, 32.19, 31.9, 31.4, 29.7, 29.5, 29.4, 28.8, 26.7, 26.4, 26.0, 25.79, 25.77, 25.7, 22.7, 22.4, 19.2, 19.0, 14.1, 13.7, 13.4, 6.31, 6.28 (Peaks of rotamers are observed); **HRMS (FAB) *m/z*:** $[M+Na]^+$ Calcd for $C_{36}H_{53}N_7O_6Na$ 702.3955; Found 702.3958.

第二章　DFT計算による反応機構解析

Methyl (2*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-2-((methoxycarbonyl)oxy)-3-phenylpropanoate (255):



254　67　255

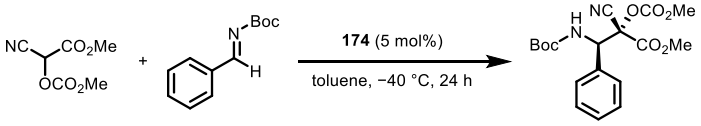
According to **GP5**, cyanohydrin **254** (17.3 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst ***ent*-53** (2.3 mg, 0.0049 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **255** as a colorless oil. The values of ee and dr of the products were determined by chiral HPLC analysis: CHIRALPAK IA-3, 1.0 mL/min, 3% ethanol/hexane, λ = 220 nm, $t_{R(ent\text{-}255')}$ = 9.5 min, $t_{R(ent\text{-}255)}$ = 10.3 min, $t_{R(255')}$ = 12.2 min, $t_{R(255)}$ = 13.5 min.

Yield: 34.7 mg, 0.0918 mmol, 92% yield

Ratio of Stereoisomers: 255:***ent*-255**:**255′**:***ent*-255′** = 95.6:0.7:2.8:0.8

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40 (5H, s), 5.49 (1H, d, J = 9.7 Hz), 5.40 (1H, d, J = 9.7 Hz), 3.83 (6H, s), 1.44 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 163.5, 154.4, 153.0, 133.8, 129.5, 128.8, 128.0, 113.8, 81.1, 77.4, 58.2, 56.2, 54.5, 28.2; **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{18}H_{22}N_2O_7Na$ 401.1319; Found 401.1323; **IR (ATR):** 3374, 2971, 1767, 1507, 1446, 1363, 1264, 1164 cm^{-1}; **Optical Rotation:** $[\alpha]^{19}_D$ −13.6 (c 1.00, $CHCl_3$).

Methyl (2*R*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-cyano-2-((methoxycarbonyl)oxy)-3-phenylpropanoate (255′):



254　67　255'

According to **GP5**, cyanohydrin **254** (17.3 mg, 0.0999 mmol, 1.0 equiv.) reacted with *N*-Boc imine **67** (30.8 mg, 0.150 mmol, 1.5 equiv.) and catalyst **174** (1.9 mg, 0.0048 mmol, 5 mol%) in toluene (0.50 + 0.50 mL) at −40 °C for 24 hours. Column chromatography (SiO_2, eluted with hexane/EtOAc = 100:0 → 90:10) afforded **255′** as a colorless oil.

Yield: 35.8 mg, 0.0946 mmol, 95% yield

Ratio of Stereoisomers: 255:***ent*-255**:**255′**:***ent*-255′** = 4.2:1.0:89.0:5.9

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45–7.37 (5H, m), 5.44 (2H, s), 3.88 (3H, s), 3.86 (3H, s), 1.42 (9H, s); **^{13}C-NMR (126 MHz, $CDCl_3$):** δ 163.0, 154.3, 153.1, 133.7, 129.4, 128.8, 128.3, 113.4, 81.0, 58.9, 56.2, 54.5, 28.1 (One aliphatic carbon peak is missing due to overlapping); **HRMS (ESI) *m/z*:** $[M+Na]^+$ Calcd for $C_{18}H_{22}N_2O_7Na$ 401.1319; Found 401.1324; **IR (ATR):** 3382, 2970,

1765, 1708, 1504, 1446, 1362, 1252, 1162 cm^{-1}; **Optical Rotation:** $[\alpha]^{19}_{D}$ −5.5 (c 0.60, $CHCl_3$).

Details for DFT calculations

DFT calculations for each structure was performed with the following protocol for lower energy conformations obtained from preliminary conformational search at SMD(toluene)/B3LYP-D3/6-311+G(2d,2p)//B3LYP-D3/6-31G(d,p) level of theory. All calculations were carried out with Gaussian 09[50,51] software.

Geometry optimization: The geometry optimizations including transition state searches were carried out at the B3LYP-D3/6-311G(d,p) level of theory.[52-54] Ultra-fine integration grid was employed in all electronic structure calculations. The nature of the stationary points was characterized via vibrational analysis. In addition, intrinsic reaction coordinate (IRC)[57] calculations were performed at the same level to connect all the transition states with the corresponding reactants and products.

Single point electronic energy calculations: For each optimized structure (potential energy minimum or transition state computed at B3LYP-D3/6-311G(d,p) level of theory), additional single-point energy calculations were performed with the 6-311+G(3d,3p) basis set.[57]

Entropic and thermal contributions: Harmonic frequencies were computed at the B3LYP-D3/6-311G(d,p) level. These data were used to estimate the zero-point energies as well as the thermal and entropic contributions to the Gibbs free energies. The thermochemical data were obtained within the ideal gas – rigid rotor – harmonic oscillator approximation for T = 298.15 K and p = 1 atm (ideal gas standard state), but corrections were applied for switching to c = 1 mol/dm^3 concentrations (0.003019 a.u.).

Solvent effects: Solvent effects were also taken into account by estimating the solvation free energies by using the integral equation formalism variant of the polarizable continuum model (IEFPCM).[55] The atomic radii and non-electrostatic terms in the IEFPCM calculations were those introduced by Truhlar and coworkers (SMD solvation model).[56] Solvation free energies (for toluene as organic solvent used experimentally) were calculated at the B3LYP-D3/6-311G(d,p) level for the gas-phase optimized geometries.

Total energies and cartesian coordinates (standard XYZ format (units are in Å)) of optimized geometries at B3LYP-D3/6-311+G(d,p) level of theory are given below.

53_A

Zero-point correction = 0.468151 (Hartree/Particle)
Thermal correction to Energy = 0.497840
Thermal correction to Enthalpy = 0.498784
Thermal correction to Gibbs Free Energy = 0.401101
Sum of electronic and zero-point Energies = −1978.077951
Sum of electronic and thermal Energies = −1978.048262
Sum of electronic and thermal Enthalpies = −1978.047318
Sum of electronic and thermal Free Energies = −1978.145001
E(RB3LYP-D3) = −1978.546102

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −1978.639944
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −1978.570369

0 1

C	3.88542900	-0.68325600	0.81759600
C	2.65986500	1.08171300	-0.92631600
C	2.51262500	-0.76390900	0.61990500
C	4.66065000	0.27320400	0.16566300
C	4.03091800	1.15895700	-0.69994100
C	1.88925100	0.11956500	-0.26878900
H	1.93106600	-1.50045900	1.15081600
H	5.72681200	0.32850700	0.33341400
H	2.19560800	1.76335200	-1.62931600
C	4.55615500	-1.68142500	1.72456400
C	4.82123500	2.25199900	-1.36599900
F	5.65399200	-1.16128000	2.31770300
F	3.73288500	-2.10941300	2.70493500
F	4.96070900	-2.77507900	1.04234500
F	6.12379400	1.93124800	-1.49812400
F	4.76806600	3.40289400	-0.65376400
F	4.34545600	2.53872200	-2.59893700
N	0.50075200	0.12257300	-0.48019800
H	0.13319200	0.99601400	-0.83185200
C	-0.37367100	-0.95129500	-0.59846700
N	-1.65734100	-0.51368100	-0.69929900
H	-1.88509500	0.33919600	-0.18629300
C	-2.82225200	-1.39183300	-0.75715500
C	-5.28861600	-1.46080500	-0.25641500
C	-4.31745100	-2.88621700	-2.12241300
C	-5.55112700	-2.12366500	-1.61836100
C	-3.06819800	-1.99465700	-2.14685800
C	-4.04844700	-0.55272800	-0.33234200
H	-5.13583600	-2.23365000	0.50487900
H	-4.12865500	-3.74480400	-1.46624300
H	-5.81696900	-1.34706500	-2.34692000

H	-3.19602000	-1.17852200	-2.86826700
H	-4.21678200	0.16130500	-1.14339400
H	-2.67118300	-2.22120200	-0.05582900
H	-6.15979600	-0.87604800	0.05358600
H	-4.50479900	-3.29301200	-3.12026300
H	-6.41262100	-2.79470700	-1.54937200
H	-2.19151600	-2.56747900	-2.45100900
N	-3.73836000	0.26329900	0.85945200
C	-3.54685300	-0.53223000	2.07545600
H	-3.06366900	0.07291200	2.84232600
H	-2.88989000	-1.37749000	1.86962700
H	-4.49006900	-0.92189100	2.48916500
C	-4.66119500	1.38823600	1.06835300
C	-4.23932100	2.32696200	2.21260300
C	-4.76208400	2.33965600	-0.14842000
H	-5.67295500	1.01326800	1.30890600
C	-5.08185500	3.58313100	1.96365700
H	-3.16980700	2.54736500	2.10910200
H	-4.40162300	1.90355500	3.20528200
C	-5.08152300	3.74793700	0.42589600
H	-5.51172000	2.01019400	-0.87033400
H	-3.79709200	2.34702700	-0.66459700
H	-6.10145500	3.41435300	2.32535400
H	-4.69795000	4.46175300	2.48602600
H	-6.03462400	4.13493500	0.05989300
H	-4.31418100	4.46234100	0.11785600
S	0.08980800	-2.55906000	-0.64080900

254

Zero-point correction = 0.136238 (Hartree/Particle)
Thermal correction to Energy = 0.149062
Thermal correction to Enthalpy = 0.150006
Thermal correction to Gibbs Free Energy = 0.095333
Sum of electronic and zero-point Energies = −663.768759
Sum of electronic and thermal Energies = −663.755935
Sum of electronic and thermal Enthalpies = −663.754991
Sum of electronic and thermal Free Energies = −663.809664
E(RB3LYP-D3) = −663.904997

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −663.950426
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −663.913674

0 1

C	0.52161900	0.76326400	0.34738200
H	0.43492300	0.63949000	1.43112200
C	1.22708100	-0.50076000	-0.20358200
O	0.76972200	-1.20631700	-1.05479900
O	2.38688800	-0.66669600	0.43139600
C	3.17429400	-1.80742100	0.01569200
H	4.07333400	-1.77336400	0.62503600
H	3.41887900	-1.72611900	-1.04399200
H	2.61731700	-2.72848600	0.19157900
C	1.30028700	1.96690700	0.05788000
N	1.93592200	2.90124700	-0.16036500
O	-0.75673700	0.91890700	-0.25224600
C	-1.69131300	0.05578900	0.21938400
O	-1.52490900	-0.71133500	1.13073800
O	-2.79616200	0.23604000	-0.48937200
C	-3.89991000	-0.61704300	-0.11822500
H	-4.71046700	-0.34017700	-0.78732200
H	-4.18023800	-0.44445100	0.92187600
H	-3.62795800	-1.66483100	-0.25265500

67

Zero-point correction = 0.248551 (Hartree/Particle)
Thermal correction to Energy = 0.263220
Thermal correction to Enthalpy = 0.264164
Thermal correction to Gibbs Free Energy = 0.205433
Sum of electronic and zero-point Energies = −671.478902
Sum of electronic and thermal Energies = −671.464232
Sum of electronic and thermal Enthalpies = −671.463288
Sum of electronic and thermal Free Energies = −671.522019
E(RB3LYP-D3) = −671.727452

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −671.763834
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −671.741767

0 1

C	4.80537000	-0.79740200	-0.17668400
C	3.46776900	-1.18056700	-0.16349100
C	2.45644800	-0.22185700	-0.01413900
C	2.80430200	1.13220700	0.11969000
C	4.13849500	1.51116600	0.10608400
C	5.14113400	0.54819100	-0.04192700
H	5.58278900	-1.54374400	-0.29159400
H	3.20015700	-2.22708700	-0.26726200
H	2.01069800	1.86063700	0.23062300
H	4.40465400	2.55686800	0.20964900
H	6.18267300	0.84941800	-0.05255200
C	1.05951400	-0.65375800	0.00066800
H	0.87378300	-1.72915800	-0.10715000
N	0.08814200	0.16849100	0.13719600
C	-1.20536500	-0.41422600	0.16494900
O	-1.45824100	-1.58224400	0.36491500
O	-2.09933600	0.55651200	-0.04565300
C	-3.54636300	0.26914800	-0.08004800
C	-4.00394700	-0.26359900	1.27947200
H	-5.09408300	-0.34414100	1.28853500
H	-3.57594700	-1.24379800	1.48119700
H	-3.70375700	0.42605700	2.07212800
C	-3.86053800	-0.70124100	-1.22073900
H	-3.43424600	-1.68416600	-1.02854100
H	-4.94418900	-0.79981100	-1.32441600
H	-3.45948700	-0.31613700	-2.16155400
C	-4.14424100	1.64758400	-0.35577500
H	-5.23355500	1.58118100	-0.40641400
H	-3.87043300	2.34549500	0.43801300
H	-3.77090400	2.04093000	-1.30349400

IM1

Zero-point correction = 0.610195 (Hartree/Particle)
Thermal correction to Energy = 0.653136
Thermal correction to Enthalpy = 0.654080
Thermal correction to Gibbs Free Energy = 0.529091
Sum of electronic and zero-point Energies = −2641.891785
Sum of electronic and thermal Energies = −2641.848845
Sum of electronic and thermal Enthalpies = −2641.847901
Sum of electronic and thermal Free Energies = −2641.972889

E(RB3LYP-D3) = −2642.501981

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −2642.633823

Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −2642.529402

0 1

C	4.21656600	1.77900700	-0.22391800
C	2.63941200	-0.49450400	-0.13721400
C	2.88319200	1.88629500	0.15618400
C	4.78311600	0.54883400	-0.55288100
C	3.98110700	-0.58385100	-0.49474400
C	2.08070200	0.74136200	0.18977900
H	2.47358800	2.84493900	0.43184600
H	5.82500800	0.47749700	-0.83029800
H	2.02428600	-1.38211400	-0.10446000
C	4.52699800	-1.94230900	-0.82800500
C	5.05526700	3.02518000	-0.31786600
F	4.98350100	3.57961100	-1.54957900
F	6.36250000	2.77163800	-0.08070100
F	4.66265100	3.97079600	0.56165900
F	4.31735800	-2.82635900	0.18193400
F	5.84994100	-1.92787400	-1.07561900
F	3.92223200	-2.47270600	-1.92111300
N	0.73627000	0.74785500	0.61838200
H	0.49072700	-0.08887700	1.15299900
C	-0.25545800	1.63085700	0.30774900
S	-0.04100900	3.00959700	-0.64991100
N	-1.46290500	1.26909700	0.82732300
H	-1.50018800	0.45627000	1.43141500
C	-2.65927400	2.09645100	0.83493800
C	-5.09797100	2.28984400	0.22720700
C	-4.21857800	3.48159800	2.28276000
C	-5.42447700	2.78184400	1.64654600
C	-2.98136200	2.57724300	2.26167700
C	-3.88821500	1.34972600	0.26756300
H	-4.88464500	3.15248200	-0.41343100
H	-4.00144800	4.40451700	1.73114800
H	-5.71695200	1.92396400	2.26311900
H	-3.14086200	1.70041400	2.89963300
H	-4.10123800	0.51719400	0.93729900
H	-2.43620700	2.96736200	0.21769200
H	-5.96794600	1.78054300	-0.19208600
H	-4.44891500	3.77566800	3.31034500
H	-6.28530800	3.45502900	1.60961300
H	-2.10531900	3.10725300	2.64355200
N	-3.58859000	0.69086200	-1.07325300
C	-3.11435500	1.65050200	-2.11772100
H	-2.87347500	1.09159500	-3.01751900
H	-2.21636300	2.15945000	-1.77299900
H	-3.90357700	2.36953300	-2.33337700
C	-4.73864100	-0.15241900	-1.60581400
C	-4.30039900	-1.06505400	-2.79361500
C	-4.74084800	-2.49131700	-2.40284100
C	-5.87167900	-2.27445200	-1.38857200
C	-5.34894300	-1.09824900	-0.55458800
H	-5.48687300	0.56429100	-1.94730800
H	-3.22527400	-1.02823500	-2.95975800
H	-4.79640700	-0.73391400	-3.70880300
H	-5.03974500	-3.08781000	-3.26676600
H	-3.90749200	-3.00306300	-1.91385400
H	-6.08044900	-3.15355700	-0.77632600
H	-6.80041400	-1.99976300	-1.90249000
H	-4.57299500	-1.45945400	0.12191900
H	-6.11632900	-0.61665900	0.05418500
H	-2.80025500	0.00618300	-0.91145800
C	-1.26621000	-2.33975500	0.87047000
C	-1.00040100	-1.96029900	-0.45165400
O	-1.69442200	-1.18509500	-1.14680900
O	0.14035800	-2.49909900	-0.95995800
C	0.46372200	-2.13440100	-2.31213100
H	-0.28290700	-2.52718800	-3.00511600
H	1.43641900	-2.58154300	-2.50344400
H	0.51839500	-1.04956300	-2.41794200
C	-2.29503500	-1.76130200	1.60348200
N	-3.14244500	-1.21330900	2.19118400
O	-0.43328000	-3.27522100	1.52752000
C	0.66044800	-2.77313200	2.11625200
O	0.95614000	-1.59987900	2.20148800
O	1.37631500	-3.77814000	2.59983400
C	2.63256900	-3.40458600	3.20659400
H	3.29895900	-2.98032700	2.45499600
H	3.04246500	-4.33113800	3.60089000
H	2.46951300	-2.68120500	4.00626600

IM2

Zero-point correction = 0.860001 (Hartree/Particle)

Thermal correction to Energy = 0.919644

Thermal correction to Enthalpy = 0.920589

Thermal correction to Gibbs Free Energy = 0.758106

Sum of electronic and zero-point Energies = −3313.391857

Sum of electronic and thermal Energies = −3313.332214

Sum of electronic and thermal Enthalpies = −3313.331269

Sum of electronic and thermal Free Energies = −3313.493752

E(RB3LYP-D3) = −3314.251858

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.416327

Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.288706

0 1

C	5.35660800	-0.32152900	-0.10044900
C	3.26313600	1.26497800	-0.95465700
C	4.17981700	-0.92544000	-0.53390600
C	5.50869200	1.06061700	-0.07773900
C	4.44310900	1.84428700	-0.51198600
C	3.11187000	-0.12878900	-0.95797300
H	6.42956000	1.51279100	0.26169600
H	2.43469600	1.88448600	-1.26753700
C	1.38613300	-1.82759900	-1.66036900
N	1.83351400	-0.59703300	-1.28732600
H	1.10749200	0.10947100	-1.10946400
N	0.02086900	-1.88753800	-1.68178900
H	-0.49344800	-1.03220400	-1.49217100
C	-0.73598200	-2.94570100	-2.33264500
C	-2.67484000	-4.53977600	-2.13329800
C	-1.96823100	-3.67977900	-4.41552000
C	-3.14133300	-4.14107700	-3.54430100
C	-1.20405900	-2.53610600	-3.74027000
C	-1.94472800	-3.36436500	-1.47677700

H	-2.01074800	-5.40921700	-2.20127400
H	-1.28797500	-4.52333200	-4.58761700
H	-3.87174100	-3.32863400	-3.45876600
H	-1.83752200	-1.64861500	-3.65813100
H	-2.61587900	-2.50864600	-1.40964200
H	-0.05306400	-3.78853600	-2.44405400
H	-3.54307600	-4.83587000	-1.54111600
H	-2.32927000	-3.36073700	-5.39705300
H	-3.65712900	-4.98775500	-4.00593600
H	-0.31742100	-2.26436800	-4.31856000
N	-1.52755700	-3.63629000	-0.02741400
H	-1.16264200	-2.73499000	0.35794700
C	-2.02286700	2.04444200	-0.98003900
C	-0.74182500	2.21819300	-0.43959300
O	0.13491300	1.33362500	-0.35531800
O	-0.53713300	3.46496500	0.07274000
C	0.81061700	3.80216000	0.42670100
H	1.26590500	3.03165900	1.04929900
H	0.74515900	4.73948300	0.97619200
H	1.41623400	3.95004900	-0.46940500
C	-2.45607200	0.79467100	-1.40268600
N	-2.80281800	-0.27826100	-1.70072700
O	-2.94698600	3.10044000	-1.02741200
C	-2.69188400	4.09302400	-1.90856200
O	-1.80718100	4.14000600	-2.71645800
O	-3.62557300	5.03501600	-1.70383000
C	-3.50950100	6.18159200	-2.56261400
H	-2.54793500	6.67682200	-2.41430800
H	-4.32734500	6.84032200	-2.27798000
H	-3.60005300	5.88895700	-3.61042800
C	-2.43064800	1.13342000	1.81556000
N	-2.17865700	-0.13145900	1.77265600
C	-0.88535100	-0.57481800	2.00115000
O	-0.45580800	-1.60619800	1.48983800
O	-0.20897700	0.15388500	2.88637600
C	1.17578200	-0.17638800	3.31384600
C	-3.76810100	1.68359000	1.66212500
C	-6.29296900	2.82690300	1.33073000
C	-4.88602000	0.86878100	1.41889400
C	-3.93099100	3.07511500	1.72127200
C	-5.18805400	3.64346100	1.55836900
C	-6.13895100	1.43919800	1.25784600
H	-4.74955100	-0.20026600	1.34138400
H	-3.05982000	3.70605200	1.85275800
H	-5.30126100	4.72037800	1.58350800
H	-6.99942200	0.80895900	1.06388000
H	-7.27363800	3.26900100	1.19437000
H	-1.63393100	1.85800600	1.99187900
C	2.10292800	-0.20495400	2.10525700
H	3.14289400	-0.24225500	2.43811600
H	1.90542800	-1.06883600	1.47601200
H	1.95622500	0.69227500	1.50422600
C	1.15761400	-1.49972100	4.07720400
H	2.14765400	-1.68717800	4.50000500
H	0.43454800	-1.45807000	4.89558000
H	0.90170100	-2.32491600	3.41414000
C	1.51104600	0.99308900	4.23531900
H	2.51383200	0.86502000	4.64850300
H	1.48138800	1.93296600	3.68009300
H	0.79527200	1.05210100	5.05792900
S	2.36382300	-3.14837500	-2.06353300
C	6.44092700	-1.19518300	0.46744000
C	4.52498200	3.34111000	-0.41930300
F	6.53249200	-2.38108600	-0.16570500
F	7.65592000	-0.60842700	0.41084900
F	6.20271500	-1.47047000	1.77739900
F	3.82958400	3.95566400	-1.40255100
F	5.79274100	3.79428700	-0.47360000
F	4.00083900	3.78925000	0.75474000
H	4.08632800	-1.99952900	-0.53250700
C	-0.40872500	-4.61940600	0.11143500
H	-0.09299500	-4.63413500	1.15073000
H	-0.75567600	-5.60762600	-0.18726400
H	0.43501100	-4.31124000	-0.50166700
C	-2.70507400	-4.00207700	0.85592600
C	-2.33534300	-4.18595500	2.33852200
C	-3.81970000	-2.92643400	0.83483900
H	-3.07772600	-4.95283500	0.47227500
C	-3.69312300	-4.02090400	3.03261400
H	-1.65206100	-3.39244700	2.65029800
H	-1.86529700	-5.14900800	2.54499800
C	-4.32792800	-2.82855400	2.29595800
H	-4.60920900	-3.20397600	0.13378900
H	-3.42188100	-1.96249500	0.51436100
H	-4.29405000	-4.92660000	2.89156400
H	-3.59572800	-3.85898900	4.10778100
H	-5.41732200	-2.82354700	2.36248500
H	-3.96352800	-1.89522700	2.73020400

TS_{Add}-1

Zero-point correction = 0.859314 (Hartree/Particle)
Thermal correction to Energy = 0.917800
Thermal correction to Enthalpy = 0.918744
Thermal correction to Gibbs Free Energy = 0.761019
Sum of electronic and zero-point Energies = −3313.385319
Sum of electronic and thermal Energies = −3313.326834
Sum of electronic and thermal Enthalpies = −3313.325889
Sum of electronic and thermal Free Energies = −3313.483614
E(RB3LYP-D3) = −3314.244633
Imaginary frequency = 74.39i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.408933
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.282025

0 1

C	4.90873000	-0.76937800	-0.39991200
C	3.17786000	1.16527700	-1.35516500
C	3.65775400	-1.14730400	-0.87685800
C	5.30742300	0.56257400	-0.37214900
C	4.42141000	1.52243300	-0.85369800
C	2.77162700	-0.17487800	-1.34695400
H	6.27783200	0.84391600	0.01189900
H	2.49523600	1.92527700	-1.70390300
C	0.85488200	-1.60444600	-2.08868300
N	1.43514900	-0.43543900	-1.68600400
H	0.81298800	0.33150300	-1.41651700
N	-0.48017400	-1.63154800	-1.84517700
H	-0.90339300	-0.84401500	-1.36029500

C	-1.39361700	-2.68642700	-2.24250800
C	-3.11325300	-4.35245800	-1.41250700
C	-3.35802400	-3.31987700	-3.71422300
C	-4.09773400	-3.86518400	-2.48825600
C	-2.38467800	-2.20635500	-3.31704900
C	-2.16733400	-3.21662900	-1.01488300
H	-2.53887300	-5.19839200	-1.80557900
H	-2.80708600	-4.13693200	-4.19664200
H	-4.73005600	-3.07657000	-2.06208400
H	-2.92403300	-1.32885400	-2.95053800
H	-2.74960900	-2.38839400	-0.61569300
H	-0.78664500	-3.48390500	-2.67259900
H	-3.67111000	-4.70995200	-0.54406200
H	-4.07240500	-2.94402500	-4.45157200
H	-4.76339500	-4.68640900	-2.76786900
H	-1.80154000	-1.86761700	-4.17616200
N	-1.22705200	-3.58138900	0.13287600
H	-0.70466000	-2.69728900	0.38491300
C	-1.79702000	2.54485000	-0.44293500
C	-0.40925500	2.66595900	-0.10511000
O	0.45335900	1.86220400	-0.45953000
O	-0.13234100	3.71988000	0.68868900
C	1.26270300	4.04176100	0.83538500
H	1.82299000	3.21145700	1.26087400
H	1.29242800	4.90076000	1.50218800
H	1.69372200	4.30216300	-0.13271900
C	-2.12490500	1.77886500	-1.57692000
N	-2.41119400	1.06860100	-2.44877600
O	-2.68644900	3.56362900	-0.06758900
C	-2.56532400	4.74752200	-0.71975400
O	-1.81257000	4.99130300	-1.62051900
O	-3.44854300	5.58586600	-0.16930400
C	-3.46432200	6.90171000	-0.75256900
H	-2.48945300	7.38011300	-0.64296200
H	-4.22541400	7.45134200	-0.20326800
H	-3.71840900	6.84728700	-1.81258100
C	-2.37377200	0.84759700	1.13009400
N	-1.66770400	-0.22589800	0.80199400
C	-0.46809800	-0.46107200	1.41269500
O	0.17996100	-1.48950300	1.16682700
O	-0.07993100	0.43008000	2.33246900
C	1.18717900	0.31386400	3.08832600
C	-3.80482300	0.91454100	0.82857600
C	-6.55498800	1.06910300	0.32339400
C	-4.41434200	0.03232900	-0.07696400
C	-4.59273300	1.88687300	1.46240200
C	-5.95829300	1.95922600	1.21567600
C	-5.77735200	0.10999500	-0.32714500
H	-3.79999600	-0.68051600	-0.60533900
H	-4.12216000	2.59659000	2.13178900
H	-6.55615300	2.71582500	1.71041800
H	-6.23464400	-0.56753900	-1.03956000
H	-7.61963200	1.12908500	0.12711200
H	-2.02168300	1.52853900	1.90222500
C	2.37404900	0.29214400	2.12780400
H	3.30199200	0.43560100	2.68614500
H	2.43137900	-0.65404700	1.59644700
H	2.27809400	1.08913700	1.39088600
C	1.14225600	-0.92531400	3.98298000
H	2.00103700	-0.91479300	4.65883400
H	0.23035200	-0.92716300	4.58585000
H	1.18155800	-1.83520200	3.38767800
C	1.16820000	1.58990400	3.92744800
H	2.07604800	1.65682100	4.53068000
H	1.10769500	2.46659100	3.28205400
H	0.30224700	1.59572400	4.59331800
S	1.68997000	-2.87189200	-2.84096000
C	5.78477600	-1.81992700	0.22187200
C	4.76656700	2.97700000	-0.71989400
F	5.68400100	-3.01159800	-0.40136600
F	7.08870100	-1.46986600	0.22246000
F	5.43923800	-2.03267300	1.52053000
F	4.10954600	3.75333000	-1.60748000
F	6.08594500	3.21198700	-0.86921400
F	4.43035000	3.44290300	0.51739800
H	3.36641500	-2.18572900	-0.86474600
C	-0.19163100	-4.59520100	-0.23976700
H	0.51361800	-4.68589600	0.58165400
H	-0.67307000	-5.55543700	-0.42101400
H	0.35303100	-4.26349400	-1.12152400
C	-1.95416600	-4.00426500	1.40328900
C	-0.98121200	-4.20297000	2.58815200
C	-3.01664300	-2.97958600	1.89149700
H	-2.42648000	-4.95608900	1.15966900
C	-1.83650900	-3.88029700	3.82026600
H	-0.16796100	-3.47790600	2.51311300
H	-0.54880800	-5.20427500	2.61556400
C	-2.66149200	-2.67097400	3.36138100
H	-4.01306900	-3.41868300	1.80689000
H	-3.00633800	-2.06503800	1.30395300
H	-2.49556900	-4.72347100	4.05643300
H	-1.22780100	-3.68115400	4.70450100
H	-3.54665200	-2.49194800	3.97385800
H	-2.04653300	-1.76736100	3.40595200

TS_{Add}-2

Zero-point correction = 0.859262 (Hartree/Particle)
Thermal correction to Energy = 0.917869
Thermal correction to Enthalpy = 0.918814
Thermal correction to Gibbs Free Energy = 0.757871
Sum of electronic and zero-point Energies = −3313.381350
Sum of electronic and thermal Energies = −3313.322743
Sum of electronic and thermal Enthalpies = −3313.321799
Sum of electronic and thermal Free Energies = −3313.482741
E(RB3LYP-D3) = −3314.240613
Imaginary frequency = 230.53i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.405275
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.275627

0 1

C	-5.65287300	-0.43342400	-0.36066600
C	-3.40578500	-1.93098400	-0.94603400
C	-4.47092600	0.21901900	-0.69902100
C	-5.73192200	-1.82005100	-0.29017600
C	-4.58863600	-2.55797500	-0.58293600
C	-3.32739600	-0.53169700	-0.99281900
H	-4.43307900	1.29569000	-0.72767800

H	-6.65268500	-2.31126000	-0.01064800
H	-2.52895600	-2.52554000	-1.17183600
N	-2.05941100	-0.00025200	-1.25050000
H	-1.30842000	-0.68150000	-1.13861800
C	-1.64040700	1.26505400	-1.56855300
S	-2.63695600	2.53657400	-2.06407000
N	-0.29213800	1.38208700	-1.45417900
H	0.22659900	0.56743100	-1.14574000
C	0.51959100	2.50179100	-1.89693300
C	2.35199100	4.09781700	-1.21769300
C	2.21700700	3.29279000	-3.61100200
C	3.15344000	3.69604400	-2.46696700
C	1.29560800	2.14795700	-3.17822200
C	1.47761500	2.92654800	-0.76526700
H	1.72495200	4.96591300	-1.44901300
H	1.61638600	4.16031000	-3.91316200
H	3.80262600	2.84912000	-2.21876800
H	1.88408600	1.24702200	-2.99862100
H	2.10973300	2.06812700	-0.52024100
H	-0.16293900	3.31684500	-2.13628200
H	3.04021700	4.39507200	-0.42330600
H	2.79633400	2.98963700	-4.48749400
H	3.79759200	4.52721500	-2.76797800
H	0.55991700	1.92188200	-3.95451000
C	-6.88361900	0.39496900	-0.10477400
C	-4.59135300	-4.05076700	-0.41092900
F	-6.58807700	1.57344700	0.48655000
F	-7.53457600	0.68642600	-1.25366000
F	-7.76764700	-0.24396100	0.69433800
F	-3.80166800	-4.67108200	-1.31380000
F	-5.82774700	-4.57899100	-0.52162600
F	-4.12441000	-4.40028000	0.81565200
N	0.71176900	3.17818200	0.53533300
C	1.62836300	3.45470900	1.68307500
H	2.27636300	2.58794800	1.79259600
C	2.93319200	-1.75028400	-0.36605700
C	3.76983100	-0.91451300	-1.24502600
O	3.38124600	0.12619000	-1.74277900
O	5.02613400	-1.36818800	-1.33304600
C	5.94732700	-0.52934100	-2.05312300
H	5.59962400	-0.37336700	-3.07537100
H	6.89225800	-1.06710400	-2.04310300
H	6.05037500	0.43045000	-1.54615100
C	1.55495500	-1.75962100	-0.71007900
N	0.41880000	-1.66416800	-0.90735800
O	3.45694200	-2.98068300	0.08030400
C	3.66098600	-3.93628700	-0.86541500
O	3.33693500	-3.86534800	-2.01783600
O	4.26878100	-4.95741400	-0.26365100
C	4.54419600	-6.08196500	-1.12249100
H	3.61710300	-6.47945700	-1.53852300
H	5.02658100	-6.81866400	-0.48463800
H	5.20577100	-5.78420900	-1.93753900
C	2.93271800	-0.66417000	1.40555600
N	2.00227800	0.31063800	1.33272100
C	0.75154800	0.07102800	1.77879300
O	-0.17188800	0.89688500	1.62734000
H	2.70764100	-1.57640300	1.95662000
C	4.36152100	-0.26250300	1.47231600
C	7.07418800	0.43853700	1.59008400
C	4.77976200	1.02665700	1.11891200
C	5.32218500	-1.19671100	1.87962000
C	6.66758500	-0.84869800	1.93854700
C	6.12514600	1.37472200	1.17917600
H	4.04208100	1.74276700	0.78668300
H	5.00855300	-2.20429500	2.12426100
H	7.39990700	-1.58218400	2.25638800
H	6.43553200	2.37743000	0.90552400
H	8.12247000	0.71119600	1.63996100
O	0.56142800	-1.08665000	2.44443000
C	-0.73300700	-1.48900700	3.02351700
C	-1.78112300	-1.62404200	1.92225100
H	-2.02999100	-0.65244800	1.50276200
H	-2.68816600	-2.08244200	2.32325900
H	-1.39864500	-2.26461500	1.12633300
C	-1.15010500	-0.49432600	4.10756500
H	-0.34839200	-0.37953000	4.84166100
H	-2.03853400	-0.86853700	4.62306300
H	-1.37696300	0.47733000	3.67274900
C	-0.40423300	-2.85266400	3.62901000
H	0.38428200	-2.75731100	4.37881600
H	-0.06169400	-3.53842000	2.85123000
H	-1.29187900	-3.27738100	4.10326000
H	0.29946100	2.23324100	0.80254600
H	2.19940400	4.36287900	1.51725400
H	1.02944800	3.56212200	2.58420100
C	-0.47016400	4.12809700	0.45707300
C	-1.52556100	3.79610800	1.53996000
C	-2.09151900	5.16423500	1.94700300
C	-0.86266500	6.08446500	1.89676200
C	-0.13478300	5.63650300	0.61497200
H	-0.92645900	3.94785200	-0.51007000
H	-1.06506500	3.30542200	2.40041400
H	-2.27437400	3.10712300	1.14861000
H	-2.83584700	5.49634500	1.21557300
H	-2.57765300	5.14306000	2.92433000
H	-0.22999200	5.90361900	2.77310600
H	-1.11329100	7.14711900	1.88859600
H	0.93372600	5.84801300	0.63656800
H	-0.53935600	6.16940000	-0.24933400

TS_{Add}-3

Zero-point correction = 0.859981 (Hartree/Particle)
Thermal correction to Energy = 0.918075
Thermal correction to Enthalpy = 0.919019
Thermal correction to Gibbs Free Energy = 0.764357
Sum of electronic and zero-point Energies = −3313.381883
Sum of electronic and thermal Energies = −3313.323790
Sum of electronic and thermal Enthalpies = −3313.322845
Sum of electronic and thermal Free Energies = −3313.477508
E (RB3LYP-D3) = −3314.241864
Imaginary frequency = 111.72i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.405185
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p)) = −3314.277390

0 1

C	4.44006500	-1.04572400	-0.60759400
C	2.12823100	-2.22356100	-1.56332700
C	3.40482100	-0.24100200	-1.06635800
C	4.34639400	-2.43500300	-0.61137200
C	3.17391800	-3.00734400	-1.09502600
C	2.22331500	-0.82617900	-1.53573400
H	3.50429600	0.83149000	-1.03556300
H	5.15689300	-3.04900900	-0.24529100
H	1.21236800	-2.68508100	-1.90376100
C	5.62585300	-0.39150500	0.04230000
C	2.96816700	-4.49135200	-1.00116800
F	6.75373000	-1.12038400	-0.08510100
F	5.41797600	-0.23162500	1.37968400
F	5.87796900	0.83984700	-0.45128300
F	2.20506600	-4.97397600	-2.00438900
F	2.32158700	-4.82031100	0.15668800
F	4.12656000	-5.17910300	-1.00016000
N	1.07085000	-0.10931200	-1.86207800
H	0.21466000	-0.62763000	-1.65040600
C	0.91797100	1.24275900	-2.05372800
S	2.07071500	2.20686900	-2.82756000
N	-0.27098700	1.67453300	-1.57466300
H	-0.81276000	1.02163900	-1.01538100
C	-0.85679600	3.00762100	-1.61767200
C	-0.64675300	5.42105400	-0.82396600
C	-1.74115800	4.91510800	-3.03800700
C	-0.84025200	5.89196200	-2.27345000
C	-1.13792500	3.50788700	-3.04496000
C	-0.02416500	4.02291200	-0.80002900
H	-1.62587300	5.41319700	-0.33484700
H	-2.73396200	4.89548900	-2.56966800
H	0.13340900	5.96067500	-2.77174900
H	-0.20687200	3.50637400	-3.61298300
H	0.96364000	4.06148100	-1.25335600
H	-1.82718500	2.88111700	-1.13255700
H	-0.01618000	6.12627400	-0.27435000
H	-1.88763100	5.25702600	-4.06603900
H	-1.26991000	6.89759500	-2.27070700
H	-1.81429100	2.78605100	-3.50698300
N	0.20204000	3.50044400	0.62557300
C	1.47337100	4.05666200	1.26397800
H	1.35632000	5.14008000	1.22022500
C	-0.98466400	3.70908400	1.51240100
H	-1.88802800	3.44256800	0.97725900
H	0.34757300	2.45916200	0.58670700
C	-3.12977700	-1.39827800	-0.50766400
C	-1.93545200	-2.19579700	-0.44993800
O	-0.84442300	-1.82560900	-0.87883900
O	-2.09356000	-3.35710300	0.20924100
C	-0.91781100	-4.18181800	0.29734600
H	-0.61339600	-4.52243300	-0.69375900
H	-1.20341800	-5.02960000	0.91603700
H	-0.09719400	-3.63036800	0.75218800
C	-3.18347300	-0.35518600	-1.45811900
N	-3.19800500	0.57939100	-2.14505200
O	-4.34817000	-1.96803100	-0.10859300
C	-4.86191200	-2.93142500	-0.91539500
O	-4.40356400	-3.30359100	-1.95881300
O	-5.97393600	-3.37851900	-0.32635200
C	-2.62755100	-0.10035500	1.33761200
H	-2.54376100	-1.01128100	1.92829800
N	-1.53756500	0.60205800	1.03083000
C	-0.31245300	0.18417200	1.45607900
O	0.70631700	0.85075900	1.21274300
O	-0.27702300	-0.93411400	2.20265700
C	0.91559200	-1.35007100	2.97282700
C	-3.94344500	0.54899800	1.38039300
C	-6.47356900	1.74407500	1.52803500
C	-4.18941300	1.77880800	0.75243900
C	-4.99110500	-0.07997800	2.06837300
C	-6.24420300	0.51630900	2.14713000
C	-5.44370300	2.36974900	0.82403000
H	-3.39900400	2.23545700	0.17670500
H	-4.82003600	-1.04758300	2.52445000
H	-7.04489900	0.01910500	2.68236500
H	-5.62545500	3.31289000	0.32100600
H	-7.45247900	2.20681200	1.58430500
H	-0.90514800	3.04865300	2.36858400
H	-1.01807700	4.74829900	1.83416500
C	2.76278600	3.60339000	0.52786900
H	3.36404200	4.48930400	0.30623500
H	2.56544400	3.11849500	-0.42721500
C	1.64335800	3.58056600	2.73096500
H	1.25952600	4.30337500	3.45299600
H	1.10413800	2.64340300	2.86950400
C	3.50688500	2.68962200	1.51447300
H	4.57891900	2.64737700	1.31985300
H	3.11365400	1.67272500	1.44292800
C	3.14546200	3.28844700	2.87869300
H	3.70540200	4.21504100	3.04770800
H	3.35112300	2.62101900	3.71819300
C	-6.66293800	-4.40935700	-1.05814100
H	-7.53295500	-4.65823100	-0.45475000
H	-6.96732600	-4.04272000	-2.03997100
H	-6.02001700	-5.28201900	-1.18569200
C	1.34057200	-0.22821600	3.92320800
H	2.06563700	-0.61879100	4.64128900
H	1.80196900	0.59198600	3.37831900
H	0.47649900	0.14694000	4.47793600
C	2.04647000	-1.75623200	2.03332100
H	2.90343500	-2.09467700	2.62135400
H	1.74055200	-2.57367800	1.38182600
H	2.35897400	-0.91716700	1.41828900
C	0.38892400	-2.54885300	3.75941600
H	1.19016900	-2.98007800	4.36367600
H	-0.42639300	-2.24604700	4.42019300
H	0.01490900	-3.31647300	3.08040500

TS_{Add}_4

Zero-point correction = 0.860978 (Hartree/Particle)

Thermal correction to Energy = 0.918759

Thermal correction to Enthalpy = 0.919703

Thermal correction to Gibbs Free Energy = 0.762725

Sum of electronic and zero-point Energies = −3313.369063

Sum of electronic and thermal Energies = −3313.311283

Sum of electronic and thermal Enthalpies = −3313.310338

Sum of electronic and thermal Free Energies = −3313.467316

E(RB3LYP-D3) = -3314.230041

Imaginary frequency = 302.51i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.391757

Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.262068

0 1

C	5.45208900	0.12013800	-0.16230100
C	3.60550800	-1.52627500	1.06914600
C	4.30496900	0.67881700	0.39402000
C	5.69708300	-1.24554500	-0.12130100
C	4.75638700	-2.05735500	0.50783800
C	3.35417100	-0.14735500	0.99834500
H	4.14479500	1.74298900	0.34377800
H	6.59096400	-1.66568000	-0.55978800
H	2.87578600	-2.18455600	1.51923300
N	2.09380200	0.27900300	1.45911200
H	1.45623800	-0.50129100	1.59326300
C	1.53506700	1.52720400	1.54008800
S	2.41226700	2.97208000	1.60556900
N	0.16945300	1.50699500	1.54931200
H	-0.31899500	0.61424800	1.59516600
C	-0.64642200	2.63972400	1.98934900
C	-2.75646100	3.99582700	1.69722200
C	-1.84953900	3.60816800	4.02151800
C	-3.11135100	3.76661700	3.17303000
C	-0.99848700	2.45985800	3.48043100
C	-1.92428900	2.82884000	1.14045400
H	-2.20556900	4.93706400	1.60810800
H	-1.27312600	4.54126200	3.99802100
H	-3.72633600	2.86262600	3.25924600
H	-1.52926200	1.51144400	3.59919500
H	-2.52406500	1.91947400	1.19727900
H	-0.02100800	3.52760000	1.89464100
H	-3.67836900	4.10415400	1.12703600
H	-2.10753500	3.42228000	5.06790000
H	-3.72222600	4.60131800	3.52835400
H	-0.05439500	2.38037800	4.02554300
C	6.37343000	1.02610000	-0.92935200
C	4.93431200	-3.54944900	0.47422000
F	5.87804000	1.27147300	-2.17355500
F	6.52982200	2.22682200	-0.33618200
F	7.60114800	0.49310500	-1.09963000
F	6.23751000	-3.90657100	0.49351900
F	4.40767500	-4.07660200	-0.66302700
F	4.32838500	-4.16760000	1.50614700
N	-1.64335000	2.93685900	-0.38010700
C	-0.30175000	3.52926000	-0.79543600
H	0.43535400	2.96359600	-0.24351600
C	-2.78026700	3.56148000	-1.12740400
H	-2.80749300	4.62974500	-0.93493100
C	-1.75247500	-2.06643300	0.51250300
C	-2.56541300	-1.17074700	1.37224700
O	-2.06420900	-0.26466200	2.01332800
O	-3.87355000	-1.38449200	1.28482000
C	-4.71718800	-0.45861600	2.00667000
H	-4.36213600	-0.34782900	3.03076800
H	-5.70967900	-0.89973200	1.98402900
H	-4.71462600	0.49916800	1.48552600
C	-0.48452700	-2.32267300	1.12699000
N	0.56658400	-2.42778900	1.59477600
O	-2.39458500	-3.21836200	-0.00811500
C	-2.87238200	-4.11732600	0.89033200
O	-2.71860500	-4.07596300	2.07944900
O	-3.53628900	-5.04299000	0.19923800
C	-4.10412000	-6.09925000	1.00007800
H	-3.31994300	-6.62646900	1.54541200
H	-4.59419300	-6.76328000	0.29233400
H	-4.82512300	-5.69116900	1.71014900
C	-1.52497000	-1.01568400	-1.15649600
N	-2.16140400	0.19663100	-1.03795000
C	-3.51197200	0.19240000	-1.24057500
O	-4.26518200	1.08085800	-0.83570000
H	-2.06758400	-1.78782100	-1.69430300
C	-0.07061900	-1.04957700	-1.48612700
C	2.62331500	-1.18170600	-2.27014400
C	0.71892800	0.09940100	-1.52723500
C	0.51757000	-2.27492000	-1.83320400
C	1.85479500	-2.34378800	-2.20753000
C	2.04824700	0.04061800	-1.93422500
H	0.28780700	1.03951100	-1.23491800
H	-0.08129400	-3.17912400	-1.79619100
H	2.30225700	-3.30165500	-2.44345800
H	2.64578500	0.94396500	-1.96651800
H	3.66666000	-1.22864800	-2.55805900
O	-3.96992400	-0.86987300	-1.95358600
C	-5.38122500	-1.08565500	-2.27957000
C	-5.87366900	0.03223100	-3.20021800
H	-5.87578600	0.98574900	-2.67426900
H	-6.88794200	-0.18905500	-3.54348100
H	-5.22281000	0.10941600	-4.07479800
C	-6.22397900	-1.19935100	-1.00830600
H	-7.23583200	-1.51956200	-1.27076700
H	-6.27699000	-0.24215700	-0.49387600
H	-5.78192200	-1.94096000	-0.34109600
C	-5.33884000	-2.42823500	-3.01073400
H	-4.93336200	-3.20007900	-2.35257700
H	-4.70035200	-2.35877700	-3.89403500
H	-6.34354900	-2.72087100	-3.32556300
H	-1.65744400	1.90832300	-0.67150300
H	-3.69844200	3.06702100	-0.83367300
H	-2.62802000	3.37822400	-2.18749400
C	-0.04030500	3.39380400	-2.31130400
H	1.02293100	3.17152600	-2.42608700
H	-0.57415800	2.55399000	-2.75946900
C	-0.12278200	5.03075300	-0.51502300
H	0.93092900	5.16422000	-0.25999000
H	-0.68907400	5.37998500	0.34690800
C	-0.46672900	5.79275500	-1.81524900
H	0.21525500	6.63161800	-1.96469000
H	-1.47158800	6.21885200	-1.76643800
C	-0.37006400	4.75646600	-2.96812800
H	0.40166800	5.02916000	-3.68980600
H	-1.30880900	4.70974800	-3.52432200

IM3

Zero-point correction = 0.861710 (Hartree/Particle)

Thermal correction to Energy = 0.919777

Thermal correction to Enthalpy = 0.920721

Thermal correction to Gibbs Free Energy = 0.764985
Sum of electronic and zero-point Energies = −3313.404793
Sum of electronic and thermal Energies = −3313.346725
Sum of electronic and thermal Enthalpies = −3313.345781
Sum of electronic and thermal Free Energies = −3313.501518
E(RB3LYP-D3) = −3314.266503

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.429667
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.301117

0 1

C	4.77280800	-1.02000200	-0.26587700
C	3.25656900	1.06755900	-1.25972500
C	3.53669700	-1.28908600	-0.84029300
C	5.26729700	0.27675000	-0.16191600
C	4.48673300	1.31350700	-0.66337200
C	2.75665800	-0.23958800	-1.33885600
H	6.22678300	0.47145100	0.29543400
H	2.66405400	1.88786400	-1.63704500
C	0.80491700	-1.54842600	-2.21690100
N	1.45610600	-0.40093800	-1.82084800
H	0.87191700	0.42496000	-1.71680000
N	-0.52250100	-1.47418700	-1.98197600
H	-0.86458500	-0.74525900	-1.33302300
C	-1.49899400	-2.48533300	-2.33685100
C	-3.30487800	-4.01500700	-1.44052000
C	-3.54359700	-3.00151800	-3.75091600
C	-4.28358000	-3.47756000	-2.49690200
C	-2.48353700	-1.95587700	-3.39472800
C	-2.27390500	-2.94094600	-1.07989400
H	-2.79894600	-4.90289400	-1.83537600
H	-3.06313200	-3.86063500	-4.23539400
H	-4.84850200	-2.64179200	-2.06599100
H	-2.95721700	-1.04115800	-3.02634300
H	-2.78940700	-2.06837200	-0.68049700
H	-0.95792300	-3.32840700	-2.76915200
H	-3.86353600	-4.32380300	-0.55455500
H	-4.24969900	-2.58599200	-4.47496800
H	-5.01125500	-4.25489500	-2.74621500
H	-1.90273500	-1.66729400	-4.27360100
N	-1.33557400	-3.35752600	0.05069600
H	-0.72451300	-2.50774300	0.29877700
C	-1.87291000	2.40805600	-0.45178900
C	-0.37819600	2.76701200	-0.50716900
O	0.39091300	2.24100800	-1.27472800
O	-0.04727600	3.63798500	0.42974900
C	1.36157500	3.96660600	0.49905500
H	1.94194400	3.06408100	0.67448400
H	1.45577100	4.65550000	1.33365000
H	1.68061900	4.43530600	-0.43203800
C	-2.29394800	1.93203300	-1.77807500
N	-2.66164200	1.52416300	-2.78953000
O	-2.69241800	3.49810100	-0.01577600
C	-2.57697300	4.65328700	-0.71222700
O	-1.84713300	4.83138300	-1.65098400
O	-3.40858000	5.53345100	-0.16692600
C	-3.41238200	6.83088400	-0.79900900
H	-2.42201300	7.28470000	-0.73926900
H	-4.13931000	7.41680000	-0.24229900
H	-3.70663600	6.74161400	-1.84562800
C	-2.04830400	1.29484100	0.65511800
N	-1.32334200	0.09292200	0.31473400
C	-0.27722200	-0.26114300	1.04205200
O	0.23592100	-1.41019500	0.98483700
O	0.26402100	0.69369600	1.86181800
C	1.23752800	0.39253700	2.92183300
C	-3.51700500	0.97730300	0.90732300
C	-6.16718400	0.26463700	1.50073900
C	-4.28008600	0.24290500	-0.00702400
C	-4.10335100	1.35620100	2.11531100
C	-5.41722000	0.99867500	2.41574900
C	-5.59445800	-0.10653600	0.28407300
H	-3.84180700	-0.05934100	-0.94766000
H	-3.52441500	1.93152000	2.82964400
H	-5.85343100	1.29632800	3.36279100
H	-6.17307100	-0.67040800	-0.43976400
H	-7.18994800	-0.01252200	1.73021000
H	-1.65443400	1.78325800	1.54966200
C	2.55199700	-0.11275500	2.32977400
H	3.30325000	-0.20165000	3.11896100
H	2.42028900	-1.08050200	1.85512900
H	2.92502400	0.59123900	1.58444600
C	0.63349100	-0.60073100	3.91555400
H	1.30850400	-0.73072500	4.76512700
H	-0.32271900	-0.22631200	4.28993000
H	0.47770300	-1.56865900	3.44511800
C	1.43591300	1.75373400	3.58991900
H	2.10136600	1.65489100	4.45070500
H	1.88359000	2.46251000	2.89241200
H	0.47904100	2.15688500	3.92901200
S	1.57573600	-2.85645800	-2.96184500
C	5.52923900	-2.15127900	0.37252000
C	4.91865400	2.73513500	-0.45627200
F	5.36325700	-3.31836200	-0.28165200
F	6.85600300	-1.90800600	0.44043200
F	5.10800800	-2.35966800	1.64888700
F	4.44998200	3.56805800	-1.41080100
F	6.25705900	2.87396500	-0.41316400
F	4.44229200	3.21860300	0.73146300
H	3.17260800	-2.30285100	-0.88733400
C	-0.39450300	-4.45658900	-0.31928200
H	0.33160500	-4.56970800	0.48139000
H	-0.94728300	-5.38647600	-0.45131600
H	0.14236400	-4.19413100	-1.22835300
C	-2.07820100	-3.68473800	1.33355900
C	-1.13202300	-3.97005700	2.51511700
C	-2.99724100	-2.52906500	1.80221400
H	-2.66148800	-4.58291100	1.12389900
C	-2.01041000	-3.67172700	3.73706700
H	-0.28942200	-3.27652000	2.47527700
H	-0.74152800	-4.98910700	2.51137000
C	-2.78464700	-2.40622700	3.33008700
H	-4.03841400	-2.73200000	1.54560100
H	-2.72495500	-1.59726100	1.31105400
H	-2.70296000	-4.50351700	3.90933800
H	-1.42349800	-3.54256500	4.64872500
H	-3.72458100	-2.29018100	3.87186000
H	-2.18109900	-1.52060900	3.53942100

TS_{Rot}

Zero-point correction = 0.861552 (Hartree/Particle)
Thermal correction to Energy = 0.918816
Thermal correction to Enthalpy = 0.919760
Thermal correction to Gibbs Free Energy = 0.766565
Sum of electronic and zero-point Energies = −3313.393274
Sum of electronic and thermal Energies = −3313.336010
Sum of electronic and thermal Enthalpies = −3313.335066
Sum of electronic and thermal Free Energies = −3313.488260
E(RB3LYP-D3) = −3314.254826
Imaginary frequency = 63.10i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.418326
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.290695

0 1

C	4.75783700	-1.40855600	-0.17281000
C	3.42033400	0.79791600	-1.16422400
C	3.50826900	-1.57612400	-0.75745100
C	5.35340400	-0.15632800	-0.05772100
C	4.66210800	0.94200400	-0.55959400
C	2.81710100	-0.46476200	-1.25335800
H	6.32269300	-0.04136200	0.40598100
H	2.89848300	1.66469300	-1.54225400
C	0.75558800	-1.59097700	-2.14603300
N	1.51261400	-0.51279200	-1.74837600
H	1.01244400	0.36963600	-1.67807600
N	-0.56525000	-1.35739100	-1.98802400
H	-0.85903700	-0.59183300	-1.35648200
C	-1.61630600	-2.25479700	-2.41390400
C	-3.57879600	-3.66061600	-1.76304200
C	-3.52630900	-2.59285300	-4.05690100
C	-4.41795500	-3.05667800	-2.90022800
C	-2.43662800	-1.63716700	-3.56271100
C	-2.56317700	-2.62759100	-1.25149400
H	-3.04581300	-4.54091700	-2.13815900
H	-3.05795000	-3.46866600	-4.52246000
H	-4.98842000	-2.20456100	-2.51037800
H	-2.87429500	-0.69118800	-3.22912500
H	-3.08253700	-1.72528300	-0.92296100
H	-1.13335700	-3.15890300	-2.78939900
H	-4.23802400	-4.00454200	-0.96336700
H	-4.12756100	-2.10792200	-4.83073900
H	-5.14820300	-3.79391600	-3.24545700
H	-1.74112900	-1.38836800	-4.36730400
N	-1.83050200	-3.08155200	0.00911900
H	-1.12872300	-2.31598700	0.28476200
C	-1.58025200	2.62151500	-0.46055300
C	-0.05488800	2.81382600	-0.50557100
O	0.65670200	2.23074500	-1.28703800
O	0.36303600	3.59985400	0.47165800
C	1.80063400	3.71550800	0.60420400
H	2.22723900	2.73384500	0.79825200
H	1.95990500	4.37949300	1.44901200
H	2.23040400	4.13305200	-0.30608500
C	-2.05530100	2.20428000	-1.78801100
N	-2.47694700	1.84173600	-2.79568700
O	-2.27994200	3.78690700	-0.01072500
C	-2.03072700	4.93344900	-0.68605300
O	-1.27502000	5.04465900	-1.61453900
O	-2.76650100	5.89114500	-0.13369600
C	-2.61981000	7.19110500	-0.74332300
H	-1.58592400	7.53109900	-0.66723900
H	-3.28315400	7.84499400	-0.18291500
H	-2.91117500	7.15193600	-1.79382400
C	-1.86422000	1.52051700	0.63351800
N	-1.26235400	0.26049000	0.26833400
C	-0.29703100	-0.23995200	1.01958000
O	0.07415100	-1.44058300	0.93848500
O	0.31280100	0.61192500	1.90229400
C	1.22441700	0.15805500	2.96203200
C	-3.35486700	1.34181700	0.89177300
C	-6.04741300	0.84081700	1.51066900
C	-4.17788500	0.65572900	-0.00833100
C	-3.90363800	1.78550000	2.09531500
C	-5.23907200	1.53343900	2.40811300
C	-5.51274000	0.40922700	0.29605500
H	-3.76830300	0.31494800	-0.94869800
H	-3.27733900	2.32444600	2.79787400
H	-5.64569800	1.87844500	3.35223300
H	-6.13820400	-0.11822500	-0.41622400
H	-7.08618000	0.64385400	1.75087000
H	-1.42056900	1.95562500	1.53214900
C	2.52099100	-0.37556800	2.35711400
H	3.23213400	-0.61798800	3.15105700
H	2.32912000	-1.27021900	1.77165400
H	2.97831000	0.37435800	1.70903700
C	0.54189000	-0.88543000	3.85043700
H	1.15196500	-1.06391500	4.73959300
H	-0.43865700	-0.52424600	4.17213700
H	0.42062700	-1.82535500	3.31571100
C	1.47764900	1.44309000	3.75106200
H	2.14612700	1.24324900	4.59171100
H	1.94238200	2.19718800	3.11409700
H	0.53854000	1.84711400	4.13618700
S	1.40268200	-3.00677100	-2.80966200
C	5.41822800	-2.60017100	0.46280300
C	5.20864100	2.32254800	-0.34510700
F	5.16595600	-3.74611700	-0.20032100
F	6.75980200	-2.46223600	0.54084500
F	4.97328900	-2.78217000	1.73498900
F	4.79824600	3.19942200	-1.28768900
F	6.55432900	2.35303700	-0.31667600
F	4.78599500	2.83158500	0.85158600
H	3.06476500	-2.55710600	-0.81417300
C	-0.96025000	-4.27789000	-0.20695400
H	-0.36571400	-4.43236500	0.68943200
H	-1.56317900	-5.15857800	-0.41574100
H	-0.28043000	-4.07432500	-1.03291900
C	-2.82004900	-3.20423300	1.17370000
C	-2.72962900	-4.46184700	2.04731900
C	-2.73825800	-2.06873000	2.19794000
H	-3.81322500	-3.18037700	0.72622600
C	-3.67579200	-4.11583300	3.21895900
H	-1.70893400	-4.58593900	2.41776800
H	-3.01418300	-5.37963200	1.52970900
C	-3.67449800	-2.55816900	3.31927300
H	-3.02075900	-1.10459300	1.78442200

H	-1.71280500	-1.99257500	2.55651800
H	-4.68327800	-4.48442000	3.01056400
H	-3.34892500	-4.59529300	4.14286400
H	-4.68200200	-2.16301200	3.17045900
H	-3.33727900	-2.20679700	4.29564500

IM3-2

Zero-point correction = 0.861992 (Hartree/Particle)
Thermal correction to Energy = 0.920142
Thermal correction to Enthalpy = 0.921086
Thermal correction to Gibbs Free Energy = 0.765207
Sum of electronic and zero-point Energies = −3313.398508
Sum of electronic and thermal Energies = −3313.340359
Sum of electronic and thermal Enthalpies = −3313.339415
Sum of electronic and thermal Free Energies = −3313.495293
E(RB3LYP-D3) = −3314.260501

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.423480
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.294882

0 1

C	4.90124100	-1.42391100	-0.12673400
C	3.48202800	0.73248600	-1.10956800
C	3.66251700	-1.64049300	-0.71968700
C	5.44710000	-0.15028100	-0.00294500
C	4.71536800	0.92309500	-0.50244400
C	2.93015900	-0.55350900	-1.21040500
H	6.40904500	0.00005500	0.46578000
H	2.92546100	1.58008300	-1.48380500
C	0.86594500	-1.72160600	-2.07289600
N	1.63700700	-0.63530400	-1.72602900
H	1.14295400	0.25283900	-1.72175400
N	-0.44910200	-1.41862400	-2.01435100
H	-0.73142100	-0.60929500	-1.44664300
C	-1.53425100	-2.27596400	-2.45134600
C	-3.84985000	-3.10873100	-1.82146600
C	-3.31123800	-2.59810900	-4.24184700
C	-4.39152200	-2.58017700	-3.15837000
C	-2.10428700	-1.77427100	-3.79127300
C	-2.62524300	-2.30927600	-1.36532300
H	-3.58837300	-4.16670000	-1.93347300
H	-3.00554300	-3.63376900	-4.43743900
H	-4.74846900	-1.55227600	-3.02103800
H	-2.38573600	-0.72266300	-3.68606800
H	-2.92175500	-1.27997200	-1.15735600
H	-1.12958300	-3.27748900	-2.60877600
H	-4.63632800	-3.04485900	-1.06949000
H	-3.70572600	-2.20206500	-5.18154000
H	-5.25717700	-3.17904200	-3.45553700
H	-1.29566500	-1.81913600	-4.52479000
N	-2.06604500	-2.78084400	-0.02054800
H	-1.27001100	-2.12345500	0.24063400
C	-1.61370200	2.51659900	-0.50580400
C	-0.08849700	2.73147400	-0.60413200
O	0.61456400	2.11792200	-1.36971500
O	0.33425400	3.57156100	0.32448400
C	1.77195800	3.69869200	0.44664700
H	2.19742000	2.73140300	0.70399800
H	1.93100000	4.41427500	1.24820200
H	2.20071800	4.05888200	-0.48815900
C	-2.10559200	2.02004700	-1.80093200
N	-2.53823200	1.60779200	-2.78466400
O	-2.32903700	3.68826800	-0.10388300
C	-2.11494700	4.80284800	-0.84329200
O	-1.38155000	4.87631600	-1.79322700
O	-2.85567600	5.77524900	-0.32597300
C	-2.74321500	7.04494200	-1.00348800
H	-1.71412900	7.40508100	-0.96479300
H	-3.40710000	7.71537400	-0.46374000
H	-3.05354400	6.94745200	-2.04471100
C	-1.81771800	1.47431500	0.65298400
N	-1.22932900	0.20833700	0.29155300
C	-0.23058900	-0.27738400	1.01453400
O	0.11782100	-1.48003000	0.94080200
O	0.42349600	0.59518200	1.84593300
C	1.31191900	0.14868400	2.92998400
C	-3.26837100	1.25114100	1.06812200
C	-5.82497100	0.55536400	2.01546500
C	-4.26168800	0.80841200	0.18672900
C	-3.58358700	1.35358200	2.42534800
C	-4.84685300	1.00347200	2.89990200
C	-5.52862300	0.46924200	0.65520100
H	-4.05263700	0.72575000	-0.87062300
H	-2.82526700	1.69835000	3.12047700
H	-5.06650300	1.08635400	3.95857500
H	-6.28652800	0.13623500	-0.04568200
H	-6.81012900	0.28630700	2.37923800
H	-1.31188300	1.95249300	1.49533200
C	2.57929900	-0.48633600	2.36233700
H	3.27082300	-0.72785900	3.17381200
H	2.34184200	-1.39563900	1.81720900
H	3.08033800	0.20707500	1.68549700
C	0.56544300	-0.80856300	3.86163300
H	1.17185100	-1.00417600	4.74957600
H	-0.38181400	-0.36591600	4.18135400
H	0.36504500	-1.75177600	3.35861500
C	1.63676600	1.45604400	3.65291100
H	2.27675300	1.25905700	4.51614000
H	2.16308900	2.14171200	2.98665200
H	0.72071900	1.94145200	3.99776200
S	1.46635300	-3.22014100	-2.56662900
C	5.60738400	-2.59087500	0.50663000
C	5.20420300	2.32379400	-0.28041400
F	5.39998900	-3.74393500	-0.15849200
F	6.94308100	-2.40035100	0.58359400
F	5.17080300	-2.78998800	1.77817100
F	4.77870700	3.18200500	-1.23476500
F	6.54632500	2.40679900	-0.22589200
F	4.73754000	2.82008600	0.90501600
H	3.25929100	-2.63795600	-0.78917200
C	-1.38663300	-4.10988300	-0.05761000
H	-1.05358400	-4.34925200	0.95006800
H	-2.06503900	-4.87901500	-0.41908200
H	-0.51105900	-4.03619800	-0.70035600
C	-3.09094300	-2.63430400	1.09599600
C	-3.95225800	-3.86008500	1.43397900
C	-2.46705000	-2.25531900	2.44897600
H	-3.73616700	-1.81452700	0.77791300

C	-4.64989700	-3.39282600	2.72113500
H	-3.31466000	-4.72199600	1.65146300
H	-4.65129400	-4.15283500	0.65163200
C	-3.56382100	-2.59391900	3.49009100
H	-2.18048100	-1.20793400	2.46438000
H	-1.56305300	-2.84130700	2.62162100
H	-5.48460300	-2.73448200	2.46243500
H	-5.05760100	-4.22500900	3.29740200
H	-3.98338000	-1.68572100	3.92532000
H	-3.14676500	-3.18292500	4.30942400

TS_{PT}-D

Zero-point correction = 0.857647 (Hartree/Particle)
Thermal correction to Energy = 0.915397
Thermal correction to Enthalpy = 0.916341
Thermal correction to Gibbs Free Energy = 0.762039
Sum of electronic and zero-point Energies = −3313.396401
Sum of electronic and thermal Energies = −3313.338652
Sum of electronic and thermal Enthalpies = −3313.337707
Sum of electronic and thermal Free Energies = −3313.492010
E(RB3LYP-D3) = −3314.254048
Imaginary frequency = 1320.16i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.415360
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p)) = −3314.287563

0 1

C	4.79967800	-1.51972200	-0.07850800
C	3.52804700	0.61578800	-1.28342600
C	3.56235100	-1.71906100	-0.67929000
C	5.41711600	-0.27194800	-0.05736300
C	4.75825600	0.79170900	-0.66471400
C	2.90807800	-0.64151800	-1.28800700
H	6.37710400	-0.13460300	0.41922000
H	3.02785300	1.45795300	-1.74113100
C	0.82003300	-1.78343300	-2.11967400
N	1.62531600	-0.70202800	-1.82961300
H	1.15525300	0.19727500	-1.84264300
N	-0.48834400	-1.45118500	-2.01902300
H	-0.70559800	-0.59639000	-1.51826100
C	-1.61336200	-2.31160200	-2.35118000
C	-3.94746700	-3.02539600	-1.71194800
C	-3.27256600	-2.94871400	-4.15607200
C	-4.41237900	-2.76399400	-3.15234900
C	-2.09665300	-2.04332500	-3.78676800
C	-2.75875600	-2.13342900	-1.32498100
H	-3.67158200	-4.07960300	-1.59877400
H	-2.94713200	-3.99660600	-4.15304400
H	-4.79164400	-1.73690600	-3.22457300
H	-2.38321900	-0.99178400	-3.87590200
H	-3.09421600	-1.09321400	-1.37550500
H	-1.25313000	-3.34166500	-2.31142200
H	-4.77924300	-2.83450500	-1.03513900
H	-3.61524200	-2.72743100	-5.17082800
H	-5.25124900	-3.42662500	-3.38529800
H	-1.24637500	-2.20905400	-4.45269800
N	-2.25657700	-2.30468000	0.09553400
H	-1.71853100	-1.15302300	0.30139100
C	-1.59153300	2.32673500	-0.47028200
C	-0.07427300	2.59747000	-0.56644800
O	0.65245800	1.96179900	-1.29088600
O	0.31156500	3.54163200	0.26915100
C	1.73591300	3.81393400	0.27746900
H	2.28153900	2.90938500	0.53478800
H	1.87655400	4.58239500	1.03206500
H	2.04932500	4.16914600	-0.70437100
C	-2.02943300	1.77144400	-1.76126200
N	-2.40809800	1.30337000	-2.74232100
O	-2.34142300	3.49581600	-0.13327900
C	-2.16800800	4.57523300	-0.93657200
O	-1.44703900	4.61525600	-1.89768000
O	-2.93345800	5.54973900	-0.46531700
C	-2.87074800	6.78368400	-1.21357600
H	-1.85409700	7.17910000	-1.20598100
H	-3.55187300	7.46002500	-0.70378100
H	-3.18763800	6.61750200	-2.24395400
C	-1.83849400	1.32767300	0.73250100
N	-1.17141000	0.05082700	0.52062600
C	-0.00198600	-0.20817300	1.17163600
O	0.53683400	-1.30651800	1.14733800
O	0.51257400	0.85295300	1.86383300
C	1.48178200	0.63905000	2.95787500
C	-3.31423200	1.19185200	1.08942400
C	-5.97626400	0.86231700	1.93842400
C	-4.32931100	0.91250100	0.16880900
C	-3.66250400	1.32954200	2.43641500
C	-4.97719000	1.16027100	2.86245300
C	-5.64768900	0.74951400	0.58945400
H	-4.10876400	0.82566100	-0.88487200
H	-2.89005900	1.56377600	3.16119800
H	-5.22050900	1.26633600	3.91358300
H	-6.41822100	0.53519200	-0.14257900
H	-7.00210300	0.73410900	2.26423500
H	-1.36831800	1.85340300	1.56324800
C	2.83378100	0.20322400	2.39869200
H	3.56337300	0.13823300	3.21039000
H	2.75826000	-0.76711100	1.91649000
H	3.20077000	0.92975900	1.67289800
C	0.91950500	-0.37566100	3.95739900
H	1.55732600	-0.40361200	4.84420000
H	-0.08741600	-0.08221900	4.26749300
H	0.88186600	-1.37258100	3.52277200
C	1.57168200	2.02296700	3.59966300
H	2.25279700	1.99414600	4.45312600
H	1.94872900	2.75608200	2.88601600
H	0.58894100	2.35086900	3.94638100
S	1.37275900	-3.29977900	-2.59206500
C	5.42806500	-2.65761500	0.67779200
C	5.31405000	2.18014600	-0.55628100
F	5.12702800	-3.85966000	0.15083700
F	6.77560700	-2.55839200	0.72206400
F	5.00023000	-2.67727000	1.96774200
F	5.01159500	2.94819100	-1.62573400
F	6.65042400	2.20050000	-0.40202800
F	4.78999300	2.83053200	0.52938300
H	3.09983900	-2.69291400	-0.66333700
C	-1.30123500	-3.43419200	0.24741100
H	-1.09477900	-3.58509600	1.30228800

H	-1.71175000	-4.35305200	-0.17573500
H	-0.35934800	-3.19599600	-0.22898000
C	-3.31824800	-2.32910000	1.17079200
C	-4.12081600	-3.64824800	1.35776900
C	-2.68363500	-2.04173100	2.57226200
H	-3.99964500	-1.52028100	0.91611300
C	-4.32416300	-3.77644000	2.87545600
H	-3.54633900	-4.50356200	0.99640800
H	-5.06500400	-3.64420000	0.81454200
C	-3.00055700	-3.26235000	3.45117600
H	-3.15588200	-1.15249200	2.98723100
H	-1.61671700	-1.83551000	2.50662700
H	-5.14625200	-3.12764400	3.19869000
H	-4.57017800	-4.79613600	3.18050300
H	-3.05775500	-3.01104400	4.51251900
H	-2.22706000	-4.03007000	3.34033100

IM4-D

Zero-point correction = 0.860829 (Hartree/Particle)
Thermal correction to Energy = 0.919453
Thermal correction to Enthalpy = 0.920397
Thermal correction to Gibbs Free Energy = 0.763533
Sum of electronic and zero-point Energies = −3313.407273
Sum of electronic and thermal Energies = −3313.348649
Sum of electronic and thermal Enthalpies = −3313.347705
Sum of electronic and thermal Free Energies = −3313.504569
E(RB3LYP-D3) = −3314.268102

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.429661
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.301756

0 1

C	4.81890900	-1.60956000	0.07689100
C	3.49369600	0.42781900	-1.23489500
C	3.54785900	-1.84645900	-0.43334200
C	5.44306200	-0.37077700	-0.04088400
C	4.75534900	0.64518900	-0.69689400
C	2.86717700	-0.81992400	-1.10048000
H	6.42879800	-0.20319600	0.36894900
H	2.97909500	1.22907100	-1.74637900
C	0.76723500	-2.01846000	-1.83536000
N	1.56050100	-0.91729200	-1.57527100
H	1.11382300	-0.01639300	-1.70688100
N	-0.54258700	-1.68407500	-1.88291100
H	-0.79064800	-0.72354100	-1.69434100
C	-1.63239600	-2.56511500	-2.28216000
C	-3.98261400	-3.33671000	-1.88446600
C	-3.04645000	-3.33321300	-4.23957800
C	-4.29848700	-3.16316900	-3.37660200
C	-1.94948200	-2.37287900	-3.77535300
C	-2.88558500	-2.36146900	-1.39611700
H	-3.66552800	-4.36750200	-1.68850800
H	-2.68372000	-4.36550100	-4.15900300
H	-4.71243600	-2.15970100	-3.53956000
H	-2.25970200	-1.33566500	-3.94214100
H	-3.25920400	-1.34427300	-1.57879200
H	-1.26677900	-3.58364300	-2.14503300
H	-4.89260500	-3.16966100	-1.30914000
H	-3.27761900	-3.16082600	-5.29502100
H	-5.07490200	-3.87505600	-3.67398600
H	-1.02518100	-2.53467300	-4.33606200
N	-2.55672400	-2.42425100	0.05017600
H	-1.69813400	-0.56158500	0.38764500
C	-1.52180800	2.39325200	-0.59165000
C	-0.00486000	2.57585200	-0.82434700
O	0.63958500	1.83756500	-1.52771900
O	0.47572000	3.56527000	-0.09667600
C	1.91255200	3.75667000	-0.17122500
H	2.41743100	2.85310700	0.15992200
H	2.12624900	4.58604900	0.49640300
H	2.20235300	3.99278500	-1.19491900
C	-2.07875000	1.67861500	-1.75162000
N	-2.53119600	1.06810300	-2.61642300
O	-2.20112900	3.62375800	-0.35685600
C	-2.03826800	4.58488800	-1.30396500
O	-1.37611900	4.46391400	-2.29981700
O	-2.73404800	5.64353600	-0.92106600
C	-2.67518800	6.76863500	-1.82706400
H	-1.64613500	7.11459500	-1.93220500
H	-3.29572300	7.53412200	-1.36895700
H	-3.06593300	6.48563100	-2.80514300
C	-1.69578100	1.57528600	0.74614200
N	-1.10577200	0.24999300	0.62588800
C	0.00345200	-0.14537400	1.34801200
O	0.30244200	-1.30716400	1.50838000
O	0.69494300	0.91689700	1.82221300
C	1.64147700	0.74900900	2.95543800
C	-3.12091300	1.56372000	1.26996900
C	-5.68430500	1.48095600	2.40075500
C	-4.21027700	1.11366300	0.52116100
C	-3.33391800	1.98509000	2.58539000
C	-4.60430400	1.94046000	3.15158000
C	-5.48342000	1.07429200	1.08380500
H	-4.07806600	0.78291500	-0.49969200
H	-2.49565500	2.34368500	3.17299800
H	-4.75015200	2.26430500	4.17558800
H	-6.31835800	0.71816400	0.49134900
H	-6.67567000	1.44397800	2.83722800
H	-1.09292000	2.13850000	1.45434900
C	2.85223200	-0.07132000	2.52350500
H	3.59177900	-0.08062900	3.32814100
H	2.57346600	-1.09513800	2.29111600
H	3.31499900	0.37567300	1.64381600
C	0.89821300	0.11804600	4.13366500
H	1.54940500	0.11058700	5.01075600
H	0.00335700	0.69847700	4.37464700
H	0.60796900	-0.90727000	3.90960500
C	2.04124900	2.18855000	3.27031000
H	2.69218100	2.20631400	4.14700200
H	2.58660700	2.62958600	2.43502100
H	1.15932300	2.79899300	3.47752700
S	1.34562200	-3.57440700	-2.10668300
C	5.48253800	-2.68712000	0.89035600
C	5.32168200	2.03314800	-0.72665700
F	5.15642000	-3.92464400	0.47552300
F	6.83023600	-2.58866900	0.86304800
F	5.11551300	-2.60135100	2.19673800
F	4.93191800	2.73318100	-1.81572300

F	6.66519900	2.05431200	-0.68508200
F	4.88956300	2.75647200	0.35390900
H	3.08135000	-2.81056500	-0.30991700
C	-1.66261700	-3.52641000	0.43024500
H	-1.56332900	-3.54627500	1.51417200
H	-2.02032700	-4.51176700	0.10117800
H	-0.66461500	-3.36664000	0.03418800
C	-3.71270400	-2.28026200	0.96647200
C	-4.58393600	-3.54395300	1.26984400
C	-3.26786800	-1.76805000	2.37828500
H	-4.35499200	-1.52397200	0.51233200
C	-5.00503600	-3.39838200	2.73887900
H	-3.98483700	-4.45012400	1.15147600
H	-5.43939800	-3.63720000	0.60014000
C	-3.75547900	-2.80624800	3.40186300
H	-3.74343000	-0.80650300	2.57439800
H	-2.19020500	-1.61200000	2.42157300
H	-5.83842400	-2.69044300	2.82289800
H	-5.33078200	-4.34216700	3.18381400
H	-3.95137300	-2.37178600	4.38528000
H	-3.00512000	-3.59332200	3.53604600

53_D

Zero-point correction = 0.468153 (Hartree/Particle)
Thermal correction to Energy = 0.497695
Thermal correction to Enthalpy = 0.498639
Thermal correction to Gibbs Free Energy = 0.401612
Sum of electronic and zero-point Energies = −1978.076636
Sum of electronic and thermal Energies = −1978.047094
Sum of electronic and thermal Enthalpies = −1978.046150
Sum of electronic and thermal Free Energies = −1978.143177
E(RB3LYP-D3) = −1978.544789

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −1978.638281
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −1978.568971

0 1

C	3.85283600	-0.44152100	1.03959400
C	2.78719500	0.80473400	-1.18960100
C	2.49307700	-0.55801100	0.77890000
C	4.69324500	0.29743600	0.21005200
C	4.14311200	0.92567100	-0.90051300
C	1.95068200	0.06167000	-0.35269600
H	1.85960000	-1.11951600	1.44673700
H	5.74811600	0.38457300	0.42810100
H	2.38653400	1.27832900	-2.07816200
C	4.43701800	-1.16770700	2.22289400
C	5.00374000	1.79278600	-1.77825700
F	5.51672500	-0.52573600	2.72244300
F	3.54532600	-1.29878800	3.22794400
F	4.84138800	-2.41255900	1.88842500
F	6.30117900	1.42918600	-1.73855800
F	4.94568800	3.09126000	-1.39719000
F	4.60880300	1.75164900	-3.07089700
N	0.57854400	0.02327600	-0.64977200
H	0.25910100	0.77379100	-1.24676200
C	-0.31818600	-1.03253300	-0.53322700
N	-1.57969000	-0.62413800	-0.83389200
H	-1.81303100	0.33913900	-0.58804000
C	-2.76505000	-1.46850600	-0.72199600
C	-5.24923200	-1.38084400	-0.34982100
C	-4.22088400	-3.26188900	-1.71769500
C	-5.45889000	-2.38152600	-1.49804100
C	-2.95451300	-2.41741900	-1.91227400
C	-3.98824200	-0.52921500	-0.59477500
H	-5.14692900	-1.92490900	0.59573800
H	-4.08174000	-3.91667400	-0.84868600
H	-5.67280800	-1.82512100	-2.41970100
H	-3.03028600	-1.82206500	-2.83024300
H	-4.10816500	-0.03799300	-1.56932200
H	-2.67415600	-2.08057500	0.18366900
H	-6.12162500	-0.73128800	-0.25141200
H	-4.36916400	-3.91737400	-2.58064300
H	-6.33781100	-3.00168500	-1.29756300
H	-2.07515400	-3.05571000	-2.00629200
N	-3.70362000	0.55995600	0.35062400
C	-3.53185000	0.14349300	1.74036100
H	-3.24114700	1.00249100	2.34664500
H	-2.72672500	-0.59044800	1.81110600
H	-4.43091900	-0.29679700	2.19349900
C	-4.48428500	1.79135100	0.14933300
C	-5.92748600	1.83301100	0.74662600
C	-3.77073600	3.05132900	0.73727800
H	-4.55396200	1.91011600	-0.93470100
C	-6.11262200	3.26914500	1.26097100
H	-6.00302000	1.13579500	1.58539300
H	-6.68491800	1.54000400	0.01666400
C	-4.71998200	3.63006300	1.79974100
H	-3.62339800	3.78331400	-0.06202200
H	-2.78047300	2.80501100	1.12459900
H	-6.37309700	3.93816300	0.43253400
H	-6.90333100	3.35502300	2.01020000
H	-4.58170600	4.70181400	1.95857500
H	-4.56126900	3.13338000	2.76368800
S	0.09932400	-2.59741600	-0.11018300

TS_{Add}-5

Zero-point correction = 0.766074 (Hartree/Particle)
Thermal correction to Energy = 0.820845
Thermal correction to Enthalpy = 0.821789
Thermal correction to Gibbs Free Energy = 0.672643
Sum of electronic and zero-point Energies = −3157.383206
Sum of electronic and thermal Energies = −3157.328436
Sum of electronic and thermal Enthalpies = −3157.327491
Sum of electronic and thermal Free Energies = −3157.476638
E(RB3LYP-D3) = −3158.149281
Imaginary frequency = 150.07i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3158.306315
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3158.183055

0 1

C	-5.15111300	0.36038300	-0.04099100
C	-3.20169000	-1.05118200	-1.38750400
C	-3.99921700	1.02132600	-0.45167300
C	-5.34450000	-0.99974900	-0.27042700
C	-4.35194700	-1.69452200	-0.95226900
C	-2.99463200	0.30624400	-1.11356300
H	-3.86700800	2.07096400	-0.24237800

H	-6.24063000	-1.49895300	0.06891500
H	-2.44194400	-1.60588900	-1.92181800
N	-1.72790700	0.79875700	-1.42980500
H	-1.02079500	0.06598100	-1.45707100
C	-1.23140000	2.07519100	-1.48904000
S	-2.17160600	3.46648100	-1.67102800
N	0.12283200	2.07891800	-1.41868900
H	0.58792700	1.18021400	-1.30170300
C	0.99552500	3.22020700	-1.63375600
C	2.94498500	4.51799100	-0.64473300
C	2.80340600	4.18140200	-3.14460100
C	3.74174000	4.28391700	-1.93810200
C	1.79128800	3.05070900	-2.94071800
C	1.94168300	3.38246100	-0.42636900
H	2.41892700	5.47706400	-0.71543000
H	2.27713100	5.13466700	-3.28330500
H	4.31340100	3.35422100	-1.84705700
H	2.31755000	2.09346700	-2.91586400
H	2.47545300	2.43897300	-0.29217800
H	0.35915300	4.10030200	-1.73144100
H	3.63264300	4.58452300	0.20171700
H	3.37768600	4.00104000	-4.05712800
H	4.45970100	5.09792600	-2.07175200
H	1.07023800	3.01252600	-3.76125000
C	-6.15367800	1.11242400	0.79137500
C	-4.44288200	-3.18180800	-1.13237400
F	-5.82504800	1.05616000	2.10861500
F	-6.22202700	2.41701600	0.46361200
F	-7.39758700	0.59820400	0.68117000
F	-5.69839700	-3.64834400	-1.00852500
F	-3.68891400	-3.82615700	-0.19467300
F	-3.97037100	-3.58389700	-2.33250900
N	1.14679200	3.52814700	0.86813300
C	0.17810800	4.66356700	0.90433300
H	0.71069000	5.60966300	0.81578900
H	-0.34304500	4.62407700	1.86016500
H	-0.55253800	4.55189400	0.10545400
C	2.01757200	3.54286900	2.08123900
H	2.68867700	2.69034000	2.03580300
C	2.69318600	-1.52908000	-0.59745700
C	1.27752300	-1.76472000	-0.78383800
O	0.50185300	-0.89611300	-1.17853700
O	0.88680700	-2.97446900	-0.36918300
C	-0.52590600	-3.23906300	-0.40610400
H	-1.06830500	-2.45153200	0.11366900
H	-0.65955000	-4.19210100	0.09902400
H	-0.86997700	-3.31435300	-1.43894300
C	3.26714700	-0.46371300	-1.33770700
N	3.74142000	0.46791900	-1.83619400
O	3.52270200	-2.63325900	-0.34002200
C	3.67772600	-3.52404100	-1.35385300
O	3.20514400	-3.43300500	-2.45250300
O	4.45224600	-4.50671400	-0.89391900
C	4.73023800	-5.54749400	-1.85071000
H	3.80375300	-6.02440200	-2.17484000
H	5.36510200	-6.25762200	-1.32613800
H	5.24653900	-5.13770400	-2.72033500
C	2.56888000	-0.64000500	1.38198400
N	1.78778900	0.44762400	1.29581800
C	0.48362300	0.38009300	1.63662800
O	-0.25355100	1.38406200	1.59201200
H	2.15947500	-1.57095000	1.77401100
C	4.01847700	-0.47024700	1.60896900
C	6.76769100	-0.20792200	2.08999300
C	4.68088700	0.73220200	1.32456600
C	4.75861900	-1.54261300	2.12540400
C	6.12126600	-1.41094500	2.36888100
C	6.04362900	0.86127600	1.56232200
H	4.12397700	1.54925600	0.89090300
H	4.26091300	-2.48500100	2.31898100
H	6.68018100	-2.24841800	2.77052100
H	6.54562100	1.79332900	1.32801200
H	7.83086300	-0.10551800	2.27641700
O	0.01371200	-0.81227400	2.07367400
C	-1.16906600	-0.91595400	2.95784500
C	-2.45050000	-0.57233500	2.20280300
H	-2.43110000	0.45733000	1.85756200
H	-3.31226700	-0.70683500	2.86144500
H	-2.58183300	-1.23017500	1.34266800
C	-0.96697400	-0.01526500	4.17787700
H	-0.00595600	-0.23153000	4.65159600
H	-1.76035500	-0.20296400	4.90523400
H	-0.99746900	1.03586300	3.89421000
C	-1.14917500	-2.38869000	3.36226300
H	-0.21261800	-2.63528100	3.86680700
H	-1.24846800	-3.02863800	2.48399700
H	-1.98033200	-2.60075800	4.03865400
H	0.57043500	2.63680600	0.98919600
H	2.56196700	4.48338000	2.14261200
H	1.37207000	3.43142500	2.95135200

TS_{Add}-6

Zero-point correction = 0.765999 (Hartree/Particle)
Thermal correction to Energy = 0.820940
Thermal correction to Enthalpy = 0.821885
Thermal correction to Gibbs Free Energy = 0.671628
Sum of electronic and zero-point Energies = −3157.375496
Sum of electronic and thermal Energies = −3157.320555
Sum of electronic and thermal Enthalpies = −3157.319610
Sum of electronic and thermal Free Energies = −3157.469867
E(RB3LYP-D3) = −3158.141495
Imaginary frequency = 141.57i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3158.299376
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3158.174875

0 1

C	5.05874800	0.15657000	-0.33089900
C	2.86282000	-1.27931300	-1.18708200
C	3.89566900	0.83942000	-0.67980000
C	5.14610900	-1.23008700	-0.38731300
C	4.02647300	-1.93569800	-0.82118700
C	2.77253000	0.11916800	-1.10046800
H	3.85354600	1.91443500	-0.61087900
H	6.05146100	-1.74385800	-0.09877600
H	1.99579700	-1.84572900	-1.49816900
N	1.51148400	0.65116800	-1.37562200
H	0.78869500	-0.06719800	-1.38145000

C	1.02380500	1.93172300	-1.36972800
S	1.96478000	3.31873900	-1.60399600
N	-0.31690900	1.93130400	-1.16831800
H	-0.74119800	1.04762900	-0.90860600
C	-1.27438700	3.02942700	-1.20268100
C	-2.02079300	5.24065700	-0.21434800
C	-2.57141800	4.68122300	-2.61725900
C	-2.21788200	5.80197400	-1.63178400
C	-1.50304400	3.58265900	-2.61917000
C	-0.92788400	4.17164500	-0.22907000
H	-2.96873700	4.81329600	0.12964000
H	-3.53958600	4.24529600	-2.34066800
H	-1.29671600	6.29959600	-1.95647100
H	-0.55657300	3.97046200	-3.00496900
H	0.00354400	4.61342100	-0.57664800
H	-2.20692900	2.56487800	-0.87582400
H	-1.75460800	6.04520800	0.47895000
H	-2.68769900	5.08693200	-3.62581500
H	-3.00207000	6.56391900	-1.61378600
H	-1.80826500	2.74537400	-3.24888500
C	6.25843800	0.96467900	0.08570200
C	4.01452500	-3.43634100	-0.79048000
F	7.14406200	0.23232700	0.79798700
F	6.92509500	1.45678900	-0.98253700
F	5.91103100	2.02488200	0.85003600
F	5.24927000	-3.96997000	-0.83356800
F	3.30245800	-3.96680300	-1.81030700
F	3.42956800	-3.89765800	0.35394200
N	-0.59486100	3.62492300	1.15802700
C	-1.75058300	3.49863600	2.09374500
H	-2.10565400	4.48604100	2.38257400
H	-1.40383200	2.95000900	2.96732800
H	-2.53209800	2.91516300	1.61936300
C	0.52339600	4.38946500	1.78585500
H	1.38315100	4.34205100	1.11960400
C	-2.64056500	-1.60973500	-0.68021700
C	-1.28033000	-2.09129600	-0.63037500
O	-0.31032900	-1.39800000	-0.92701900
O	-1.16514600	-3.32962300	-0.13141600
C	0.17690200	-3.84008900	-0.02876400
H	0.60652400	-3.98883100	-1.02074500
H	0.08757800	-4.79287700	0.48760700
H	0.80206500	-3.15315700	0.53766700
C	-2.89774200	-0.52268400	-1.55183600
N	-3.09479500	0.44001200	-2.16620600
O	-3.68424500	-2.52608000	-0.47591400
C	-3.87155000	-3.45885300	-1.44516500
O	-3.26270900	-3.54223700	-2.47486900
O	-4.86008100	-4.25463900	-1.03339200
C	-5.20238600	-5.30749900	-1.95473000
H	-5.52797600	-4.88900900	-2.90853100
H	-6.01295500	-5.85408600	-1.47834800
H	-4.34428300	-5.96021900	-2.12390900
C	-2.62958800	-0.52798900	1.26905900
N	-1.71653500	0.44668800	1.18954400
C	-0.47519200	0.26916700	1.70388900
O	0.36550600	1.18622000	1.69031200
H	-2.39065900	-1.46113800	1.77836800
C	-4.06136900	-0.17841400	1.26142100
C	-6.79474600	0.43986400	1.30033700
C	-4.52103000	1.05427700	0.77615900
C	-4.99479500	-1.10112500	1.75310500
C	-6.35019500	-0.79200000	1.77769900
C	-5.87583400	1.35969400	0.79395400
H	-3.80792400	1.74835900	0.35671800
H	-4.65167100	-2.06844900	2.09940100
H	-7.06073000	-1.51488900	2.16182000
H	-6.21961600	2.31113700	0.40374900
H	-7.85207500	0.67946900	1.31497600
O	-0.20970400	-0.92145500	2.28015500
C	0.96943700	-1.13427500	3.14689700
C	0.95626800	-0.12135900	4.29446400
H	1.16428200	0.88319800	3.93116300
H	1.71855700	-0.39464100	5.02819800
H	-0.01728400	-0.12977700	4.79175700
C	2.25930400	-1.06246900	2.33140000
H	2.25714300	-1.80452100	1.53377800
H	3.11084500	-1.27641600	2.98282200
H	2.38982000	-0.07657200	1.89158300
C	0.73295400	-2.54681300	3.67900600
H	0.68115500	-3.26298000	2.85787900
H	-0.20477000	-2.59336500	4.23696700
H	1.55126900	-2.83841600	4.34121100
H	-0.22824900	2.63351200	1.07662000
H	0.21490700	5.42325000	1.94308700
H	0.77058200	3.92017100	2.73676700

TS_{Add}-7

Zero-point correction = 0.760487 (Hartree/Particle)
Thermal correction to Energy = 0.809397
Thermal correction to Enthalpy = 0.810342
Thermal correction to Gibbs Free Energy = 0.677452
Sum of electronic and zero-point Energies = −2687.690935
Sum of electronic and thermal Energies = −2687.642025
Sum of electronic and thermal Enthalpies = −2687.641081
Sum of electronic and thermal Free Energies = −2687.773971
E(RB3LYP-D3) = −2688.451422
Imaginary frequency = 197.30i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −2688.618457
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −2688.490754

0 1

H	-6.70505500	-1.49734100	-0.29342400
C	-5.75952100	-1.93669600	-0.58718700
C	-3.29536400	-2.99388300	-1.37781400
C	-4.62666500	-1.12908600	-0.63198800
C	-5.65747000	-3.28168900	-0.91902900
C	-4.41973700	-3.80408500	-1.30609500
C	-3.38740600	-1.63781300	-1.03668800
H	-6.53237000	-3.91889700	-0.88157500
H	-4.33512900	-4.85199900	-1.57022400
H	-2.34361500	-3.39395900	-1.70870700
S	-4.68233300	0.57192700	-0.09481400
O	-5.93420800	1.17571400	-0.53899600
O	-4.37224100	0.60710200	1.34140000
N	-3.43681800	1.25235600	-0.92263400
C	-2.34154700	0.55557100	-1.12890800

N	-2.27381300	-0.81215600	-1.12397600
H	-1.35702000	-1.23338500	-1.25934400
N	-1.18762800	1.19420100	-1.42660500
H	-0.35649400	0.62810300	-1.56995500
C	-1.05132500	2.64315900	-1.46917600
C	-0.13239100	4.70830000	-0.30032100
C	-0.00252700	4.54161300	-2.81197500
C	0.69845600	5.04389000	-1.54670800
C	-0.24938900	3.03369400	-2.72402600
C	-0.36886100	3.19859200	-0.19615100
H	-1.09489200	5.22936400	-0.35991600
H	-0.95578100	5.07115500	-2.93688400
H	1.68327900	4.57015800	-1.46682300
H	0.71221000	2.51338800	-2.70917500
H	0.58049200	2.67014200	-0.08424900
H	-2.05611000	3.05757800	-1.55565700
H	0.37869800	5.07451400	0.59328500
H	0.60137000	4.76331600	-3.69589000
H	0.86183300	6.12414500	-1.59498500
H	-0.80252000	2.67432700	-3.59551300
N	-1.14166700	2.82302500	1.06031800
H	-1.22736900	1.75814900	1.07376600
C	-0.35704500	3.07533500	2.30828800
H	-0.21538700	4.14412300	2.45581600
C	-2.51456600	3.40370700	1.18689300
H	-3.05802500	2.81028300	1.92100300
H	-3.04167700	3.31326300	0.24372300
H	-2.44140700	4.44424800	1.50146600
C	2.71955500	-0.80004200	-0.78194000
C	1.56558500	-1.64882200	-1.02224800
O	0.47968200	-1.21413700	-1.39599700
O	1.76601400	-2.92503400	-0.67833800
C	0.61397000	-3.77966900	-0.75316900
H	-0.16822900	-3.40181500	-0.09491800
H	0.95537100	-4.75641800	-0.41881600
H	0.24766300	-3.83456700	-1.78032400
C	2.73737700	0.43898900	-1.48222900
N	2.72867300	1.49813000	-1.94791700
O	3.96571200	-1.42852200	-0.60208900
C	4.47782200	-2.07974700	-1.67759200
O	3.97630900	-2.14941400	-2.76541900
O	5.63403200	-2.61965900	-1.29300100
C	6.32796700	-3.34820500	-2.32431700
H	5.71589000	-4.17753300	-2.68280900
H	7.23664200	-3.71619700	-1.85386400
H	6.56641900	-2.68974300	-3.16112700
C	2.27417700	-0.19752600	1.18926600
N	1.06725200	0.40168500	1.18791200
C	-0.03647200	-0.28371700	1.53330100
O	-1.16310200	0.24275500	1.56450200
O	0.11531000	-1.58612000	1.89496200
C	-0.86404200	-2.24953200	2.78461200
C	3.46964200	0.63861100	1.45034700
C	5.74959000	2.17829000	1.98547900
C	3.44437100	2.03008000	1.28567800
C	4.65646700	0.03015600	1.87941200
C	5.78675300	0.79452300	2.14882500
C	4.57558000	2.79271800	1.54991000
H	2.53693100	2.49945700	0.93490600
H	4.69133700	-1.04724300	1.98496700
H	6.69758100	0.31049500	2.48258300
H	4.54538800	3.86765600	1.41083100
H	6.63110000	2.77459900	2.19300600
H	2.36492600	-1.22489800	1.54392600
C	-2.19425400	-2.48378600	2.06950800
H	-2.84947600	-3.07627500	2.71421000
H	-2.68975800	-1.54436800	1.83438800
H	-2.04300100	-3.04608500	1.14629100
C	-1.04624400	-1.41560400	4.05489300
H	-1.62915000	-1.98458300	4.78331500
H	-0.07355300	-1.18354200	4.49661900
H	-1.57485600	-0.48907400	3.83692400
C	-0.16787200	-3.57181200	3.10403500
H	-0.78903300	-4.17017400	3.77443100
H	0.00702500	-4.14519600	2.19162000
H	0.79559800	-3.39043200	3.58511600
H	-0.92334200	2.66015900	3.14053100
H	0.59110000	2.54901500	2.22529900

TS_{Add}-8

Zero-point correction = 0.760179 (Hartree/Particle)
Thermal correction to Energy = 0.809389
Thermal correction to Enthalpy = 0.810333
Thermal correction to Gibbs Free Energy = 0.675981
Sum of electronic and zero-point Energies = −2687.686667
Sum of electronic and thermal Energies = −2687.637457
Sum of electronic and thermal Enthalpies = −2687.636513
Sum of electronic and thermal Free Energies = −2687.770865
E(RB3LYP-D3) = −2688.446846
Imaginary frequency = 192.51i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −2688.614524
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −2688.487514

0 1

H	6.60523200	-1.94151900	-1.02634700
C	5.60332400	-2.35312900	-1.03083100
C	2.98526500	-3.34002400	-1.06907200
C	4.52185000	-1.49667300	-0.84591600
C	5.37680000	-3.71095100	-1.21628400
C	4.06562900	-4.19710100	-1.22420500
C	3.20474500	-1.96914400	-0.87847000
H	6.21131100	-4.38729100	-1.35430300
H	3.88438100	-5.25586800	-1.36988400
H	1.96820200	-3.71290600	-1.10890500
S	4.75538000	0.23025600	-0.47523400
O	4.77764400	0.37483200	0.99039200
O	5.89210900	0.74260100	-1.23125000
N	3.37340900	0.91847700	-1.03865400
C	2.23630200	0.26505300	-0.91083800
N	2.13388300	-1.09371900	-0.75171900
H	1.19615500	-1.48532300	-0.71915800
N	1.06197800	0.92618200	-0.94621100
H	0.21565600	0.37039500	-0.94898400
C	0.88128100	2.37303700	-1.03146800
C	1.47775500	4.66078300	-0.11314500
C	0.94156900	4.40481600	-2.56271700
C	1.79311500	5.15494100	-1.53250100

C	1.15610200	2.89256300	-2.45503300
C	1.72899400	3.15439900	-0.00776100
H	0.43019900	4.88818900	0.11062800
H	-0.11842900	4.63492700	-2.39765000
H	2.85608200	4.99522900	-1.74700300
H	2.18552400	2.63529000	-2.72133900
H	2.77356300	2.94911100	-0.23066800
H	-0.17636400	2.52596900	-0.80669500
H	2.09083600	5.19383900	0.62026500
H	1.18219800	4.74236400	-3.57451500
H	1.61416100	6.23230900	-1.59016300
H	0.48727300	2.35727400	-3.13155000
N	1.52570400	2.62038100	1.40533900
C	0.38409400	3.21997700	2.15519400
H	0.23534400	2.62186000	3.05187900
H	-0.51668800	3.14805500	1.55506400
H	0.61016200	4.25136200	2.41948000
C	2.79005900	2.68420400	2.20178900
H	2.58664000	2.28536500	3.19450400
H	3.11992300	3.72073700	2.27558000
H	3.54548300	2.06450700	1.71971700
H	1.27907900	1.58641800	1.37640100
C	-2.76808800	-0.66579200	-0.77344900
C	-1.81920300	-1.76883300	-0.73677000
O	-0.61421500	-1.61807300	-0.90874000
O	-2.37708800	-2.94389800	-0.42157100
C	-1.50662400	-4.08579600	-0.46480400
H	-1.10932500	-4.21554700	-1.47341600
H	-2.12856200	-4.93423200	-0.18910100
H	-0.68426800	-3.97095200	0.24031600
C	-2.38907200	0.42367200	-1.60897100
N	-2.04101000	1.35933300	-2.19462400
O	-4.13761600	-0.99040300	-0.75760300
C	-4.62393100	-1.63185100	-1.85030700
O	-4.00253600	-1.92132500	-2.83530800
O	-5.91479700	-1.87250700	-1.62002100
C	-6.60066700	-2.54156900	-2.69563800
H	-6.56144500	-1.94010500	-3.60526800
H	-7.62689200	-2.65601400	-2.35462700
H	-6.14782900	-3.51542600	-2.88958300
C	-3.55409600	1.19843400	1.09895700
C	-5.59032100	3.12239600	1.02992000
C	-3.27828400	2.51325200	0.70091700
C	-4.86680200	0.85974600	1.45015700
C	-5.87675900	1.81579500	1.42135000
C	-4.28850500	3.46646900	0.66471500
H	-2.27272100	2.76473800	0.39669600
H	-5.09346600	-0.16147700	1.73208200
H	-6.88790400	1.54030800	1.69876200
H	-4.06442000	4.47799400	0.34477100
H	-6.37755700	3.86758600	1.00380900
C	-2.49336600	0.16562200	1.15779600
H	-2.80724000	-0.76516100	1.63122200
N	-1.21430300	0.57393700	1.26903800
C	-0.29458100	-0.22698500	1.83775300
O	0.88948900	0.12705000	1.99016200
O	-0.71338800	-1.43899100	2.28015400
C	0.15623500	-2.32293900	3.07611600
C	-0.77415700	-3.49397800	3.39180300
H	-0.24452600	-4.24983500	3.97616200
H	-1.13888400	-3.95435800	2.47232600
H	-1.63796200	-3.14918000	3.96413100
C	0.58333600	-1.61927400	4.36665300
H	1.08441000	-2.33531900	5.02327600
H	-0.29489300	-1.23046500	4.88854700
H	1.26599800	-0.79916200	4.15483400
C	1.36013100	-2.78020000	2.24933000
H	1.91396000	-3.54466300	2.80028400
H	2.02581100	-1.94885900	2.02946600
H	1.02848900	-3.21621400	1.30520100

TS_{Add}-9

Zero-point correction = 0.765846 (Hartree/Particle)

Thermal correction to Energy = 0.820805

Thermal correction to Enthalpy = 0.821750

Thermal correction to Gibbs Free Energy = 0.670596

Sum of electronic and zero-point Energies = −3157.379634

Sum of electronic and thermal Energies = −3157.324674

Sum of electronic and thermal Enthalpies = −3157.323730

Sum of electronic and thermal Free Energies = −3157.474884

E(RB3LYP-D3) = −3157.145480

Imaginary frequency = 226.81i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3158.303443

Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3158.178487

0 1

C	5.77890000	-0.25814200	-0.19300100
C	3.57387000	1.22202900	-0.95324700
C	4.57005000	-0.90960300	-0.42065000
C	5.90585000	1.12109500	-0.31825500
C	4.78320900	1.85115900	-0.69732000
C	3.44718000	-0.16652900	-0.80161500
H	4.49539900	-1.97766600	-0.29740800
H	6.84740000	1.61320700	-0.12200300
H	2.71426700	1.81006800	-1.25103500
N	2.15707300	-0.67950500	-0.97474200
H	1.43955300	0.04542700	-0.98550700
C	1.67636000	-1.95869900	-1.07081700
S	2.60348100	-3.34804000	-1.32057100
N	0.32229700	-1.98831100	-0.95158500
H	-0.15677500	-1.10553800	-0.81429600
C	-0.54340600	-3.12273800	-1.22911000
C	-2.56839800	-4.39008400	-0.38177200
C	-2.20829000	-4.11436400	-2.87050700
C	-3.24701400	-4.18731800	-1.74661100
C	-1.21139500	-2.98132700	-2.60838200
C	-1.59232300	-3.24355900	-0.10783100
H	-2.03895900	-5.35040100	-0.37798600
H	-1.67563700	-5.07150900	-2.94001800
H	-3.81732000	-3.25244000	-1.72458500
H	-1.72578500	-2.01970200	-2.65293700
H	-2.14205400	-2.30090700	-0.04915700
H	0.08733100	-4.01195700	-1.24937400
H	-3.33053900	-4.43497900	0.39962900
H	-2.70151300	-3.95761700	-3.83377800
H	-3.95489800	-5.00212600	-1.92346800
H	-0.41623000	-2.97470900	-3.35830800

C	6.98819900	-1.08430500	0.15641600
C	4.83721900	3.35225500	-0.73893400
F	6.66737800	-2.16927100	0.89349300
F	7.61770100	-1.53592300	-0.95231800
F	7.89920000	-0.37525600	0.86099000
F	4.06781800	3.86421000	-1.72387800
F	6.09049200	3.81752600	-0.91917800
F	4.38327100	3.88836500	0.42350600
N	-0.90804000	-3.34064000	1.25433100
C	-1.87670400	-3.44604200	2.38509400
H	-2.61198700	-2.65328200	2.27974800
C	-2.73825300	1.44056300	-0.53244300
C	-3.57746900	0.50911500	-1.30616900
O	-3.21885500	-0.61404800	-1.61136200
O	-4.80423500	0.99458900	-1.52964800
C	-5.73236800	0.09336100	-2.15961400
H	-5.34231200	-0.24279400	-3.12137400
H	-6.64551800	0.66863100	-2.29137100
H	-5.91418200	-0.76499700	-1.51232200
C	-1.34916500	1.33050500	-0.80676500
N	-0.21380800	1.15034800	-0.93763700
O	-3.21541400	2.74934600	-0.31876500
C	-3.33038400	3.54392300	-1.41669900
O	-2.96493700	3.26798800	-2.52501500
O	-3.90627000	4.67719000	-1.01959400
C	-4.08702800	5.65589700	-2.06263800
H	-3.12420400	5.93618200	-2.49269500
H	-4.55466200	6.50915200	-1.57734100
H	-4.73042700	5.25813800	-2.84904300
C	-2.87180400	0.66606600	1.39564300
N	-2.00760500	-0.36151300	1.53150300
C	-0.75998000	-0.12374900	1.98634900
O	0.10730200	-1.02279800	2.03026000
H	-2.60633500	1.64294100	1.79782600
C	-4.32623400	0.37022400	1.45498800
C	-7.08412700	-0.13067700	1.54783500
C	-4.82114400	-0.92773200	1.27548000
C	-5.23342100	1.41428000	1.67453400
C	-6.60124100	1.16549200	1.72151300
C	-6.18867000	-1.17652900	1.32327800
H	-4.12439200	-1.73043300	1.08198100
H	-4.85943200	2.42510400	1.78269200
H	-7.29145500	1.98362400	1.89337000
H	-6.55834500	-2.18692000	1.18505200
H	-8.15001900	-0.32527300	1.58849100
O	-0.50671700	1.11941600	2.43820500
C	0.79940300	1.53856800	2.98264700
C	1.87947200	1.40752700	1.91185800
H	2.06433500	0.36346200	1.66990000
H	2.80894800	1.86180200	2.26311200
H	1.56610600	1.92978300	1.00718300
C	1.12151400	0.73289900	4.24153600
H	0.29658800	0.80414800	4.95515500
H	2.02059500	1.13869600	4.71267800
H	1.29197400	-0.31384500	3.99729600
C	0.54874400	3.00703200	3.32160700
H	-0.26039400	3.09827400	4.04963900
H	0.27020600	3.56024600	2.42224500
H	1.45223400	3.45494400	3.74138600
H	-0.43862200	-2.39147300	1.42728300
H	-2.33817800	-4.43185200	2.39820900
H	-1.32289400	-3.28381000	3.30889500
C	0.15207300	-4.38373300	1.36901800
H	0.95240200	-4.18711400	0.65865000
H	-0.27689400	-5.36990200	1.19219500
H	0.55843700	-4.33807500	2.37875200

TS_{Add}-10

Zero-point correction = 0.859123 (Hartree/Particle)
Thermal correction to Energy = 0.917632
Thermal correction to Enthalpy = 0.918576
Thermal correction to Gibbs Free Energy = 0.758753
Sum of electronic and zero-point Energies = −3313.379805
Sum of electronic and thermal Energies = −3313.321297
Sum of electronic and thermal Enthalpies = −3313.320352
Sum of electronic and thermal Free Energies = −3313.480176
E(RB3LYP-D3) = −3314.238929
Imaginary frequency = 274.90i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.403668
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.274845

0 1

C	5.60280900	-0.25420400	0.12672800
C	3.76969200	1.49465500	-0.98903500
C	4.37489900	-0.73922000	-0.30712100
C	5.93497000	1.09290400	0.01487300
C	5.00255300	1.95941700	-0.54497600
C	3.44679100	0.13886500	-0.87257300
H	4.13654500	-1.78542200	-0.20013900
H	6.89637900	1.45535800	0.34981800
H	3.04886400	2.18343500	-1.40929300
N	2.14027300	-0.23659500	-1.22909500
H	1.46387400	0.50994500	-1.06809600
C	1.66203500	-1.42183900	-1.70609200
S	2.64158400	-2.68582000	-2.26119500
N	0.30106700	-1.48138300	-1.70688000
H	-0.23697900	-0.67051000	-1.41256600
C	-0.46938900	-2.50854700	-2.38946000
C	-2.38039500	-4.14049500	-2.22659000
C	-1.81308100	-3.08643000	-4.46063200
C	-2.93246700	-3.62581600	-3.56536900
C	-1.01805600	-1.99763600	-3.73434300
C	-1.61604100	-3.02730600	-1.49941300
H	-1.71441200	-4.99078500	-2.41265200
H	-1.14197300	-3.90876400	-4.73768000
H	-3.65704200	-2.82654600	-3.36697400
H	-1.64765100	-1.12369500	-3.55050000
H	-2.28715200	-2.19157400	-1.30239200
H	0.22284700	-3.32261800	-2.60570400
H	-3.20717500	-4.50353000	-1.61396900
H	-2.22720900	-2.69097900	-5.39243600
H	-3.47720900	-4.43118300	-4.06610900
H	-0.16437700	-1.67220700	-4.33412400
C	6.53992300	-1.19348600	0.83383200
C	5.29587700	3.43269000	-0.61204600
F	6.24000900	-1.27425700	2.15657100
F	6.47493800	-2.44894000	0.34623200

F	7.82657800	-0.79159200	0.75278100
F	6.62145800	3.68573200	-0.67044100
F	4.82213000	4.07970500	0.47999700
F	4.72481700	4.01710600	-1.68740900
N	-1.11444700	-3.44704200	-0.11705300
C	-2.15950900	2.09206000	-0.31296000
C	-2.82748400	1.17321400	-1.24351700
O	-2.30696100	0.14765500	-1.65252400
O	-4.09708600	1.51654100	-1.48540400
C	-4.85764700	0.59502300	-2.28221400
H	-4.40299400	0.47796500	-3.26744300
H	-5.84840400	1.03496700	-2.36393700
H	-4.91357600	-0.37623300	-1.78742700
C	-0.73977000	2.07872400	-0.43570600
N	0.41259300	1.99555000	-0.47597600
O	-2.71556600	3.36816000	-0.10235000
C	-2.79749800	4.18394700	-1.18610200
O	-2.38712400	3.93542200	-2.28609400
O	-3.40544100	5.29987600	-0.78997000
C	-3.56803800	6.29404000	-1.82098900
H	-2.59631200	6.59929600	-2.21231300
H	-4.06774100	7.12965500	-1.33701400
H	-4.17697900	5.89977500	-2.63610600
C	-2.46856200	1.13845700	1.47137700
N	-2.00344200	-0.12473700	1.33756200
C	-0.77525900	-0.44080700	1.76928100
O	-0.19991500	-1.50663200	1.45408500
H	-1.86779200	1.86927600	2.01389700
C	-3.93204400	1.33978900	1.64612900
C	-6.68325200	1.75907800	1.99682500
C	-4.85344700	0.33607400	1.32425300
C	-4.41021200	2.55670800	2.14606700
C	-5.77490800	2.76478800	2.32091300
C	-6.21671900	0.54251100	1.49815900
H	-4.48710000	-0.60337700	0.93939700
H	-3.70758000	3.34617900	2.38226500
H	-6.12913200	3.71292700	2.70932600
H	-6.91783900	-0.24652400	1.24808200
H	-7.74663000	1.92011400	2.13518100
O	-0.19672900	0.42943500	2.62837200
C	1.12184700	0.20750600	3.24660600
C	2.20634800	0.13367200	2.17551800
H	2.06679900	-0.74075700	1.54491700
H	3.19162800	0.07489900	2.64511500
H	2.17504800	1.02607200	1.54858600
C	1.08093900	-1.04697500	4.12171500
H	0.23792100	-0.99390200	4.81556600
H	2.00342900	-1.11634100	4.70409300
H	0.98241300	-1.94190000	3.51012800
C	1.29190700	1.46197000	4.10243400
H	0.48920700	1.53324000	4.83984300
H	1.26532300	2.35344500	3.47241800
H	2.25025500	1.43269100	4.62608800
H	-0.77809400	-2.56404400	0.38244300
C	0.05310700	-4.37837600	-0.14601000
H	0.85870200	-3.95744000	-0.74212400
H	-0.25465900	-5.34084300	-0.55473600
H	0.41126700	-4.50706700	0.87156300
C	-2.21713000	-3.99441800	0.77209300
C	-1.75718800	-4.25043400	2.22106300
C	-3.07702400	-4.21582800	3.00169200
C	-3.82817500	-3.02781600	2.37886000
C	-3.41772500	-3.02495500	0.88580900
H	-2.52015100	-4.94318900	0.32570000
H	-1.10717300	-3.43440900	2.54584300
H	-1.21894600	-5.19279900	2.33667100
H	-3.63107900	-5.14790600	2.83997700
H	-2.92186800	-4.11120500	4.07727000
H	-3.49138200	-2.09218500	2.83200700
H	-4.90890800	-3.08826300	2.51894300
H	-3.10598600	-2.01761300	0.60838400
H	-4.23149500	-3.33533900	0.22646400

TS_{Add}-11

Zero-point correction = 0.859720 (Hartree/Particle)
Thermal correction to Energy = 0.917955
Thermal correction to Enthalpy = 0.918899
Thermal correction to Gibbs Free Energy = 0.761159
Sum of electronic and zero-point Energies = −3313.384983
Sum of electronic and thermal Energies = −3313.326748
Sum of electronic and thermal Enthalpies = −3313.325804
Sum of electronic and thermal Free Energies = −3313.483544
E(RB3LYP-D3) = −3314.244703
Imaginary frequency = 147.92i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −3314.408477
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −3314.280537

0 1

C	-5.07866500	-0.36055300	-0.21363100
C	-3.03160500	-1.82258200	-1.34410800
C	-3.95952300	0.30531000	-0.69968200
C	-5.19155600	-1.74792100	-0.26117900
C	-4.15072600	-2.46802300	-0.83667800
C	-2.90524800	-0.43124500	-1.25137700
H	-6.06299900	-2.24894400	0.13494800
H	-2.23383200	-2.39798700	-1.79427300
C	-1.24654200	1.37256500	-1.85480800
N	-1.66409800	0.08882200	-1.61872300
H	-0.91323900	-0.59568700	-1.53965200
N	0.10333500	1.47318700	-1.77761500
H	0.62408200	0.63356600	-1.52972000
C	0.89766400	2.63195400	-2.14026400
C	2.64452200	4.27272400	-1.33397500
C	2.67828300	3.49987500	-3.73739500
C	3.53280600	3.91348800	-2.53522700
C	1.76988400	2.32303500	-3.37090800
C	1.77015900	3.07748200	-0.94659900
H	2.00878700	5.12529700	-1.59567400
H	2.07053600	4.35314000	-4.06508600
H	4.19610600	3.08554000	-2.26217200
H	2.38224300	1.44216600	-3.16410700
H	2.40056200	2.23035800	-0.66455800
H	0.19978000	3.42553400	-2.40770500
H	3.27083000	4.58155400	-0.49396000
H	3.31698300	3.22317600	-4.58032800
H	4.16615000	4.76929500	-2.78531600
H	1.09701200	2.07321400	-4.19525700

N	0.92196900	3.31927000	0.30184600
H	0.39990500	2.41305200	0.48050600
C	1.76811300	3.44950300	1.52898000
H	2.26172800	2.49235900	1.68009300
C	2.87437200	-1.83940000	-0.46994400
C	1.48060700	-2.18337000	-0.64851200
O	0.66488600	-1.42387600	-1.16810400
O	1.15113400	-3.34846400	-0.07989200
C	-0.24420200	-3.69387200	-0.08854800
H	-0.83378900	-2.87781400	0.32538500
H	-0.33091100	-4.58075300	0.53379200
H	-0.57254900	-3.91932400	-1.10451600
C	3.40921900	-0.84401900	-1.32710400
N	3.84864100	0.04301400	-1.92818700
O	3.75927400	-2.84672400	-0.05021200
C	3.99468600	-3.85298300	-0.93150700
O	3.54862300	-3.93926700	-2.04150700
O	4.81273800	-4.71568800	-0.32785300
C	5.17809500	-5.85535600	-1.12985400
H	4.29076900	-6.42793800	-1.40502100
H	5.83883200	-6.44842100	-0.50195100
H	5.69342600	-5.53400800	-2.03646300
C	2.63350000	-0.71115300	1.37279200
N	1.78311300	0.29662300	1.12550400
C	0.47671400	0.18768500	1.44825700
O	-0.32364500	1.11969600	1.25254200
O	0.07728900	-0.96618400	2.03996600
C	-1.09370600	-1.01789800	2.94212100
C	4.05970900	-0.40645000	1.60558200
C	6.76709100	0.12213200	2.10193900
C	4.63474300	0.80701400	1.20229300
C	4.86549200	-1.35444400	2.25139800
C	6.20743900	-1.09041700	2.50157000
C	5.97711000	1.06771200	1.44809200
H	4.02583900	1.52886600	0.67878200
H	4.43607500	-2.30610000	2.53956300
H	6.81816400	-1.83235500	3.00321900
H	6.41217400	2.00605500	1.12266100
H	7.81429900	0.32745900	2.29390700
H	2.27736100	-1.61089800	1.87432700
C	-2.39669200	-0.85903500	2.16292700
H	-3.24634800	-0.95415400	2.84387300
H	-2.44101800	0.11283500	1.68027100
H	-2.48972500	-1.63509900	1.40206900
C	-0.94343200	0.05363000	4.02404300
H	-1.72183700	-0.07784300	4.77938700
H	0.03046600	-0.03648800	4.51199800
H	-1.03844100	1.05158400	3.59782200
C	-0.98367000	-2.41684900	3.54532900
H	-1.79903600	-2.58361100	4.25297700
H	-1.04546900	-3.17610000	2.76386000
H	-0.03271900	-2.53502700	4.06900400
H	2.48977100	4.25284700	1.41868000
H	1.12106700	3.65668000	2.37777900
C	-0.15311600	4.38712900	0.18754000
C	-1.32359100	4.10606700	1.15713700
C	0.30574100	5.84709800	0.46346600
H	-0.53736200	4.29774700	-0.82385600
C	-1.84652200	5.50279400	1.51512300
H	-0.97293100	3.59485500	2.05696500
H	-2.06307600	3.45648700	0.69022300
C	-0.56089200	6.33376100	1.64262800
H	0.10440100	6.44872800	-0.42615300
H	1.37245000	5.93894700	0.66279900
H	-2.46694800	5.89287200	0.70103900
H	-2.45499200	5.50408500	2.42154100
H	-0.73274800	7.41166700	1.61947600
H	-0.06736900	6.10201300	2.59311400
S	-2.26972400	2.66150700	-2.23846800
C	-6.13225600	0.43821900	0.50378200
C	-4.15433900	-3.96884200	-0.81771500
F	-6.27815600	1.67640600	-0.00729900
F	-7.34125200	-0.16197000	0.47030800
F	-5.81045000	0.59255200	1.81505600
F	-3.64360400	-4.49814100	-1.95087900
F	-5.38288700	-4.48717800	-0.64018600
F	-3.37767400	-4.43810700	0.20182100
H	-3.89177500	1.37944800	-0.63340200

TS_{Add}-12

Zero-point correction = 0.760290 (Hartree/Particle)
Thermal correction to Energy = 0.809239
Thermal correction to Enthalpy = 0.810184
Thermal correction to Gibbs Free Energy = 0.677120
Sum of electronic and zero-point Energies = −2687.691084
Sum of electronic and thermal Energies = −2687.642134
Sum of electronic and thermal Enthalpies = −2687.641190
Sum of electronic and thermal Free Energies = −2687.774254
E(RB3LYP-D3) = −2688.45137385
Imaginary frequency = 255.71i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = − 2688.618134
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −2688.489582

0 1

H	-6.78887700	-1.48310300	-0.82436200
C	-5.82183800	-1.92129100	-1.03899300
C	-3.29172100	-2.97808900	-1.60903800
C	-4.68232700	-1.12841200	-0.92973200
C	-5.69466100	-3.25075300	-1.41864600
C	-4.42591500	-3.77313000	-1.69049900
C	-3.41339100	-1.63547400	-1.22727100
H	-6.57365800	-3.87814100	-1.50233000
H	-4.32187600	-4.81174600	-1.98283200
H	-2.30954500	-3.37590200	-1.83391500
S	-4.77061300	0.53920400	-0.30962100
O	-5.96878300	1.19001900	-0.82999700
O	-4.58914100	0.49577200	1.14867700
N	-3.44703900	1.24266800	-0.98509200
C	-2.33914700	0.54521400	-1.11780800
N	-2.28561100	-0.81774700	-1.17046600
H	-1.38302900	-1.28700500	-1.20014900
N	-1.16356600	1.20214900	-1.26769800
H	-0.29608700	0.69290600	-1.41558500
C	-1.05825400	2.65278600	-1.18669500
C	-0.28590200	4.63215600	0.21319000
C	-0.01934700	4.69873900	-2.29350000
C	0.58666200	5.11878000	-0.95140800

C	-0.19806600	3.17957300	-2.35029400
C	-0.46553700	3.11126700	0.16614700
H	-1.26563200	5.11871500	0.15045000
H	-0.98934800	5.19448300	-2.42388200
H	1.59224900	4.69078700	-0.85460200
H	0.77726300	2.68810800	-2.32003000
H	0.49413000	2.60330700	0.27744400
H	-2.06674800	3.05134200	-1.29719500
H	0.16360000	4.93365900	1.16229200
H	0.61593800	5.02872100	-3.12039300
H	0.69723500	6.20533700	-0.89572800
H	-0.68014600	2.87569900	-3.28281500
N	-1.28008200	2.59709600	1.34036900
C	-0.56178000	2.75698300	2.64234700
H	0.41280200	2.28158900	2.55365000
H	-1.33392500	1.52990000	1.25924500
O	3.94983200	0.27625600	-1.55516100
C	4.21814100	1.51742700	-2.23004500
H	3.83375700	2.35171000	-1.64188000
H	3.75957600	1.51896700	-3.21996900
H	5.30124500	1.57547900	-2.30310700
C	2.66117000	-0.02764000	-1.37624300
O	1.73523300	0.67000300	-1.75854600
C	2.46510000	-1.23028300	-0.55542000
C	1.24686900	-1.90816000	-0.84718900
N	0.21092800	-2.38340500	-1.04164800
O	3.57264300	-2.06718900	-0.31121600
C	4.13477500	-2.67128500	-1.39080300
O	3.72238200	-2.62905900	-2.51623500
O	5.21411600	-3.32029900	-0.95571400
C	5.93472000	-4.03814200	-1.97683000
H	6.29386900	-3.34971000	-2.74349900
H	5.29258900	-4.78901400	-2.43996400
H	6.76842200	-4.50962200	-1.46208500
H	2.31875400	2.28413500	1.04523200
C	3.28214200	1.84185900	1.25351400
C	5.74640600	0.67514800	1.79981500
C	4.42036100	2.63544100	1.34478200
C	3.36058800	0.45451200	1.42823200
C	4.60711000	-0.11826800	1.70866100
C	5.65906600	2.05398000	1.61503000
H	4.34245100	3.70908200	1.20974500
H	4.68199700	-1.19126700	1.83013000
H	6.54727200	2.67152500	1.68898100
H	6.70472800	0.21629100	2.01551000
C	2.15309200	-0.40877700	1.30735200
N	0.94810800	0.20064100	1.33699700
C	-0.13990900	-0.49258000	1.73165700
O	0.06515200	-1.73841300	2.20377200
C	-1.02107300	-2.56774500	2.76434600
O	-1.28288200	0.00367700	1.70612500
H	2.26891600	-1.39087600	1.76584800
C	-2.09948400	-2.83217400	1.71454900
H	-2.78711400	-3.59581200	2.08778400
H	-2.66621200	-1.93047600	1.49549200
H	-1.64139400	-3.20051600	0.79580100
C	-1.58710600	-1.89266800	4.01441200
H	-2.12027400	-0.98123800	3.74958000
H	-2.28299200	-2.57288500	4.51253700
H	-0.78025700	-1.65286700	4.71222300
C	-0.28133000	-3.85635300	3.12044000
H	0.52210500	-3.65216400	3.83198700
H	-0.97196400	-4.57507600	3.56756000
H	0.15442200	-4.30003000	2.22269000
H	-1.14314900	2.23683200	3.40158300
H	-0.47501800	3.81079500	2.90002000
C	-2.67629200	3.12456400	1.45061900
H	-3.14663500	3.12648300	0.47355300
H	-3.24211900	2.43941000	2.07988100
H	-2.65383600	4.12575000	1.88007400

TS_{Add}-13

Zero-point correction = 0.841902 (Hartree/Particle)
Thermal correction to Energy = 0.895205
Thermal correction to Enthalpy = 0.896150
Thermal correction to Gibbs Free Energy = 0.754684
Sum of electronic and zero-point Energies = −2918.732252
Sum of electronic and thermal Energies = −2918.678949
Sum of electronic and thermal Enthalpies = −2918.678004
Sum of electronic and thermal Free Energies = −2918.819470
E(RB3LYP-D3) = −2919.574154
Imaginary frequency = 197.33i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −2919.750607
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −2919.617113

0 1

H	6.62057800	-0.70204300	0.66217700
C	5.90305900	0.06802100	0.40750200
C	4.00018700	2.00041400	-0.38174500
C	4.60913200	-0.30180800	0.06035200
C	6.24188900	1.41258500	0.40873000
C	5.29581500	2.35419300	0.01304100
C	3.63803700	0.63403100	-0.32158600
H	7.24166600	1.72675900	0.68215200
H	5.58106400	3.39760100	-0.04801600
S	4.14990500	-2.02594400	0.10759200
O	5.26187800	-2.82216700	-0.40290100
O	3.64443300	-2.34079800	1.45070000
N	2.91516500	-2.08967500	-0.96627200
C	2.06137600	-1.09103900	-1.02189500
N	2.35104600	0.20053400	-0.65436000
H	1.58528100	0.86923600	-0.66190100
N	0.83292900	-1.30135700	-1.53835700
H	0.16733500	-0.53182100	-1.51526400
C	0.37744100	-2.60186800	-2.01817000
C	-1.11040200	-4.62028600	-1.57151500
C	-0.95403000	-3.69397800	-3.90625500
C	-1.87823700	-4.33841400	-2.86996500
C	-0.35944600	-2.39622300	-3.35490700
C	-0.52499200	-3.32892600	-0.99148100
H	-0.30307900	-5.33199800	-1.78007200
H	-0.15058600	-4.39464000	-4.16836500
H	-2.71340000	-3.66153400	-2.66140600
H	-1.16397100	-1.67165900	-3.21046300
H	-1.32446900	-2.63894000	-0.71388600
H	1.26755500	-3.20255000	-2.20549500
H	-1.77622200	-5.09097300	-0.84428800

H	-1.50275600	-3.48142500	-4.82767800
H	-2.30007300	-5.27218300	-3.25246400
H	0.35386700	-1.96021600	-4.05938900
N	0.21179700	-3.57752600	0.32061600
H	0.54014400	-2.62534000	0.67351600
C	-0.70851100	-4.00631000	1.42020000
H	-1.49260700	-3.25912500	1.51564500
C	1.38523800	-4.50282900	0.25349500
H	1.98954800	-4.33152500	1.14328100
H	1.99791300	-4.26450100	-0.60819600
H	1.03200600	-5.53271800	0.21486300
C	-2.73614000	1.02583100	-0.40182600
C	-1.43603500	1.67580900	-0.34595700
O	-0.40287000	1.17480200	-0.78293400
O	-1.46868000	2.81222100	0.35225000
C	-0.19801100	3.45152000	0.56351200
H	0.45682200	2.78729100	1.12416900
H	-0.41594500	4.34947800	1.13674300
H	0.25569500	3.70526000	-0.38981300
C	-2.91900400	0.03700900	-1.40590400
N	-3.08182900	-0.84670300	-2.13541500
O	-3.86753300	1.81276200	-0.11033200
C	-4.14578900	2.81837500	-0.97656900
O	-3.54163900	3.07516300	-1.98144300
O	-5.21372300	3.45993000	-0.50084000
C	-5.65986400	4.56355500	-1.31126000
H	-4.87445600	5.31661800	-1.39596300
H	-6.52612600	4.96854500	-0.79341600
H	-5.93446600	4.21766300	-2.30917200
C	-2.55796600	-0.12400300	1.35790600
N	-1.49229900	-0.93345900	1.21474600
C	-0.29395600	-0.59828000	1.72470000
O	0.71328000	-1.31317200	1.57927400
O	-0.21888400	0.54292400	2.45968300
C	0.86965900	0.75289100	3.43862600
C	-3.90762000	-0.73575100	1.37029600
C	-6.47640100	-1.85518400	1.43911100
C	-4.14386700	-2.01020500	0.83729000
C	-4.97954200	-0.02774000	1.92912600
C	-6.25334600	-0.58478000	1.96743200
C	-5.41803200	-2.56399500	0.87077000
H	-3.32492000	-2.54965000	0.38433400
H	-4.81017700	0.96859500	2.31894900
H	-7.07282300	-0.02626100	2.40546200
H	-5.58917400	-3.54774500	0.44797500
H	-7.46967100	-2.28928600	1.46632700
H	-2.47384800	0.77924200	1.96372400
H	-0.12679900	-4.03345900	2.34048000
H	-1.11081400	-4.99527500	1.21012700
C	3.11279600	3.06824600	-0.91681000
C	1.67568900	5.20487500	-2.05217100
C	3.03403800	4.31023700	-0.26743500
C	2.43608400	2.91246600	-2.13547700
C	1.72242500	3.96891300	-2.69452000
C	2.33186700	5.37031300	-0.83331400
H	3.53240100	4.44213500	0.68626900
H	2.49079700	1.96779700	-2.66219600
H	1.20832100	3.82659800	-3.63782100
H	2.28977000	6.32313000	-0.31765800
H	1.12442400	6.02751300	-2.49248300
C	2.21658400	0.94507400	2.74025700
H	2.96444500	1.24939500	3.47785600
H	2.54631000	0.02351500	2.26719600
H	2.15365900	1.73194500	1.98564000
C	0.91138400	-0.42160000	4.41934400
H	1.26283900	-1.32560400	3.92499000
H	1.59394300	-0.18626300	5.23983600
H	-0.08313200	-0.59785500	4.83765000
C	0.42630200	2.03153400	4.14870800
H	-0.55472400	1.89175400	4.60763400
H	1.14486200	2.29485500	4.92833600
H	0.35988900	2.86271300	3.44440800

TS_{Add}-14

Zero-point correction = 0.840707 (Hartree/Particle)
Thermal correction to Energy = 0.894478
Thermal correction to Enthalpy = 0.895423
Thermal correction to Gibbs Free Energy = 0.750715
Sum of electronic and zero-point Energies = −2918.730242
Sum of electronic and thermal Energies = −2918.676471
Sum of electronic and thermal Enthalpies = −2918.675527
Sum of electronic and thermal Free Energies = −2918.820234
E(RB3LYP-D3) = −2919.570949
Imaginary frequency = 256.94i

Relative energy (RB3LYP-D3/6-311+G(3d,3p)) = −2919.747578
Relative energy (SMD(toluene)/RB3LYP-D3/6-311G(d,p) = −2919.614519

0 1

H	6.92204000	-0.11993200	0.19619100
C	6.10973800	0.56176900	-0.02350900
C	3.95884200	2.26614500	-0.67569500
C	4.83379200	0.04936500	-0.23609000
C	6.30661700	1.93328700	-0.09651700
C	5.23395900	2.76777400	-0.41404600
C	3.75046600	0.87405600	-0.55789900
H	7.28988500	2.35348100	0.07665900
H	5.38882500	3.83721800	-0.50040600
S	4.51038200	-1.69214000	-0.02434300
O	5.62991400	-2.45764800	-0.56367600
O	4.12875100	-1.92302400	1.37622700
N	3.19408300	-1.92954600	-0.97831400
C	2.26298400	-0.99974200	-1.01169100
N	2.48241500	0.32463500	-0.76467500
H	1.67534200	0.95081100	-0.71889000
N	1.00259700	-1.34676700	-1.37350900
H	0.27977600	-0.63986600	-1.43006600
C	0.61048700	-2.71607200	-1.68917400
C	-0.73638300	-4.74397700	-0.94013000
C	-0.67899100	-4.12466100	-3.38086000
C	-1.53891300	-4.68723400	-2.24631100
C	-0.16853500	-2.72817100	-3.01821400
C	-0.21847000	-3.35550500	-0.54992900
H	0.10812000	-5.43029400	-1.07143000
H	0.16672900	-4.79926900	-3.56501000
H	-2.41739300	-4.04670500	-2.10408100
H	-1.01293400	-2.04154400	-2.93886000
H	-1.04834300	-2.67751300	-0.33697700

H	1.53097800	-3.28130900	-1.83145000	C	-3.73428600	-0.71667100	1.48351300
H	-1.36146100	-5.15115500	-0.14207900	C	-6.25619400	-1.94012800	1.36421000
H	-1.25289600	-4.07788000	-4.31073100	C	-3.86450300	-2.04122100	1.04731600
H	-1.90570300	-5.68769200	-2.49285300	C	-4.88550400	-0.01525000	1.86144700
H	0.49888500	-2.34199200	-3.79319800	C	-6.13599400	-0.62205600	1.80189100
N	0.56702100	-3.39070700	0.75471100	C	-5.11471600	-2.64816000	0.98842200
H	0.80966400	-2.37657300	1.00303500	H	-2.97686700	-2.58118400	0.75022600
C	-0.27884700	-3.78682400	1.92356000	H	-4.79618100	1.01683100	2.17702500
H	-1.14292200	-3.12757400	1.95632400	H	-7.01844700	-0.06563800	2.09719700
C	1.82784300	-4.19627400	0.74743300	H	-5.20012600	-3.67596100	0.65185100
H	2.43137800	-3.87334300	1.59436200	H	-7.23065400	-2.41382400	1.32139900
H	2.39739600	-3.98804300	-0.15089500	H	-2.39099700	0.85356800	2.14855700
H	1.58278300	-5.25527200	0.82398700	H	0.31704700	-3.63325400	2.82181000
C	-2.52970000	1.11804500	-0.16592800	H	-0.56467800	-4.83395000	1.84565000
C	-2.98586300	0.15206600	-1.17735300	C	2.85796400	3.18016300	-1.08494200
O	-2.24512100	-0.67558400	-1.67950900	C	0.74212400	4.85732600	-1.83604600
O	-4.30509300	0.21244500	-1.39226000	C	2.42345000	4.20079300	-0.23303900
C	-4.84830400	-0.80104100	-2.25609800	C	2.23308900	3.02632000	-2.32852600
H	-4.37455900	-0.75882300	-3.23809100	C	1.18297600	3.85791000	-2.70068900
H	-5.90999900	-0.57785100	-2.32768700	C	1.37009000	5.03198700	-0.60530100
H	-4.69754800	-1.78640500	-1.81375700	H	2.89729000	4.32103600	0.73440900
C	-1.17819600	1.51257200	-0.35350500	H	2.56775100	2.24085300	-2.99681600
N	-0.04360100	1.69950000	-0.45649100	H	0.69749500	3.71719600	-3.65945900
O	-3.41820600	2.13473300	0.23984500	H	1.03212600	5.80746200	0.07310500
C	-3.74564600	3.06538600	-0.69197900	H	-0.09206900	5.48911800	-2.11837800
O	-3.28064500	3.15446800	-1.79489800	C	2.16785000	1.56142000	2.39425000
O	-4.66364600	3.86173000	-0.14436600	H	2.93839600	2.14948900	2.90067500
C	-5.11898700	4.92895700	-0.99814100	H	2.61016300	0.63125600	2.04731500
H	-4.28690900	5.57997700	-1.27168100	H	1.80644500	2.13087100	1.53772000
H	-5.85475100	5.47283800	-0.41057200	C	1.41415100	0.33545100	4.48154200
H	-5.57168800	4.52437900	-1.90483000	H	2.20266000	0.78506600	5.09094900
C	-2.40786600	-0.04194400	1.52669900	H	0.55558200	0.12724800	5.12554200
N	-1.30880800	-0.82122900	1.45402500	H	1.78783800	-0.59760800	4.06256700
C	-0.13682800	-0.38074200	1.95649900	C	0.48090300	2.61557200	3.93164200
O	0.92329000	-1.02272600	1.82541700	H	-0.38016700	2.43110500	4.57802000
O	-0.16660700	0.77056500	2.65931800	H	1.25653100	3.11749900	4.51489400
C	1.01596200	1.30114400	3.36494300	H	0.16968400	3.27551500	3.11869800

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論文目録

Divergent and Scalable Synthesis of α-Hydroxy/Keto-β-amino Acid Analogues by the Catalytic Enantioselective Addition of Glyoxylate Cyanohydrin to Imines
Takeshi, Nanjo, Xuan Zhang, Yusuke Tokuhiro, Yoshiji Takemoto
ACS Catal. **2019**, *9*, 10087–10092.

Highly Stereoselective, Organocatalytic Mannich-type Addition of Glyoxylate Cyanohydrin: A Versatile Building Block for the Asymmetric Synthesis of β-Amino-α-ketoacids
Yusuke Tokuhiro, Kosuke Yoshikawa, Sei Murayama, Takeshi Nanjo, Yoshiji Takemoto
ACS Catal. **2022**, *12*, 5292–5304.

その他関連研究における発表論文

Bifunctional-Benzothiadiazine-Catalyzed Regio- and Stereoselective Aldol Reactions Using A 1,3-Acetonedicarboxylic Acid Monoester
Yusuke Tokuhiro, Noboru Hayama, Yusuke Kobayashi, Yoshiji Takemoto
Heterocycles **2021**, *103*, 484–493.

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