

博 士 論 文

ラジカルの安定化効果を活用した複雑かつ
嵩高い分子合成法の開発

2 0 2 4 年

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略語表

Ac	Acetyl
Acr	Acridinium
Ar	Aryl
BDE	Bond Dissociation Energy
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
bpy	2,2'-Bipyridyl
Bu	Butyl
Bz	Benzoyl
Cbz	Carbobenzoxo
Cy	Cyclohexyl
Cz	Carbazole
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
Dha	Dehydroalanine
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMA	<i>N,N</i> -Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
dmp	2,9-Dimethyl-1,10-phenanthroline
DMPU	<i>N,N'</i> -Dimethylpropyleneurea
DMSO	Dimethyl Sulfoxide
DMTr	4,4'-Dimethoxytrityl
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridine
e	Electron
Et	Ethyl
EWG	Electron Withdrawing Group
FG	Functional Group
HAT	Hydrogen Atom Transfer
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
Im	Imidazolium
IPN	Isophthalodinitrile
iPr	Isopropyl
LED	Light Emitting Diode
Me	Methyl

Mes	Mesityl
MTBE	Methyl <i>tert</i> -Butyl Ether
NHC	<i>N</i> -Heterocyclic Carbene
NHPI	<i>N</i> -Hydroxyphthalimide
PC	Photocatalyst
PG	Protecting Group
Ph	Phenyl
Phth	Phthaloyl
ppy	2-Phenylpyridinato
PRE	Persistent Radical Effect
PTH	Phenothiazine
RSE	Radical Stabilization Energy
SCE	Saturated Calomel Electrode
SET	Single Electron Transfer
TBAF	Tetrabutylammonium Fluoride
TBS	<i>tert</i> -Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-Oxyl
Tf	Trifluoromethanesulfonyl
TFT	2,3,7,8-Tetrafluorothianthrene
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

序論

第一節 ラジカル反応

不対電子をもつラジカルは、高い反応性を示し、有機合成化学における重要な活性種の一つである。¹ ラジカルが関与する素過程として、1) 原子引き抜き、2) 二重結合へのラジカル付加、3) β -開裂、4) ラジカル-ラジカルカップリング、などがある。このような素過程を経るラジカル反応は、穏和な条件下にて、イオン反応では達成困難とされる嵩高い分子同士の結合形成を可能にする。また、高い官能基許容性を有するため、複雑な分子の合成・変換に有用である。

1800 年代に、Kolbe 電解反応²、ピナコールカップリング反応³、Borodin-Hundsdiecker 反応⁴、Hofmann-Löffler-Freytag 反応⁵などのラジカル反応が既に報告されている。1900 年代に入り、Birch 還元反応⁶や Kharasch 付加反応⁷、またフェノールの工業的製法であるクメン法⁸が見出されている。ラジカル化学における重要な発見として、1957 年 van der Kerk らによって有機スズヒドريدを用いたアルキルラジカル発生法が報告され、以降炭素ラジカルを活用した分子変換反応の開発が急速に進展していく。⁹ 1900 年代後半には、近年でも有機合成に利用されている Giese 反応¹⁰や Minisci 反応¹¹、Barton-McCombie 反応¹²などが開発されている。これらのラジカル反応の多くは、原子引き抜きや二重結合へのラジカル付加を経る分子変換であった。一方で、ラジカル-ラジカルカップリングは、拡散律速に近い過程であるため、異なる二種のラジカルの選択的なクロスカップリングは困難であり、有機合成化学的に価値がない素過程とされていた。

1900 年に Gomberg によって世界で最初に発見されたラジカルであるトリフェニルラジカル¹³が選択的なクロスカップリングを起こすことを 1936 年 Bachmann と Wiselogle らは報告している。¹⁴ その後、Perkins らによるフェニルアゾトリフェニルメタンのベンゼン中での熱分解¹⁵や Huber らによる *N*-ニトロソジメチルアミンの光分解¹⁶の報告を基に、1986 年 Fischer はこのラジカル-ラジカルカップリングの選択性を説明する一般的な原理を定式化した。¹⁷ また、1976 年 Griller と Ingold らによって、半減期が 10^{-3} 秒以下の反応性の高い炭素ラジカル種は短寿命ラジカル、より半減期の長い安定化された炭素ラジカル種は長寿命ラジカルと定義付けされた。¹⁸ Fischer の原理は、後に Finke によって長寿命ラジカル効果 (PRE : persistent radical effect) と命名されている。¹⁹ この PRE は、二種のラジカルが同じ速度で等量発生する場合において、長寿命ラジカルと短寿命ラジカルが選択的にクロスカップリングする速度論的な事象である (Figure P1)。²⁰ すなわち、長寿命ラジカル同士のホモカップリングは遅いのに対し、短寿命ラジカル同士のホモカップリングは速いため、長寿命ラジカルと短寿命ラジカルの濃度差が生まれ、選択的なクロスカップリングが進行するようになる。

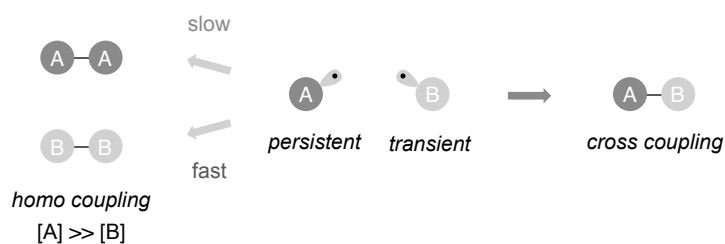


Figure P1. 長寿命ラジカル効果

この PRE は、高分子材料の合成法である原子移動ラジカル重合 (ATRP: Atom Transfer Radical Polymerization) で重要な現象である。^{20a} また、近年急速に発展している光酸化還元触媒反応²¹においても、PRE に基づく反応設計により高度な分子変換が実現されている。すなわち、光酸化還元触媒系で発生した二種のラジカルの内、一方のラジカル種がもう一方のラジカル種よりも長寿命であれば PRE が作動するため、選択的なクロスカップリングを達成できる。第二節では、長寿命ラジカルの要因となるラジカルの安定化について示す。

第二節 ラジカルの安定化

ラジカルの安定化には、共鳴効果や誘起効果といった電子的な要因による熱力学的安定化と嵩高い置換基に由来した立体的な要因による速度論的安定化がある。1900 年に Gomberg によって発見されたトリフェニルメチルラジカルは、隣接したフェニル基の π 軌道との相互作用に由来した非局在化による熱力学的安定化と三つのフェニル基の立体的な嵩高さに由来した速度論的安定化を受けている (**Figure P2**)。また、ガルビノキシルラジカル²² や 2,2,6,6-テトラメチルピペリジン 1-オキシルラジカル (TEMPO)²³ は単離可能なフリーラジカルであり、共鳴効果による熱力学的な安定化と嵩高い置換基による速度論的な安定化を受けている。これらのラジカルは、試薬として販売されており、ラジカル捕捉剤や酸化反応の触媒として利用されている。

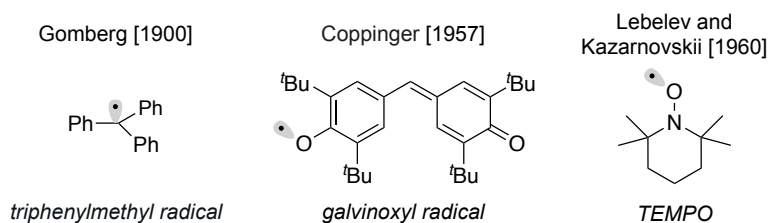


Figure P2. 代表的な安定ラジカル

炭素ラジカルの重要な安定化効果として、captodative 効果がある。²⁴ これは、電子求引性基 (capto) と電子供与性基 (dative) の極性の異なる置換基を有するラジカル中心が大きな安定化を受ける電子的な効果である。隣接した電子求引性基の最低空軌道 (LUMO) および電子供与性基の最高被占軌道 (HOMO) との相互作用により、ラジカルが非局在化し、熱力学的な安定性が増加すると考えられる。

炭素ラジカルの安定性の指標として、ラジカル安定化エネルギー (RSE: radical stabilization energy) がある。²⁵ この RSE は、メチルラジカルのエネルギーを基準とし、ある炭素ラジカルが生じる炭素-水素結合の結合解離エネルギー (BDE: bond dissociation energy) を求めることで、相対的な安定性を評価することができる (**Figure P3**)。例えば、トリフェニルメタンの炭素-水素結合の BDE は 81 kcal/mol であり、メタンの炭素-水素結合の BDE は 105 kcal/mol であることから、トリフェニルメチルラジカルの RSE は 24 kcal/mol と算出できる。^{20c}

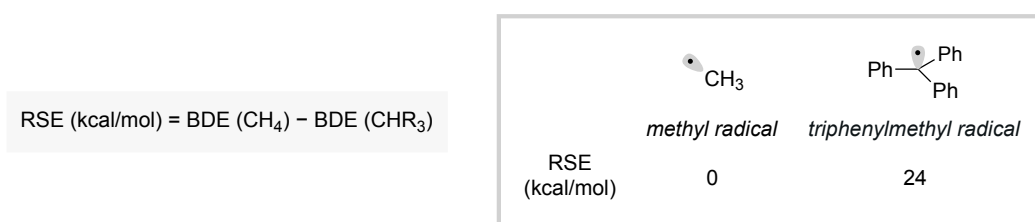


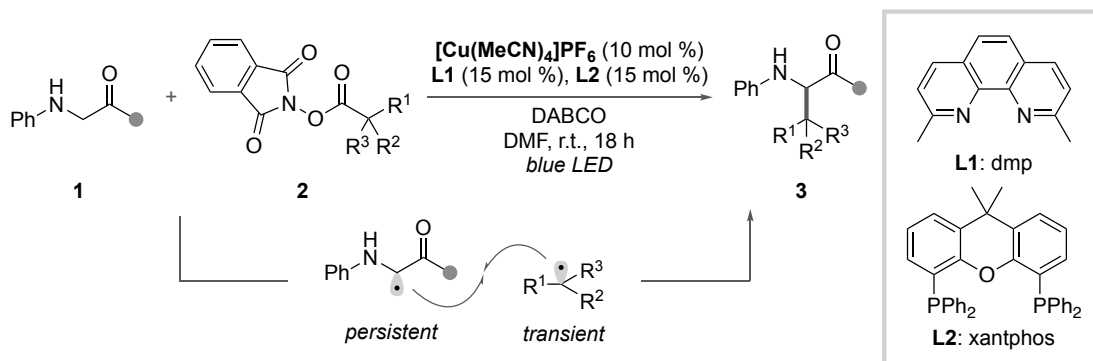
Figure P3. ラジカル安定化エネルギー

他には、遷移金属による有機ラジカルの安定化がある。すなわち、遷移金属錯体が有機ラジカルを捕捉あるいは配位することで生じる有機遷移金属錯体は、長寿命ラジカルとなる。そのため、PRE に基づいた遷移金属触媒による多様なクロスカップリング反応が開発されている。^{20d}

第三節では、近年見出された光酸化還元触媒や有機分子触媒による PRE のようなラジカルの安定化効果を活用した分子変換反応について示す。

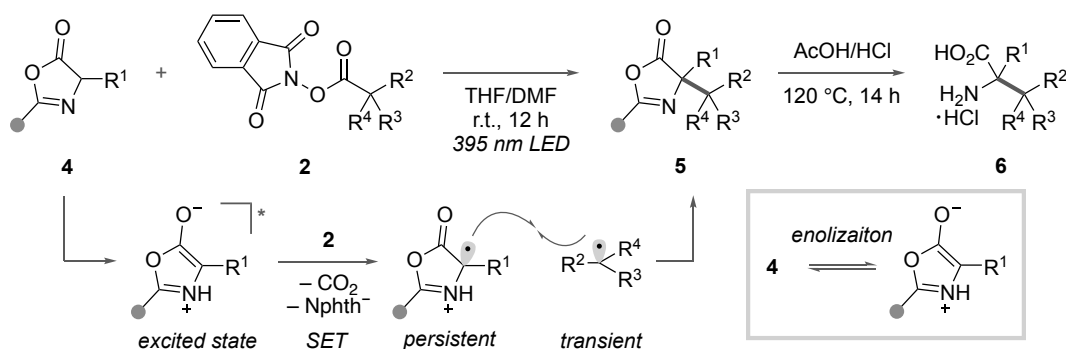
第三節 長寿命な炭素ラジカルを活用した分子変換反応

長寿命な炭素ラジカルの代表例として、グリシルラジカルがある。グリシルラジカルは、電子供与性の窒素原子と電子求引性のカルボニル基が隣接しており、第二節で述べた **captodative** 効果が働くことで、安定化されている。このグリシルラジカルを活用した先駆的な研究として、1969 年に Elad らは、グリシンジペプチドを基質として用い、アセトンおよびトルエン中で紫外光を照射することで、グリシルラジカルを経てグリシン残基の C-H アルキル化が進行することを見出している。²⁶ 近年では、より穏和な可視光エネルギーによって発生させたグリシルラジカルを活用した分子変換が達成されている。例えば、2018 年 Xu らは、青色 LED で駆動する銅錯体と脂肪族カルボン酸誘導体であるレドックス活性エステル **2** を用いることで、グリシンやペプチド **1** の脱炭酸型 C(sp³)-H アルキル化反応を報告している (**Scheme P1**)。²⁷ 本反応では、可視光によって励起された Cu^I 錯体がレドックス活性エステルへの一電子移動を起こすことで、Cu^{II} 錯体と脱炭酸を経てアルキルラジカルが生じる。一方で、Cu^{II} 錯体がグリシン誘導体を一電子酸化することで、基底状態の Cu^I 錯体が再生し、脱プロトン化を経てグリシルラジカルが発生する。最後に、長寿命なグリシルラジカルと短寿命なアルキルラジカルのクロスカップリングにより、C(sp³)-H アルキル化体 **3** が生成する。



Scheme P1. 銅触媒によるグリシンやペプチドの脱炭酸型 C(sp³)-H アルキル化反応

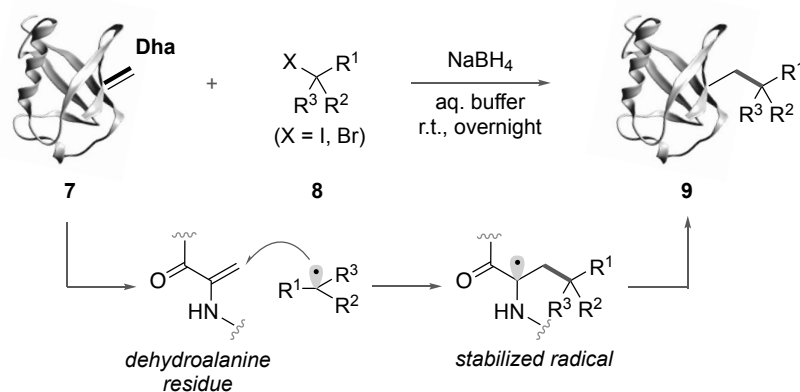
2022 年 Zheng らは、紫外光とレドックス活性エステル **2** を用いたオキサゾロン **4** の脱炭酸型アルキル化反応を報告している (**Scheme P2**)。²⁸ この反応では、まず系中で生じたオキサゾロン **4** のエノラート体が紫外光によって励起される。次に、励起状態のエノラート体からレドックス活性エステル **2** への一電子移動が進行し、オキサゾロンラジカルと脱炭酸を経てアルキルラジカルが発生する。オキサゾロンラジカルは、グリシルラジカルと類似した構造であり、captodative 効果が働くことで長寿命ラジカルになると考えられる。最後に、長寿命なオキサゾロンラジカルと短寿命なアルキルラジカルの PRE に基づく選択的なラジカル-ラジカルカップリングにより目的物 **5** が生成する。クロスカップリング体 **5** は、酸性条件下反応させることで、 α -第三級アミノ酸 **6** へと誘導することが可能である。



Scheme P2. ラジカル-ラジカルカップリングを経た α -第三級アミノ酸の合成

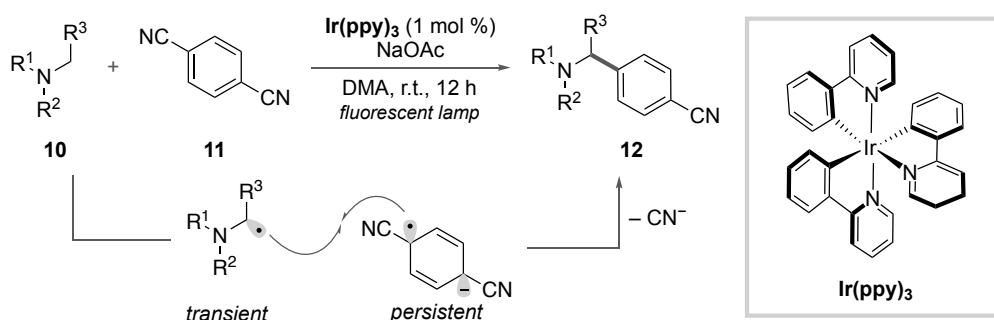
アルケンへのラジカル付加過程においてもラジカルの安定化効果が重要である。すなわち、アルケンへのラジカル付加において、グリシルラジカルのような captodative 効果が働く炭素ラジカルが生じる場合、遷移状態が安定化されるため、その反応速度は大きくなる。²⁹ このような安定化されたラジカルを経るアルケンへのラジカル付加を活用した手法として、2016 年 Davis らは、デヒドロアラニン (Dha) **7** を経由したタンパク質の化学修飾法を開発している (**Scheme P3**)。³⁰ この反応では、まず水素化ホウ素ナト

リウムとハロゲン化アルキル **8** からアルキルラジカルが発生する。このアルキルラジカルがタンパク質のデヒドロアラニン部位に付加することで、**captodative** 効果によって安定化されたラジカルを経て $C(sp^3)-C(sp^3)$ 結合形成反応が進行し、翻訳後修飾タンパク質 **9** が生成する。同年、Lee と Park らは、亜鉛と酢酸銅を用いることで、上記と同様の過程を経たタンパク質の化学修飾法を報告している。³¹



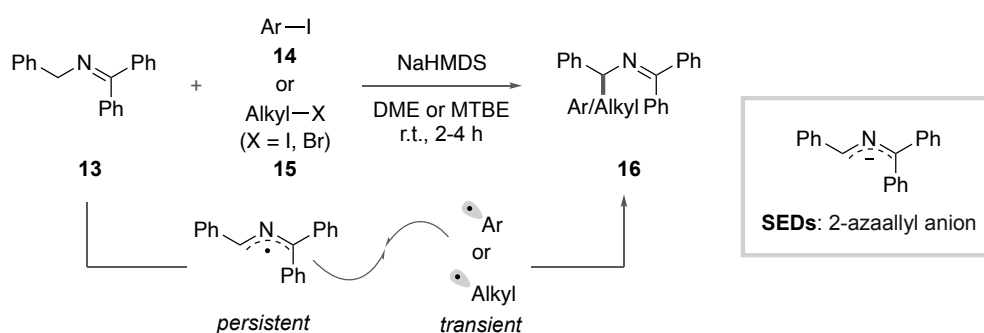
Scheme P3. デヒドロアラニンを経由したタンパク質の化学修飾法

シアノアレーンの一電子還元によって生じるラジカルアニオンは、**captodative** 効果が働き、長寿命ラジカルとなる。³² 例えば、ジシアノベンゼンのラジカルアニオンは、30 ナノ秒程度の長い寿命を有する。³³ この長寿命なアレーンラジカルアニオンを活用した先駆的な研究として、2011 年 MacMillan らは、光酸化還元触媒によるシアノアレーン **11** を用いたアミン **10** の α 位 C-H アリール化反応を報告している (**Scheme P4**)。³⁴ 本反応では、まず励起された Ir^{III} 錯体が、シアノアレーンへの一電子移動を起こし、 Ir^{IV} 錯体と長寿命なアレーンラジカルアニオンが生成する。次に、 Ir^{IV} 錯体がアミンを一電子酸化することで、アミンラジカルカチオンが生じると共に基底状態の Ir^{III} 錯体が再生する。その後、脱プロトン化を経て生じた短寿命な α -アミノラジカルと長寿命なシアノアレーンのラジカルアニオンがクロスカップリングし、シアノ基の脱離を経て目的のベンジルアミン体 **12** が生成する。本反応が報告されて以降、この長寿命なシアノアレーンラジカルアニオンを活用した多様なアリール化反応が開発されている。³⁵



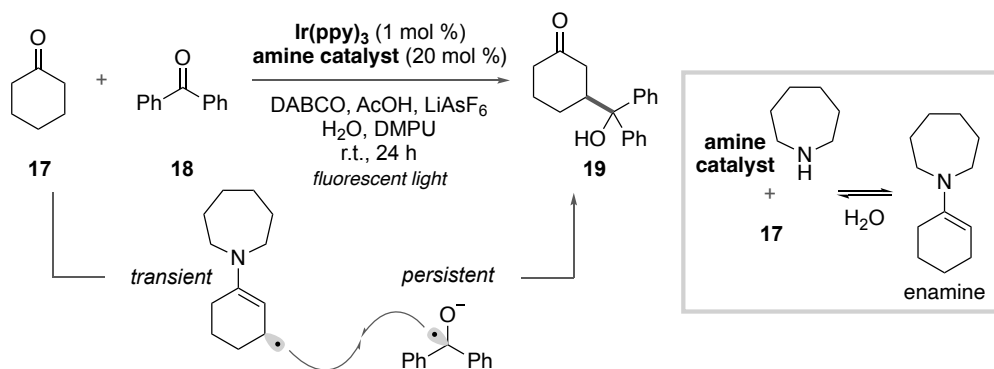
Scheme P4. 光酸化還元触媒によるアミンの α 位 C-H アリール化反応

2017 年 Walsh らは、*N*-ベンジルケチミン **13** とアリールハライド **14** またはアルキルハライド **15** を塩基存在下で反応させることで、 $C(sp^3)-C(sp^2)$ や $C(sp^3)-C(sp^3)$ カップリングが進行することを見出している (Scheme P5)。³⁶ *N*-ベンジルケチミンの脱プロトン化によって生じる 2-アザアリルアニオンは super-electron-donors (SEDs) であり、アリールまたはアルキルハライドへの一電子移動を起こす。その後、生じたアザアリルラジカルが長寿命であるため、短寿命な炭素ラジカルとの選択的なクロスカップリングが進行し、カップリング体 **16** を与える。*N*-ベンジルケチミン **13** は、対応するベンジルアミンから合成できるため、本手法はベンジルアミンの形式的な α 位アリール化またはアルキル化反応と言える。本報告以降、2-アザアリルアニオンからの一電子移動を起点とした様々な分子変換が達成されている。³⁷



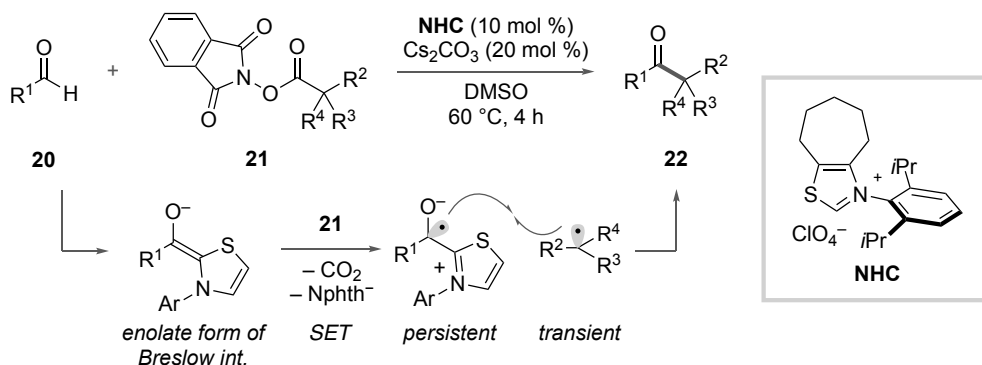
Scheme P5. メタルフリーなケチミンのアリールおよびアルキル化反応

長寿命なケチルラジカルの代表例として、ベンゾフェノンの一電子還元によって生じるベンゾフェノンケチルがある。ベンゾフェノンケチルは青色を示し、水や酸素と反応すると色が消えるため、エーテル系溶媒の脱酸素・脱水溶媒を調整する際の指示薬として利用されてきた。このような長寿命なケチルラジカルを活用した分子変換として、2013 年 MacMillan らは、光酸化還元触媒と有機分子触媒の協働触媒系によるアリールケトン **18** を用いた環状ケトン **17** の β 位 C-H 官能基化反応を報告している (Scheme P6)。³⁸ 本反応では、励起された Ir^{III} 錯体がベンゾフェノンへの一電子移動を起こし、長寿命なケチルラジカルが生成する。また、一電子移動を経て生じた酸化力の高い Ir^{IV} 錯体が、有機分子触媒であるアミンと環状ケトンから形成されるエナミンを一電子酸化することで、基底状態の Ir^{III} 錯体が再生すると共に、エナミンラジカルカチオンが生じる。その後、脱プロトン化を経て生じる短寿命な β -エナミルラジカルと長寿命なケチルラジカルがクロスカップリングすることで、 γ -ヒドロキシケトン体 **19** を与える。



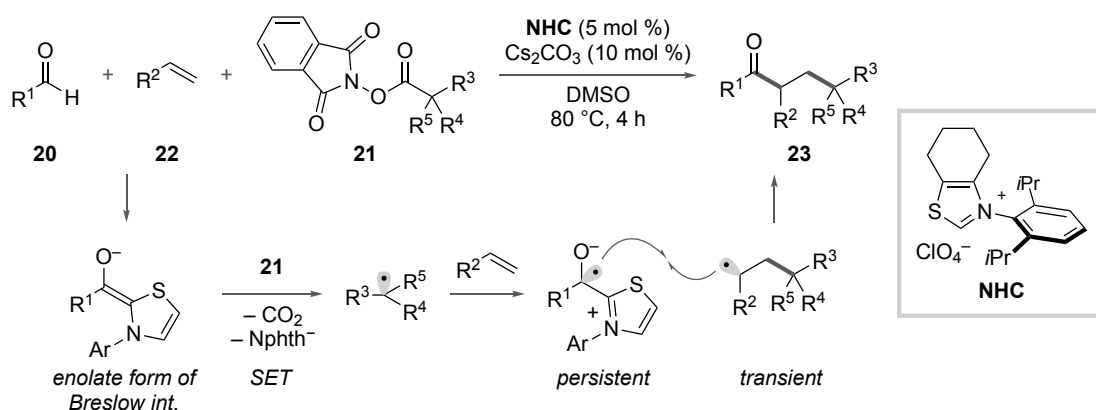
Scheme P6. アリールケトンを用いた環状ケトンのβ位官能基化反応

2019 年大宮らは、有機分子である *N*-ヘテロ環カルベン (NHC) 触媒と脂肪族カルボン酸誘導体であるレドックス活性エステル **21** を用いた芳香族アルデヒド **20** の脱炭酸型アルキル化反応を報告している (**Scheme P7**)。³⁹ 本反応では、まずアルデヒドと NHC から Breslow 中間体が形成される。その後、塩基による脱プロトン化によって生成する高還元力のエノラート型 Breslow 中間体からレドックス活性エステルへの一電子移動が起きる。生じたエノラート型 Breslow 中間体由来のケチルラジカルは、電子供与性のアルコキシ基と電子求引性のチアゾリウム環による captodative 効果とチアゾリウム触媒の嵩高い置換基による速度論的な安定化を受けることで、長寿命ラジカルになると考えられる。最後に、脱炭酸を経て生じたアルキルラジカルと長寿命なケチルラジカルとのクロスカップリングにより、ケトン体 **22** が生成すると共に NHC 触媒が再生する。



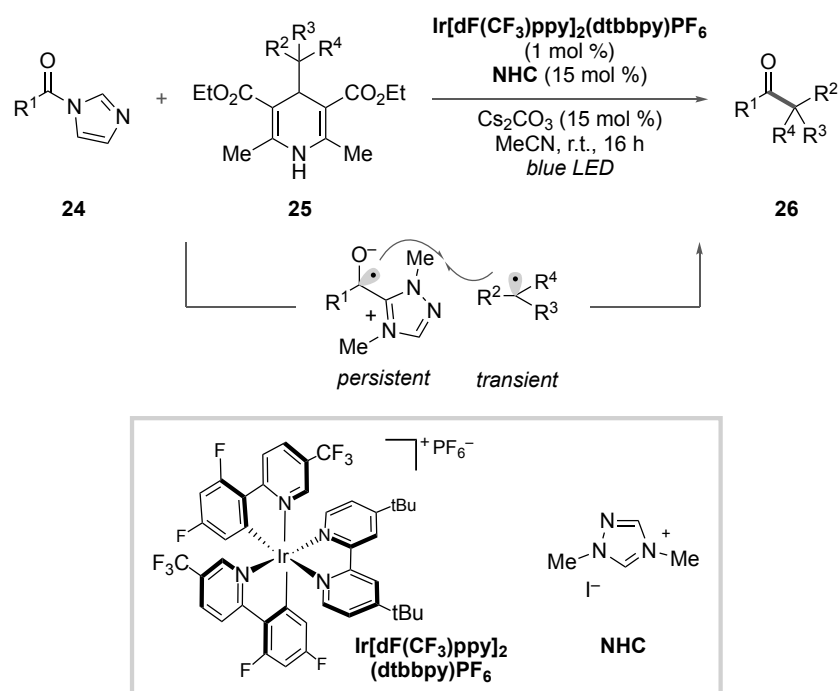
Scheme P7. NHC 触媒によるアルデヒドの脱炭酸型アルキル化反応

大宮らは、この Breslow 中間体由来の長寿命なケチルラジカルを活用することで、ラジカルリレー型アルケンの二炭素官能基化反応へ展開している (**Scheme P8**)。⁴⁰ 上に述べた NHC 触媒系にアルケン **22** を加えることで、生じたアルキルラジカルが Breslow 中間体由来のケチルラジカルとカップリングするより先にアルケンへ付加する。その後、生じた炭素ラジカルと長寿命なケチルラジカルとのクロスカップリングにより、アルケンのアルキルアシル化体 **23** を与える。



Scheme P8. NHC 触媒によるアルケンのビシナルアルキルアシル化反応

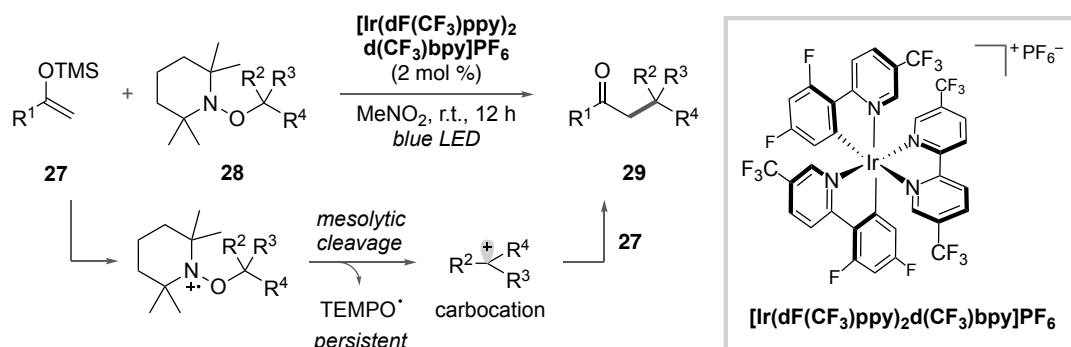
2020 年 Scheidt らは、NHC とカルボン酸誘導体から形成されるアシルアゾリウム中間体の一電子還元によって長寿命なケチルラジカルを発生させる、上記の大宮らと相補的な手法を報告している (**Scheme P9**)。⁴¹ 具体的には、光酸化還元触媒とトリアゾリウム型 NHC 触媒存在下、基質としてカルボン酸誘導体 **24** と Hantzsch エステル **25** を用い、可視光照射することで、カルボン酸誘導体由来のアシルアゾリウムの還元的なアルキル化が進行する。本反応では、まず可視光により励起した Ir^{III} 錯体が Hantzsch エステルの一電子酸化を起こし、ラジカルカチオンと Ir^{II} 錯体が生じる。このラジカルカチオンから芳香族化を駆動力としてアルキルラジカルが生成する。一方で、生じた Ir^{II} 錯体が NHC 触媒とカルボン酸誘導体から形成されるアシルアゾリウム中間体に対して一電子移動を起こすことで、ケチルラジカルが生成すると共に基底状態の Ir^{III} 錯体が再生する。最後に、長寿命なケチルラジカルと短寿命なアルキルラジカルの選択的なクロスカップリングにより、目的のケトン体 **26** が生成する。大宮、Scheidt らの報告以降、長寿命なケチルラジカルを経た NHC 触媒によるラジカル介在型アシル化反応が種々報告されている。⁴²



Scheme P9. 光酸化還元触媒と NHC 触媒によるカルボン酸を用いたケトン合成

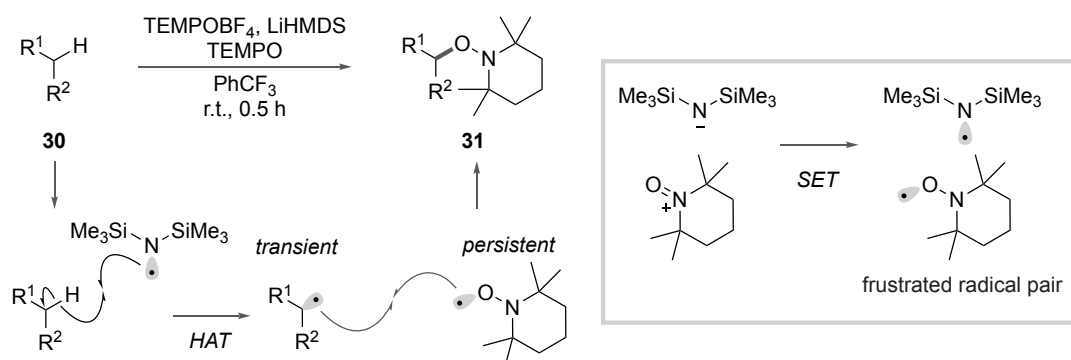
第四節 長寿命なヘテロ原子ラジカルを活用した分子変換反応

長寿命な酸素ラジカルとして、単離可能なほど安定な TEMPO ラジカルがある。この TEMPO ラジカルの安定性を活用した分子変換として、2016 年 Knowles らは、光酸化還元触媒存在下、基質としてアルコキシアミン **28** を使い、ニトロメタン中で可視光照射することで、カルボカチオンが発生することを見出している (**Scheme P10**)。⁴³ 本反応では、まず可視光によって励起された Ir^{III} 錯体がアルコキシアミン **28** を一電子酸化する。ここで、生じたアルコキシアミンラジカルカチオンにおいて、安定な TEMPO ラジカルの生成を駆動力としたメソリティック開裂が進行することで、カルボカチオンが発生する。生じたカルボカチオンと求核剤であるシリルエノールエーテル **27** が反応し、目的のカップリング体 **29** が生成する。一方で、 Ir^{II} 錯体と TEMPO ラジカル間の一電子移動により、基底状態の Ir^{III} 錯体が再生する。本手法では、求核剤として、アリルシランやビニルトリフルオロボレート塩のような炭素求核剤だけでなく、スルホンアミドやアニリン、アルコールといったヘテロ原子求核剤の適用も可能である。



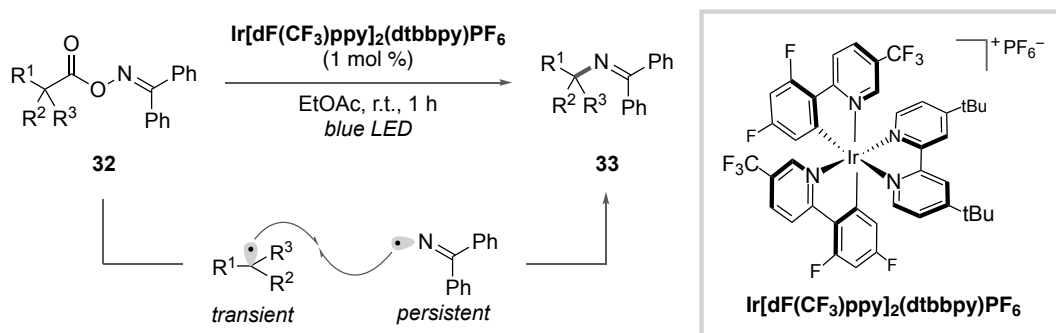
Scheme P10. 光酸化還元触媒によるアルコキシアミンからのカルボカチオン発生法

TEMPO ラジカルを活用した分子変換として、2023 年 Lin らは、frustrated radical pairs (FRPs) による $\text{C}(\text{sp}^3)\text{-H}$ 官能基化反応を報告している (**Scheme P11**)。⁴⁴ 本反応では、まずヘキサメチルジシラジドアニオンと *N*-オキソアンモニウム間の一電子移動により、窒素ラジカルと TEMPO ラジカルの FRPs が生じる。この窒素ラジカルが脂肪族化合物 **30** の $\text{C}(\text{sp}^3)\text{-H}$ 結合の水素を引き抜くことで、アルキルラジカルが発生する。ここで、長寿命な TEMPO ラジカルと短寿命なアルキルラジカルが PRE により選択的にクロスカップリングすることで、 $\text{C}(\text{sp}^3)\text{-H}$ アミノオキシ化体 **31** を与える。



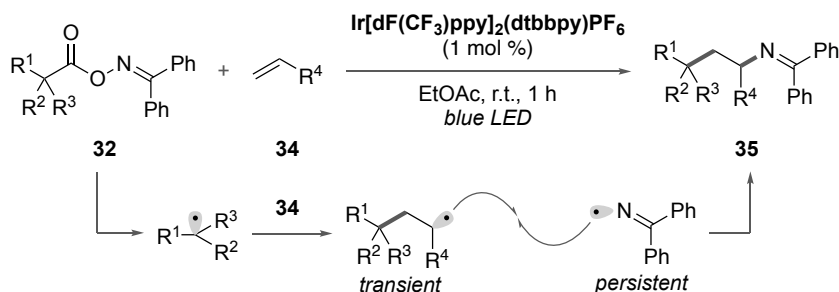
Scheme P11. Frustrated radical pairs を用いた $\text{C}(\text{sp}^3)\text{-H}$ 官能基化反応

長寿命な窒素ラジカルとして、ジフェニルイミニルラジカルがある。2019 年 You と Cho らは、Ir 型光触媒存在下、基質としてオキシムエステル **32** を用い、可視光照射することで、脱炭酸型 $\text{C}(\text{sp}^3)\text{-N}$ カップリング反応が進行することを見出した (**Scheme P12**)。⁴⁵ この反応では、可視光によって励起された Ir 型光触媒からオキシムエステルへのエネルギー移動が起きることで、 N-O 結合がホモリティックに開裂する。その後、脱炭酸を経て生じる短寿命なアルキルラジカルと長寿命なジフェニルイミニルラジカルが PRE により選択的にクロスカップリングすることで、イミン体 **33** が生成する。



Scheme P12. 光触媒による脱炭酸型 C(sp³)–N カップリング反応

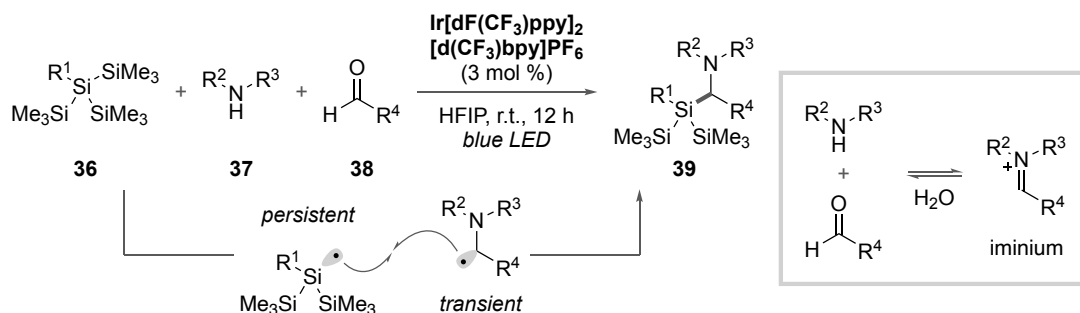
同年 Glorius らは、上記と同様の反応機構を経てオキシムエステルから生じたアルキルラジカルと長寿命なイミニルラジカルを活用することで、アルケン **34** のビシナルカルボイミノ化反応を達成している (**Scheme P13**)。⁴⁶ 本反応では、生じたアルキルラジカルがイミニルラジカルとカップリングするより先にアルケン **34** へ付加する。その後、付加によって生じた炭素ラジカルと長寿命なイミニルラジカルが PRE に基づき選択的にクロスカップリングすることで、ビシナルカルボイミノ化体 **35** を与える。本手法によって合成した三成分カップリング体は、加水分解することで、容易に脂肪族一級アミンや α -アミノ酸へと誘導できる。



Scheme P13. 光触媒によるアルケンのビシナルカルボイミノ化反応

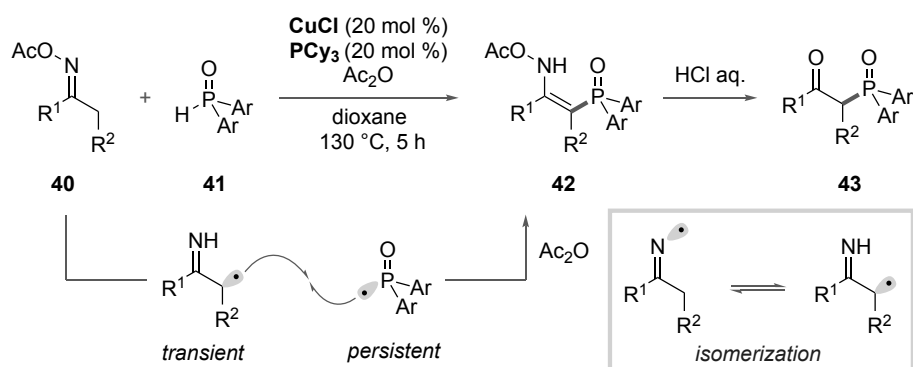
2021 年 Studer らは、有機トリストリメチルシリルシランから生じる長寿命なシリルラジカルを活用することで、 α -アミノシランの合成に成功している (**Scheme P14**)。⁴⁷ 具体的には、Ir 型光酸化還元触媒存在下、基質として有機トリストリメチルシリルシラン **36**、アミン **37**、アルデヒド **38** を用い、HFIP 中で可視光を照射することで、三成分カップリング反応が進行する。本反応では、可視光によって励起された Ir^{III} 錯体が、有機トリストリメチルシリルシラン **36** を一電子酸化することで、長寿命なシリルラジカルが生成する。次に、還元型の Ir^{II} 錯体が、アミン **37** とアルデヒド **38** から形成されたイミニウムを一電子還元することで、 α -アミノアルキルラジカルが生じると共に、基底状態の Ir^{III} 錯体が再生する。最後に、長寿命なシリルラジカルと短寿命な α -アミノ

アルキルラジカルが、PREにより選択的にクロスカップリングすることで、目的の α -アミノシラン **39** が生成する。本反応において、キラルなアミンであるプロリノール誘導体を用いることで、不斉反応も達成している。



Scheme P14. 光酸化還元触媒による三成分カップリングを経た α -アミノシランの合成

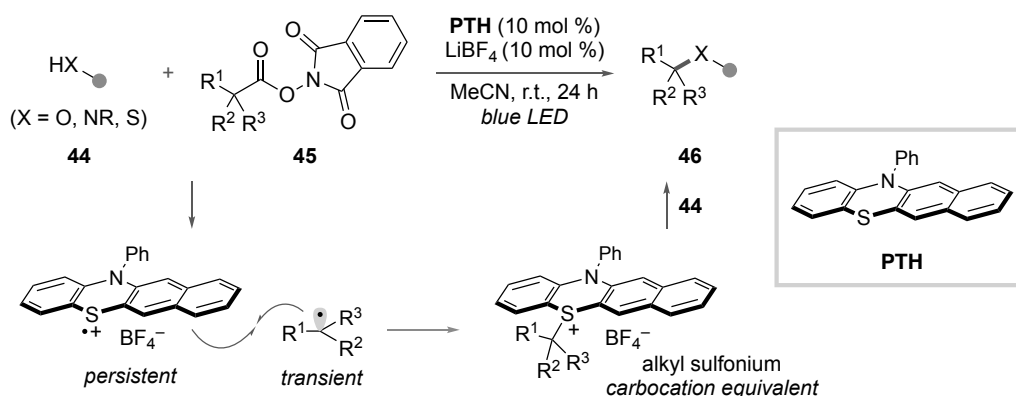
2015 年 Lei らは、長寿命なリンラジカルを活用した銅触媒によるアリールケトン *O*-アセチルオキシムの α 位ホスホリル化反応を報告している (**Scheme P15**)。⁴⁸ 触媒量の塩化銅およびリガンドであるトリシクロヘキシルホスフィン存在下、アリールケトン *O*-アセチルオキシム **40** とジアリールホスフィンオキシド **41** をジオキサン中 130°C で 5 時間反応させることで、C-P 結合形成が進行する。本反応では、銅触媒によりジアリールホスフィンオキシド **41** とアリールケトン *O*-アセチルオキシム **40** が各々電子酸化・還元され、リンラジカルとイミニルラジカルが生成する。最後に、長寿命なリンラジカルとイミニルラジカルの異性化により生じた短寿命な炭素ラジカルが選択的にクロスカップリングすることで、**42** が生成する。生成したカップリング体 **42** を塩酸処理することで、多様な β -ケトホスフィンオキシド **43** を合成している。



Scheme P15. 銅触媒によるアリールケトン *O*-アセチルオキシムの α 位ホスホリル化反応

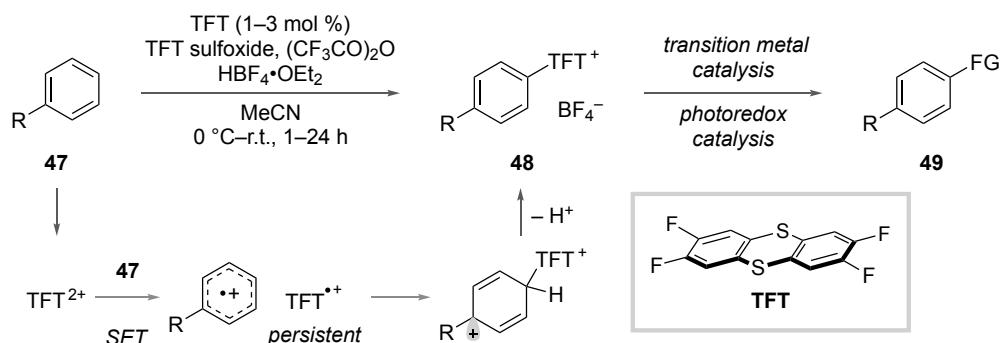
テトラチアフルバレン (TTF) の一電子酸化によって生じるラジカルカチオンは長寿命であることが知られている。⁴⁹ 1993 年 Murphy らは、TTF を触媒として用いることで、

アリールジアゾニウム塩への一電子移動を起点とした $C(sp^3)$ -ヘテロ原子結合形成反応の開発に成功している。⁵⁰ この Murphy らの手法を基に、2020 年大宮らは、可視光と有機光酸化還元触媒であるフェノチアジン (PTH) を用いることで、ヘテロ原子求核剤 **44** と脂肪族カルボン酸誘導体 **45** の脱炭酸型クロスカップリング反応の開発に成功している (Scheme P16)。⁵¹ 本手法では、可視光照射下、PTH から脂肪族カルボン酸誘導体への一電子移動が起こり、脱炭酸を伴って PTH 由来のラジカルカチオンとアルキルラジカルが生成する。ここで長寿命な PTH ラジカルカチオンと短寿命なアルキルラジカルが選択的にクロスカップリングすることで、アルキルスルホニウムを形成する。このアルキルスルホニウムがカルボカチオン等価体として、ヘテロ原子求核剤 **44** と反応することで、アルキル化体 **46** が生成する。



Scheme P16. 有機光酸化還元触媒による $C(sp^3)$ -ヘテロ原子結合形成反応

チアントレンラジカルカチオンは、単離できるほど安定であり、1970 年代から Shine らによってその反応性が研究されている。⁵² この長寿命な硫黄ラジカルカチオンを活用した分子変換として、2019 年 Ritter らは、チアントレン化を経たアレーンの位置選択的な $C(sp^2)$ -H 官能基化反応を報告している (Scheme P17)。⁵³ 具体的には、基質としてアレーン **47** を用い、テトラフルオロチアントレン (TFT) および TFT-S-オキシド存在下、トリフルオロ酢酸無水物とテトラフルオロホウ酸ジエチルエーテル錯体を加えアセトニトリル中で反応させることで、位置選択的な C-H チアントレン化が進行し、対応するチアントレニウム塩 **48** を与える。本反応では、TFT-S-オキシドのトリフルオロアセチル化体から生じた TFT ジカチオンが、アレーンを一電子酸化することで、長寿命な TFT ラジカルカチオンとアレーンラジカルカチオンが発生する。⁵⁴ これら二種のラジカルが再結合し、続く不可逆的な脱プロトン化を経てチアントレニウム塩 **48** が生成する。得られたチアントレニウム塩を種々の遷移金属触媒反応や光酸化還元触媒反応条件に付すことで、多様なアレーンの C-H 官能基化体 **49** を合成している。



Scheme P17. チアントレン化を経たアレーンの位置選択的な C(sp²)-H 官能基化反応

本論文概要

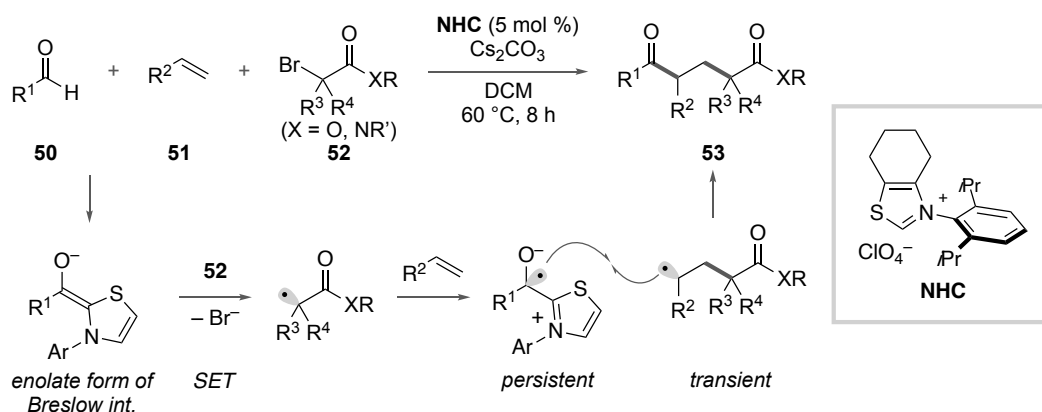
上述のように、PRE のようなラジカルの安定化効果を活用した反応設計により、ラジカルが関与する素過程を制御することで、効率的かつ選択的な結合形成を実現できる。しかし、長寿命なラジカルの多様性は未だに乏しく、構築可能な分子骨格に制限がある。また、依然として、ラジカル反応の制御のために稀少かつ残留に伴う毒性が問題となる遷移金属を用いることが主流である。そのため、持続可能な社会の実現に向けて、遷移金属を用いないラジカルの発生・制御による新たな結合形成反応の開発が重要である。

このような背景を踏まえ、本論文では、ラジカルの安定化効果を活用した有機分子触媒や有機光酸化還元触媒による新規分子変換反応の開発に取り組んだ（第一章から第三章）。また、ラジカルの安定化という観点から、リン中心へのアルキルラジカル付加反応の制御へと応用した（第四章）。これらの反応により、多様なアルキル基が置換した複雑かつ嵩高い分子を合成でき、創薬において重要な Fsp³ の高い新たなケミカルスペースの開拓を達成した。⁵⁵

第一章 *N*-ヘテロ環カルベン触媒によるラジカルリレー反応を用いた

δ-ケトカルボニルの合成

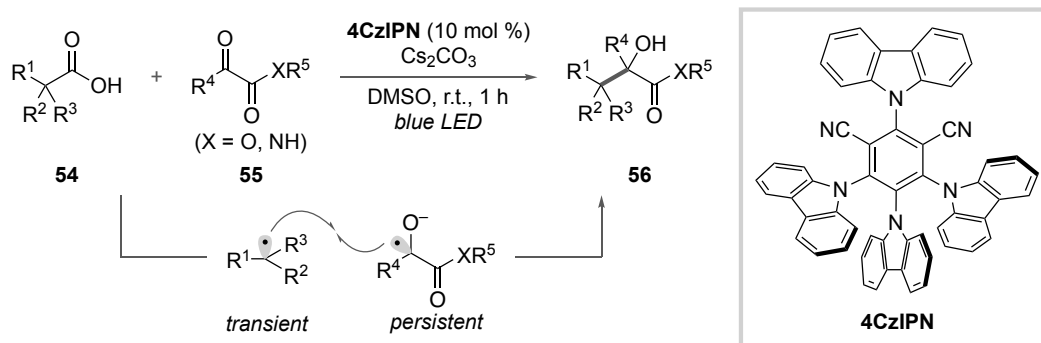
第一章では、*N*-ヘテロ環カルベン（NHC）とアルデヒドから形成するエノラート型 Breslow 中間体由来の長寿命なケチルラジカルを活用することで、アルデヒド **50**、アルケン **51**、α-ブロモカルボニル **52** の三成分カップリングによるδ-ケトカルボニル **53** 合成法を開発した（Scheme P18）。⁵⁶ 本反応は、1) エノラート型 Breslow 中間体からα-ブロモカルボニルへの一電子移動、2) 生じたアルキルラジカルのアルケンへの付加、3) 付加によって生じた炭素ラジカルと Breslow 中間体由来の長寿命なケチルラジカルのラジカル-ラジカルカップリング、というラジカルリレー機構を経て進行していると考えられる。本手法では、アルキル求電子剤として第三級α-ブロモエステルやα-ブロモアミドを適用でき、有機分子触媒のみで第四級炭素を有する複雑なδ-ケトカルボニルを一挙に構築することが可能である。



Scheme P18. NHC 触媒によるラジカルリレー機構を経た
 δ -ケトカルボニルの合成

第二章 有機光酸化還元触媒と脂肪族カルボン酸を用いた α -ケトカルボニルの アルキル化反応

第二章では、量子化学計算を活用することで α -ケトカルボニルの一電子還元によって生じるケチルラジカルが長寿命ラジカルとなり得ることを見出した。そして、PREに基づく有機光酸化還元触媒系を用いることで、脂肪族カルボン酸 **54** と α -ケトカルボニル **55** の脱炭酸型クロスカップリング反応の開発に成功した (**Scheme P19**)。⁵⁷ 本反応では、可視光励起された光酸化還元触媒が脂肪族カルボン酸 **54** と α -ケトカルボニル **55** を各々一電子酸化・還元する。その後、脱炭酸により生じた短寿命なアルキルラジカルと長寿命なケチルラジカルが、PREにより選択的にクロスカップリングすることで進行していると考えられる。本手法では、第一級から第三級脂肪族カルボン酸や α -アミノ酸が許容され、多様な嵩高いアルキル置換基を有する α -ヒドロキシカルボニル **56** の合成が可能である。



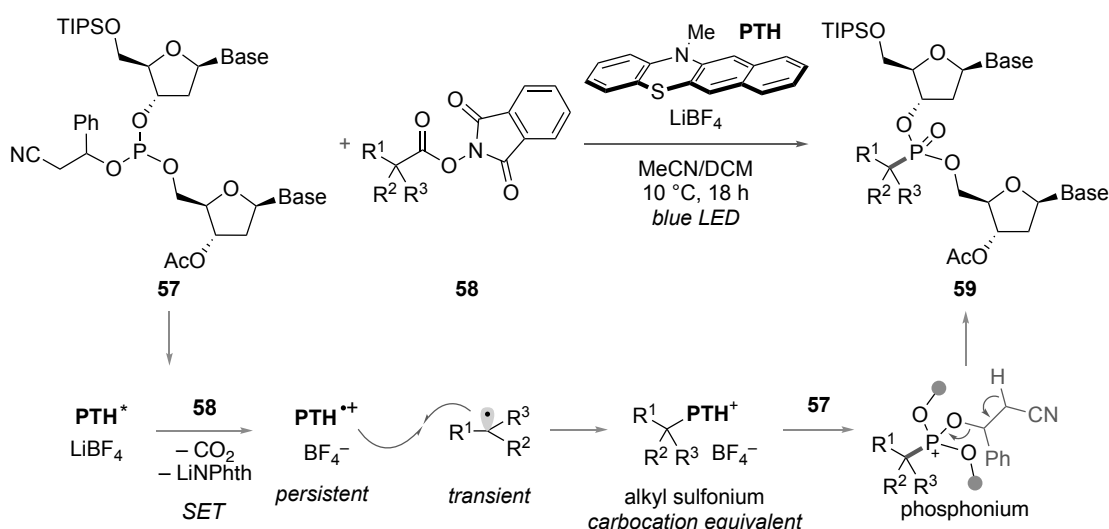
Scheme P19. 有機光酸化還元触媒による α -ケトカルボニル化合物の
脱炭酸型アルキル化反応

第三章 光駆動型ラジカル-極性交差機構を活用した核酸リン原子の

第三級アルキル化反応

第三章では、高い化学的安定性を有する堅牢な電荷中性ホスホジエステル化学修飾核酸の創出を目指し、光駆動型ラジカル-極性交差機構 (RPC: radical-polar crossover) を活用した核酸リン原子の第三級アルキル化反応の開発に取り組んだ。本 RPC 機構では、可視光照射下、酸化還元メディエーターである *N*-メチルベンゾ[*b*]フェノチアジン (PTH) から第三級脂肪族カルボン酸誘導体 **58** への一電子移動が進行し、長寿命な PTH ラジカルカチオンと脱炭酸を経てアルキルラジカルが発生する。これら二種のラジカルが PRE に基づき選択的にクロスカップリングすることで、カルボカチオン等価体であるアルキルスルホニウムを形成する。この穏和な条件下で発生させたカルボカチオン等価体を活用することで、二つのデオキシヌクレオシド構造と脱離基の置換した亜リン酸エステル **57** のリン原子第三級アルキル化反応が進行することを見出した (Scheme P20)。

⁵⁸ 本反応は、1) 光駆動型ラジカル-極性交差機構で形成したカルボカチオン等価体への核酸リン原子の求核攻撃、2) 生成したホスホニウムからのβ-脱離、を経て進行していると考えられる。本手法により、従来法では合成困難な嵩高い第三級アルキルホスホン酸ジエステル **59** を構築できる。

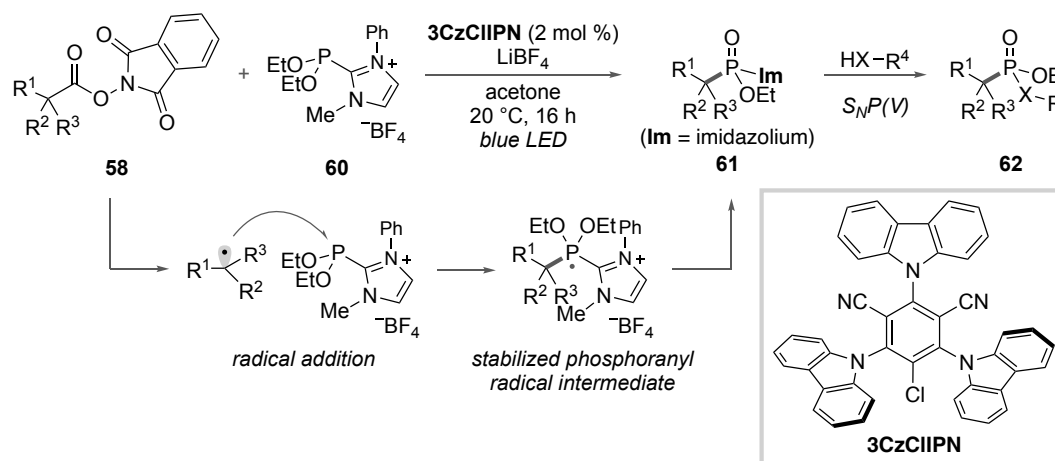


Scheme P20. 光駆動型ラジカル-極性交差機構を活用した
第三級アルキルホスホン酸ジエステルの合成

第四章 イミダゾリウムホスホナイトを用いたアルキルリン(V)化合物の合成

第四章では、二官能性リン(III)試薬であるイミダゾリウムホスホナイトを活用することで、多様な置換様式を有するアルキルリン(V)化合物の合成法の開発に成功した (Scheme P21)。本手法では、1) 有機光酸化還元触媒と脂肪族カルボン酸誘導体 **58** を用いたイミダゾリウムホスホナイト **59** の脱炭酸型アルキル化反応による C(sp³)-P 結合形成、2) リン(V)の求核置換反応 (S_NP(V): nucleophilic substitution at phosphorus(V)) による P-X (X = ヘテロ原子: 酸素、窒素、フッ素) 結合形成、と

いう二段階の過程を経る。本反応において、イミダゾリウム置換基は、ホスホナイト試薬へのアルキルラジカルが付加により生じるホスホラニルラジカル中間体の安定化および $C(sp^3)-P$ 結合形成体 **61** に対する $S_NP(V)$ 反応における良好な脱離基として機能する。本手法により、リン(V)中心に第一級から第三級のアシル基と様々なヘテロ原子置換基を一挙に導入することが可能であり、従来法では達成が困難な非対称アルキルリン(V)化合物 **62** を構築できた。



Scheme P21. イミダゾリウムホスホナイトを用いたアルキルリン(V)化合物の合成

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第一章 *N*-ヘテロ環カルベン触媒によるラジカルリレー反応を用いた δ-ケトカルボニルの合成

第一節 着想背景および作業仮説

δ-ケトエステルは、還元的な環化反応を経てラクトンやラクタムへの容易な変換が可能であり、価値の高い合成中間体である。このようなδ-ケトエステル合成の古典的なアプローチとして、ルイス酸を用いたケテンシリルアセタールのビニルケトンへの共役付加反応がある (**Figure 1-1**)。¹ しかし、エステルのα位に第四級炭素を有するようなδ-ケトエステル合成は、炭素-炭素結合形成段階において立体反発が生じることから困難であった。

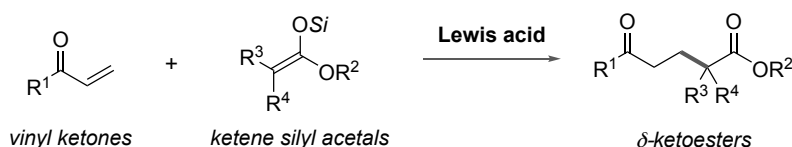


Figure 1-1. δ-ケトエステルの従来の合成法

2018 年 Dai らは、第四級炭素中心を有するδ-ケトエステルの新たな合成法として、銅触媒によるシクロプロパノールの開環を経た第三級α-ブロモエステルとのクロスカップリング反応を報告している (**Figure 1-2**)。² 本手法は、第四級炭素中心を有するδ-ケトエステルの有用な合成法であるが、基質合成の困難さから制限があった。

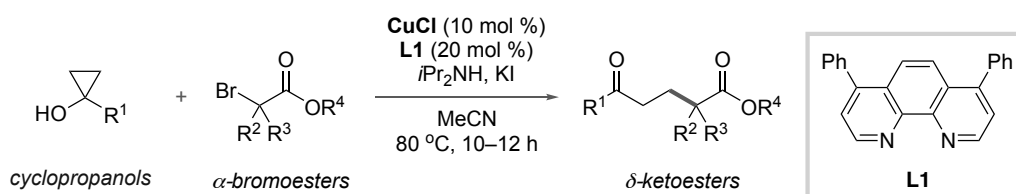


Figure 1-2. 銅触媒によるシクロプロパノールの開環を経た第三級α-ブロモエステルとのクロスカップリング反応

著者の所属研究室では、*N*-ヘテロ環カルベン (NHC) 触媒による芳香族アルデヒドと第三級脂肪族カルボン酸誘導体であるレドックス活性エステルを用いたラジカルリレー機構によるアルケンのビシナルアルキル化を報告している (**Figure 1-3**)。³ 本反応では、まず NHC と芳香族アルデヒドから形成されるエノラート型 Breslow 中間体からレドックス活性エステルへの一電子移動が起きることで、Breslow 中間体由来のケチルラジカルと脱炭酸を経てアルキルラジカルが生成する。発生したアルキルラジカルがスチレンへラジカル付加し、その後、付加によって生じたベンジルラジカルと Breslow

中間体由来の長寿命なケチルラジカルがラジカル-ラジカルカップリングすることで、アルキルアシル化体を与える。本手法は、アルケンへ第三級アルキル基とアシル基を位置選択的に導入することが可能であり、遷移金属を用いずに複雑なケトン体を一挙に構築できる。

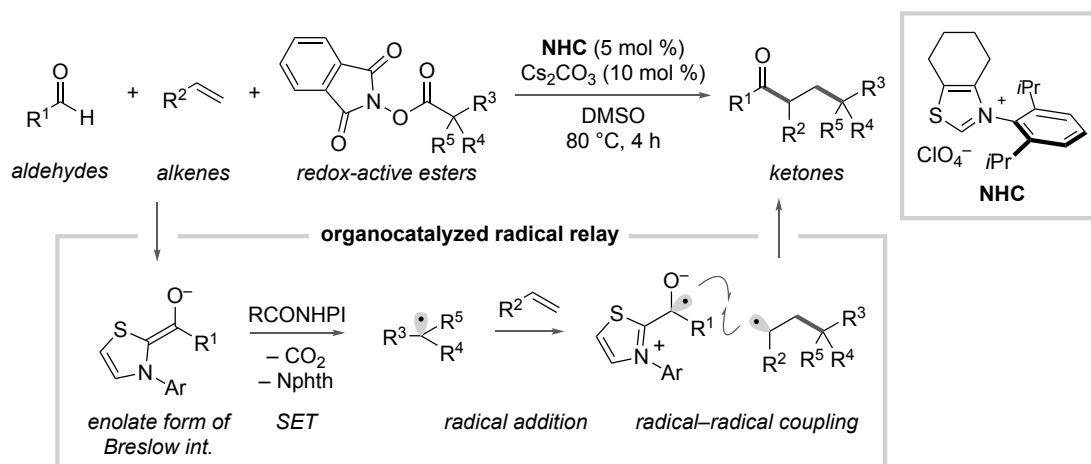


Figure 1-3. NHC 触媒によるラジカルリレー機構を経たアルケンのビシナルアルキルアシル化反応

そこで、本 NHC 触媒反応系において、アルキル求電子剤としてレドックス活性エステルの代わりに α -ブromoエステルを用いることで、嵩高い δ -ケトエステルの効率的な合成法に展開できると考えた (Figure 1-4)。 α -ブromoエステルは、テトラキス(ジメチルアミノ)エチレン ($E^{\circ}_{\text{ox}} = -0.78 \text{ V vs SCE in MeCN}$) によって一電子還元され、対応する炭素ラジカルが生成することが知られている。⁴ そのため、エノラート型 Breslow 中間体 ($E^{\circ}_{\text{ox}} = -1.38 \text{ V vs SCE in MeCN}$)⁵ からの一電子移動が容易に進行し、NHC 触媒によるラジカルリレー機構に適用できると考えられる。

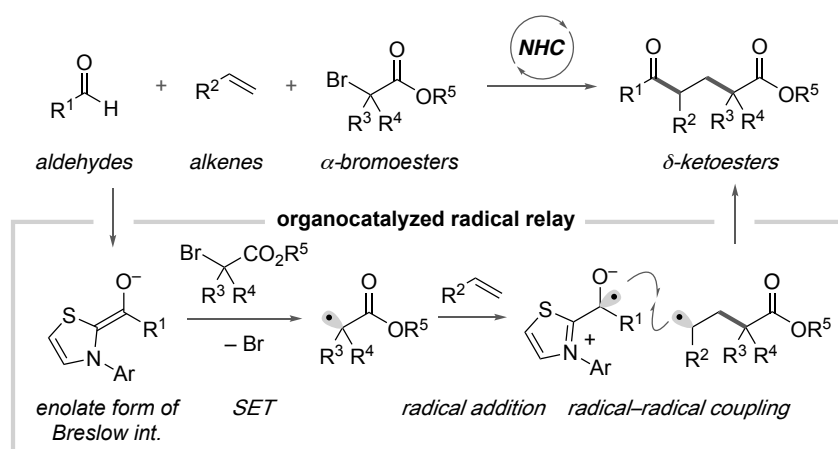
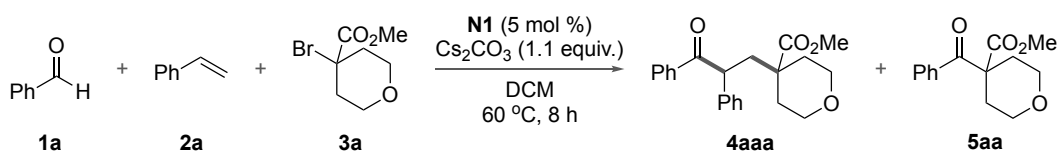


Figure 1-4. NHC 触媒によるラジカルリレー機構を経た δ -ケトエステル合成

第二節 反応条件の最適化および基質適用範囲の検討

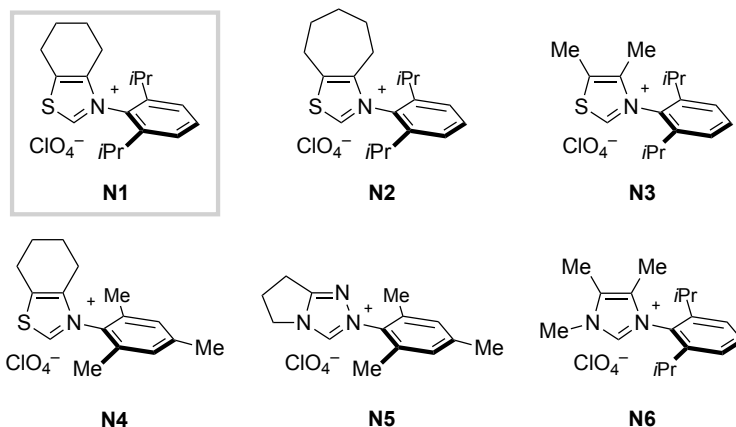
上記の作業仮説に基づき、NHC 触媒によるアルデヒドと α -ブロモエステルを用いたアルケンのビシナルアルキルアシル化反応の検討を行った。前報の反応条件を基に、³ベンズアルデヒド **1a**、スチレン **2a** および α -ブロモエステル **3a** を NHC 前駆体である触媒量のチアゾリウム塩 **N1**⁶ および化学量論量の炭酸セシウムの存在下、ジクロロメタン中 60°Cで反応させたところ、三成分カップリング生成物である δ -ケトエステル **4aaa** を高収率で与えた (Table 1-1, entry 1)。この際、副生成物として **1a** と **3a** の二成分カップリング生成物であるケトン体 **5aa** も少量生成した。副生成物 **5aa** は、 α -ブロモエステル **3a** の一電子還元によって生じたラジカルが求電子的であるため、**2a** へのラジカル付加より Breslow 中間体由来の求核的なケチルラジカルとのラジカル-ラジカルカップリングが速く進行することで、生成したと考えられる。次に、NHC 触媒の検討を行った (entries 2–6)。チアゾリウム環のバックボーンに七員環骨格を持つ **N2** やジメチル骨格を持つ **N3** を用いた場合、**4aaa** の収率はわずかに低下した (entries 2 and 3)。窒素上の置換基を 2,6-ジイソプロピルフェニル基から嵩の小さいメシチル基に変更した **N4** を用いたところ、化学選択性は向上したが、目的物の収率は低下した (entry 4)。トリアゾリウム塩 **N5** やイミダゾリウム塩 **N6** を用いた場合では、反応は全く進行せず目的物 **4aaa** も副生成物 **5aa** も得られなかった。 (entries 5 and 6)。塩基として、炭酸セシウムの代わりに炭酸カリウムやジアザビシクロウンデセン (DBU: 1,8-Diazabicyclo[5.4.0]-7-undecene) を用いたところ、二成分カップリング体 **5aa** を優先的に与えた (entries 7 and 8)。これは、エノラート型 Breslow 中間体のカウンターカチオンが本反応の化学選択性に影響を与えることが示唆された。溶媒として、ジメチルスルホキシドやアセトニトリルのような高極性溶媒を用いた際には、 δ -ケトエステル **4aaa** は低収率に留まった一方で、テトラヒドロフランを用いた場合、中程度の収率で **4aaa** を与えた (entries 9–11)。

Table 1-1. 反応条件の最適化^a



entry	change from standard conditions	yield of 4aaa (%) ^b	yield of 5aa (%) ^b
1	none	74	22
2	N2 instead of N1	60	20
3	N3 instead of N1	64	24
4	N4 instead of N1	45	6
5	N5 instead of N1	0	0

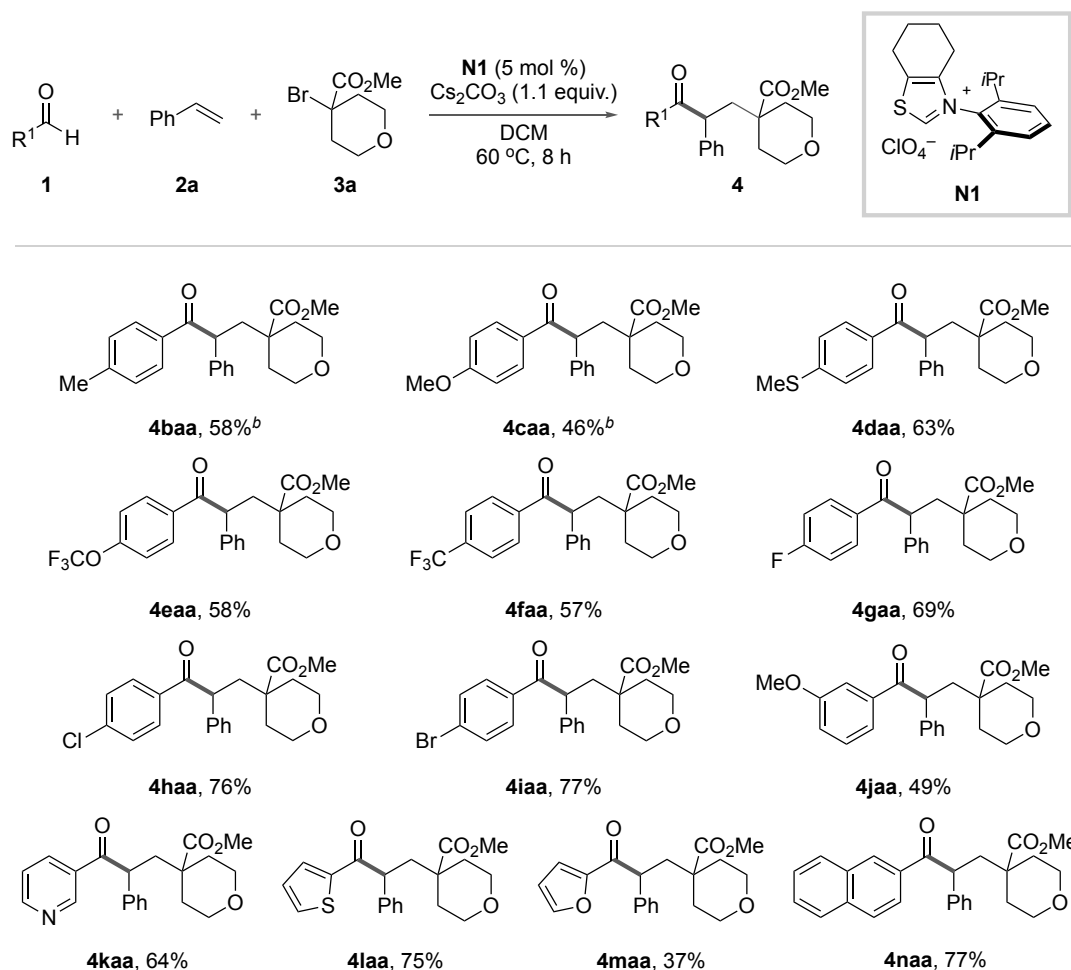
6	N6 instead of N1	1	0
7	K ₂ CO ₃ instead of Cs ₂ CO ₃	26	56
8	DBU instead of Cs ₂ CO ₃	14	67
9	DMSO instead of DCM	31	64
10	MeCN instead of DCM	22	63
11	THF instead of DCM	55	14



^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), **N1** (5 mol %), Cs₂CO₃ (0.22 mmol), DCM (400 μ L), 60 $^{\circ}$ C, 8 h. ^b¹H NMR yield based on **1a**.

得られた最適条件を基に、基質適用範囲の検討を行った。まず、芳香族アルデヒド **1** を検討した (Table 1-2)。パラ位にメチル基、メトキシ基やメチルチオ基のような電子供与性基やトリフルオロメトキシ基やトリフルオロメチル基のような電子求引性基を有する芳香族アルデヒドの適用が可能であり、目的の三成分カップリング体 **4** を良好な収率で与えた (**4baa–4faa**)。遷移金属触媒反応において反応点となり得る C(sp²)–ハロゲン結合を有する基質でも問題なく反応が進行した (**4gaa–4iaa**)。パラ位だけでなく、メタ位に置換基を有する芳香族アルデヒドも許容された (**4jaa**)。他にも、ピリジンやチオフェン、フランといったヘテロ芳香族や π 共役系の広がった 2-ナフトアルデヒドも本反応に適用可能であった (**4kaa–4naa**)。

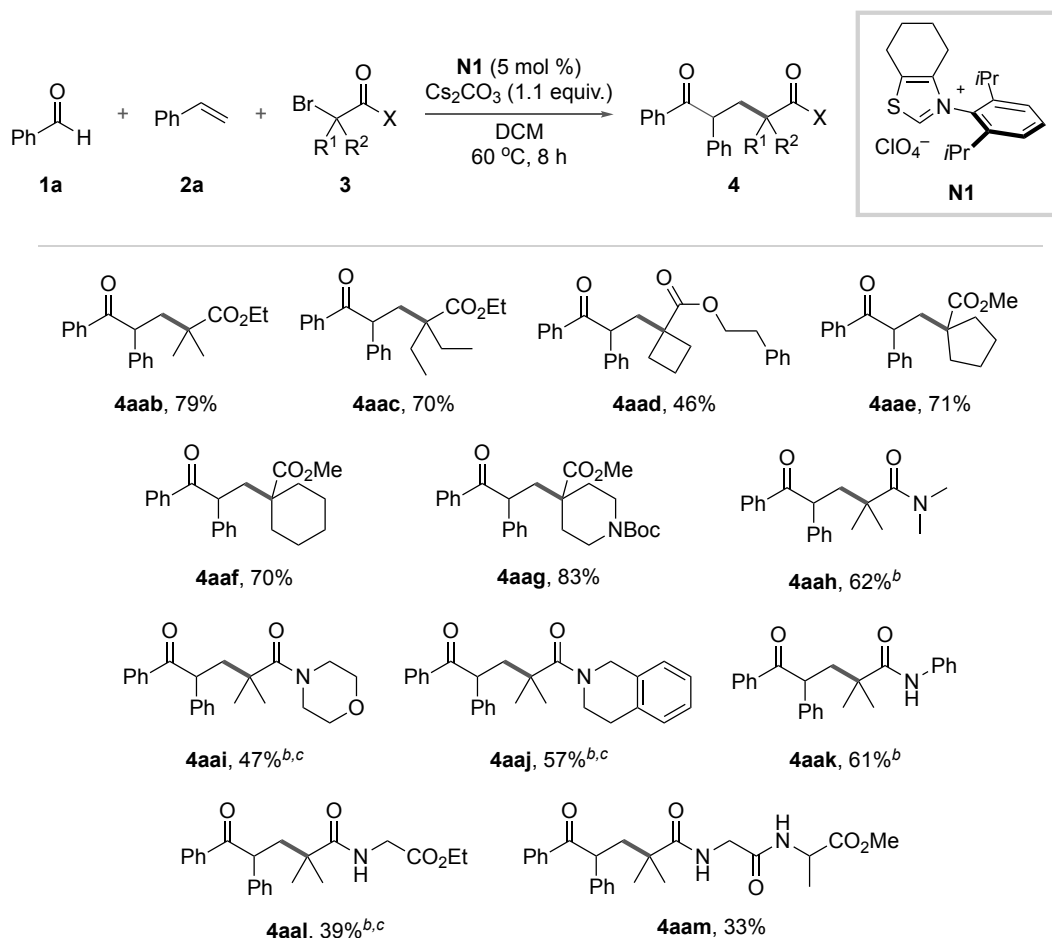
Table 1-2. アルデヒドの検討^a



^aReaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), **N1** (5 mol %), Cs_2CO_3 (0.22 mmol) DCM (400 μL), 60 °C, 8 h. ^b**N1** (10 mol%) was used.

次に、 α -ブロモカルボニル化合物 **3** の検討を行った (Table 1-3)。本反応では、ジメチル基やジエチル基を有する非環状の第四級炭素を含む骨格の導入が可能であり、対応する δ -ケトエステル体を高収率で与えた (**4aab** and **4aac**)。また、エステルの α 位にシクロブチル基やシクロペンチル基やピペラジン環のような様々な環状炭素骨格を有する基質が許容された (**4aad**–**4aag**)。さらに、本反応では α -ブロモアミドも適用でき、 δ -ケトアミドの合成が可能であった。ジメチルアミン、モルホリン、テトラヒドロイソキノリン有する基質の適用が可能であり、対応する δ -ケトアミド体を良好な収率で与えた (**4aah**–**4ajj**)。酸性度の高いプロトンを持つアニリドを用いた場合でも、問題なく反応が進行した (**4aak**)。また、 α -アミノ酸やジペプチド由来の α -ブロモアミドも適用できた (**4aal** and **4aam**)。

Table 1-3. α -ブロモカルボニル化合物の検討^a

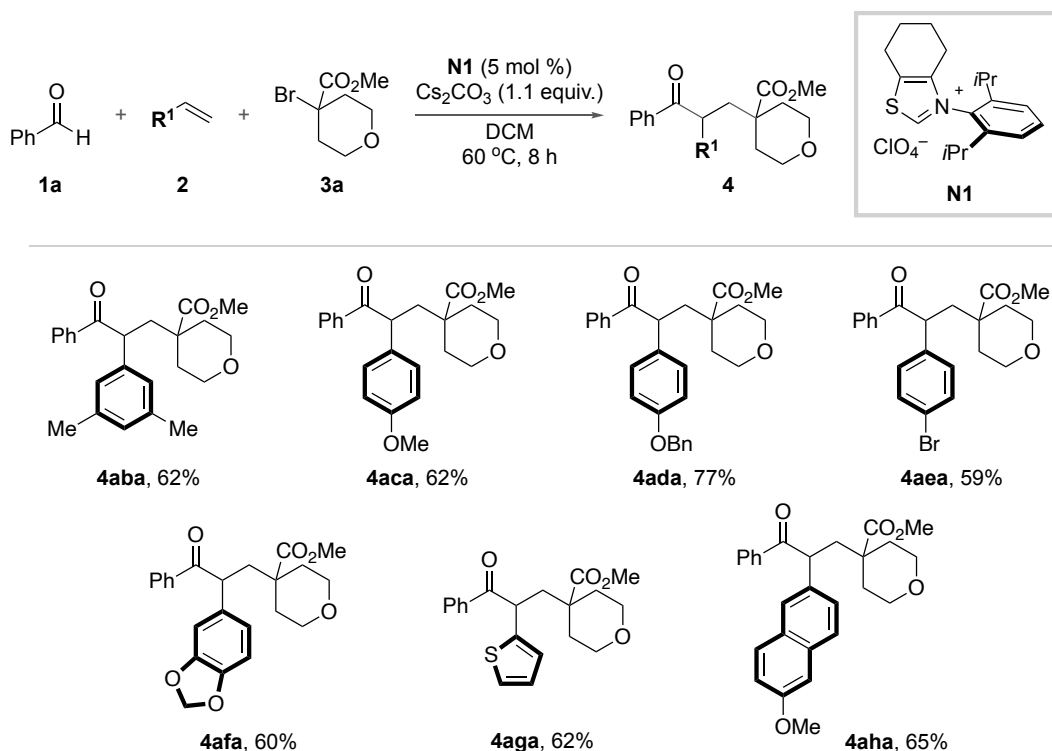


^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3** (0.3 mmol), **N1** (5 mol %), Cs_2CO_3 (0.22 mmol), DCM (400 μL), 60 °C, 8 h. ^b**2a** (0.6 mmol) was used. ^cMeCN (400 μL) was used instead of DCM (400 μL).

続いて、スチレン類を検討した。(Table 1-4)。ベンゼン環上に3,5-ジメチル基や

-メトキシ基、またベンジルオキシ基のような電子供与性基を有するスチレンを用いた場合では、目的の三成分カップリング体を良好な収率で与えた(**4aba–4ada**)。また、*p* 位にブロモ基のようなハロゲンを有する基質でも問題なく反応が進行した(**4aea**)。さらに、1,3-ベンゾジオキサールやチオフエン環のようなヘテロ環やナフタレン環を有するアルケンも適用でき、ケトンの α 位にこれらの置換基を有する δ -ケトエステル体を構築することができた(**4afa–4aha**)。

Table 1-4. アルケンの検討^a



^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3** (0.3 mmol), **N1** (5 mol %), Cs_2CO_3 (0.22 mmol), DCM (400 μL), 60 °C, 8 h.

第三節 推定反応機構

本反応の推定反応機構を以下に示す (Figure 1-5)。本反応の触媒サイクルは、アルデヒド **1** と NHC から形成される Breslow 中間体 **A** の形成によって開始される。その後、炭酸セシウムによる Breslow 中間体 **A** の脱プロトン化により、高い還元力を有するエノラート型 Breslow 中間体 **B** を形成する。このエノラート **B** から α -ブロモカルボニル **3** への一電子移動により、それぞれケチルラジカル **C** とアルキルラジカル **D** が生成する。この発生したアルキルラジカル **D** のスチレン **2** への付加によって、第二級ベンジルラジカル **E** が生じる。⁷ 最後に、長寿命なケチルラジカル **C** と短寿命なベンジルラジカル **E** のラジカル-ラジカルカップリングと続く NHC の脱離により、目的の δ -ケトカルボニル体 **4** が生成し、NHC は次の触媒サイクルへと再生される。

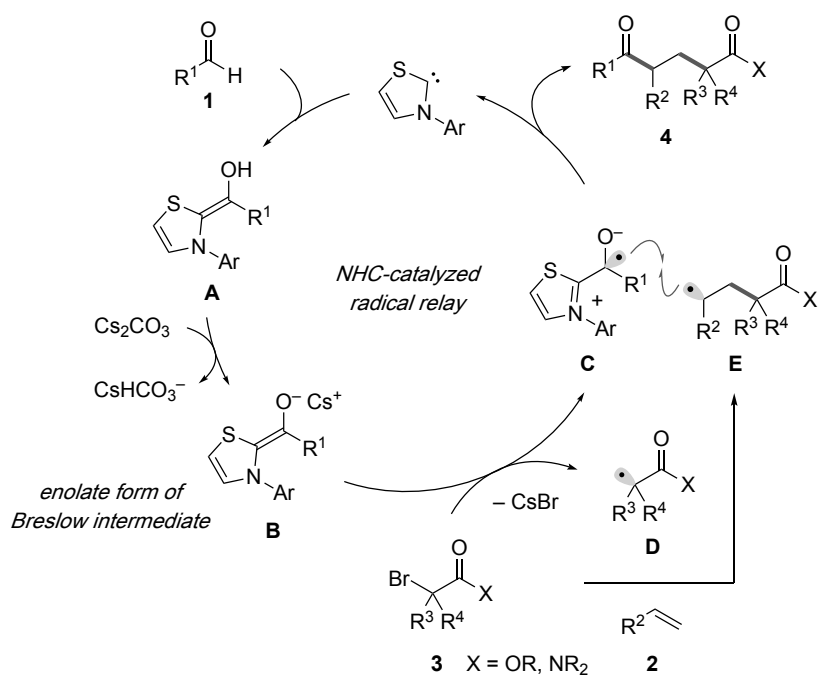


Figure 1-5. 推定反応機構

第四節 結論

NHC 触媒によるアルデヒドと第三級 α -ブロモエステルを用いたアルケンのビシナルアルキルアシル化反応を開発した。本反応は、エノラート型 Breslow 中間体から α -ブロモエステルへの一電子移動を起点としたラジカルリレー機構を経て進行する。本反応では、 α -ブロモエステルだけでなく α -ブロモアミドも適用でき、ペプチド構造を含む多様な δ -ケトアミドの構築を可能とした。本手法により、エステルやアミドの α 位に第四級炭素中心を有する複雑な δ -ケトカルボニル化合物の効率的な合成を達成した。

第一章 参考文献

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第一章 実験項

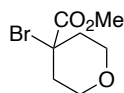
1. Instrumentation and Chemicals

NMR spectra were recorded on a JNM-ECS400, operating at 400 MHz for ^1H NMR and 100.5 MHz for ^{13}C NMR, and JNM-ECA600, operating at 600 MHz for ^1H NMR and 150.9 MHz for ^{13}C NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si and the residual solvent resonances, respectively. Chemical shifts are reported in δ ppm. DART-Mass spectra were measured with JMS-T100TD (JEOL Ltd.). FAB-MS spectra were measured with JMS-700 (JEOL Ltd.). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F₂₅₄. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. IR spectra were measured with a Thermo Scientific iD7 ATR Accessory for the Thermo Scientific Nicolet iS5 FT-IR Spectrometer. Melting points were measured on a Yanaco MP-500D apparatus.

All reactions were carried out under nitrogen or argon atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. K_2CO_3 and DBU were purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Cs_2CO_3 was purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. DCM, DMSO and THF were purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. MeCN was purchased from Kanto Chemical Co., stored under nitrogen, and used as received. Thiazolium salt **N1–N4** were prepared by the reported procedure.¹ Triazolium salt **N5**² and imidazolium salt **N6**³ were prepared by the reported procedure. Aldehydes **1a**, **1c**, **1h** and **1i** were purchased from Nacalai Tesque Inc., **1b**, **1g**, **1j** and **1n** were purchased from FUJIFILM Wako Pure Chemical Co., **1d**, **1e**, **1f**, **1k**, **1l** and **1m** were purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Alkene **2a** was purchased from FUJIFILM Wako Pure Chemical Co., distilled before use. Alkenes **2b–2h** were prepared by Wittig reaction from the corresponding aldehydes. α -Bromoesters **3a**, **3c–3g** were prepared by the reported procedure.⁴ α -Bromoester **3b** was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. α -Bromoamides **3h–3m** were prepared by the reported procedure.^{5–7}

2. Characterization Data for α -Bromoesters and α -Bromoamides

Methyl 4-Bromotetrahydro-2H-pyran-4-carboxylate (**3a**)

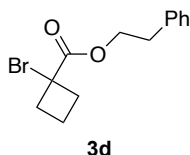


3a

3a was prepared by bromination of the corresponding ester with LDA and CBr_4 (20 mmol scale; 3.11 g, 70% yield). Brown oil. IR (neat) 1060, 1106, 1131, 1164, 1201, 1263, 1437, 1736 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.19–2.28 (m, 4H), 3.71–3.76 (m, 2H), 3.82–3.88 (m, 5H).

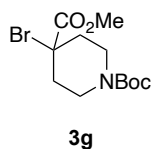
^{13}C NMR (100.5 MHz, CDCl_3) δ 37.2, 53.1, 58.8, 64.5, 170.8. The spectrum data of **3a** was consistent with that of commercially available one.

Phenethyl 1-Bromocyclobutane-1-carboxylate (**3d**)



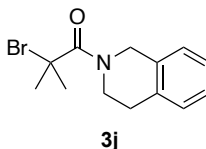
3d was prepared by bromination of the corresponding ester with LDA and CBr_4 (3.7 mmol scale; 380 mg, 36% yield). Pale yellow oil. **IR** (neat) 1075, 1118, 1193, 1247, 1287, 1454, 1730 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ 1.80 (m, 1H), 2.17 (m, 1H), 2.57–2.62 (m, 2H), 2.82–2.86 (m, 2H), 3.00 (t, $J = 7.2$ Hz, 2H), 4.41 (t, $J = 7.2$ Hz, 2H), 7.22–7.25 (m, 3H), 7.30 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (150.9 MHz, CDCl_3) δ 16.7, 34.8, 37.2, 54.1, 66.3, 126.6, 128.5, 128.9, 137.3, 171.4. **HRMS–FAB** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{BrO}_2$, 283.0328; found, 283.0329.

1-(*tert*-Butyl) 4-Methyl 4-bromopiperidine-1,4-dicarboxylate (**3g**)



3g was prepared by bromination of the corresponding ester with LDA and CBr_4 (20 mmol scale; 1.88 g, 56% yield). Brown solid. **M.p.** 63–66 °C. **IR** (neat) 1057, 1121, 1165, 1236, 1366, 1418, 1694, 1738 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ 1.46 (s, 9H), 2.06–2.10 (m, 2H), 2.19–2.22 (m, 2H), 3.36–3.39 (m, 2H), 3.70–3.78 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (150.9 MHz, CDCl_3) δ 28.4, 36.3, 40.6, 53.2, 60.4, 80.0, 154.5, 170.8. **HRMS–FAB** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{21}\text{BrNO}_4$, 322.0648; found, 322.0648.

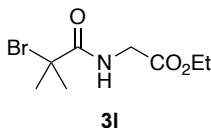
2-Bromo-1-[3,4-dihydroisoquinolin-2(1H)-yl]-2-methylpropan-1-one (**3j**)



3j was prepared by reaction of 2-bromoisobutyryl bromide and amine (6 mmol scale; 1.68 g, 99% yield). White solid. **M.p.** 59–61 °C. **IR** (neat) 1106, 1164, 1248, 1281, 1369, 1425, 1633 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.01 (s, 6H), 2.94–2.96 (m, 2H), 4.01 (brs, 2H), 4.87 (brs, 2H), 7.13–7.21 (m, 4H). ^{13}C NMR (150.9 MHz, CDCl_3) δ 28.7 ($\times 3\text{C}$), 32.6, 57.0, 126.4, 126.4 ($\times 2\text{C}$),

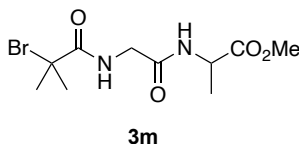
126.7, 128.6, 133.0, 169.4. **HRMS–DART** (m/z): $[M]^+$ calcd for $C_{13}H_{16}BrNO$, 281.0410; found, 281.0401.

Ethyl (2-Bromo-2-methylpropanoyl)glycinate (**3l**)



3l was prepared by reaction of 2-bromoisobutyryl bromide and amine (5 mmol scale; 1.03 g, 82% yield). Brown oil. **IR** (neat) 1019, 1113, 1185, 1373, 1520, 1659, 1740 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 1.30 (t, $J = 7.2$ Hz, 3H), 1.98 (s, 6H), 4.04 (d, $J = 4.8$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 7.21 (brs, 1H). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ 14.1, 32.3, 42.1, 61.6, 61.7, 169.4, 172.2. **HRMS–FAB** (m/z): $[M+H]^+$ calcd for $C_8H_{15}BrNO_3$, 252.0230; found, 252.0254.

Methyl (2-Bromo-2-methylpropanoyl)glycylalaninate (**3m**)



3m was prepared by reaction of 2-bromoisobutyryl bromide and amine (1.5 mmol scale; 427 mg, 92% yield). Pale yellow oil. **IR** (neat) 1114, 1158, 1211, 1371, 1453, 1523, 1651, 1741 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 1.43 (d, $J = 6.8$ Hz, 3H), 1.98 (s, 6H), 3.75 (s, 3H), 4.03–4.04 (m, 2H), 4.59 (m, 1H), 7.01 (brs, 1H), 7.49 (brs, 1H). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ 18.1, 32.1, 43.6, 48.1, 52.5, 60.9, 167.9, 172.5, 173.1. **HRMS–FAB** (m/z): $[M+H]^+$ calcd for $C_{10}H_{18}BrN_2O_4$, 309.0444; found, 309.0451.

3. Procedure for Synthesis of δ -Ketocarboxyls

The reaction in Table 1-1, entry 1 is representative. Thiazolium salt **N1** (4.0 mg, 0.01 mmol) was placed in a schlenk tube containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum, and then the vial was evacuated and filled with nitrogen. Degassed DCM (400 μ L) was added to the vial. Next, benzaldehyde **1a** (20.3 μ L, 0.2 mmol), styrene **2a** (45.9 μ L, 0.4 mmol) and α -bromoester **3a** (66.9 mg, 0.3 mmol) were added. Then, Cs_2CO_3 (71.7 mg, 0.22 mmol) was added. After 8 h stirring at 60 $^{\circ}C$ with oil bath, the reaction mixture was treated with saturated NH_4Cl aqueous solution (400 μ L), then extracted with diethylether (4 times) and dried over sodium sulfate. After filtration, the resulting solution was evaporated under reduced pressure. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (98:2–80:20, hexane/EtOAc) gave **4aaa** (52.2 mg, 0.15

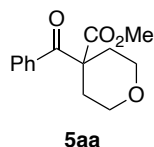
mmol) in 74% yield.

1.0 mmol scale reaction. Thiazolium salt **N1** (20.0 mg, 0.05 mmol) was placed in a schlenk tube containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum, and then the vial was evacuated and filled with nitrogen. Degassed DCM (2.0 mL) was added to the vial. Next, benzaldehyde **1a** (102 μ L, 1.0 mmol), styrene **2a** (229 μ L, 2.0 mmol) and α -bromoester **3b** (220 μ L, 1.5 mmol) were added. Then, Cs₂CO₃ (358 mg, 1.1 mmol) was added. After 8 h stirring at 60 °C with oil bath, the reaction mixture was treated with saturated NH₄Cl aqueous solution (2.0 mL), then extracted with diethylether (4 times) and dried over sodium sulfate. After filtration, the resulting solution was evaporated under reduced pressure. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (Biotage Selekt, 98:2–75:25, hexane/EtOAc) gave **4aab** (204 mg, 0.63 mmol) in 63% yield.

4. Characterization Data for δ -Ketocarboxyls

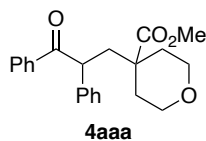
Due to the difficulty of purification, ketone **4aab** was isolated as the corresponding alcohol **4aab'** by treating the crude ketone with NaBH₄ followed by column chromatography.

Methyl 4-Benzoyltetrahydro-2H-pyran-4-carboxylate (**5aa**)



The product **5aa** was purified by flash chromatography on silica gel (98:2–80:20, hexane/EtOAc) (Table 1-1, entry 1; 10.9 mg, 0.044 mmol, 22% isolated yield). Pale yellow oil. **IR** (neat) 1078, 1107, 1137, 1198, 1253, 1447, 1683, 1735 cm⁻¹. **¹H NMR** (600 MHz, CDCl₃) δ 2.24–2.26 (m, 4H), 3.67–3.71 (m, 5H), 3.78–3.81 (m, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.54 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 2H). **¹³C NMR** (150.9 MHz, CDCl₃) δ 31.9, 52.8, 55.4, 64.2, 128.5, 128.7, 132.9, 135.5, 173.5, 196.6. **HRMS–DART** (m/z): [M]⁺ calcd for C₁₄H₁₆O₄, 248.1043; found, 248.1043.

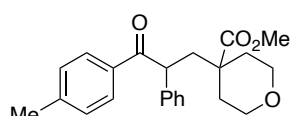
Methyl 4-(3-Oxo-2,3-diphenylpropyl)tetrahydro-2H-pyran-4-carboxylate (**4aaa**)



The product **4aaa** was purified by flash chromatography on silica gel (98:2–80:20, hexane/EtOAc) (Table 1-1, entry 1; 52.2 mg, 0.15 mmol, 74% isolated yield). White solid. **M.p.**

90–92 °C. **IR** (neat) 1107, 1138, 1195, 1298, 1447, 1597, 1682, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.49–1.58 (m, 2H), 1.90 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.06–2.17 (m, 2H), 2.85 (dd, $J = 14.4, 8.8$ Hz, 1H), 3.27–3.43 (m, 2H), 3.51 (s, 3H), 3.78–3.84 (m, 2H), 4.74 (dd, $J = 8.8, 3.6$ Hz, 1H), 7.18 (m, 1H), 7.23–7.29 (m, 4H), 7.38–7.42 (m, 2H), 7.49 (m, 1H), 7.93–7.95 (m, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.3, 34.9, 44.1, 44.8, 48.4, 51.8, 65.3, 65.4, 127.2, 128.2, 128.6, 128.6, 129.0, 133.0, 136.4, 139.6, 175.5, 198.6. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{24}\text{O}_4$, 352.1669; found, 352.1662.

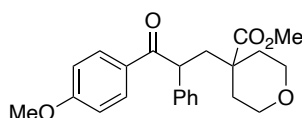
Methyl 4-[3-Oxo-2-phenyl-3-(p-tolyl)propyl]tetrahydro-2H-pyran-4-carboxylate (4baa)



4baa

The product **4baa** was purified by flash chromatography on silica gel (97:3–88:12, hexane/EtOAc) (Table 1-2; 45.4 mg, 0.12 mmol, 62% isolated yield). White solid. **M.p.** 79–81 °C. **IR** (neat) 1107, 1138, 1195, 1297, 1446, 1606, 1678, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.47–1.58 (m, 2H), 1.89 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.05–2.17 (m, 2H), 2.35 (s, 3H), 2.84 (dd, $J = 14.4, 8.4$ Hz, 1H), 3.27–3.42 (m, 2H), 3.51 (s, 3H), 3.78–3.83 (m, 2H), 4.71 (dd, $J = 8.4, 3.6$ Hz, 1H), 7.15–7.20 (m, 3H), 7.22–7.28 (m, 4H), 7.85 (d, $J = 8.0$ Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 21.6, 34.3, 34.9, 44.0, 44.8, 48.2, 51.8, 65.3, 65.4, 127.1, 128.1, 128.8, 129.0, 129.3, 133.8, 139.8, 143.8, 175.5, 198.1. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{26}\text{O}_4$, 366.1826; found, 366.1827.

Methyl 4-[3-(4-Methoxyphenyl)-3-oxo-2-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4caa)

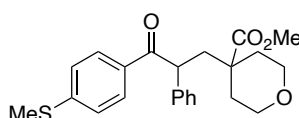


4caa

The product **4caa** was purified by flash chromatography on silica gel (98:2–84:16, hexane/EtOAc) (Table 1-2; 34.4 mg, 0.09 mmol, 45% isolated yield). Colorless oil. **IR** (neat) 1031, 1168, 1245, 1446, 1510, 1600, 1673, 1725 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.47–1.57 (m, 2H), 1.89 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.04–2.16 (m, 2H), 2.84 (dd, $J = 14.4, 8.4$ Hz, 1H), 3.27–3.42 (m, 2H), 3.52 (s, 3H), 3.78–3.82 (m, 5H), 4.68 (dd, $J = 8.4, 3.6$ Hz, 1H), 6.87 (d, $J = 9.2$ Hz, 2H), 7.17 (m, 1H), 7.23–7.28 (m, 4H), 7.94 (d, $J = 9.2$ Hz, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 34.3, 34.9, 44.1, 44.8, 48.0, 51.8, 55.4, 65.3, 65.4, 113.8, 127.0, 128.1, 129.0, 129.3, 130.9,

140.0, 163.4, 175.5, 197.0. **HRMS–DART** (m/z): $[M]^+$ calcd for $C_{23}H_{26}O_5$, 382.1775; found, 382.1778.

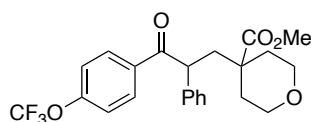
Methyl 4-{3-[4-(Methylthio)phenyl]-3-oxo-2-phenylpropyl}tetrahydro-2H-pyran-4-carboxylate (4daa)



4daa

The product **4daa** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–84:16, DCM/MeOH) (Table 1-2; 50.2 mg, 0.13 mmol, 63% isolated yield). White solid. **M.p.** 86–88 °C. **IR** (neat) 1094, 1139, 1193, 1245, 1445, 1588, 1674, 1724 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 1.47–1.56 (m, 2H), 1.88 (dd, J = 14.4, 3.6 Hz, 1H), 2.04–2.17 (m, 2H), 2.47 (s, 3H), 2.85 (dd, J = 14.4, 8.8 Hz, 1H), 3.28–3.41 (m, 2H), 3.52 (s, 3H), 3.79–3.83 (m, 2H), 4.68 (dd, J = 8.8, 3.6 Hz, 1H), 7.16–7.28 (m, 7H), 7.86 (d, J = 8.8 Hz, 2H). **^{13}C NMR** (150.9 MHz, $CDCl_3$) δ 14.7, 34.3, 34.9, 44.0, 44.8, 48.1, 51.8, 65.3, 65.4, 125.0, 127.2, 128.1, 129.0, 129.1, 132.6, 139.7, 145.9, 175.5, 197.5. **HRMS–DART** (m/z): $[M]^+$ calcd for $C_{23}H_{26}O_4S$, 398.1546; found, 398.1548.

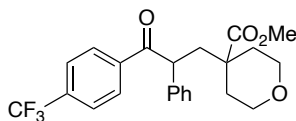
Methyl 4-{3-Oxo-2-phenyl-3-[4-(trifluoromethoxy)phenyl]propyl}tetrahydro-2H-pyran-4-carboxylate (4eaa)



4eaa

The product **4eaa** was purified by flash chromatography on silica gel (98:2–80:20, hexane/EtOAc) (Table 1-2; 50.6 mg, 0.12 mmol, 58% isolated yield). Colorless oil. **IR** (neat) 1107, 1162, 1206, 1251, 1447, 1601, 1685, 1723 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 1.48–1.58 (m, 2H), 1.88 (dd, J = 14.4, 3.2 Hz, 1H), 2.04–2.18 (m, 2H), 2.86 (dd, J = 14.4, 8.4 Hz, 1H), 3.28–3.42 (m, 2H), 3.54 (s, 3H), 3.80–3.84 (m, 2H), 4.68 (dd, J = 8.4, 3.2 Hz, 1H), 7.20–7.30 (m, 7H), 7.98 (d, J = 9.2 Hz, 2H). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ 34.4, 34.8, 44.1, 44.8, 48.5, 51.8, 65.3, 65.4, 120.2 (q, J_{C-F} = 259.3 Hz), 120.3, 127.4, 128.1, 129.2, 130.6, 134.6, 139.2, 152.4, 175.5, 197.0. **HRMS–DART** (m/z): $[M]^+$ calcd for $C_{23}H_{23}F_3O_5$, 436.1492; found, 436.1492.

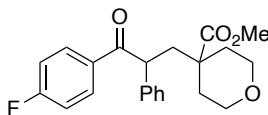
Methyl 4-{3-Oxo-2-phenyl-3-[4-(trifluoromethyl)phenyl]propyl}tetrahydro-2H-pyran-4-carboxylate (4faa)



4faa

The product **4faa** was purified by flash chromatography on silica gel (98:2–84:16, hexane/EtOAc) (Table 1-2; 47.9 mg, 0.11 mmol, 57% isolated yield). White solid. **M.p.** 70–72 °C. **IR** (neat) 1067, 1110, 1130, 1169, 1324, 1447, 1690, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.48–1.58 (m, 2H), 1.88 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.05–2.20 (m, 2H), 2.88 (dd, $J = 14.4, 9.2$ Hz, 1H), 3.27–3.42 (m, 2H), 3.54 (s, 3H), 3.80–3.84 (m, 2H), 4.72 (dd, $J = 9.2, 3.6$ Hz, 1H), 7.18–7.22 (m, 3H), 7.26–7.30 (m, 2H), 7.66 (d, $J = 8.4$ Hz, 2H), 8.02 (d, $J = 8.4$ Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.8, 44.0, 44.7, 48.8, 51.9, 65.3, 65.4, 123.5 (q, $J_{\text{C-F}} = 273.1$ Hz), 125.7 (q, $J_{\text{C-F}} = 3.0$ Hz), 127.5, 128.1, 128.9, 129.3, 134.1 (q, $J_{\text{C-F}} = 33.2$ Hz), 138.8, 139.2, 175.5, 197.6. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{23}\text{F}_3\text{O}_4$, 420.1543; found, 420.1540.

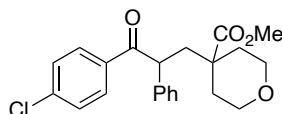
Methyl 4-[3-(4-Fluorophenyl)-3-oxo-2-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4gaa)



4gaa

The product **4gaa** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–84:16, hexane/EtOAc) (Table 1-2; 51.1 mg, 0.14 mmol, 69% isolated yield). White solid. **M.p.** 79–81 °C. **IR** (neat) 1107, 1139, 1156, 1234, 1506, 1597, 1683, 1724 cm^{-1} . **^1H NMR** (600 MHz, CDCl_3) δ 1.49–1.56 (m, 2H), 1.88 (dd, $J = 13.8, 3.6$ Hz, 1H), 2.06 (m, 1H), 2.15 (m, 1H), 2.85 (dd, $J = 13.8, 9.0$ Hz, 1H), 3.30 (m, 1H), 3.39 (m, 1H), 3.53 (s, 3H), 3.79–3.82 (m, 2H), 4.68 (dd, $J = 9.0, 3.6$ Hz, 1H), 7.05–7.08 (m, 2H), 7.18–7.22 (m, 3H), 7.26–7.28 (m, 2H), 7.95–7.98 (m, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.8, 44.1, 44.8, 48.4, 51.8, 65.3, 65.4, 115.7 (d, $J_{\text{C-F}} = 21.1$ Hz), 127.3, 128.1, 129.1, 131.3 (d, $J_{\text{C-F}} = 9.1$ Hz), 132.8 (d, $J_{\text{C-F}} = 3.0$ Hz), 139.4, 165.6 (d, $J_{\text{C-F}} = 253.5$ Hz), 175.5, 197.0. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{23}\text{FO}_4$, 370.1575; found, 370.1577.

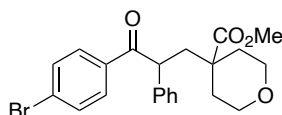
Methyl 4-[3-(4-Chlorophenyl)-3-oxo-2-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4haa)



4haa

The product **4haa** was purified by flash chromatography on silica gel (Biotage Selekt, 96:4–80:20, hexane/EtOAc) (Table 1-2; 58.8 mg, 0.15 mmol, 76% isolated yield). White solid. **M.p.** 110–113 °C. **IR** (neat) 1093, 1201, 1219, 1296, 1445, 1588, 1674, 1709 cm^{-1} . **^1H NMR** (600 MHz, CDCl_3) δ 1.48–1.56 (m, 2H), 1.87 (dd, J = 14.4, 3.6 Hz, 1H), 2.05–2.17 (m, 2H), 2.85 (dd, J = 14.4, 9.0 Hz, 1H), 3.28–3.41 (m, 2H), 3.52 (s, 3H), 3.79–3.83 (m, 2H), 4.67 (dd, J = 9.0, 3.6 Hz, 1H), 7.18–7.21 (m, 3H), 7.26–7.28 (m, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.8, 44.0, 44.8, 48.4, 51.8, 65.3, 65.4, 127.3, 128.1, 128.9, 129.2, 130.0, 134.7, 139.3, 139.4, 175.5, 197.3. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{23}\text{ClO}_4$, 386.1279; found, 386.1275.

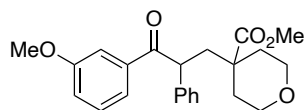
Methyl 4-[3-(4-Bromophenyl)-3-oxo-2-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4iaa)



4iaa

The product **4iaa** was purified by flash chromatography on silica gel (Biotage Selekt, 96:4–79:21, hexane/EtOAc) (Table 1-2; 66.4 mg, 0.15 mmol, 77% isolated yield). White solid. **M.p.** 108–110 °C. **IR** (neat) 1071, 1139, 1196, 1223, 1446, 1584, 1683, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.46–1.57 (m, 2H), 1.87 (dd, J = 14.4, 3.2 Hz, 1H), 2.04–2.18 (m, 2H), 2.85 (dd, J = 14.4, 8.8 Hz, 1H), 3.27–3.42 (m, 2H), 3.52 (s, 3H), 3.78–3.84 (m, 2H), 4.66 (dd, J = 8.8, 3.2 Hz, 1H), 7.17–7.21 (m, 3H), 7.25–7.29 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.8, 44.0, 44.8, 48.4, 51.9, 65.3, 65.4, 127.4, 128.1, 128.2, 129.2, 130.1, 131.9, 135.2, 139.2, 175.5, 197.5. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{23}\text{BrO}_4$, 430.0774; found, 430.0773.

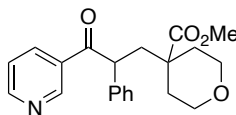
Methyl 4-[3-(3-Methoxyphenyl)-3-oxo-2-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4jaa)



4jaa

The product **4jaa** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–80:20, hexane/EtOAc) (Table 1-2; 37.5 mg, 0.10 mmol, 49% isolated yield). Colorless oil. **IR** (neat) 1138, 1196, 1262, 1430, 1448, 1596, 1683, 1725 cm^{-1} . **^1H NMR** (600 MHz, CDCl_3) δ 1.48–1.56 (m, 2H), 1.91 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.07 (m, 1H), 2.14 (m, 1H), 2.83 (dd, $J = 14.4, 8.4$ Hz, 1H), 3.30 (m, 1H), 3.40 (m, 1H), 3.52 (s, 3H), 3.79–3.83 (m, 5H), 4.71 (dd, $J = 8.4, 3.6$ Hz, 1H), 7.03 (d, $J = 7.2$ Hz, 1H), 7.18 (t, $J = 7.2$ Hz, 1H), 7.23–7.28 (m, 4H), 7.31 (m, 1H), 7.45 (s, 1H), 7.54 (d, $J = 7.2$ Hz, 1H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 34.3, 34.9, 44.1, 44.8, 48.5, 51.8, 55.4, 65.3, 65.4, 113.2, 119.3, 121.2, 127.2, 128.2, 129.1, 129.6, 137.8, 139.6, 159.8, 175.5, 198.4. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{26}\text{O}_5$, 382.1775; found, 382.1778.

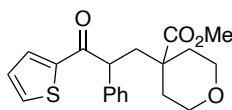
Methyl 4-[3-Oxo-2-phenyl-3-(pyridin-3-yl)propyl]tetrahydro-2H-pyran-4-carboxylate (4kaa)



4kaa

The product **4kaa** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–82:18, DCM/MeOH) (Table 1-2; 45.2 mg, 0.13 mmol, 64% isolated yield). White solid. **M.p.** 102–104 $^{\circ}\text{C}$. **IR** (neat) 1154, 1196, 1255, 1308, 1440, 1583, 1678, 1721 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.48–1.59 (m, 2H), 1.89 (dd, $J = 14.0, 3.6$ Hz, 1H), 2.06–2.19 (m, 2H), 2.86 (dd, $J = 14.0, 8.8$ Hz, 1H), 3.27–3.43 (m, 2H), 3.53 (s, 3H), 3.81–3.84 (m, 2H), 4.69 (dd, $J = 8.8, 3.6$ Hz, 1H), 7.18–7.23 (m, 3H), 7.26–7.30 (m, 2H), 7.35 (dd, $J = 8.0, 4.4$ Hz, 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 8.70 (d, $J = 4.4$ Hz, 1H), 9.15 (s, 1H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.8, 43.8, 44.7, 49.0, 51.9, 65.3, 65.4, 123.6, 127.5, 128.2, 129.3, 131.7, 135.9, 138.6, 150.0, 153.2, 175.4, 197.4. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_4$, 353.1622; found, 353.1625.

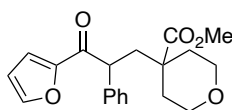
Methyl 4-[3-Oxo-2-phenyl-3-(thiophen-2-yl)propyl]tetrahydro-2H-pyran-4-carboxylate (4laa)



4laa

The product **4laa** was purified by flash chromatography on silica gel (Biotage Selekt, 96:4–86:24, hexane/EtOAc) (Table 1-2; 53.8 mg, 0.15 mmol, 75% isolated yield). White solid. **M.p.** 105–107 °C. **IR** (neat) 1066, 1107, 1138, 1196, 1413, 1446, 1660, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.48–1.57 (m, 2H), 1.93 (dd, J = 14.0, 4.0 Hz, 1H), 2.07–2.15 (m, 2H), 2.79 (dd, J = 14.0, 8.4 Hz, 1H), 3.28–3.43 (m, 2H), 3.52 (s, 3H), 3.79–3.82 (m, 2H), 4.51 (dd, J = 8.4, 4.0 Hz, 1H), 7.07 (dd, J = 4.8, 3.6 Hz, 1H), 7.21 (m, 1H), 7.26–7.29 (m, 4H), 7.58 (dd, J = 4.8, 1.2 Hz, 1H), 7.73 (dd, J = 3.6, 1.2 Hz, 1H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.2, 34.9, 43.8, 44.8, 50.2, 51.8, 65.3, 65.4, 127.3, 128.1, 128.2, 129.0, 132.4, 133.9, 139.6, 143.5, 175.4, 191.4. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}$, 358.1233 ; found, 358.1228.

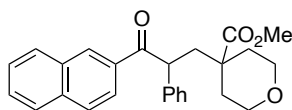
Methyl 4-[3-(Furan-2-yl)-3-oxo-2-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4maa)



4maa

The product **4maa** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–80:20, hexane/EtOAc) (Table 1-2; 25.3 mg, 0.07 mmol, 37% isolated yield). White solid. **M.p.** 86–88 °C. **IR** (neat) 1107, 1139, 1155, 1196, 1465, 1566, 1673, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.48–1.56 (m, 2H), 1.94 (dd, J = 14.4, 4.0 Hz, 1H), 2.06–2.14 (m, 2H), 2.76 (dd, J = 14.4, 8.4 Hz, 1H), 3.28–3.43 (m, 2H), 3.51 (s, 3H), 3.78–3.83 (m, 2H), 4.52 (dd, J = 8.4, 4.0 Hz, 1H), 6.48 (dd, J = 3.6, 1.6 Hz, 1H), 7.18 (d, J = 3.6 Hz, 1H), 7.20 (m, 1H), 7.25–7.30 (m, 4H), 7.55 (d, J = 1.6 Hz, 1H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.2, 34.8, 43.0, 44.7, 48.7, 51.7, 65.3, 65.3, 112.4, 117.9, 127.3, 128.3, 128.8, 139.1, 146.5, 152.1, 175.4, 187.6. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_5$, 342.1462; found, 342.1469.

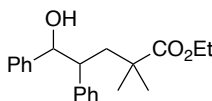
Methyl 4-[3-(Naphthalen-2-yl)-3-oxo-2-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4naa)



4naa

The product **4naa** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–80:20, hexane/EtOAc) (Table 1-2; 62.0 mg, 0.15 mmol, 77% isolated yield). White solid. **M.p.** 85–88 °C. **IR** (neat) 1107, 1124, 1138, 1194, 1446, 1677, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.51–1.62 (m, 2H), 1.95 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.10–2.22 (m, 2H), 2.92 (dd, $J = 14.4, 8.8$ Hz, 1H), 3.29–3.43 (m, 2H), 3.52 (s, 3H), 3.79–3.85 (m, 2H), 4.90 (dd, $J = 8.8, 3.6$ Hz, 1H), 7.17 (m, 1H), 7.24–7.32 (m, 4H), 7.50–7.59 (m, 2H), 7.81–7.84 (m, 2H), 7.93 (d, $J = 7.8$ Hz, 1H), 8.00 (d, $J = 7.8$ Hz, 1H), 8.47 (s, 1H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.9, 44.1, 44.8, 48.5, 51.8, 65.3, 65.4, 124.4, 126.7, 127.2, 127.7, 128.2, 128.46, 128.49, 129.1, 129.7, 130.3, 132.4, 133.7, 135.5, 139.7, 175.5, 198.5. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{26}\text{H}_{26}\text{O}_4$, 402.1826; found, 402.1830.

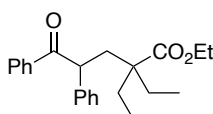
Ethyl 5-Hydroxy-2,2-dimethyl-4,5-diphenylpentanoate (4aab')



4aab'

The product **4aab'** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–75:25, hexane/EtOAc) (Table 1-3; 51.6 mg, 0.16 mmol, 79% isolated yield in 2 steps, dr >99:1). Colorless oil. **IR** (neat) 1029, 1136, 1191, 1387, 1453, 1475, 1723 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 0.94–1.03 (m, 9H), 1.69 (m, 1H), 1.92 (s, 1H), 2.09 (m, 1H), 2.95 (m, 1H), 3.49 (m, 1H), 3.65 (m, 1H), 4.64 (d, $J = 8.4$ Hz, 1H), 7.20–7.34 (m, 10H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 13.8, 24.8, 26.7, 41.4, 42.1, 50.8, 60.1, 78.8, 127.0, 127.1, 127.8, 128.2, 128.3, 129.4, 140.7, 142.2, 177.3. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{O}_3$, 326.1876; found, 326.1875.

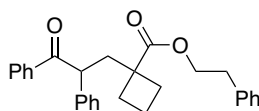
Ethyl 2,2-Diethyl-5-oxo-4,5-diphenylpentanoate (4aac)



4aac

The product **4aac** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–89:11, hexane/EtOAc) (Table 1-3; 49.3 mg, 0.14 mmol, 70% isolated yield). Colorless oil. **IR** (neat) 1030, 1128, 1191, 1235, 1448, 1597, 1683, 1721 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 0.72–0.78 (m, 6H), 1.12 (t, $J = 7.2$ Hz, 3H), 1.48–1.72 (m, 4H), 1.97 (dd, $J = 14.4, 4.0$ Hz, 1H), 2.78 (dd, $J = 14.4, 7.6$ Hz, 1H), 3.83 (m, 1H), 3.96 (m, 1H), 4.66 (dd, $J = 14.4, 7.6$ Hz, 1H), 7.17 (m, 1H), 7.23–7.30 (m, 4H), 7.39 (t, $J = 7.2$ Hz, 2H), 7.48 (t, $J = 7.2$ Hz, 1H), 7.95 (d, $J = 7.2$ Hz, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 8.0, 8.1, 14.1, 25.5, 26.8, 38.7, 49.1, 49.3, 60.1, 126.9, 128.3, 128.5, 128.6, 128.8, 132.8, 136.7, 140.1, 176.5, 199.1. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{O}_3$, 352.2033; found, 352.2032.

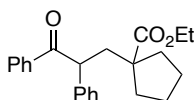
Phenethyl 1-(3-Oxo-2,3-diphenylpropyl)cyclobutane-1-carboxylate (**4aad**)



4aad

The product **4aad** was purified by flash chromatography on silica gel (100:0–90:10, hexane/EtOAc) (Table 1-3; 38.0 mg, 0.09 mmol, 46% isolated yield). Colorless oil. **IR** (neat) 1029, 1104, 1173, 1319, 1447, 1597, 1680, 1719 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.69–1.86 (m, 3H), 1.93 (m, 1H), 2.16 (m, 1H), 2.29–2.41 (m, 2H), 2.77–2.83 (m, 3H), 3.96 (m, 1H), 4.14 (m, 1H), 4.54 (t, $J = 6.4$ Hz, 1H), 7.14–7.28 (m, 10H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.46 (t, $J = 7.2$ Hz, 1H), 7.90 (d, $J = 7.2$ Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 15.7, 30.4, 31.0, 34.9, 41.4, 47.3, 50.3, 64.8, 126.5, 127.1, 128.37, 128.44 ($\times 2\text{C}$), 128.7, 128.8, 128.8, 132.8, 136.4, 137.8, 139.2, 176.7, 199.1. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{28}\text{H}_{28}\text{O}_3$, 412.2033; found, 412.2035.

Ethyl 1-(3-Oxo-2,3-diphenylpropyl)cyclopentane-1-carboxylate (**4aae**)

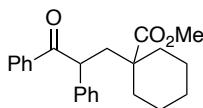


4aae

The product **4aae** was purified by flash chromatography on silica gel (99:1–95:5, hexane/EtOAc) (Table 1-3; 49.8 mg, 0.14 mmol, 71% isolated yield). Colorless oil. **IR** (neat) 1030, 1121, 1185, 1366, 1448, 1597, 1683, 1720 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.11 (t, $J = 7.2$ Hz, 3H), 1.40–1.48 (m, 2H), 1.51–1.63 (m, 4H), 2.04 (m, 1H), 2.14–2.20 (m, 2H), 2.77 (dd, $J = 14.0, 7.2$ Hz, 1H), 3.80 (m, 1H), 3.95 (m, 1H), 4.67 (dd, $J = 7.2, 4.8$ Hz, 1H), 7.16 (m, 1H), 7.23–7.29 (m, 4H), 7.38 (t, $J = 7.2$ Hz, 2H), 7.47 (t, $J = 7.2$ Hz, 1H), 7.94 (d, $J = 7.2$ Hz, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 14.0, 24.3, 24.4, 35.6, 37.0, 42.3, 50.9, 54.1, 60.4, 127.0, 128.4,

128.5, 128.6, 128.8, 132.8, 136.6, 139.8, 177.2, 199.4. **HRMS–DART** (m/z): $[M]^+$ calcd for $C_{23}H_{26}O_3$, 350.1876; found, 350.1874.

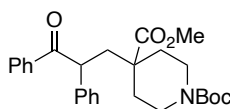
Methyl 1-(3-Oxo-2,3-diphenylpropyl)cyclohexane-1-carboxylate (4aaf)



4aaf

The product **4aaf** was purified by flash chromatography on silica gel (99:1–96:4, hexane/EtOAc) (Table 1-3; 49.1 mg, 0.14 mmol, 70% isolated yield). White solid. **M.p.** 69–71 °C. **IR** (neat) 1132, 1199, 1216, 1447, 1597, 1681, 1721 cm^{-1} . **1H NMR** (600 MHz, $CDCl_3$) δ 1.15–1.25 (m, 4H), 1.31 (m, 1H), 1.55–1.58 (m, 3H), 1.86 (dd, J = 14.4, 3.6 Hz, 1H), 2.07 (m, 1H), 2.19 (m, 1H), 2.81 (dd, J = 14.4, 8.4 Hz, 1H), 3.47 (s, 3H), 4.75 (dd, J = 8.4, 3.6 Hz, 1H), 7.16 (m, 1H), 7.23–7.26 (m, 4H), 7.39 (t, J = 7.8 Hz, 2H), 7.48 (t, J = 7.8 Hz, 1H), 7.95 (d, J = 7.8 Hz, 2H). **^{13}C NMR** (150.9 MHz, $CDCl_3$) δ 23.2, 23.4, 25.7, 34.3, 35.0, 44.2, 46.9, 48.6, 51.4, 127.0, 128.2, 128.5, 128.7, 128.9, 132.8, 136.6, 140.1, 176.5, 199.0. **HRMS–DART** (m/z): $[M]^+$ calcd for $C_{23}H_{26}O_3$, 350.1876; found, 350.1873.

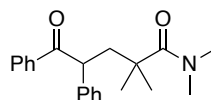
1-(*tert*-Butyl) 4-Methyl 4-(3-oxo-2,3-diphenylpropyl)piperidine-1,4-dicarboxylate (4aag)



4aag

The product **4aag** was purified by flash chromatography on silica gel (98:2–80:20, hexane/EtOAc) (Table 1-3; 54.2 mg, 0.12 mmol, 60% isolated yield). White solid. **M.p.** 135–137 °C. **IR** (neat) 1031, 1107, 1138, 1195, 1447, 1597, 1682, 1724 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 1.34–1.40 (m, 2H), 1.43 (s, 9H), 1.88 (m, 1H), 2.07–2.19 (m, 2H), 2.72 (m, 1H), 2.80–2.86 (m, 2H), 3.51 (s, 3H), 3.88 (brs, 2H), 4.73 (m, 1H), 7.18 (m, 1H), 7.22–7.28 (m, 4H), 7.40 (t, J = 7.6 Hz, 2H), 7.49 (t, J = 7.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 2H). **^{13}C NMR** (150.9 MHz, $CDCl_3$) δ 28.4, 33.5, 34.0, 40.8, 41.7, 43.7, 45.6, 48.6, 51.8, 79.5, 127.2, 128.1, 128.6, 128.6, 129.1, 133.0, 136.4, 139.6, 154.7, 175.3, 198.5. **HRMS–DART** (m/z): $[M]^+$ calcd for $C_{27}H_{33}NO_5$, 451.2353; found, 451.2355.

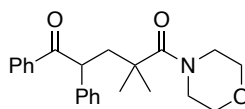
N,N,2,2-Tetramethyl-5-oxo-4,5-diphenylpentanamide (4aah)



4aah

The product **4aah** was purified by flash chromatography on silica gel (96:4–80:20, hexane/EtOAc) (Table 1-3; 33.0 mg, 0.10 mmol, 51% isolated yield). White solid. **M.p.** 82–84 °C. **IR** (neat) 1108, 1214, 1365, 1392, 1447, 1491, 1618, 1678 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.30 (d, J = 5.6 Hz, 6H), 2.03 (dd, J = 14.0, 4.0 Hz, 1H), 2.79 (s, 6H), 2.88 (dd, J = 14.0, 6.8 Hz, 1H), 4.74 (dd, J = 6.8, 4.0 Hz, 1H), 7.16 (m, 1H), 7.23–7.30 (m, 4H), 7.36–7.40 (m, 2H), 7.47 (m, 1H), 7.93–7.95 (m, 2H). **¹³C NMR** (150.9 MHz, CDCl₃) δ 27.3, 27.3, 38.1 ($\times$ 2C), 42.5, 43.8, 49.7, 126.9, 128.2, 128.5, 128.7, 128.8, 132.9, 136.6, 140.2, 175.6, 199.6. **HRMS–DART** (m/z): [M]⁺ calcd for C₂₁H₂₅NO₂, 323.1880; found, 323.1896.

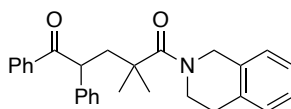
2,2-Dimethyl-1-morpholino-4,5-diphenylpentane-1,5-dione (4aai)



4aai

The product **4aai** was purified by flash chromatography on silica gel (Biotage Selekt, 95:5–80:20, hexane/EtOAc) (Table 1-3; 30.0 mg, 0.08 mmol, 41% isolated yield). Colorless oil. **IR** (neat) 1035, 1116, 1202, 1267, 1415, 1447, 1625, 1680 cm⁻¹. **¹H NMR** (600 MHz, CDCl₃) δ 1.29 (d, J = 4.2 Hz, 6H), 1.99 (dd, J = 14.4, 3.6 Hz, 1H), 2.90 (dd, J = 14.4, 7.2 Hz, 1H), 3.40–3.52 (m, 6H), 3.57–3.60 (m, 2H), 4.73 (dd, J = 7.2, 3.6 Hz, 1H), 7.17 (m, 1H), 7.25–7.29 (m, 4H), 7.39 (t, J = 7.2 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.95 (d, J = 7.2 Hz, 2H). **¹³C NMR** (150.9 MHz, CDCl₃) δ 27.1, 27.4, 42.7, 43.8, 45.6, 49.7, 66.6, 127.1, 128.2, 128.6, 128.7, 129.0, 133.0, 136.4, 140.2, 174.9, 199.6. **HRMS–DART** (m/z): [M]⁺ calcd for C₂₃H₂₇NO₃, 365.1985; found, 365.1981.

1-[3,4-Dihydroisoquinolin-2(1H)-yl]-2,2-dimethyl-4,5-diphenylpentane-1,5-dione (4aaj)

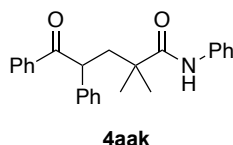


4aaj

The product **4aaj** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–77:23, hexane/EtOAc) (Table 1-3; 46.9 mg, 0.11 mmol, 57% isolated yield). Colorless oil. **IR** (neat) 1109, 1158, 1243, 1366, 1418, 1447, 1622, 1680 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.32

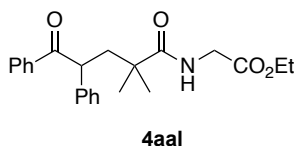
(d, $J = 2.8$ Hz, 6H), 2.08 (dd, $J = 14.8, 4.0$ Hz, 1H), 2.73–2.83 (m, 2H), 2.94 (dd, $J = 14.8, 6.8$ Hz, 1H), 3.58 (m, 1H), 3.69 (m, 1H), 4.47–4.58 (m, 2H), 4.75 (dd, $J = 6.8, 4.0$ Hz, 1H), 7.06–7.26 (m, 9H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.46 (t, $J = 7.2$ Hz, 1H), 7.92 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (150.9 MHz, CDCl_3) δ 27.2, 27.4, 28.8, 42.9, 43.4, 44.1, 49.8, 126.2, 126.4, 126.5 ($\times 2\text{C}$), 127.0, 128.2, 128.5 ($\times 2\text{C}$), 128.7, 128.9, 132.9, 133.5, 136.5, 140.2, 175.0, 199.7. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{28}\text{H}_{29}\text{NO}_2$, 411.2193; found, 411.2190.

2,2-Dimethyl-5-oxo-N,4,5-triphenylpentanamide (4aak)



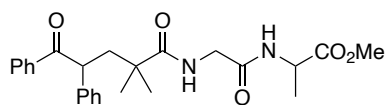
The product **4aak** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–80:20, hexane/EtOAc) (Table 1-3; 45.3 mg, 0.12 mmol, 61% isolated yield). White solid. **M.p.** 124–126 °C. **IR** (neat) 1133, 1240, 1313, 1438, 1500, 1524, 1597, 1679 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.27 (s, 6H), 2.04 (dd, $J = 14.4, 3.6$ Hz, 1H), 2.92 (dd, $J = 14.4, 8.4$ Hz, 1H), 4.81 (dd, $J = 8.4, 3.6$ Hz, 1H), 7.08–7.17 (m, 2H), 7.22–7.37 (m, 9H), 7.43–7.48 (m, 3H), 7.91–7.94 (m, 2H). ^{13}C NMR (150.9 MHz, CDCl_3) δ 25.8, 26.6, 43.3, 44.6, 50.0, 120.1, 124.3, 127.0, 128.1, 128.5, 128.7, 128.9, 129.0, 132.9, 136.5, 137.7, 140.2, 175.1, 199.5. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_2$, 371.1880; found, 371.1877.

Ethyl (2,2-Dimethyl-5-oxo-4,5-diphenylpentanoyl)glycinate (4aal)



The product **4aal** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–85:15, DCM/MeOH) (Table 1-3; 29.8 mg, 0.08 mmol, 39% isolated yield). Colorless oil. **IR** (neat) 1027, 1197, 1374, 1448, 1523, 1648, 1681, 1746 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.17 (s, 6H), 1.30 (t, $J = 7.2$, 3H), 2.01 (dd, $J = 14.4, 4.0$ Hz, 1H), 2.78 (dd, $J = 14.4, 8.0$ Hz, 1H), 3.91 (d, $J = 5.6$ Hz, 2H), 4.23 (q, $J = 7.2$ Hz, 2H), 4.85 (dd, $J = 8.0, 4.0$ Hz, 1H), 6.11 (brs, 1H), 7.15 (m, 1H), 7.22–7.26 (m, 2H), 7.30–7.32 (m, 2H), 7.38 (t, $J = 7.2$ Hz, 2H), 7.47 (t, $J = 7.2$ Hz, 1H), 8.00 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ 14.1, 25.3, 26.7, 41.5, 42.3, 44.4, 49.7, 61.5, 126.9, 128.3, 128.5, 128.8, 128.9, 132.8, 136.6, 140.2, 170.1, 177.2, 199.6. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4$, 381.1935; found, 381.1934.

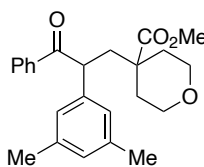
Methyl (2,2-Dimethyl-5-oxo-4,5-diphenylpentanoyl)glycylalaninate (**4aam**)



4aam

The product **4aam** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–88:12, DCM/MeOH) (Table 1-3; 28.9 mg, 0.07 mmol, 33% isolated yield, dr 1:1). Colorless oil. **IR** (neat) 1161, 1213, 1478, 1526, 1643, 1680, 1743 cm^{-1} . **^1H NMR** (600 MHz, CDCl_3) δ 1.20 (s, 6H), 1.43 (t, $J = 7.2$ Hz, 3H), 1.98 (m, 1H), 2.78 (m, 1H), 3.71–3.91 (m, 5H), 4.56 (m, 1H), 4.81 (m, 1H), 6.39 (brs, 1H), 6.79 (d, $J = 7.2$ Hz, $0.50 \times 1\text{H}$), 6.87 (d, $J = 7.2$ Hz, $0.50 \times 1\text{H}$), 7.15 (m, 1H), 7.23–7.29 (m, 4H), 7.38 (t, $J = 7.2$ Hz, 2H), 7.47 (t, $J = 7.2$ Hz, 1H), 7.96–7.98 (m, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 18.1, 18.1, 25.4, 25.5, 26.4, 26.5, 42.1, 42.1, 43.2, 43.2, 44.4, 44.5, 48.2 ($\times 2\text{C}$), 49.75, 49.76, 52.5 ($\times 2\text{C}$), 127.0 ($\times 2\text{C}$), 128.2 ($\times 2\text{C}$), 128.5 ($\times 2\text{C}$), 128.7 ($\times 2\text{C}$), 128.9 ($\times 2\text{C}$), 132.8 ($\times 2\text{C}$), 136.6, 136.6, 140.1 ($\times 2\text{C}$), 168.6, 168.7, 173.07, 173.14, 177.5, 177.6, 199.4, 199.5. **HRMS–FAB** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_5$, 439.2227; found, 439.2220.

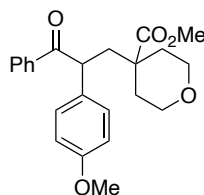
Methyl 4-[2-(3,5-Dimethylphenyl)-3-oxo-3-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (**4aba**)



4aba

The product **4aba** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–80:20, hexane/EtOAc) (Table 1-4; 47.2 mg, 0.12 mmol, 62% isolated yield). White solid. **M.p.** 70–72 $^{\circ}\text{C}$. **IR** (neat) 1108, 1138, 1195, 1298, 1446, 1597, 1683, 1727 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.46–1.58 (m, 2H), 1.81 (dd, $J = 14.0, 3.2$ Hz, 1H), 2.05 (m, 1H), 2.16 (m, 1H), 2.24 (s, 6H), 2.87 (dd, $J = 14.0, 9.2$ Hz, 1H), 3.28–3.41 (m, 2H), 3.53 (s, 3H), 3.78–3.83 (m, 2H), 4.66 (dd, $J = 9.2, 3.2$ Hz, 1H), 6.81 (s, 1H), 6.83 (s, 2H), 7.40 (t, $J = 6.8$ Hz, 2H), 7.49 (t, $J = 6.8$ Hz, 1H), 7.95 (d, $J = 6.8$ Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 21.2, 34.4, 34.7, 44.3, 44.8, 48.2, 51.7, 65.3, 65.4, 125.8, 128.5, 128.7, 128.8, 132.9, 136.5, 138.6, 139.5, 175.5, 198.6. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{24}\text{H}_{28}\text{O}_4$, 380.1982; found, 380.1975.

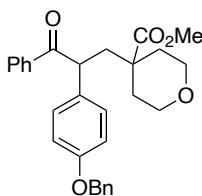
Methyl 4-[2-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4aca)



4aca

The product **4aca** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–80:20, hexane/EtOAc) (Table 1-4; 47.4 mg, 0.12 mmol, 62% isolated yield). White solid. **M.p.** 60–62 °C. **IR** (neat) 1031, 1108, 1179, 1251, 1447, 1510, 1683, 1725 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.47–1.57 (m, 2H), 1.89 (dd, J = 14.0, 3.6 Hz, 1H), 2.05–2.17 (m, 2H), 2.80 (dd, J = 14.0, 8.8 Hz, 1H), 3.28–3.42 (m, 2H), 3.52 (s, 3H), 3.73 (s, 3H), 3.79–3.82 (m, 2H), 4.68 (dd, J = 8.8, 3.6 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.93 (d, J = 7.2 Hz, 2H). **¹³C NMR** (150.9 MHz, CDCl₃) δ 34.4, 34.9, 44.1, 44.7, 47.5, 51.8, 55.2, 65.3, 65.4, 114.4, 128.56, 128.60, 129.2, 131.4, 132.9, 136.4, 158.7, 175.5, 198.7. **HRMS–DART** (m/z): [M]⁺ calcd for C₂₃H₂₆O₅, 382.1775; found, 382.1775.

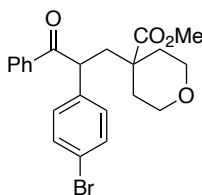
Methyl 4-[2-[4-(Benzyloxy)phenyl]-3-oxo-3-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4ada)



4ada

The product **4ada** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–80:20, hexane/EtOAc) (Table 1-4; 70.6 mg, 0.15 mmol, 77% isolated yield). Colorless oil. **IR** (neat) 1027, 1107, 1177, 1242, 1446, 1508, 1680, 1722 cm⁻¹. **¹H NMR** (600 MHz, CDCl₃) δ 1.48–1.57 (m, 2H), 1.89 (dd, J = 14.4, 4.2 Hz, 1H), 2.07 (m, 1H), 2.13 (m, 1H), 2.79 (dd, J = 14.4, 8.4 Hz, 1H), 3.30 (m, 1H), 3.39 (m, 1H), 3.49 (s, 3H), 3.79–3.82 (m, 2H), 4.68 (dd, J = 8.4, 4.2 Hz, 1H), 4.98 (s, 2H), 6.87 (d, J = 9.0 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H), 7.31 (m, 1H), 7.34–7.41 (m, 6H), 7.49 (t, J = 7.2 Hz, 1H), 7.93 (d, J = 7.2 Hz, 2H). **¹³C NMR** (150.9 MHz, CDCl₃) δ 34.4, 34.9, 44.1, 44.7, 47.5, 51.8, 65.3, 65.4, 70.0, 115.3, 127.5, 128.0 (× 2C), 128.57, 128.62, 129.3, 131.7, 132.9, 136.5, 136.8, 157.9, 175.5, 198.7. **HRMS–DART** (m/z): [M]⁺ calcd for C₂₉H₃₀O₅, 458.2088; found, 458.2083.

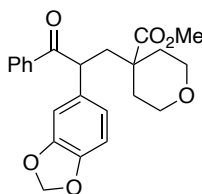
Methyl 4-[2-(4-Bromophenyl)-3-oxo-3-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4aea)



4aea

The product **4aea** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–84:16, hexane/EtOAc) (Table 1-4; 50.9 mg, 0.12 mmol, 59% isolated yield). Colorless oil. **IR** (neat) 1011, 1106, 1139, 1196, 1447, 1486, 1683, 1724 cm^{-1} . **^1H NMR** (600 MHz, CDCl_3) δ 1.48–1.55 (m, 2H), 1.87 (dd, $J = 14.4, 4.2$ Hz, 1H), 2.07 (m, 1H), 2.13 (m, 1H), 2.81 (dd, $J = 14.4, 8.4$ Hz, 1H), 3.30 (m, 1H), 3.39 (m, 1H), 3.52 (s, 3H), 3.79–3.83 (m, 2H), 4.70 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.38–7.42 (m, 4H), 7.51 (t, $J = 7.2$ Hz, 1H), 7.91 (d, $J = 7.2$ Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.3, 34.9, 43.9, 44.8, 47.7, 51.8, 65.2, 65.3, 121.2, 128.6, 128.7, 129.9, 132.1, 133.2, 136.1, 138.5, 175.4, 198.2. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{23}\text{BrO}_4$, 430.0774; found, 430.0783.

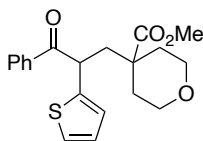
Methyl 4-[2-(Benzo[d][1,3]dioxol-5-yl)-3-oxo-3-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4afa)



4afa

The product **4afa** was purified by flash chromatography on silica gel (Biotage Selekt, 96:4–78:22, hexane/EtOAc) (Table 1-4; 47.6 mg, 0.12 mmol, 60% isolated yield). White solid. **M.p.** 109–112 $^{\circ}\text{C}$. **IR** (neat) 1036, 1140, 1195, 1245, 1444, 1486, 1680, 1722 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.46–1.57 (m, 2H), 1.85 (dd, $J = 14.0, 3.6$ Hz, 1H), 2.03–2.17 (m, 2H), 2.81 (dd, $J = 14.0, 8.8$ Hz, 1H), 3.28–3.42 (m, 2H), 3.55 (s, 3H), 3.78–3.84 (m, 2H), 4.64 (dd, $J = 8.8, 3.6$ Hz, 1H), 5.88 (d, $J = 1.4$ Hz, 1H), 5.90 (d, $J = 1.4$ Hz, 1H), 6.69 (s, 2H), 6.72 (s, 1H), 7.41 (t, $J = 7.2$ Hz, 2H), 7.50 (t, $J = 7.2$ Hz, 1H), 7.93 (d, $J = 7.2$ Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.8, 44.1, 44.8, 47.9 ($\times$ 2C), 51.8, 65.3, 65.4, 101.1, 108.3, 108.7, 121.5, 128.6, 133.0, 133.3, 136.4, 146.7, 148.1, 175.5, 198.5. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{24}\text{O}_6$, 396.1567; found, 396.1576.

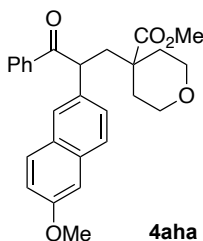
Methyl 4-[3-Oxo-3-phenyl-2-(thiophen-2-yl)propyl]tetrahydro-2H-pyran-4-carboxylate (4aga)



4aga

The product **4aga** was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–80:20, hexane/EtOAc) (Table 1-4; 44.4 mg, 0.12 mmol, 62% isolated yield). White solid. **M.p.** 102–105 °C. **IR** (neat) 1107, 1140, 1196, 1234, 1298, 1446, 1684, 1723 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.47–1.61 (m, 2H), 2.01 (dd, J = 14.4, 3.6 Hz, 1H), 2.04–2.18 (m, 2H), 2.87 (dd, J = 14.4, 8.8 Hz, 1H), 3.29–3.41 (m, 2H), 3.56 (s, 3H), 3.78–3.85 (m, 2H), 5.03 (dd, J = 8.8, 3.6 Hz, 1H), 6.82 (d, J = 3.2 Hz, 1H), 6.86 (dd, J = 4.8, 3.2 Hz, 1H), 7.15 (d, J = 4.8 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.98 (d, J = 7.6 Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.6, 42.8, 44.6, 44.8, 51.9, 65.28, 65.34, 125.1, 125.7, 127.1, 128.7, 128.7, 133.2, 135.9, 141.9, 175.4, 197.3. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}$, 358.1233; found, 358.1229.

Methyl 4-[2-(6-Methoxynaphthalen-2-yl)-3-oxo-3-phenylpropyl]tetrahydro-2H-pyran-4-carboxylate (4aha)



4aha

The product **4aha** was purified by flash chromatography on silica gel (Biotage Selekt, 96:4–76:24, hexane/EtOAc) (Table 1-4; 56.2 mg, 0.13 mmol, 65% isolated yield). White solid. **M.p.** 107–109 °C. **IR** (neat) 1030, 1198, 1223, 1392, 1446, 1604, 1681, 1724 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.52–1.60 (m, 2H), 1.98 (dd, J = 14.4, 3.6 Hz, 1H), 2.09–2.19 (m, 2H), 2.92 (dd, J = 14.4, 8.8 Hz, 1H), 3.29–3.44 (m, 2H), 3.49 (s, 3H), 3.80–3.83 (m, 2H), 3.88 (s, 3H), 4.86 (dd, J = 8.8, 3.6 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 9.2, 2.4 Hz, 1H), 7.33–7.40 (m, 3H), 7.47 (t, J = 7.2 Hz, 1H), 7.58 (s, 1H), 7.65 (dd, J = 9.2, 5.2 Hz, 2H), 7.97 (d, J = 7.2 Hz, 2H). **^{13}C NMR** (150.9 MHz, CDCl_3) δ 34.4, 34.9, 44.1, 44.8, 48.3, 51.8, 55.3, 65.3, 65.4, 105.5, 119.2, 126.6, 126.9, 127.7, 128.6, 128.7, 129.0, 129.2, 132.9, 133.6, 134.6, 136.5, 157.8, 175.6, 198.6. **HRMS–DART** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{27}\text{H}_{28}\text{O}_5$, 432.1931; found, 432.1940.

第一章 実験項 参考文献

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第二章 有機光酸化還元触媒と脂肪族カルボン酸を用いた α -ケトカルボニルのアルキル化反応

第一節 着想背景および作業仮説

異なる二種のラジカルクロスカップリングは、嵩高い置換基を有する分子同士の結合形成反応における重要な素過程として期待される。しかし、高活性なラジカル種の反応制御は困難であり、しばしばホモカップリング体の副生が問題となる。この問題の解決策として、序論で述べた長寿命ラジカル効果 (PRE : persistent radical effect) を利用した手法がある。¹ 本効果を活用した反応設計により、異なる二種のラジカルの選択的なクロスカップリングが可能となり、嵩高い分子同士の結合形成反応が実現されている。

著者の所属研究室では、*N*-ヘテロ環カルベン (NHC) 触媒による脂肪族カルボン酸誘導体であるレドックス活性エステルを用いた芳香族アルデヒドの脱炭酸型アルキル化反応を報告している (Figure 2-1)。² この反応では、NHC とアルデヒドから形成する Breslow 中間体由来のケチルラジカルとレドックス活性エステルから脱炭酸を経て生じるアルキルラジカルのクロスカップリングにより嵩高いケトン体を与える。Breslow 中間体由来のケチルラジカルが captodative 効果³ により長寿命ラジカルとなり、PRE による選択的なラジカル-ラジカルカップリングが進行したと考えられる。また、この長寿命なケチルラジカルを活用することで、ラジカルリレー型アルケンの二炭素官能基化反応へと展開している。⁴ そこで、Breslow 中間体由来のケチルラジカルと類似した構造であれば、captodative 効果が働くことで長寿命ラジカルとなり、新たな分子変換へと応用できると考えた。

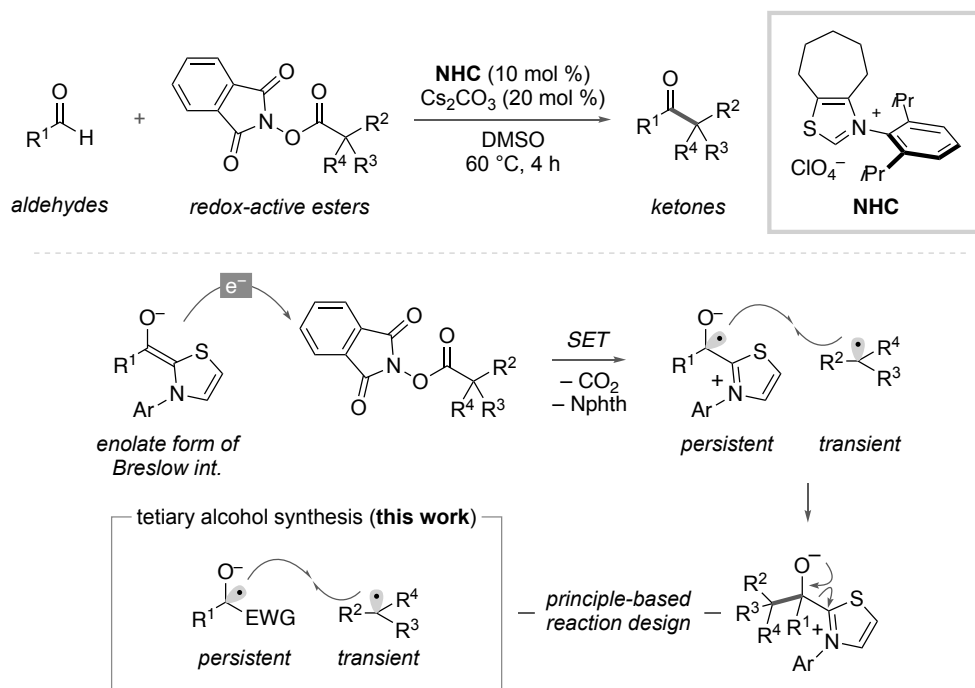


Figure 2-1. ラジカル-ラジカルカップリングを経た嵩高いアルコール合成の反応設計

量子化学計算により、メチルラジカルのエネルギーを基準としてラジカルの安定化エネルギー (RSE) を算出し、種々のケチルラジカルの長寿命性を評価した。⁵ その結果、 α -ケトカルボニルの一電子還元によって生じるケチルラジカルは、短寿命な *tert*-ブチルラジカルと比較して、Breslow 中間体由来のケチルラジカルと同程度の高い安定化エネルギーを有しており、長寿命ラジカルとなり得ることを見出した (Figure 2-2)。

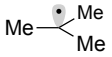
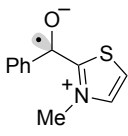
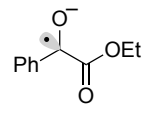
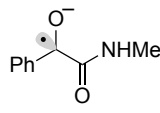
					
RSE (kcal/mol)	0	11.4	63.7	59.9	53.5

Figure 2-2. 種々のケチルラジカルのラジカルの安定化エネルギー

以上を踏まえ著者は、PREに基づく有機光酸化還元触媒系を用いた脂肪族カルボン酸と α -ケトカルボニルの脱炭酸型クロスカップリング反応の開発を目指した (Figure 2-3)。本手法により、極性反応では達成困難であった嵩高いアルコールの合成が可能となると考えられる。

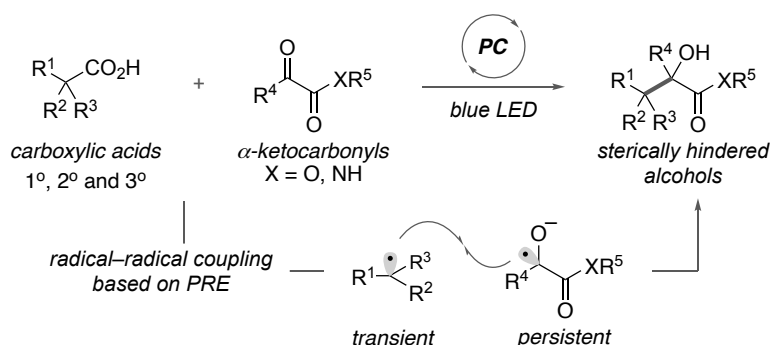


Figure 2-3. 有機分子触媒による α -ケトカルボニルの脱炭酸型アルキル化反応

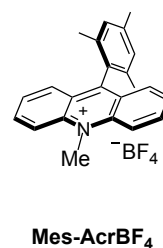
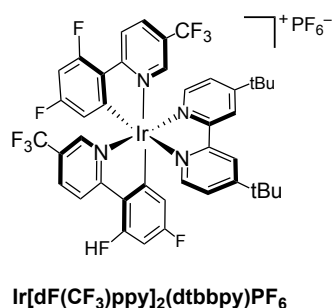
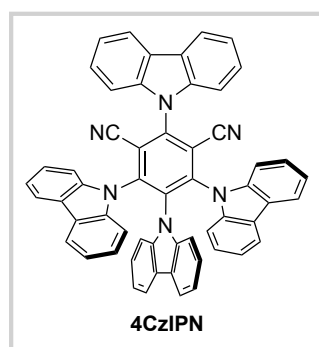
第二節 反応条件の最適化および基質適用範囲の検討

2-フェニルイソ酪酸 (**1a**) とベンゾイルギ酸エチル (**2a**) を基質として用い、光酸化還元触媒、塩基、溶媒の検討を行った (Table 2-1)。基質に対し、光酸化還元触媒として 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)⁶ を 1 mol %, 塩基として二当量の炭酸セシウムを加え、ジメチルスルホキシド溶媒中可視光照射下で一時間反応させたところ、目的のアルキル化体 **3aa** を高収率で与えた (entry 1)。4CzIPN と同程度の酸化還元電位を有する Ir 型光酸化還元触媒 ($[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$)⁷ を用いた場合でも高収率で目的物を与えた (entry 2)。一方で、メシチルアクリジニウム型の光酸化還元触媒 (Mes-AcrBF_4)⁸ を用いた場合では目的物は全く得られなかった (entry 3)。塩基

として、炭酸ナトリウムや炭酸カリウム、またフッ化セシウムや酢酸セシウムを用いた場合には、目的物の収率は低下した一方で、副生成物 **4aa** の生成量は増加した (entries 4–7)。溶媒として、他の高極性溶媒であるアセトニトリルやジメチルホルムアミドを用いた場合には、**3aa** の収率が低下した (entries 8 and 9)。ジクロロメタンを溶媒として用いた場合には、炭酸セシウムの溶解性の低さのため、収率が大幅に低下した (entry 10)。対照実験を行った結果、本反応には可視光照射、光酸化還元触媒、塩基が必須であることが示された (entries 11–13)。

Table 2-1. 反応条件の最適化 ^a

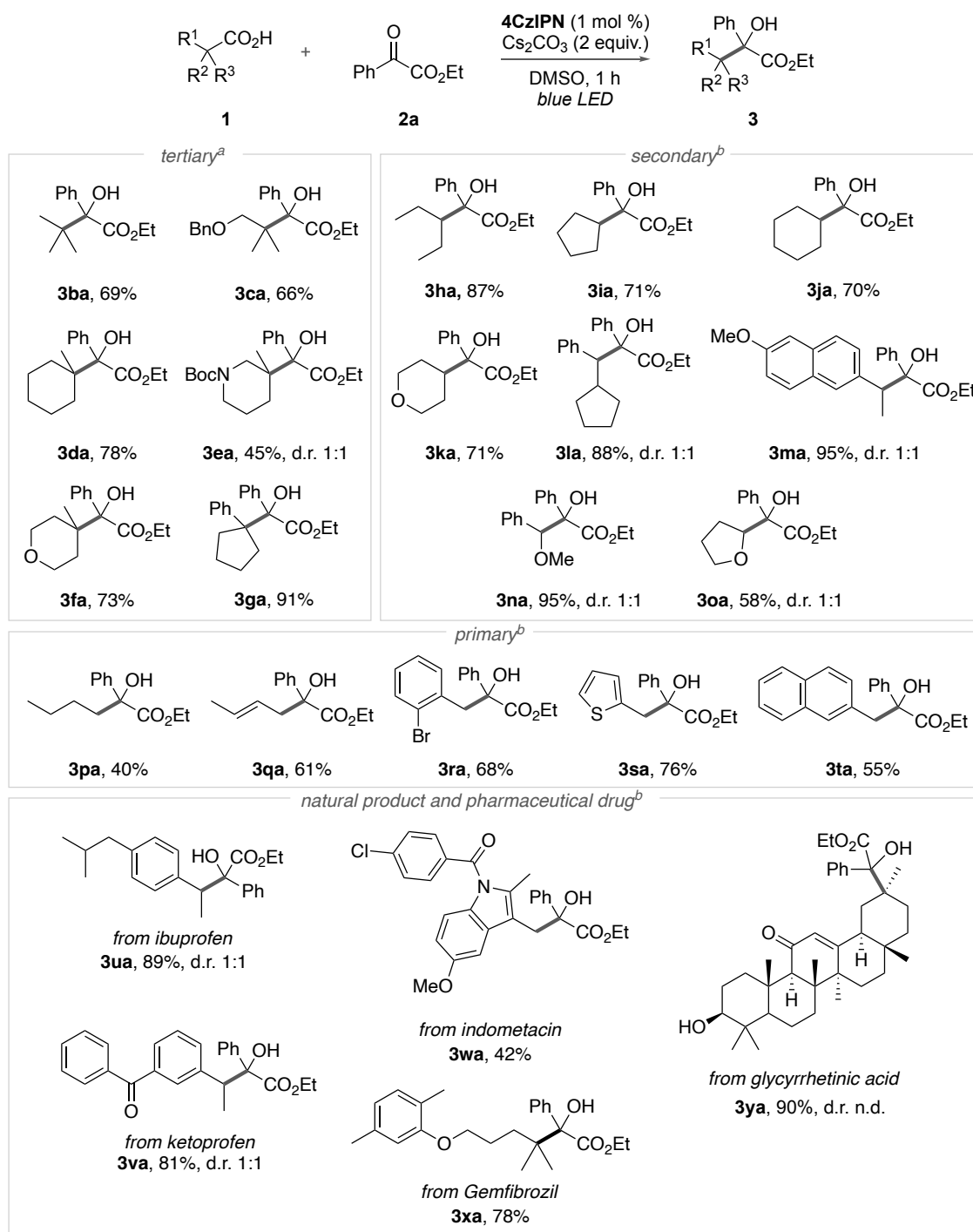
entry	change from standard conditions	yield (%) of 3aa ^b	yield (%) of 4aa ^b
1	none	96 (90)	2
2	Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆ instead of 4Cz-IPN	92	3
3	Mes-AcrBF ₄ instead of 4Cz-IPN	0	0
4	Na ₂ CO ₃ instead of Cs ₂ CO ₃	75	12
5	K ₂ CO ₃ instead of Cs ₂ CO ₃	77	11
6	CsF instead of Cs ₂ CO ₃	68	16
7	CsOAc instead of Cs ₂ CO ₃	70	15
8	MeCN instead of DMSO	53	4
9	DMF instead of DMSO	62	19
10	DCM instead of DMSO	11	10
11	without Blue LED	0	0
12	without 4Cz-IPN	0	0
13	without Cs ₂ CO ₃	11	0



^aReaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), 4CzIPN (0.002 mmol), Cs₂CO₃ (0.4 mmol) DMSO (1.0 mL), 1 h under blue LED irradiation. ^b¹H NMR yield. Yield of the isolated product is given in parentheses.

上記の検討で得られた最適条件に基づき、本反応における脂肪族カルボン酸および α -ケトカルボニルの適用範囲の検討を行った。まず、 α -ケトエステル **2a** を用いて、脂肪族カルボン酸の検討を行った (**Table 2-2**)。本反応では、種々の第三級脂肪族カルボン酸の適用が可能であり、多様な嵩高い第三級アルキル骨格を有するアルコール体を合成できた (**3ba–3da, 3ga**)。また、ピペリジンやテトラヒドロピランのようなヘテロ環を有するカルボン酸の適用も可能であった (**3ea and 3fa**)。本光酸化還元触媒系では、第三級カルボン酸だけでなく、第二級および第一級脂肪族カルボン酸の適用も可能であった。本手法は、多くのムスカリン受容体拮抗薬に見られる α -ヒドロキシエステルの合成を可能とする (**3ha–3ka**)。⁹ さらに、ベンジル位や酸素原子の α 位にラジカルが生成する基質の適用も可能であり、高い収率で目的物を与えた (**3la–3oa**)。収率は低下するが、第一級脂肪族カルボン酸も許容された (**3pa–3ta**)。本反応は、高い官能基許容性を有しているため、カルボン酸部位を含む天然物や医薬品の後期修飾が可能であった (**3ua–3ya**)。

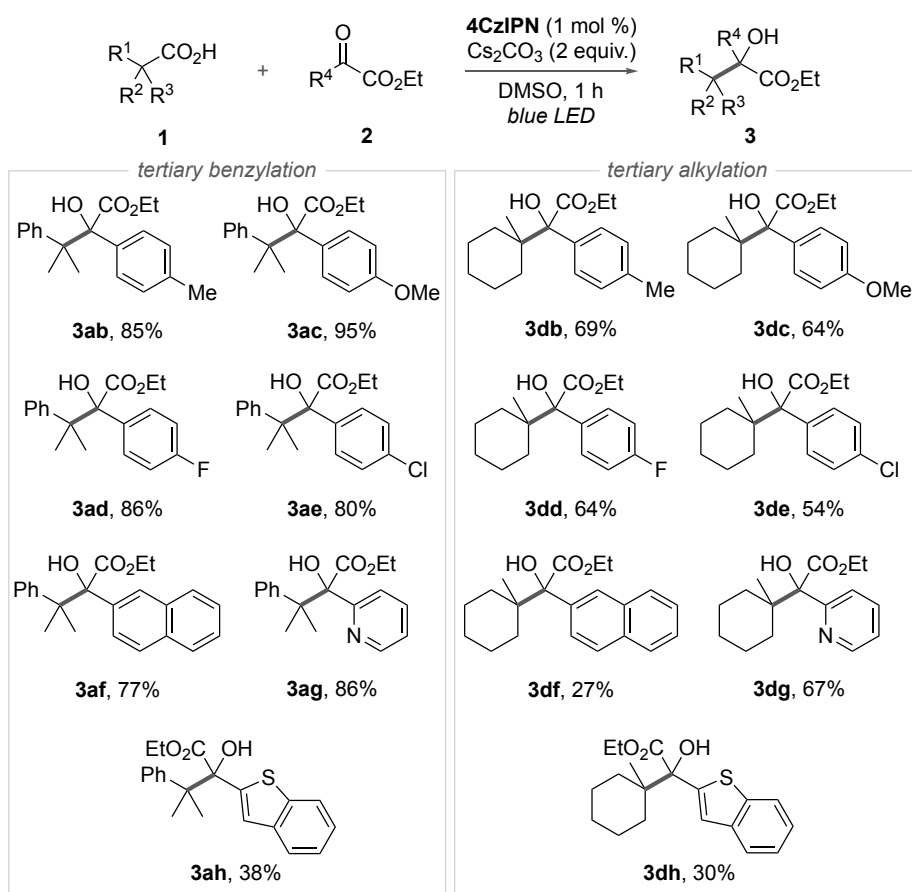
Table 2-2. 脂肪族カルボン酸の検討



^aReaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), 4CzIPN (0.002 mmol), Cs₂CO₃ (0.4 mmol), DMSO (1.0 mL), 1 h under blue LED irradiation. ^b**1** (0.2 mmol), **2** (0.2 mmol), 4CzIPN (0.004 mmol), Cs₂CO₃ (0.4 mmol), DMSO (1.0 mL), 1 h under blue LED irradiation.

次に、2-フェニルイソ酪酸 (**1a**) あるいは 1-メチル-1-シクロヘキサンカルボン酸 (**1d**) を用いて、 α -ケトエステルの検討を行った (Table 2-3)。本反応では、ベンゼン環上に電子供与性基や電子求引性基を有する α -ケトエステルの適用が可能であり、高い収率で対応する α -ヒドロキシエステル体を与えた (**3ab–3ae**)。また、ナフタレンやピリジン環を有する α -ケトエステルの適用も可能であった (**3af–3ah**)。一方で、第三級アルキル化の場合では、第三級ベンジル化に比べ収率が低下した (**3db–3dh**)。

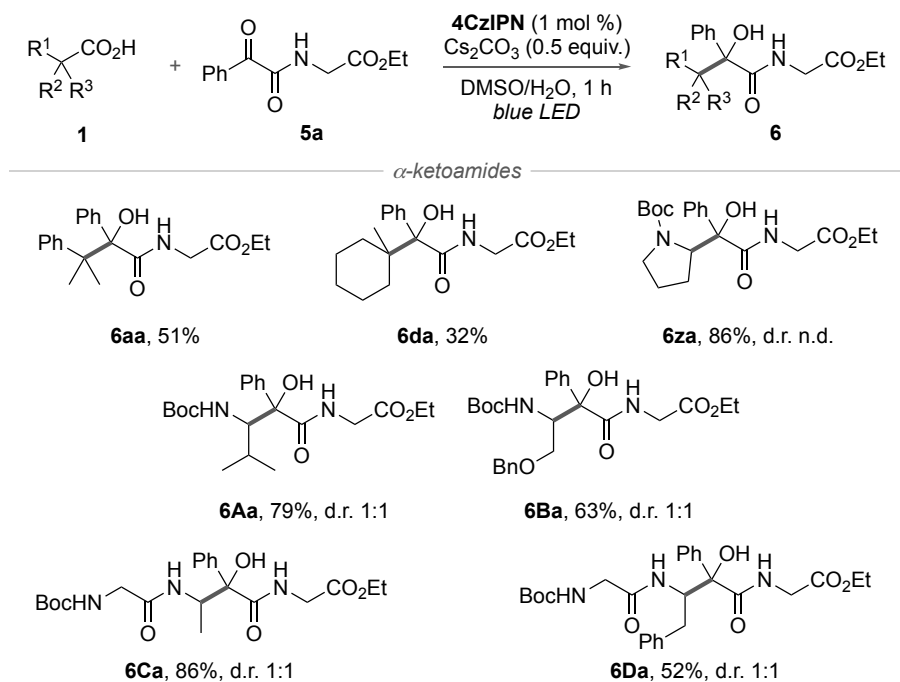
Table 2-3. α -ケトエステルの検討^a



^aReaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), 4CzIPN (0.002 mmol), Cs₂CO₃ (0.4 mmol), DMSO (1.0 mL), 1 h under blue LED irradiation.

続いて、求電子剤として、 α -ケトエステルの代わりに α -ケトアミドを用いた検討を行った (Table 2-4)。 α -ケトエステル **2a** に比べ、 α -ケトアミド **5a** 由来のケチルラジカルは RSE が低いため、目的物の収率は低下する結果となった (**6aa** and **6da**)。また、 α -ケトアミド **5a** とアミノ酸やペプチドとのカップリング反応も可能であった。プロリン、バリン、セリン誘導体とのカップリングが可能であり、良好な収率で対応する α -ヒドロキシアミド体を与えた (**6za–6Ba**)。また、カルボン酸部位を有するジペプチドとのカップリング反応も可能であった (**6Ca** and **6Da**)。

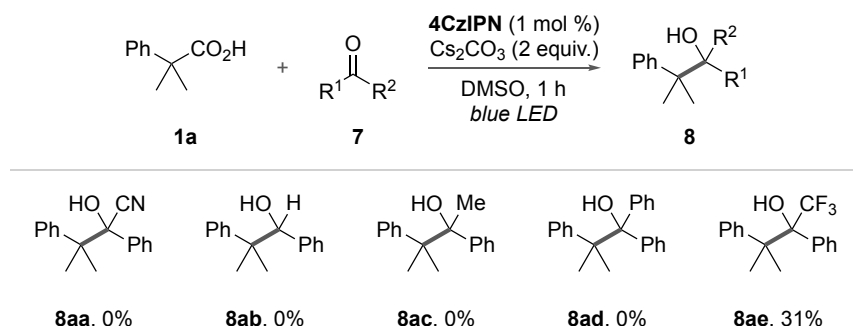
Table 2-4. α -ケトアミドの検討^a



^aReaction conditions: **1** (0.2 mmol), **5a** (0.2 mmol), 4CzIPN (0.002 mmol), Cs₂CO₃ (0.1 mmol), H₂O (1.0 mmol), DMSO (1.0 mL), 1 h under blue LED irradiation.

本有機酸化還元触媒系において、求電子剤として他のカルボニル化合物も適用できないか検討を行った (Table 2-5)。アシルシアニド (**7a**)、ベンズアルデヒド (**7b**)、アセトフェノン (**7c**)、ベンゾフェノン (**7d**) を用いた場合には、目的のカップリング体は全く得られなかった (**8aa–8ad**)。一方で、トリフルオロアセトフェノン (**7e**) を用いた場合には、低収率ではあるが **1a** とのカップリング体を与えた (**8ae**)。

Table 2-5. 他のカルボニル化合物の検討^a



^aReaction conditions: **1a** (0.2 mmol), **7** (0.2 mmol), 4CzIPN (0.002 mmol), Cs₂CO₃ (0.4 mmol), DMSO (1.0 mL), 1 h under blue LED irradiation.

第三節 ラジカルリレー型アルケンの二炭素官能基化反応

本反応系にアルケン **9** を加えることで、ラジカルリレー型アルケンの二炭素官能基化が進行することを見出した (Figure 2-4)。基質として脂肪族カルボン酸 **1d**、 α -ケトエステル **2a**、スチレン (**9a**) を用い、最適反応条件下で反応させたところ、ラジカルリレー機構が進行し、三成分カップリング体 **10daa** を高収率で得られた。この際、副生成物である二成分カップリング体 **3da** がわずかに生成していた。他のスチレン類として、*p*-メトキシスチレンや *p*-ブロモスチレンの適用が可能であり、高い化学選択性および収率で目的物を与えた (**10dba** and **10dca**)。

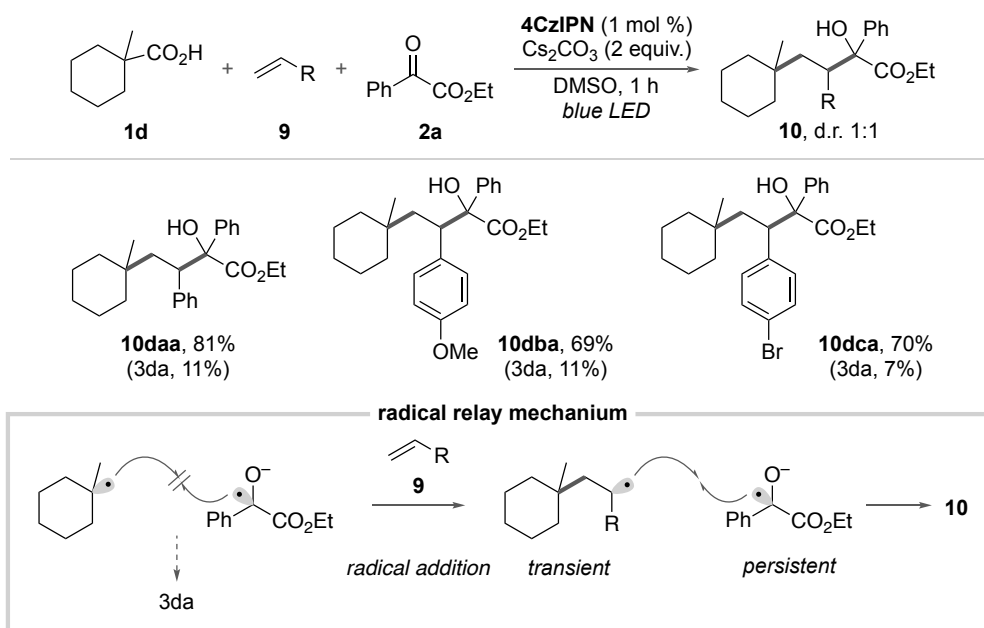


Figure 2-4. ラジカルリレー機構による三成分カップリング反応

第四節 反応機構解析

本有機酸化還元触媒系の反応機構を明らかにすべく、機構実験を行った。シトロネラ酸 **1E** を基質として用いてラジカルクロック実験を行ったところ、5-*exo* ラジカル環化した生成物 **3Ea'** のみが得られた (Figure 2-5)。この結果より、本反応では、脂肪族カルボン酸由来のアルキルラジカルを経由して進行していることが示唆された。また、第一級アルキルラジカルと **2a** 由来のケチルラジカルのラジカル-ラジカルカップリングの速度は、5-*exo* ラジカル環化の速度 ($k = 1.1 \times 10^5 \text{ s}^{-1}$) より遅いことが示唆された。¹⁰

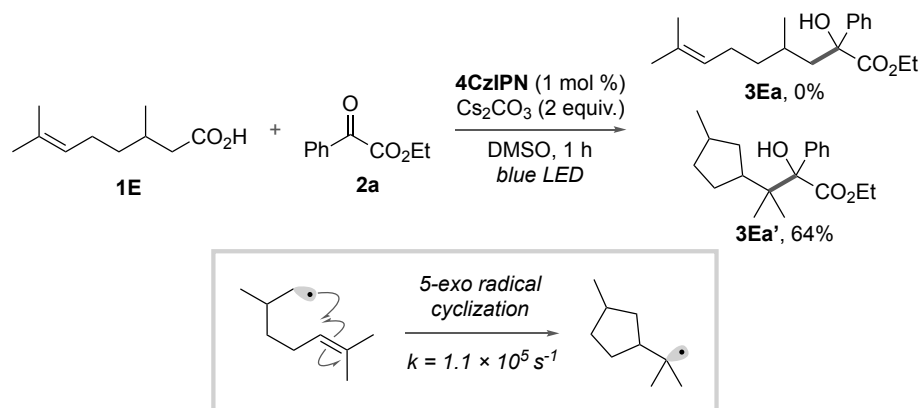


Figure 2-5. ラジカルクロック実験

次に、消光剤としてカルボン酸塩あるいは α -ケトエステル **2a** を用いて Stern–Volmer 消光実験を行った (Figure 2-6)。その結果、**2a** による消光は全く確認されなかった一方で、カルボン酸塩の濃度増加に従い、大きな消光度合いを示した。この結果より、本反応では、励起された有機光酸化還元触媒がカルボン酸塩との一電子移動を起こす、すなわち還元的消光によって進行していることが示唆された。

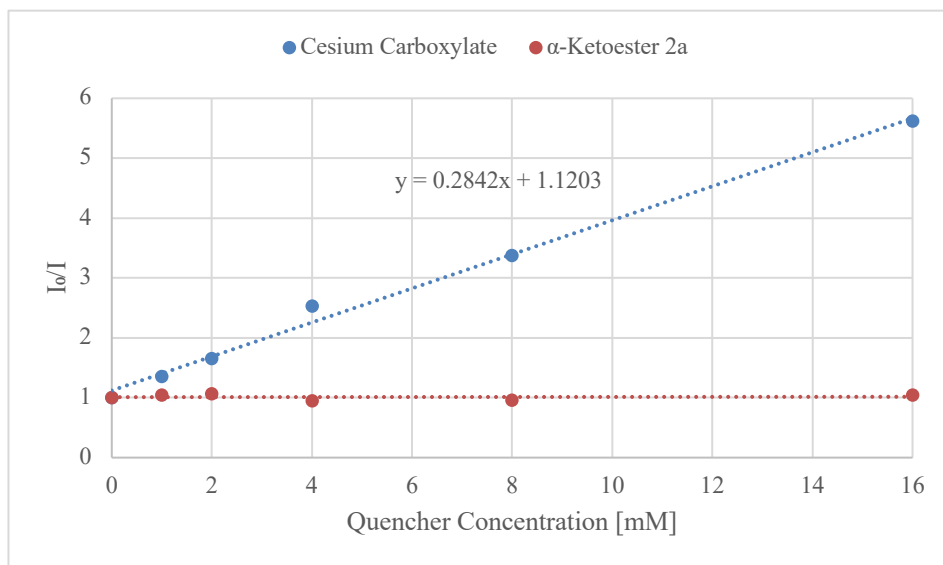


Figure 2-6. Stern–Volmer 消光実験

第五節 推定反応機構

以上の機構実験結果に基づき、推定される反応機構を以下に示す (Figure 2-7)。まず、基底状態の **4CzIPN** が、可視光照射により励起状態となる。また、塩基により脂肪族カルボン酸 **1** が脱プロトン化されカルボン酸塩へと変換される。このカルボン酸塩 ($E_{\text{red}, 1/2} = +1.16 \text{ V vs. SCE for hexanonate}$)¹¹ と励起状態の **4Cz-IPN** [$E_{1/2} (^*\text{4Cz-IPN}/\text{4Cz-IPN}^-) = +1.35 \text{ V vs. SCE}$]¹² 間の一電子移動により、脱炭酸を経てアルキルラジカルが生成する。

続いて、ラジカルアニオンとなった 4CzIPN^- [$E_{1/2}(4\text{Cz-IPN}^-/4\text{Cz-IPN}) = -1.21 \text{ V vs. SCE}$]¹² から、 α -ケトカルボニル **2** ($E_{\text{red},1/2} = -1.23 \text{ V vs SCE for 2a}$) への一電子移動が起きることで、基底状態の 4CzIPN が再生すると共に、ケチルラジカルが生成する。最後に、PRE による短寿命なアルキルラジカルと長寿命なケチルラジカルの選択的なラジカル-ラジカルカップリングが進行することで、プロトン化を経て目的のアルコール体 **3** が生成する。

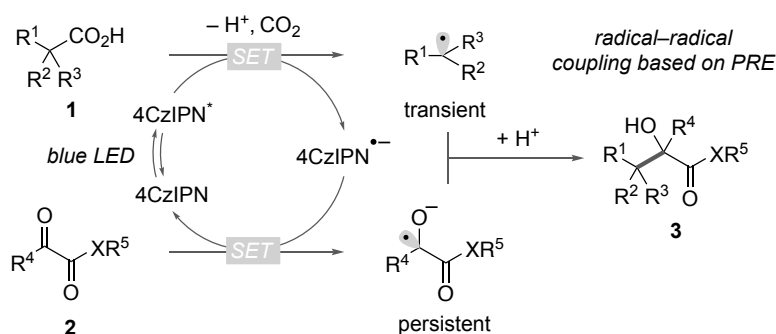


Figure 2-6. 推定反応機構

最後に、芳香族あるいは脂肪族 α -ケトエステルを用いて、本反応における RSE と反応性の評価を行った (Figure 2-7)。脂肪族 α -ケトエステル由来のケチルラジカルは、芳香族 α -ケトエステル由来のものと比較して、RSE はわずかに小さいことが量子化学計算により明らかとなった。実際に、脂肪族カルボン酸 **1a** とのカップリング反応を検討したところ、メチル基が置換した α -ケトエステル **B** を用いた場合では、目的物は得られなかった。一方で、*tert*-ブチル基が置換した α -ケトエステル **C** との反応では、対応するケチルラジカルの RSE は **B** より小さいものの脱炭酸型アルキル化が進行し、低収率ではあるが目的のアルコール体を与えた。 α -ケトエステル **C** の場合では、対応するケチルラジカルが *tert*-ブチル基の立体的な嵩高さにより安定化されたため、**1a** とのカップリング反応が進行したと考えられる。

	$\text{Ph}-\text{C}(=\text{O})-\text{CO}_2\text{R}$ A	$\text{Me}-\text{C}(=\text{O})-\text{CO}_2\text{R}$ B	$\text{C}(\text{Me})_3-\text{C}(=\text{O})-\text{CO}_2\text{R}$ C
Yield (%) ^[a,b]	90	0	30
$E_{\text{red},1/2}$ (vs. SCE) ^[a]	-1.26	-1.43	-1.61
RSE (kcal/mol) ^[c]	59.9	53.5	50.2

^aR = 2-phenylethyl. ^bThe reaction with **1a** under standard conditions. ^cR = ethyl.

Figure 2-7. RSE と反応性の関係

第五節 結論

PRE に基づく有機光酸化還元触媒系を用いることで、脂肪族カルボン酸を用いた α -ケトカルボニルの脱炭酸型アルキル化を達成した。本反応は、可視光励起された光酸化還元触媒が脂肪族カルボン酸と α -ケトカルボニルを各々電子酸化・還元し、その後、脱炭酸により生じた短寿命なアルキルラジカルと長寿命なケチルラジカルがラジカル-ラジカルカップリングすることで進行する。本反応により、極性反応では達成困難であった嵩高いアルコールを合成できる。また、本手法は、アルケンを加えた三成分カップリング反応や医薬品・生理活性物質の後期修飾への応用が可能であった。

第二章 参考文献

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第二章 実験項

1. Instrumentation and Chemicals

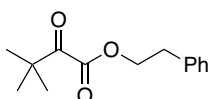
NMR spectra were recorded on a Bruker AVANCE NEO 400N spectrometer, operating at 400 MHz for ^1H NMR, 100.6 MHz for ^{13}C NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si and the residual solvent resonances, respectively. Chemical shifts were reported in δ ppm. DART-Mass and ESI-Mass spectra were measured with JMS-T100TD (JEOL Ltd.). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F₂₅₄. Silica gel (Wakosil[®] 60, 64–210 μm) was used for column chromatography. Biotage Selekt was used for purification. IR spectra were measured with a Thermo Scientific iD7 ATR Accessory for the Thermo Scientific Nicolet iS5 FT-IR Spectrometer. Melting points were measured on a Stanford Research Systems MPA100. CV measurements were recorded with a Hokuto Denko HZ-7000 potentiostat. Kessil A160W Tuna Blue (highest blue and intensity setting) was used as a light source. TEKNOS MG9 was used as a fan.

All reactions were carried out under nitrogen or argon atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. Cs_2CO_3 , K_2CO_3 and CsF were purchased from FUJIFILM Wako Pure Chemical Co., Na_2CO_3 and CsOAc were purchased from Nacalai Tesque Inc., stored under nitrogen, and used as received. DMSO, MeCN, DMF and DCM were purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. 4Cz-IPN was prepared by the reported procedure ⁹. $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ was purchased from Sigma-Aldrich Japan., Mes-AcrBF₄ was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Carboxylic acids **1a**, **1b**, **1d**, **1g–1k**, **1n–1s**, **1v–x**, **1z**, **1A** and **1B** were purchased from Tokyo Chemical Industry Co., **1f**, **1u** and **1y** were purchased from FUJIFILM Wako Pure Chemical Co., **1l**, **1m** and **1t** were purchased from Sigma-Aldrich Japan., stored under nitrogen, and used as received. **1c** was prepared by *tert*-butoxycarbonyl (Boc) protection of the corresponding carboxylic acid. **1e** was prepared by benzyl protection of the hydroxypivalic acid. Peptides **1C** and **1D** were prepared from the corresponding amino acids through condensation reactions. Citronellic acid **1E** was prepared according to the reported procedure ¹⁰. α -Ketoester **2a** was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. **2b–2e** were prepared by Friedel–Crafts reaction from the corresponding arenes. **2f** was prepared according to the reported procedure ¹¹. **2g** was prepared according to the reported procedure ¹². **2h** was prepared according to the reported procedure ¹³. **2A–C** were prepared from the corresponding alcohol and α -keto acids through condensation reactions. α -Ketoamide **5a** was prepared from the corresponding amine and α -keto acids through condensation reaction. Other carbonyls **7a**, **7d** and **7e** were purchased from Tokyo Chemical Industry Co., **7b** was purchased

from Nacalai Tesque Inc., **7c** was purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. Styrene **9a** was purchased from FUJIFILM Wako Pure Chemical Co., distilled before using. Alkenes **9b** and **9c** were prepared by Wittig reaction from the corresponding aldehydes.

2. Characterization Data for α -Ketoester

Phenethyl 3,3-Dimethyl-2-oxobutanoate (**2C**)



2C was synthesized by DCC condensation and purified by flash chromatography on silica gel (Biotage Selekt, 98:2–81:19, hexane/EtOAc) (5 mmol scale; 955 mg, 4.07 mmol, 82% isolated yield). Colorless oil. **IR** (neat) 1007, 1052, 1238, 1290, 1368, 1455, 1715, 1736, 2971 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 7.33–7.22 (m, 5H), 4.47 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 1.19 (s, 9H). **¹³C NMR** (100.6 MHz, CDCl_3) δ 201.9, 163.7, 136.9, 128.9, 128.6, 126.8, 65.9, 42.5, 34.8, 25.5. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_3$, 252.1594; found, 252.1596.

3. Procedure for Synthesis of α -Hydroxyesters

The reaction in Table 2-1, entry 1 is representative. In a glovebox, to an oven-dried vial with a stirring bar was added photocatalyst 4Cz-IPN (1.6 mg, 0.002 mmol), 2-phenylisobutyris acid **1a** (32.8 mg, 0.2 mmol) and ethyl benzylformate **2a** (31.8 μL , 0.2 mmol) and DMSO (1.0 ml). Then, Cs_2CO_3 (130.3 mg, 0.4 mmol) was added to the reaction mixture. The reaction was stirred and irradiated with a 34W blue LED (0.5 cm away) with a cooling fan to keep the temperature around 40 $^\circ\text{C}$ (Figure S2-1). After 1 h, the reaction mixture was treated with saturated NH_4Cl aqueous solution (1.0 mL), then extracted with diethyl ether (3 times) and dried over sodium sulfate. After filtration, the resulting solution was evaporated under reduced pressure. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (100:0–97:3, hexane/EtOAc) gave **3aa** (53.7 mg, 0.18 mmol) in 90% yield.

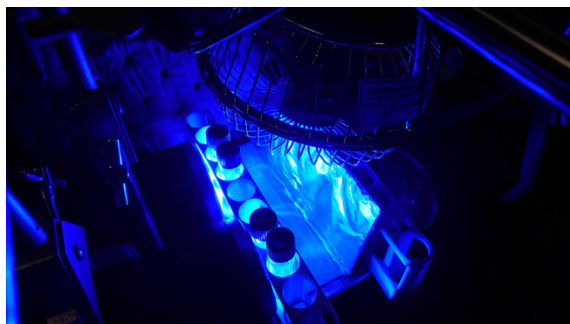
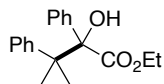


Figure S2-1. Light set up

1 mmol scale reaction. In a glovebox, to an oven-dried vial with a stirring bar was added photocatalyst 4Cz-IPN (7.9 mg, 0.01 mmol), 2-phenylisobutyris acid **1a** (164.2 mg, 1.0 mmol) and ethyl benzylformate **2a** (159.1 μ L, 1.0 mmol) and DMSO (5.0 ml). Then, Cs₂CO₃ (651.6 mg, 2.0 mmol) was added to the reaction mixture. The reaction was stirred and irradiated with a 34W blue LED with a cooling fan to keep the temperature around 40 °C. After 1 h, the reaction mixture was treated with saturated NH₄Cl aqueous solution (5.0 mL), then extracted with diethylether (3 times) and dried over sodium sulfate. After filtration, the resulting solution was evaporated under reduced pressure. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (Biotage Selekt, 100:0–80:20, hexane/EtOAc) gave **3aa** (259.6 mg, 0.87 mmol) in 87% yield.

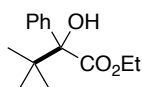
4. Characterization Data for α -Hydroxycarbonyls

Ethyl 2-Hydroxy-3-methyl-2,3-diphenylbutanoate (**3aa**)



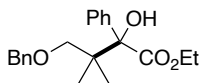
The product **3aa** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-1, entry 1; 53.7 mg, 0.18 mmol, 90% isolated yield). Colorless oil. **IR** (neat) 1031, 1063, 1169, 1246, 1446, 1716, 2980, 3489 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.72–7.69 (m, 2H), 7.39–7.36 (m, 2H), 7.31–7.20 (m, 6H), 4.13–4.08 (m, 2H), 3.69 (s, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 173.5, 144.9, 138.7, 128.3, 127.8, 127.6, 127.2, 127.1, 126.3, 82.6, 62.3, 46.0, 25.1, 24.4, 13.9. **HRMS–DART** (m/z): [M+NH₄]⁺ calcd for C₁₉H₂₆NO₃, 316.1907; found, 316.1905.

Ethyl 2-Hydroxy-3,3-dimethyl-2-phenylbutanoate (**3ba**)



The product **3ba** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 32.6 mg, 0.14 mmol, 69% isolated yield). Colorless oil. **IR** (neat) 1017, 1068, 1174, 1208, 1249, 1713, 2960, 3502 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.72–7.75 (m, 2H), 7.27–7.34 (m, 3H), 4.34 (q, J = 7.2 Hz, 2H), 3.76 (s, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.00 (s, 9H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 174.6, 139.2, 127.4, 127.4, 127.2, 82.8, 62.3, 39.0, 25.7, 14.2. **HRMS–DART** (m/z): [M+NH₄]⁺ calcd for C₁₄H₂₄NO₃, 254.1751; found, 254.1755.

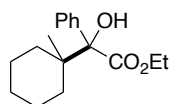
Ethyl 4-(Benzyloxy)-2-hydroxy-3,3-dimethyl-2-phenylbutanoate (**3ca**)



The product **3ca** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 45.2 mg, 0.13 mmol, 66% isolated yield). Colorless oil. **IR** (neat)

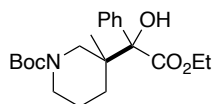
1027, 1066, 1095, 1244, 1447, 1710, 2977, 3475 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.73–7.71 (m, 2H), 7.35–7.27 (m, 8H), 4.47 (s, 2H), 4.18–4.11 (m, 2H), 3.49 (d, J = 8.8 Hz, 1H), 3.43 (d, J = 8.8 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.16 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 174.1, 138.7, 137.9, 128.4, 127.7, 127.7, 127.5, 127.4, 127.3, 81.8, 78.0, 73.7, 61.7, 43.0, 22.1, 21.3, 14.0. HRMS–DART (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{O}_4$, 343.1904; found, 343.1898.

Ethyl 2-Hydroxy-2-(1-methylcyclohexyl)-2-phenylacetate (3da)



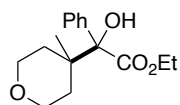
The product **3da** was purified by flash chromatography on silica gel (100:0 – 97:3, hexane/EtOAc) (Table 2-2; 43.1 mg, 0.16 mmol, 78% isolated yield). Colorless oil. IR (neat) 1027, 1058, 1215, 1241, 1446, 1710, 2925, 3497 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, J = 7.2 Hz, 2H), 7.33–7.27 (m, 3H), 4.34 (q, J = 7.2 Hz, 2H), 3.82 (s, 1H), 1.65–1.31 (m, 12H), 1.02–0.95 (m, 4H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 174.6, 138.7, 127.8, 127.3, 127.1, 83.6, 62.4, 41.9, 31.4, 30.9, 25.9, 22.0, 21.8, 17.4, 14.2. HRMS–DART (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{17}\text{H}_{28}\text{NO}_3$, 294.2064; found, 294.2066.

tert-Butyl 3-(2-Ethoxy-1-hydroxy-2-oxo-1-phenylethyl)-3-methylpiperidine-1-carboxylate (3ea)



The product **3ea** was purified by flash chromatography on silica gel (100:0–90:10, hexane/EtOAc) (Table 2-2; 34.0 mg, 0.09 mmol, 45% isolated yield). The diastereomeric ratio (1:1) is determined by ^1H NMR. Pale yellow oil. IR (neat) 1064, 1156, 1244, 1429, 1677, 1716, 2977, 3489 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J = 6.8 Hz, 2H), 7.33–7.31 (m, 3H), 4.39–4.35 (m, 2H), 4.08–3.79 (m, 3H), 2.91 (d, J = 12.8 Hz, 0.5H), 2.78 (d, J = 12.8 Hz, 0.5H), 1.71–1.40 (m, 15H), 1.27 (m, 1H), 1.02 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 174.0, 173.8, 155.3, 155.2, 138.0, 138.0, 127.8 ($\times$ 2C), 127.8 ($\times$ 2C), 127.4 ($\times$ 2C), 82.3, 82.2, 79.1, 79.0, 62.7, 62.7, 50.0, 49.1, 44.5, 43.4, 42.0 ($\times$ 2C), 30.5, 29.5, 28.4 ($\times$ 2C), 21.4, 21.1, 16.5 ($\times$ 2C), 14.2 ($\times$ 2C). HRMS–DART (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_5$, 378.2275; found, 378.2272.

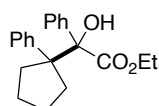
Ethyl 2-Hydroxy-2-(4-methyltetrahydro-2H-pyran-4-yl)-2-phenylacetate (3fa)



The product **3fa** was purified by flash chromatography on silica gel (100:0–94:6,

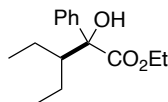
hexane/EtOAc) (Table 2-2; 40.6 mg, 0.15 mmol, 73% isolated yield). Colorless oil. **IR** (neat) 1029, 1062, 1095, 1167, 1222, 1714, 2960, 3493 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.72–7.70 (m, 2H), 7.33–7.31 (m, 3H), 4.38–4.33 (m, 2H), 3.79–3.73 (m, 3H), 3.57–3.51 (m, 2H), 2.02 (m, 1H), 1.83 (m, 1H), 1.46 (m, 1H), 1.39 (t, $J = 7.2$ Hz, 3H), 1.23 (m, 1H), 1.15 (s, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.1, 138.0, 127.7, 127.7, 127.4, 83.1, 63.9, 63.7, 62.6, 39.7, 32.2, 31.0, 17.0, 14.2. **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{O}_4$, 279.1591; found, 279.1604.

Ethyl 2-Hydroxy-2-phenyl-2-(1-phenylcyclopentyl)acetate (**3ga**)



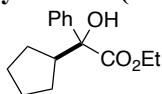
The product **3ga** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-2; 59.0 mg, 0.18 mmol, 91% isolated yield). Pale yellow oil. **IR** (neat) 1033, 1059, 1173, 1244, 1446, 1720, 2873, 2956, 3494 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.79–7.78 (m, 2H), 7.47 (d, $J = 7.6$ Hz, 2H), 7.32–7.20 (m, 6H), 4.14–4.02 (m, 2H), 3.63 (s, 1H), 2.53 (m, 1H), 2.29 (m, 1H), 1.86–1.78 (m, 2H), 1.38–1.33 (m, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.77 (m, 1H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.7, 141.7, 138.9, 129.0, 128.0, 127.6, 127.3, 127.2, 126.4, 82.9, 62.2, 59.0, 33.2, 32.9, 22.4, 21.4, 13.9. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_3$, 342.2064; found, 342.2065.

Ethyl 3-Ethyl-2-hydroxy-2-phenylpentanoate (**3ha**)



The product **3ha** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 43.6 mg, 0.17 mmol, 87% isolated yield). Colorless oil. **IR** (neat) 1026, 1052, 1143, 1239, 1447, 1717, 2962, 3506 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.70–7.65 (m, 2H), 7.36–7.32 (m, 2H), 7.26 (m, 1H), 4.25–4.16 (m, 2H), 3.71 (s, 1H), 2.16 (m, 1H), 1.55–1.38 (m, 2H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.18–1.13 (m, 2H), 0.99 (t, $J = 7.2$ Hz, 3H), 0.72 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 176.0, 141.6, 128.0, 127.3, 126.0, 82.0, 62.4, 48.4, 23.1, 21.4, 14.0, 13.0, 12.7. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{15}\text{H}_{26}\text{NO}_3$, 268.1907; found, 268.1911.

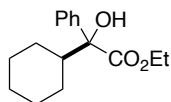
Ethyl 2-Cyclopentyl-2-hydroxy-2-phenylacetate (**3ia**)



The product **3ia** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 35.3 mg, 0.14 mmol, 71% isolated yield). Colorless oil. **IR** (neat)

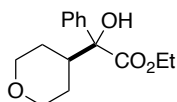
1034, 1070, 1098, 1172, 1244, 1446, 1717, 2953, 3507 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.66 (d, $J = 7.6$ Hz, 2H), 7.35–7.32 (m, 2H), 7.26 (m, 1H), 4.30–4.15 (m, 2H), 3.76 (s, 1H), 2.91 (m, 1H), 1.68–1.43 (m, 6H), 1.34–1.26 (m, 5H). $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ 175.7, 141.9, 128.0, 127.3, 125.9, 79.1, 62.4, 47.2, 26.8, 26.4, 26.3, 26.0, 14.1. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_3$, 266.1751; found, 266.1750.

Ethyl 2-Cyclohexyl-2-hydroxy-2-phenylacetate (**3ja**)



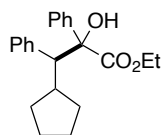
The product **3ja** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-2; 36.7 mg, 0.14 mmol, 70% isolated yield). Colorless oil. **IR** (neat) 1028, 1072, 1122, 1148, 1233, 1446, 1718, 2930, 3505 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 (d, $J = 7.6$ Hz, 2H), 7.36–7.32 (m, 2H), 7.26 (m, 1H), 4.26–4.19 (m, 2H), 3.70 (s, 1H), 2.22 (m, 1H), 1.80 (m, 1H), 1.65–1.63 (m, 2H), 1.47–1.41 (m, 2H), 1.30–1.26 (m, 4H), 1.18–1.09 (m, 4H). $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ 175.6, 140.9, 128.0, 127.3, 126.0, 80.8, 62.4, 45.7, 27.3, 26.3, 26.2 ($\times 2$ C), 25.5, 14.1. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_3$, 280.1907; found, 280.1906.

Ethyl 2-Hydroxy-2-phenyl-2-(tetrahydro-2H-pyran-4-yl)acetate (**3ka**)



The product **3ka** was purified by flash chromatography on silica gel (100:0–90:10, hexane/EtOAc) (Table 2-2; 37.5 mg, 0.14 mmol, 71% isolated yield). Colorless oil. **IR** (neat) 1020, 1091, 1149, 1235, 1446, 1720, 2952, 3503 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 (d, $J = 7.2$ Hz, 2H), 7.37–7.33 (m, 2H), 7.28 (m, 1H), 4.30–4.21 (m, 2H), 4.03 (m, 1H), 3.90 (m, 1H), 3.71 (s, 1H), 3.43 (m, 1H), 3.29 (m, 1H), 2.44 (m, 1H), 1.76 (m, 1H), 1.48 (m, 1H), 1.31–1.28 (m, 4H), 1.01 (m, 1H). $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ 174.8, 140.0, 128.2, 127.6, 125.9, 79.9, 68.1, 67.6, 62.7, 43.3, 27.2, 25.6, 14.1. **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{O}_4$, 265.1434; found, 265.1432.

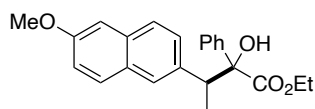
Ethyl 3-Cyclopentyl-2-hydroxy-2,3-diphenylpropanoate (**3la**)



The product **3la** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 59.6 mg, 0.18 mmol, 88% isolated yield). The diastereomeric ratio

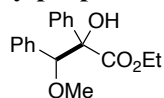
(1:1) is determined by ^1H NMR. Colorless oil. **IR** (neat) 1032, 1069, 1120, 1240, 1447, 1717, 2955, 3490 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.85 (d, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.39–7.08 (m, 5H), 6.99–6.95 (m, 2H), 4.28 (m, 1H), 4.10 (s, 0.5H), 4.02 (s, 0.5H), 3.79 (m, 1H), 3.52 (d, $J = 9.2$ Hz, 0.5H), 3.41 (d, $J = 9.2$ Hz, 0.5H), 2.45 (m, 0.5H), 2.30 (m, 0.5H), 1.82 (m, 0.5H), 1.66–0.91 (m, 10H), 0.51 (m, 0.5H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 176.3, 174.9, 141.8, 141.7, 141.6, 141.1, 129.9, 129.7, 127.8, 127.7, 127.5, 127.4, 127.2, 126.8, 126.6, 126.5, 126.0, 125.7, 81.0, 80.9, 62.7, 62.3, 58.6, 57.9, 43.3, 42.1, 32.5 ($\times 2\text{C}$), 32.3, 31.1, 25.3, 25.1, 23.5, 23.4, 14.0, 13.6. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{NO}_3$, 356.2220; found, 356.2199.

Ethyl 2-Hydroxy-3-(6-methoxynaphthalen-2-yl)-2-phenylbutanoate (3ma)



The product **3ma** was purified by flash chromatography on silica gel (100:0–91:9, hexane/EtOAc) (Table 2-2; 69.2 mg, 0.19 mmol, 95% isolated yield). The diastereomeric ratio (1:1) is determined by ^1H NMR. White solid. **M.p.** 84–86 $^{\circ}\text{C}$. **IR** (neat) 1032, 1135, 1176, 1237, 1485, 1606, 1722, 2979, 3502 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.85 (d, $J = 7.6$ Hz, 1H), 7.79 (s, 0.5H), 7.69 (m, 1H), 7.58–7.51 (m, 2H), 7.44–7.40 (m, 2H), 7.34 (m, 0.5H), 7.24 (m, 0.5H), 7.14–7.03 (m, 3H), 6.98 (s, 0.5H), 4.35 (m, 1H), 3.98–3.79 (m, 6H), 1.45 (d, $J = 6.8$ Hz, 1.5H), 1.38 (t, $J = 7.2$ Hz, 1.5H), 1.18–1.11 (m, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 175.2, 174.6, 157.4, 157.1, 140.9, 140.7, 137.1, 136.5, 133.7, 133.1, 129.2 ($\times 2\text{C}$), 128.7, 128.5, 128.2, 128.1, 127.9, 127.9, 127.7 ($\times 2\text{C}$), 127.6, 127.2, 126.3, 126.3, 125.9, 125.6, 118.7, 118.2, 105.5, 105.3, 81.2, 81.0, 62.8, 62.4, 55.3, 55.2, 47.6, 47.5, 17.1, 15.2, 14.1, 13.9. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4$, 382.2013; found, 382.2011.

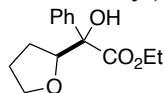
Ethyl 2-Hydroxy-3-methoxy-2,3-diphenylpropanoate (3na)



The product **3na** was purified by flash chromatography on silica gel (100:0–95:5, hexane/EtOAc) (Table 2-2; 57.1 mg, 0.19 mmol, 95% isolated yield). The diastereomeric ratio (1:1) is determined by ^1H NMR. Pale yellow oil. **IR** (neat) 1033, 1073, 1095, 1135, 1242, 1448, 1726, 2982, 3502 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.79 (d, $J = 7.6$ Hz, 1H), 7.53–7.46 (m, 2H), 7.41–7.25 (m, 3H), 7.22–7.10 (m, 3H), 7.03 (m, 1H), 4.98 (s, 0.5H), 4.91 (s, 0.5H), 4.37 (m, 1H), 4.05 (m, 1H), 3.78 (s, 0.5H), 3.63 (s, 0.5H), 3.30 (s, 1.5H), 3.13 (s, 1.5H), 1.38 (t, $J = 7.2$ Hz, 1.5H), 1.17 (t, $J = 7.2$ Hz, 1.5H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.7, 172.3, 139.5, 137.6, 136.1, 134.9, 128.9, 128.7, 128.5, 128.1, 127.9, 127.81, 127.8, 127.8, 127.7, 127.3, 126.2, 126.0,

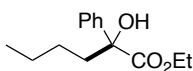
87.7, 86.4, 81.4, 81.0, 62.5, 62.4, 57.5, 57.4, 14.2, 13.9. **HRMS–DART** (m/z): $[M+NH_4]^+$ calcd for $C_{18}H_{24}NO_4$, 318.1700; found, 318.1694.

Ethyl 2-Hydroxy-2-phenyl-2-(tetrahydrofuran-2-yl)acetate (3oa)



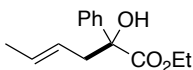
The product **3oa** was purified by flash chromatography on silica gel (100:0–90:10, hexane/EtOAc) (Table 2-2; 29.0 mg, 0.12 mmol, 58% isolated yield). The diastereomeric ratio (1:1) is determined by 1H NMR. The spectrum data of product **3oa** was consistent with the literature ¹⁴.

Ethyl 2-Hydroxy-2-phenylhexanoate (3pa)



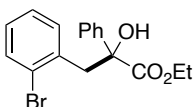
The product **3pa** was purified by flash chromatography on silica gel (100:0–95:5, hexane/EtOAc) (Table 2-2; 18.9 mg, 0.08 mmol, 40% isolated yield). The spectrum data of product **3pa** was consistent with the literature ¹⁵.

Ethyl 2-Hydroxy-2-phenylhex-4-enoate (3qa)



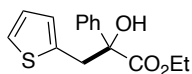
The product **3qa** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 28.6 mg, 0.12 mmol, 61% isolated yield). The spectrum data of product **3qa** was consistent with the literature ¹⁶.

Ethyl 3-(2-Bromophenyl)-2-hydroxy-2-phenylpropanoate (3ra)



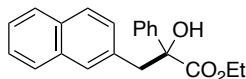
The product **3ra** was purified by flash chromatography on silica gel (100:0–95:5, hexane/EtOAc) (Table 2-2; 47.5 mg, 0.14 mmol, 68% isolated yield). Colorless oil. **IR** (neat) 1023, 1070, 1095, 1210, 1252, 1440, 1470, 1720, 2980, 3494 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.39–7.31 (m, 4H), 7.17 (t, J = 7.2 Hz, 1H), 7.07 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.84 (d, J = 14.4 Hz, 1H), 3.76 (s, 1H), 3.48 (d, J = 14.4 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.3, 141.6, 135.7, 132.8, 131.6, 128.3, 128.2, 127.9, 127.0, 126.2, 125.7, 78.6, 62.7, 44.2, 13.9. **HRMS–DART** (m/z): $[M+NH_4]^+$ calcd for $C_{17}H_{21}BrNO_3$, 366.0699; found, 366.0698.

Ethyl 2-Hydroxy-2-phenyl-3-(thiophen-2-yl)propanoate (3sa)



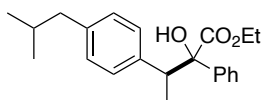
The product **3sa** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 42.0 mg, 0.15 mmol, 76% isolated yield). Brown oil. **IR** (neat) 1070, 1097, 1148, 1208, 1240, 1447, 1722, 2980, 3502 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.70 (d, J = 7.2 Hz, 2H), 7.40–7.32 (m, 3H), 7.17 (d, J = 4.8 Hz, 1H), 6.94–6.91 (m, 2H), 4.21–4.18 (m, 2H), 3.86 (s, 1H), 3.83 (d, J = 14.8 Hz, 1H), 3.39 (t, J = 14.8 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.0, 141.0, 137.2, 128.3, 128.0, 127.5, 126.4, 125.6, 125.0, 78.3, 62.6, 40.5, 14.0. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3\text{S}$, 294.1158; found, 294.1163.

Ethyl 2-Hydroxy-3-(naphthalen-2-yl)-2-phenylpropanoate (3ta)



The product **3ta** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-2; 35.2 mg, 0.11 mmol, 55% isolated yield). White solid. **M.p.** 71–73 °C. **IR** (neat) 1072, 1101, 1198, 1220, 1447, 1508, 1724, 2980, 3502 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.81–7.71 (m, 6H), 7.45–7.31 (m, 6H), 4.22–4.14 (m, 2H), 3.75 (d, J = 13.6 Hz, 1H), 3.70 (s, 1H), 3.37 (d, J = 13.6 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.2, 141.7, 133.4, 133.2, 132.4, 129.3, 128.9, 128.3, 127.9, 127.7, 127.6, 127.4, 125.8, 125.7, 125.6, 78.8, 62.5, 46.0, 14.1. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_3$, 338.1751; found, 338.1756.

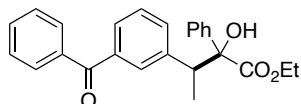
Ethyl 2-Hydroxy-3-(4-isobutylphenyl)-2-phenylbutanoate (3ua)



The product **3ua** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-2; 60.6 mg, 0.18 mmol, 89% isolated yield). The diastereomeric ratio (1:1) is determined by ^1H NMR. Colorless oil. **IR** (neat) 1020, 1133, 1176, 1242, 1366, 1447, 1511, 1721, 2954, 3502 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.82 (d, J = 7.6 Hz, 1H), 7.47–7.31 (m, 3.5H), 7.16–7.05 (m, 2.5H), 6.94 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 4.33 (m, 1H), 3.97 (q, J = 7.2 Hz, 1H), 3.78 (s, 0.5H), 3.71–3.64 (m, 1.5H), 2.44 (d, J = 7.2 Hz, 1H), 2.31 (d, J = 7.2 Hz, 1H), 1.84 (m, 0.5H), 1.73 (m, 0.5H), 1.39–1.35 (m, 3H), 1.14–1.07 (m, 3H), 0.90–0.87 (m, 3H), 0.81–0.78 (m, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 175.2, 174.6, 141.0, 140.7, 140.3, 139.4, 139.0, 138.1, 128.9, 128.7 ($\times$ 2C), 128.1 ($\times$ 2C), 127.6, 127.5, 127.1, 126.3, 125.8, 81.2, 80.8, 62.7, 62.3, 47.5, 47.3, 45.1, 44.9, 30.2, 30.1, 22.4, 22.3, 22.3, 22.2, 16.7, 15.1, 14.1, 13.9.

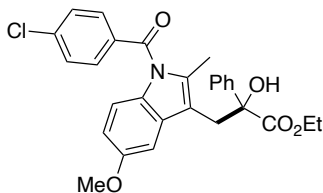
HRMS–DART (m/z): $[M+NH_4]^+$ calcd for $C_{22}H_{32}NO_3$, 358.2377; found, 358.2383.

Ethyl 3-(3-Benzoylphenyl)-2-hydroxy-2-phenylbutanoate (3va)



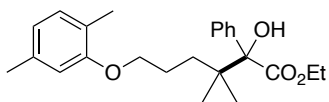
The product **3va** was purified by flash chromatography on silica gel (100:0–92:8, hexane/EtOAc) (Table 2-2; 62.9 mg, 0.16 mmol, 81% isolated yield). The diastereomeric ratio (1:1) is determined by 1H NMR. Pale yellow oil. **IR** (neat) 1132, 1177, 1245, 1284, 1447, 1597, 1655, 1720, 2979, 3491 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 7.90 (s, 0.5H), 7.80 (d, J = 7.6 Hz, 2H), 7.69 (m, 1H), 7.59–7.32 (m, 8.5H), 7.24–7.17 (m, 2H), 4.34 (m, 1H), 4.01 (q, J = 7.2 Hz, 1H), 3.89 (s, 0.5H), 3.82–3.72 (m, 1.5H), 1.40–1.35 (m, 3H), 1.16–1.11 (m, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 196.81, 196.76, 174.9, 174.5, 142.3, 141.2, 140.7, 140.4, 137.7, 137.6, 137.2, 136.6, 133.3, 133.2, 132.4, 132.2, 131.4, 130.9, 130.1, 130.0, 128.9, 128.3, 128.2, 128.1, 127.94, 127.86 ($\times$ 2C), 127.70, 127.65, 127.4, 126.2, 125.8, 80.9, 80.6, 62.9, 62.7, 47.6, 47.5, 16.9, 15.1, 14.1, 13.8. **HRMS–DART** (m/z): $[M+NH_4]^+$ calcd for $C_{25}H_{28}NO_4$, 406.2013; found, 406.2013.

Ethyl 3-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-2-hydroxy-2-phenylpropanoate (3wa)



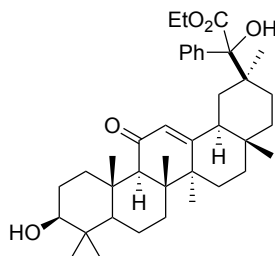
The product **3wa** was purified by flash chromatography on silica gel (90:10–80:20, hexane/EtOAc) (Table 2-2; 41.3 mg, 0.08 mmol, 42% isolated yield). Off white solid. **M.p.** 115–117 $^{\circ}C$. **IR** (neat) 1089, 1232, 1357, 1476, 1595, 1683, 1725, 2364, 2980, 3503 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.45–7.33 (m, 5H), 7.08 (s, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 4.28–4.12 (m, 2H), 3.82 (s, 3H), 3.67–3.63 (m, 2H), 3.30 (m, 1H), 2.14 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.4, 168.3, 155.7, 141.7, 139.1, 136.7, 134.1, 131.8, 131.2, 130.9, 129.0, 128.2, 127.9, 125.7, 114.5, 114.1, 111.3, 103.0, 79.2, 62.6, 55.7, 35.3, 14.0, 13.9. **HRMS–DART** (m/z): $[M+NH_4]^+$ calcd for $C_{28}H_{30}ClN_2O_5$, 509.1838; found, 509.1832.

Ethyl 6-(2,5-Dimethylphenoxy)-2-hydroxy-3,3-dimethyl-2-phenylhexanoate (3xa)



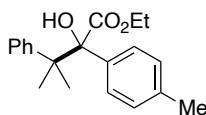
The product **3xa** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-2; 60.0 mg, 0.16 mmol, 78% isolated yield). Colorless oil. **IR** (neat) 1032, 1129, 1156, 1245, 1388, 1508, 1712, 2971, 3502 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.75–7.73 (m, 2H), 7.34–7.28 (m, 3H), 6.99 (d, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 7.6$ Hz, 1H), 6.60 (s, 1H), 4.34 (q, $J = 7.2$ Hz, 2H), 3.88 (t, $J = 6.0$ Hz, 2H), 3.80 (s, 1H), 2.30 (s, 3H), 2.14 (s, 3H), 1.75–1.71 (m, 3H), 1.49 (m, 1H), 1.38 (t, $J = 7.2$ Hz, 3H), 1.05 (s, 3H), 0.99 (s, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.5, 157.0, 139.0, 136.4, 130.2, 127.6, 127.5, 127.3, 123.6, 120.5, 112.0, 83.4, 68.5, 62.4, 41.5, 32.9, 24.5, 22.1, 21.7, 21.4, 15.7, 14.2. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{24}\text{H}_{36}\text{NO}_4$, 402.2639; found, 402.2640.

Ethyl 2-Hydroxy-2-(10-hydroxy-2,4a,6a,6b,9,12a-heptamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydricen-2-yl)-2-phenylacetate (3ya)



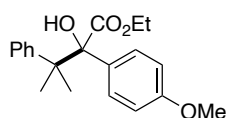
The product **3ya** was purified by flash chromatography on silica gel (90:10–70:30, hexane/EtOAc) (Table 2-2; 108.9 mg, 0.18 mmol, 90% isolated yield). The diastereomeric ratio is not determined. Pale yellow oil. **IR** (neat) 994, 1029, 1207, 1386, 1453, 1651, 1743, 2929, 3491 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.75 (m, 1H), 7.46 (m, 1H), 7.34–7.30 (m, 3H), 5.13 (s, 0.5H), 4.94 (s, 0.5H), 4.33 (m, 1H), 4.17–4.13 (m, 1.5H), 3.75 (m, 0.5H), 3.23 (brs, 1H), 2.77 (m, 1H), 2.30 (m, 1H), 2.09–1.97 (m, 2H), 1.84–1.00 (m, 34H), 0.85–0.70 (m, 8H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 200.4, 200.3, 200.2, 200.1, 174.2, 174.14, 174.06, 174.0, 172.5, 172.3, 172.2, 170.3, 170.1, 169.6, 169.5, 168.8, 168.6, 168.5, 128.7, 128.6, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.6, 127.6, 127.5, 127.4, 127.2, 126.6, 126.5, 126.5, 126.4, 78.68, 78.65, 78.6, 78.2, 75.9, 75.8, 72.9, 61.74, 61.72, 61.67, 61.1, 61.03, 61.02, 60.98, 54.9, 54.84, 54.79, 48.8, 46.0, 45.31, 45.30, 43.23, 43.17, 43.1, 39.1, 37.01, 36.99, 35.3, 32.6, 32.52, 32.50, 32.0, 31.6, 28.4, 28.3, 28.2, 28.0, 27.2, 26.4, 26.33, 26.26, 26.2, 23.34, 23.25, 23.2, 20.9, 18.7, 18.62, 18.57, 17.4, 16.30, 16.27, 15.6, 15.5, 14.1, 14.0 (only observed peaks). **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{39}\text{H}_{57}\text{O}_5$, 605.4201; found, 605.4195.

Ethyl 2-Hydroxy-3-methyl-3-phenyl-2-(*p*-tolyl)butanoate (3ab)



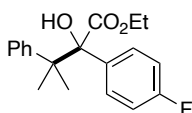
The product **3ab** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-3; 53.1 mg, 0.17 mmol, 85% isolated yield). Colorless oil. **IR** (neat) 1032, 1068, 1216, 1243, 1364, 1510, 1715, 2979, 3492 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.58 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.26–7.20 (m, 3H), 7.11 (d, J = 8.0 Hz, 2H), 4.11–4.07 (m, 2H), 3.64 (s, 1H), 2.35 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.6, 145.0, 137.2, 135.8, 128.3, 127.9, 127.7, 127.1, 126.3, 82.5, 62.2, 45.9, 25.1, 24.4, 21.0, 13.9. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_3$, 330.2064; found, 330.2063.

Ethyl 2-Hydroxy-2-(4-methoxyphenyl)-3-methyl-3-phenylbutanoate (**3ac**)



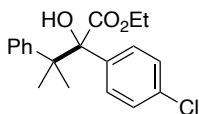
The product **3ac** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-3; 62.4 mg, 0.19 mmol, 95% isolated yield). Colorless oil. **IR** (neat) 1031, 1067, 1087, 1175, 1244, 1508, 1608, 1715, 2979, 3489 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.61 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.26–7.21 (m, 3H), 6.83 (d, J = 8.4 Hz, 2H), 4.14–4.07 (m, 2H), 3.82 (s, 3H), 3.65 (s, 1H), 1.50 (s, 3H), 1.36 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.7, 159.0, 144.9, 130.8, 129.1, 128.3, 127.1, 126.3, 112.4, 82.3, 62.2, 55.2, 46.1, 25.1, 24.4, 13.9. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_4$, 346.2013; found, 346.2010.

Ethyl 2-(4-Fluorophenyl)-2-hydroxy-3-methyl-3-phenylbutanoate (**3ad**)



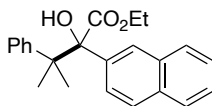
The product **3ad** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-3; 54.4 mg, 0.17 mmol, 86% isolated yield). Colorless oil. **IR** (neat) 1015, 1031, 1068, 1162, 1223, 1505, 1602, 1716, 2980, 3487 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.69–7.66 (m, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.26–7.20 (m, 3H), 7.00–6.95 (m, 2H), 4.14–4.08 (m, 2H), 3.72 (s, 1H), 1.50 (s, 3H), 1.35 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.3, 162.4 (d, $J_{\text{C-F}}$ = 246.5 Hz), 144.5, 134.3 (d, $J_{\text{C-F}}$ = 3.0 Hz), 129.7 (d, $J_{\text{C-F}}$ = 8.0 Hz), 128.2, 127.2, 126.4, 113.8 (d, $J_{\text{C-F}}$ = 21.1 Hz), 82.2, 62.4, 46.1, 25.0, 24.3, 13.9. **^{19}F NMR** (376.5 MHz, CDCl_3) δ –115.5 (s). **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{19}\text{H}_{25}\text{FNO}_3$, 334.1813; found, 334.1809.

Ethyl 2-(4-Chlorophenyl)-2-hydroxy-3-methyl-3-phenylbutanoate (3ae)



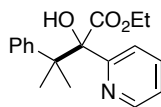
The product **3ae** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-3; 53.3 mg, 0.16 mmol, 80% isolated yield). Colorless oil. **IR** (neat) 1013, 1068, 1093, 1167, 1242, 1489, 1717, 2980, 3490 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.64 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.28–7.23 (m, 5H), 4.12–4.10 (m, 2H), 3.71 (s, 1H), 1.50 (s, 3H), 1.35 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.2, 144.4, 137.2, 133.7, 129.4, 128.2, 127.2, 127.2, 126.5, 82.3, 62.5, 46.1, 25.9, 24.3, 13.9. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{19}\text{H}_{25}\text{ClNO}_3$, 350.1517; found, 350.1517.

Ethyl 2-Hydroxy-3-methyl-2-(naphthalen-2-yl)-3-phenylbutanoate (3af)



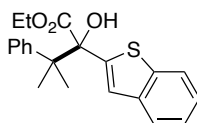
The product **3af** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-3; 53.7 mg, 0.15 mmol, 77% isolated yield). Colorless oil. **IR** (neat) 1031, 1068, 1091, 1227, 1364, 1714, 2977, 3488 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 8.19 (s, 1H), 7.85–7.82 (m, 3H), 7.76 (m, 1H), 7.49–7.47 (m, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.27–7.21 (m, 3H), 4.17–4.13 (m, 2H), 3.80 (s, 1H), 1.57 (s, 3H), 1.42 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.4, 144.8, 136.3, 132.7, 132.4, 128.6, 128.3, 127.3, 127.2, 126.4, 126.3, 126.1 ($\times$ 2C), 125.9, 125.8, 82.8, 62.4, 46.3, 25.2, 24.5, 14.0. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_3$, 366.2064; found, 366.2066.

Ethyl 2-Hydroxy-3-methyl-3-phenyl-2-(pyridin-2-yl)butanoate (3ag)



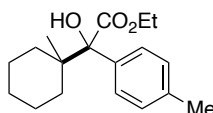
The product **3ag** was purified by flash chromatography on silica gel (98:2–90:10, hexane/EtOAc) (Table 2-3; 51.5 mg, 0.17 mmol, 86% isolated yield). White solid. **M.p.** 89–91 $^{\circ}\text{C}$. **IR** (neat) 1033, 1094, 1240, 1435, 1590, 1719, 2979, 3304 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 8.43 (d, J = 4.8 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.26–7.19 (m, 6H), 6.36 (s, 1H), 4.14–4.02 (m, 2H), 1.54 (s, 3H), 1.43 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 172.3, 155.6, 146.4, 144.4, 135.8, 128.2, 127.1, 126.2, 123.9, 123.0, 82.3, 61.3, 47.0, 24.9, 24.5, 13.9. **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_3$, 300.1594; found, 300.1591.

Ethyl 2-(Benzo[*b*]thiophen-2-yl)-2-hydroxy-3-methyl-3-phenylbutanoate (**3ah**)



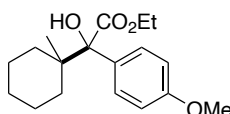
The product **3ah** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-3; 26.9 mg, 0.08 mmol, 38% isolated yield). Colorless oil. **IR** (neat) 1014, 1066, 1098, 1125, 1244, 1366, 1458, 1719, 2979, 3481 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.80 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.45–7.43 (m, 3H), 7.34–7.23 (m, 5H), 4.16 (q, J = 7.2 Hz, 2H), 4.07 (s, 1H), 1.66 (s, 3H), 1.52 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 172.6, 144.4, 144.1, 139.5, 128.0, 127.4 ($\times$ 2C), 126.7, 124.03, 123.99, 123.5, 123.1, 121.8, 82.2, 62.9, 46.3, 24.8, 24.4, 13.9. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_3\text{S}$, 372.1628; found, 372.1631.

Ethyl 2-Hydroxy-2-(1-methylcyclohexyl)-2-(*p*-tolyl)acetate (**3db**)

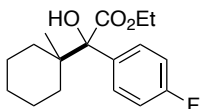


The product **3db** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-3; 40.1 mg, 0.14 mmol, 69% isolated yield). Colorless oil. **IR** (neat) 1010, 1065, 1182, 1213, 1240, 1446, 1510, 1709, 2923, 3496 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.61 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.77 (s, 1H), 2.33 (s, 3H), 1.64–1.31 (m, 12H), 1.04–0.95 (m, 4H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.7, 137.0, 135.7, 127.8, 127.7, 83.5, 62.3, 41.9, 31.4, 30.9, 25.9, 22.0, 21.8, 20.9, 17.5, 14.2. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{18}\text{H}_{30}\text{NO}_3$, 308.2220; found, 308.2224.

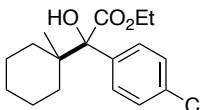
Ethyl 2-Hydroxy-2-(4-methoxyphenyl)-2-(1-methylcyclohexyl)acetate (**3dc**)



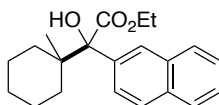
The product **3dc** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-3; 39.2 mg, 0.13 mmol, 64% isolated yield). Colorless oil. **IR** (neat) 1033, 1064, 1178, 1239, 1508, 1608, 1709, 2925, 3496 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.65 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 1H), 1.62–1.49 (m, 5H), 1.42–1.30 (m, 7H), 1.01–0.97 (m, 4H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.7, 158.8, 130.7, 129.0, 112.4, 83.3, 62.3, 55.2, 41.9, 31.4, 30.9, 25.9, 22.0, 21.8, 17.4, 14.2. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{18}\text{H}_{30}\text{NO}_4$, 342.2169; found, 342.2165.

Ethyl 2-(4-Fluorophenyl)-2-hydroxy-2-(1-methylcyclohexyl)acetate (3dd)

The product **3dd** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Table 2-3; 37.7 mg, 0.13 mmol, 64% isolated yield). Colorless oil. **IR** (neat) 1015, 1064, 1162, 1221, 1505, 1602, 1711, 2926, 3492 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.73–7.69 (m, 2H), 7.01–6.97 (m, 2H), 4.34 (q, $J = 7.2$ Hz, 2H), 3.85 (s, 1H), 1.61–1.41 (m, 5H), 1.39–1.28 (m, 7H), 1.04–0.94 (m, 4H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.4, 162.2 (d, $J_{\text{C-F}} = 246.5$ Hz), 134.2 (d, $J_{\text{C-F}} = 3.0$ Hz), 129.6 (d, $J_{\text{C-F}} = 8.0$ Hz), 113.8 (d, $J_{\text{C-F}} = 21.1$ Hz), 83.3, 62.5, 42.0, 31.4, 30.8, 25.9, 21.9, 21.7, 17.4, 14.2. **^{19}F NMR** (376.5 MHz, CDCl_3) δ –116.0 (s). **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{17}\text{H}_{27}\text{FNO}_3$, 312.1969; found, 312.1967.

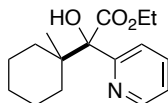
Ethyl 2-(4-Chlorophenyl)-2-hydroxy-2-(1-methylcyclohexyl)acetate (3de)

The product **3de** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-3; 33.6 mg, 0.11 mmol, 54% isolated yield). Colorless oil. **IR** (neat) 1014, 1065, 1094, 1216, 1240, 1490, 1712, 2926, 3491 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.68 (d, $J = 7.6$ Hz, 2H), 7.27 (d, $J = 7.6$ Hz, 2H), 4.34 (q, $J = 7.2$ Hz, 2H), 3.85 (s, 1H), 1.60–1.28 (m, 12H), 1.00–0.94 (m, 4H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.3, 137.1, 133.4, 129.3, 127.2, 83.3, 62.6, 42.1, 31.4, 30.8, 25.9, 21.9, 21.7, 17.4, 14.2. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{17}\text{H}_{27}\text{ClNO}_3$, 328.1674; found, 328.1671.

Ethyl 2-Hydroxy-2-(1-methylcyclohexyl)-2-(naphthalen-2-yl)acetate (3df)

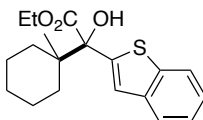
The product **3df** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-3; 17.6 mg, 0.05 mmol, 27% isolated yield). Colorless oil. **IR** (neat) 1018, 1067, 1084, 1157, 1216, 1237, 1446, 1710, 2924, 3494 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 8.21 (s, 1H), 7.89–7.76 (m, 4H), 7.48–7.46 (m, 2H), 4.40–4.35 (m, 2H), 3.92 (s, 1H), 1.73–1.26 (m, 12H), 1.08 (s, 3H), 0.98 (m, 1H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 174.5, 136.3, 132.6, 132.5, 128.5, 127.3, 127.0, 126.3, 126.0, 126.0, 125.8, 83.9, 62.4, 42.4, 31.6, 31.0, 25.9, 22.0, 21.8, 17.6, 14.3. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{21}\text{H}_{30}\text{NO}_3$, 344.2220; found, 344.2216.

Ethyl 2-Hydroxy-2-(1-methylcyclohexyl)-2-(pyridin-2-yl)acetate (3dg)



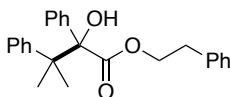
The product **3dg** was purified by flash chromatography on silica gel (100:0–95:5, hexane/EtOAc) (Table 2-3; 37.2 mg, 0.13 mmol, 67% isolated yield). Colorless oil. **IR** (neat) 1030, 1088, 1234, 1434, 1590, 1718, 2924, 3315 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 8.53 (d, J = 4.8 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.71 (m, 1H), 7.27 (m, 1H), 6.36 (s, 1H), 4.32–4.18 (m, 2H), 1.62–1.26 (m, 12H), 1.03–0.96 (m, 4H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 172.8, 155.7, 146.4, 135.9, 123.9, 122.9, 83.1, 61.3, 43.3, 31.6, 31.0, 25.9, 22.0, 21.8, 17.4, 14.2. **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_3$, 278.1751; found, 278.1752.

Ethyl 2-(Benzo[*b*]thiophen-2-yl)-2-hydroxy-2-(1-methylcyclohexyl)acetate (3dh)



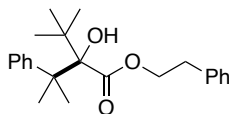
The product **3dh** was purified by flash chromatography on silica gel (100:0–96:4, hexane/EtOAc) (Table 2-3; 19.9 mg, 0.06 mmol, 30% isolated yield). Brown oil. **IR** (neat) 1013, 1066, 1086, 1242, 1458, 1716, 2924, 3484 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.79 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.43 (s, 1H), 7.34–7.26 (m, 2H), 4.42–4.34 (m, 2H), 4.30 (s, 1H), 1.72–1.56 (m, 7H), 1.44–1.26 (m, 5H), 1.14 (s, 3H), 1.03 (m, 1H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.7, 144.9, 139.7, 139.4, 124.0, 123.9, 123.4, 122.7, 121.8, 83.1, 63.0, 42.5, 31.4, 30.9, 25.9, 22.0, 21.8, 17.5, 14.2. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_3\text{S}$, 350.1784; found, 350.1782.

Phenethyl 2-Hydroxy-3-methyl-2,3-diphenylbutanoate (3aA)



The product **3aA** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Figure 2-7; 67.4 mg, 0.18 mmol, 90% isolated yield). Colorless oil. **IR** (neat) 1012, 1032, 1062, 1166, 1241, 1447, 1714, 3026, 3496 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.58 (d, J = 7.6 Hz, 2H), 7.34–7.15 (m, 13H), 4.33–4.17 (m, 2H), 3.65 (s, 1H), 2.89 (t, J = 6.8 Hz, 2H), 1.43 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.7, 144.8, 138.5, 137.3, 128.8, 128.6, 128.2, 127.8, 127.5, 127.2, 127.1, 126.8, 126.4, 82.8, 66.9, 45.9, 34.7, 25.1, 24.4. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_3$, 392.2220; found, 392.2221.

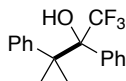
Phenethyl 2-(*tert*-Butyl)-2-hydroxy-3-methyl-3-phenylbutanoate (**3aC**)



The product **3aC** was purified by flash chromatography on silica gel (100:0 - 97:3, hexane/EtOAc) (Figure 2-7, Scheme D; 21.3 mg, 0.06 mmol, 30% isolated yield). Colorless oil. **IR** (neat) 1023, 1068, 1089, 1247, 1386, 1497, 1708, 2560, 3494 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.32–7.16 (m, 10H), 4.33 (brs, 1H), 4.09 (m, 1H), 3.67 (brs, 1H), 3.02 (brs, 2H), 1.57 (s, 6H), 0.98 (s, 9H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 176.8, 147.5, 137.5, 128.8, 128.6, 128.1, 127.1, 126.8, 126.1, 84.6, 67.0, 46.4, 40.4, 34.8, 28.5, 27.5, 27.1. **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{23}\text{H}_{34}\text{NO}_3$, 372.2533; found, 372.2531.

5. Characterization Data for Other Coupling Product

1,1,1-Trifluoro-3-methyl-2,3-diphenylbutan-2-ol (**8ae**)



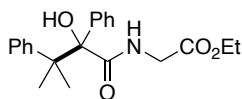
The product **8ae** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–82:18, hexane/EtOAc) (Table 2-5; 18.2 mg, 0.06 mmol, 31% isolated yield). Colorless oil. **IR** (neat) 1033, 1059, 1143, 1259, 1448, 1484, 2985, 3556 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.43–7.42 (m, 2H), 7.32–7.26 (m, 8H), 2.62 (s, 1H), 1.60 (s, 3H), 1.36 (s, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 143.6, 136.4, 128.3, 128.1, 127.7, 127.3, 127.1 (q, $J_{\text{C-F}} = 2.1$ Hz), 126.9, 126.8 (q, $J_{\text{C-F}} = 233.1$ Hz), 81.6 (q, $J_{\text{C-F}} = 25.7$ Hz), 44.8, 25.8 (q, $J_{\text{C-F}} = 2.4$ Hz), 25.0 (q, $J_{\text{C-F}} = 2.9$ Hz). **^{19}F NMR** (376.5 MHz, CDCl_3) δ –67.3 (s). **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{F}_3\text{NO}$, 312.1570; found, 312.1572.

6. Procedure for Synthesis of α -Hydroxyamides

The reaction to produce 6aa in Table 2-4 is representative. In a glovebox, to an oven-dried vial with a stirring bar was added photocatalyst 4Cz-IPN (1.6 mg, 0.002 mmol), 2-phenylisobutyric acid **1a** (32.8 mg, 0.2 mmol) and α -ketoamide **5a** (47.0 mg, 0.2 mmol) and DMSO (1.0 ml). Then, Cs_2CO_3 (32.6 mg, 0.1 mmol) and H_2O (18.0 μL , 1.0 mmol) were added to the reaction mixture. The reaction was stirred and irradiated with a 34W blue LED (0.5 cm away) with a cooling fan to keep the temperature around 40 $^\circ\text{C}$ (Figure S2-1). After 1 h, the reaction mixture was treated with saturated NH_4Cl aqueous solution (1.0 mL), then extracted with ethyl acetate (3 times) and dried over sodium sulfate. After filtration, the resulting solution was evaporated under reduced pressure. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (98:2–90:10, hexane/EtOAc) gave **6aa** (36.3 mg, 0.10 mmol) in 51% yield.

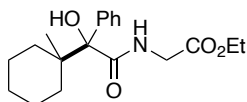
7. Characterization Data for α -Hydroxyamides

Ethyl (2-Hydroxy-3-methyl-2,3-diphenylbutanoyl)glycinate (**6aa**)



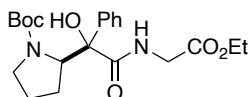
The product **6aa** was purified by flash chromatography on silica gel (98:2–90:10, hexane/EtOAc) (Table 2-4; 36.3 mg, 0.10 mmol, 51% isolated yield). Colorless oil. **IR** (neat) 1032, 1059, 1202, 1375, 1445, 1510, 1660, 1743, 2981, 3417 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.62 (d, $J = 7.2$ Hz, 2H), 7.35 (brs, 1H), 7.28–7.18 (m, 8H), 4.15 (q, $J = 7.2$ Hz, 2H), 3.96 (m, 1H), 3.80 (m, 1H), 2.64 (s, 1H), 1.66 (s, 3H), 1.48 (s, 3H), 1.22 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.0, 169.6, 143.3, 138.6, 128.2, 128.0, 127.6, 127.4, 127.1, 127.1, 81.5, 61.3, 46.8, 41.2, 24.83, 24.78, 14.1. **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_4$, 356.1856; found, 356.1858.

Ethyl [2-Hydroxy-2-(1-methylcyclohexyl)-2-phenylacetyl]glycinate (**6da**)



The product **6da** was purified by flash chromatography on silica gel (98:2–90:10, hexane/EtOAc) (Table 2-4; 21.3 mg, 0.06 mmol, 32% isolated yield). Colorless oil. **IR** (neat) 1022, 1060, 1199, 1376, 1510, 1647, 1746, 2912, 3330 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.80 (d, $J = 7.2$ Hz, 2H), 7.62 (brs, 1H), 7.32–7.26 (m, 3H), 4.21–4.09 (m, 3H), 3.84 (m, 1H), 2.82 (s, 1H), 1.73–1.23 (m, 12H), 1.07–0.99 (m, 4H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 173.6, 169.9, 138.4, 127.5, 127.4, 127.2, 83.7, 61.4, 42.0, 41.1, 31.6, 30.9, 25.7, 21.9, 21.7, 17.3, 14.1. **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{NO}$, 334.2013; found, 334.2016.

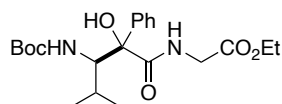
tert-Butyl 2-[2-[(2-Ethoxy-2-oxoethyl)amino]-1-hydroxy-2-oxo-1-phenylethyl]pyrrolidine-1-carboxylate (**6za**)



The product **6za** was purified by flash chromatography on silica gel (95:5–75:25, hexane/EtOAc) (Table 2-4; 69.9 mg, 0.17 mmol, 86% isolated yield). The diastereomeric ratio is not determined. Colorless oil. **IR** (neat) 1029, 1062, 1196, 1390, 1520, 1684, 1750, 2978, 3410 cm^{-1} . Signals for two rotamers were given: **^1H NMR** (400 MHz, CDCl_3) δ 7.47–7.43 (m, 2H), 7.34–7.27 (m, 3H), 5.41 (m, 1H), 5.10 (m, 1H), 4.22–4.20 (m, 2H), 4.07–3.88 (m, 2H), 3.54 (m, 1H), 3.40 (m, 1H), 3.21 (m, 1H), 2.17–1.78 (m, 4H), 1.47 (s, 4.5H), 1.37–1.25 (m, 7.5H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 172.4, 171.6, 171.3, 169.7, 169.4, 155.1, 154.6, 139.2, 138.6, 137.8,

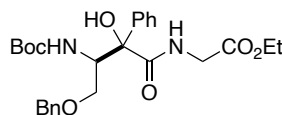
137.6, 128.7, 128.5, 128.34, 128.26, 128.1, 128.0, 127.6, 127.3, 126.8, 126.5, 126.3, 87.8, 87.1, 80.8, 80.4, 78.9, 78.6, 78.4, 74.1, 61.5, 61.1, 46.4, 45.5, 41.2, 41.0, 40.9, 33.6, 33.0, 32.6, 31.4, 28.3, 28.1, 22.6, 22.3, 21.6, 14.1 (only observed peaks). **HRMS–DART** (m/z): $[M+H]^+$ calcd for $C_{21}H_{31}N_2O_6$, 407.2177; found, 407.2175.

Ethyl {3-[(*tert*-Butoxycarbonyl)amino]-2-hydroxy-4-methyl-2-phenylpentanoyl}glycinate (6Aa)



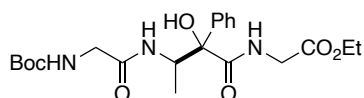
The product **6Aa** was purified by flash chromatography on silica gel (90:10–70:30, hexane/EtOAc) (Table 2-4; 64.5 mg, 0.16 mmol, 79% isolated yield). The diastereomeric ratio (1:1) is determined by 1H NMR. White solid. **M.p.** 98–100 °C. **IR** (neat) 1058, 1155, 1194, 1246, 1512, 1659, 1687, 1757, 2972, 3362 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.36–7.15 (m, 3H), 5.26 (d, J = 10.4 Hz, 0.5H), 5.10 (s, 0.5H), 5.04 (m, 1H), 4.81 (m, 0.5H), 4.72 (d, J = 10.0 Hz, 0.5H), 4.24–4.09 (m, 3H), 3.94 (m, 1H), 1.96 (m, 1H), 1.45–1.26 (m, 13H), 1.08–1.03 (m, 3H), 0.97–0.94 (m, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.5, 170.9, 170.2, 169.7, 155.4, 155.1, 138.7, 137.0, 128.4, 128.2, 127.9, 127.4, 127.0, 126.5, 86.3, 84.2, 80.0, 80.0, 79.4, 78.2, 61.6, 61.5, 41.1, 40.7, 33.3, 32.9, 28.23, 28.15, 17.7, 17.6, 17.4, 17.2, 14.1 ($\times$ 2C). **HRMS–DART** (m/z): $[M+H]^+$ calcd for $C_{21}H_{33}N_2O_6$, 409.2333; found, 409.2338.

Ethyl {4-(Benzyloxy)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-2-phenylbutanoyl}glycinate (6Ba)



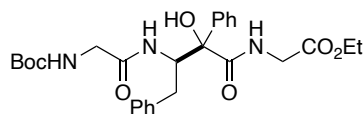
The product **6Ba** was purified by flash chromatography on silica gel (90:10–70:30, hexane/EtOAc) (Table 2-4; 61.3 mg, 0.13 mmol, 63% isolated yield). The diastereomeric ratio (1:1) is determined by 1H NMR. Colorless oil. **IR** (neat) 1024, 1056, 1201, 1367, 1522, 1674, 1715, 2979, 3332 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.35–7.26 (m, 8H), 6.05 (d, J = 9.6 Hz, 0.5H), 5.43 (brs, 0.5H), 5.25 (m, 1H), 5.07 (m, 1H), 4.60–4.56 (m, 2H), 4.20–4.09 (m, 2.5H), 3.88–3.57 (m, 3.5H), 1.45–1.40 (m, 9H), 1.29–1.23 (m, 4H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.6, 171.2, 170.0, 169.5, 154.8 ($\times$ 2C), 137.5, 137.3, 128.5, 128.4 ($\times$ 2C), 128.4 ($\times$ 2C), 128.1 ($\times$ 2C), 128.0, 127.9, 127.8, 127.4 ($\times$ 2C), 127.2 ($\times$ 2C), 80.9, 80.5, 80.4, 80.1, 78.8, 78.0, 73.62, 73.60, 71.3, 71.0, 61.4, 61.2, 40.6 ($\times$ 2C), 28.2, 28.1, 14.1 ($\times$ 2C). **HRMS–DART** (m/z): $[M+H]^+$ calcd for $C_{26}H_{35}N_2O_7$, 487.2439; found, 487.2433.

Ethyl (3-{2-[(*tert*-Butoxycarbonyl)amino]acetamido}-2-hydroxy-2-phenylbutanoyl)glycinate (6Ca)



The product **6Ca** was purified by flash chromatography on silica gel (100:0–95:5, DCM/MeOH) (Table 2-4; 75.2 mg, 0.17 mmol, 86% isolated yield). The sample contains unseparable impurities. The diastereomeric ratio (1:1) is determined by ^1H NMR. Pale yellow oil. **IR** (neat) 1026, 1081, 1169, 1202, 1367, 1521, 1669, 2980, 3311 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.45–7.41 (m, 2H), 7.36–7.20 (m, 3H), 7.13 (m, 0.5H), 6.94 (brs, 0.5H), 5.53 (brs, 1H), 5.30 (s, 1H), 5.01 (m, 1H), 4.25–4.17 (m, 3H), 4.13–3.78 (m, 3.5H), 3.48 (m, 0.5H), 1.49–1.43 (m, 10.5H), 1.31–1.24 (m, 4.5H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 171.6 ($\times$ 2C), 170.6, 170.6, 170.1 ($\times$ 2C), 169.7, 169.6, 136.9 ($\times$ 2C), 128.5, 128.4, 128.3, 128.2, 127.0, 126.9, 80.1, 79.5, 78.9 ($\times$ 2C), 76.1 ($\times$ 2C), 61.7, 61.5, 41.0, 40.9, 40.7 ($\times$ 2C), 28.3, 28.2, 21.4, 21.3, 14.1 ($\times$ 2C). **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{32}\text{N}_3\text{O}_7$, 438.2235; found, 438.2237.

Ethyl (3-{2-[(*tert*-Butoxycarbonyl)amino]acetamido}-2-hydroxy-2,4-diphenylbutanoyl)glycinate (6Da)



The product **6Da** was purified by flash chromatography on silica gel (90:10–60:40, hexane/EtOAc) (Table 2-4; 53.4 mg, 0.10 mmol, 52% isolated yield). White solid. **M.p.** 123–125 $^{\circ}\text{C}$. **IR** (neat) 1026, 1063, 1168, 1203, 1248, 1520, 1676, 2979, 3305 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.35–7.26 (m, 10H), 7.06 (d, J = 10.0 Hz, 1H), 6.69 (brs, 1H), 5.77 (m, 0.5H), 5.28 (brs, 0.5H), 4.95 (m, 1H), 4.22–4.09 (m, 3H), 3.89–3.77 (m, 2H), 3.53 (m, 1H), 3.14 (m, 1H), 2.97 (m, 1H), 1.47–1.42 (m, 9H), 1.30–1.27 (m, 4H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 172.0 ($\times$ 2C), 170.5 ($\times$ 2C), 170.2 ($\times$ 2C), 169.5, 169.3, 136.4, 135.1 ($\times$ 2C), 130.3, 129.8, 128.8, 128.6 ($\times$ 2C), 128.4, 128.4, 128.33, 128.3, 127.1 ($\times$ 2C), 127.0, 126.6, 80.7, 80.2, 78.5, 78.2, 61.8 ($\times$ 2C), 61.3 ($\times$ 2C), 41.9 ($\times$ 2C), 41.1, 40.8, 40.5 ($\times$ 2C), 28.3, 28.2, 14.1 ($\times$ 2C). **HRMS–DART** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{36}\text{N}_3\text{O}_7$, 514.2548; found, 514.2545.

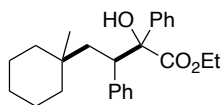
8. Procedure for Three-Component Coupling

The reaction to produce 10daa in Figure 2-4 is representative. In a glovebox, to an oven-dried vial with a stirring bar was added photocatalyst 4Cz-IPN (1.6 mg, 0.002 mmol), 1-methyl-1-cyclohexanecarboxylic acid **1d** (28.4 mg, 0.2 mmol) and styrene **9** (68.7 μL , 0.6 mmol) and ethyl benzylformate **2a** (31.8 μL , 0.2 mmol) and DMSO (1.0 ml). Then, Cs_2CO_3 (130.3 mg, 0.4 mmol) was added to the reaction mixture. The reaction was stirred and irradiated with a 34W blue LED

(0.5 cm away) with a cooling fan to keep the temperature around 40 °C (Figure S2-1). After 1 h, the reaction mixture was treated with saturated NH₄Cl aqueous solution (1.0 mL), then extracted with diethyl ether (3 times) and dried over sodium sulfate. After filtration, the resulting solution was evaporated under reduced pressure. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (100:0–97:3, hexane/EtOAc) gave **10daa** (61.6 mg, 0.16 mmol) in 81% yield.

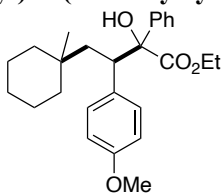
9. Characterization Data for Three-Component Coupling Products

Ethyl 2-Hydroxy-4-(1-methylcyclohexyl)-2,3-diphenylbutanoate (**10daa**)



The product **10daa** was purified by flash chromatography on silica gel (100:0–97:3, hexane/EtOAc) (Figure 2-4; 61.6 mg, 0.16 mmol, 81% isolated yield). The diastereomeric ratio (1:1) is determined by ¹H NMR. Colorless oil. **IR** (neat) 1024, 1070, 1104, 1234, 1447, 1719, 2923, 3497 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.47–7.30 (m, 3H), 7.28–7.20 (m, 2H), 7.13–6.97 (m, 4H), 4.33 (m, 1H), 3.96–3.87 (m, 1.5H), 3.77 (s, 0.5H), 3.63 (m, 1H), 2.21 (m, 0.5H), 1.85 (m, 0.5H), 1.41–1.32 (m, 4H), 1.23–0.94 (m, 9H), 0.84 (m, 1H), 0.70 (s, 1.5H), 0.49 (s, 1.5H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 175.4, 174.4, 141.7, 140.8 (× 2C), 140.6, 130.3 (× 2C), 128.0, 127.7, 127.6, 127.5, 127.0, 127.0, 126.8, 126.7, 125.9, 125.8, 82.8, 82.2, 62.8, 62.4, 49.5, 49.4, 43.8, 40.8, 38.8, 38.4, 38.3, 38.2, 33.4, 33.0, 26.3, 26.2, 25.1 (× 2C), 22.0, 21.8, 21.8, 21.7, 14.1, 13.9. **HRMS–DART** (*m/z*): [M+NH₄]⁺ calcd for C₂₅H₃₆NO₃, 398.2690; found, 398.2691.

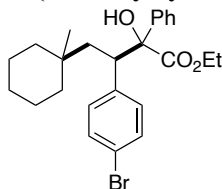
Ethyl 2-Hydroxy-3-(4-methoxyphenyl)-4-(1-methylcyclohexyl)-2-phenylbutanoate (**10dba**)



The product **10dba** was purified by flash chromatography on silica gel (100:0–95:5, hexane/EtOAc) (Figure 2-4; 56.7 mg, 0.14 mmol, 69% isolated yield). The diastereomeric ratio (1:1) is determined by ¹H NMR. Colorless oil. **IR** (neat) 1033, 1116, 1177, 1243, 1446, 1510, 1719, 2924, 3502 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.82 (d, *J* = 7.6 Hz, 1H), 7.44–7.26 (m, 3H), 7.15–6.99 (m, 3H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 4.31 (m, 1H), 3.95–3.85 (m, 1.5H), 3.79 (s, 1.5H), 3.75 (s, 0.5H), 3.66 (s, 1.5H), 3.59 (m, 1H), 2.15 (m, 0.5H), 1.79 (m, 0.5H), 1.39–0.94 (m, 13H), 0.85 (m, 1H), 0.70 (s, 1.5H), 0.50 (s, 1.5H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 175.5, 174.6, 158.3, 157.7, 140.9, 140.7, 133.7, 132.8, 131.1 (× 2C), 128.0, 127.5 (× 2C), 127.0, 126.7, 125.8, 113.0, 112.4, 82.9, 82.4, 62.7, 62.3, 55.1, 54.9, 48.5, 48.5, 43.8, 40.9,

38.8, 38.5, 38.3, 38.2, 33.3, 33.0, 26.3, 26.2, 25.3 ($\times 2C$), 22.0, 21.9, 21.8, 21.7, 14.1, 13.9. **HRMS–DART** (m/z): $[M+NH_4]^+$ calcd for $C_{26}H_{38}NO_4$, 428.2795; found, 428.2801.

Ethyl 3-(4-Bromophenyl)-2-hydroxy-4-(1-methylcyclohexyl)-2-phenylbutanoate (**10dca**)



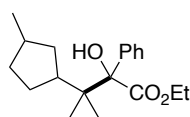
The product **10dca** was purified by flash chromatography on silica gel (100:0–95:5, hexane/EtOAc) (Figure 2-4; 64.3 mg, 0.14 mmol, 70% isolated yield). The diastereomeric ratio (1:1) is determined by 1H NMR. Colorless oil. **IR** (neat) 1010, 1024, 1070, 1233, 1446, 1487, 1719, 2924, 3496 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, $J = 7.6$ Hz, 1H), 7.42–7.31 (m, 4H), 7.16–6.98 (m, 4H), 4.32 (m, 1H), 3.97–3.85 (m, 1.5H), 3.78 (s, 0.5H), 3.60 (m, 1H), 2.13 (m, 0.5H), 1.77 (m, 0.5H), 1.40–1.32 (m, 4H), 1.21–0.93 (m, 9H), 0.83 (m, 1H), 0.70 (s, 1.5H), 0.48 (s, 1.5H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.2, 174.3, 141.0, 140.5, 140.4, 140.0, 132.0 ($\times 2C$), 130.8, 130.1, 128.1, 127.72, 127.66, 127.2, 126.5, 125.7, 120.7, 119.9, 82.5, 82.0, 62.9, 62.5, 48.8, 48.8, 44.0, 40.9, 38.8, 38.5, 38.4, 38.2, 33.4, 33.0, 26.3, 26.2, 25.3, 25.1, 22.0, 21.8, 21.73, 21.69, 14.1, 13.9. **HRMS–DART** (m/z): $[M+NH_4]^+$ calcd for $C_{25}H_{35}BrNO_3$, 476.1795; found, 476.1801.

10. Procedure for Radical Clock Experiment

In a glovebox, to an oven-dried vial with a stirring bar was added photocatalyst 4Cz-IPN (3.2 mg, 0.002 mmol), citronellic acid **1E** (36.6 μL , 0.2 mmol) and ethyl benzylformate **2a** (31.8 μL , 0.2 mmol) and DMSO (1.0 ml). Then, Cs_2CO_3 (130.3 mg, 0.4 mmol) was added to the reaction mixture. The reaction was stirred and irradiated with a 34W blue LED (0.5 cm away) with a cooling fan to keep the temperature around 40 $^{\circ}C$ (Figure S2-1). After 1 h, the reaction mixture was treated with saturated NH_4Cl aqueous solution (1.0 mL), then extracted with diethyl ether (3 times) and dried over sodium sulfate. After filtration, the resulting solution was evaporated under reduced pressure. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (100:0–97:3, hexane/EtOAc) gave **3Ea'** (39.0 mg, 0.13 mmol) in 64% yield.

11. Characterization Data for Cyclized Product

Ethyl 2-Hydroxy-3-methyl-3-(3-methylcyclopentyl)-2-phenylbutanoate (**3Ea'**)

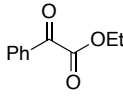
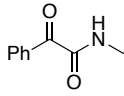
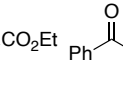
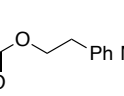
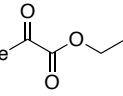


The product **3Ea'** was purified by flash chromatography on silica gel (100:0–80:20,

hexane/EtOAc) (Figure 2-5; 39.0 mg, 0.13 mmol, 64% isolated yield). The diastereomeric ratio (1:1:1:1) is determined by $^1\text{H-NMR}$. Colorless oil. **IR** (neat) 1019, 1064, 1166, 1242, 1365, 1446, 1710, 2949, 3499 cm^{-1} . **$^1\text{H NMR}$** (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.2$ Hz, 2H), 7.32–7.26 (m, 3H), 4.33–4.30 (m, 2H), 3.77 (s, 1H), 2.27 (m, 1H), 1.87–1.36 (m, 7H), 1.25 (m, 1H), 1.12–0.85 (m, 11H). **$^{13}\text{C NMR}$** (100.6 MHz, CDCl_3) δ 175.2, 175.12, 175.10, 175.07, 140.1 ($\times 2\text{C}$), 140.0 ($\times 2\text{C}$), 127.9 ($\times 2\text{C}$), 127.8 ($\times 2\text{C}$), 127.3 ($\times 4\text{C}$), 127.1 ($\times 4\text{C}$), 83.5 ($\times 4\text{C}$), 62.4 ($\times 4\text{C}$), 46.1, 46.0, 44.4, 44.3, 44.07, 44.05, 43.94, 43.93, 38.8, 38.3, 36.2, 35.8, 34.8, 34.7, 33.8, 33.7, 33.46, 33.45, 33.3, 33.2, 29.8, 29.3, 27.4, 26.9, 21.7, 21.6, 21.4, 21.3, 20.9, 20.83, 20.79 ($\times 2\text{C}$), 20.6, 20.5, 20.2, 20.1, 14.1 ($\times 4\text{C}$). **HRMS–DART** (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{19}\text{H}_{32}\text{NO}_3$, 322.2377; found, 322.2383.

12. Cyclic Voltammetry (CV) Experiments

CV measurements were carried out under nitrogen atmosphere in acetonitrile solutions with 0.1 M of tetrabutylammonium hexafluorophosphate (Bu_4NPF_6) as a supporting electrolyte. Measurements were made with a glassy carbon electrode (area = 0.07 cm^2), an Ag/AgCl reference electrode, and a Pt wire counter electrode. The concentration of the sample solution was fixed at 10 mM and the sweep rates were set to 100 mV/s.

					
$E_{1/2}$ (vs. Ag/AgCl)	−1.27	−1.29	−1.30	−1.47	−1.66
$E_{1/2}$ (vs. SCE) ^a	−1.23	−1.25	−1.26	−1.43	−1.61

$$^a E_{1/2} (\text{V vs. SCE}) = E_{1/2} (\text{V vs. Ag/AgCl}) + 0.045 \text{ V}$$

Figure S2-2. Summary of redox potetials

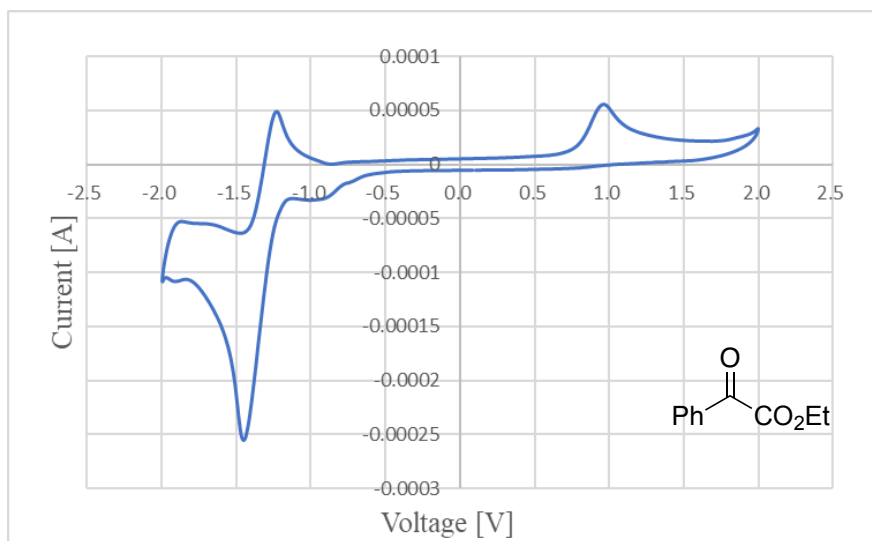


Figure S2-3. Cyclic voltammogram of **2a**

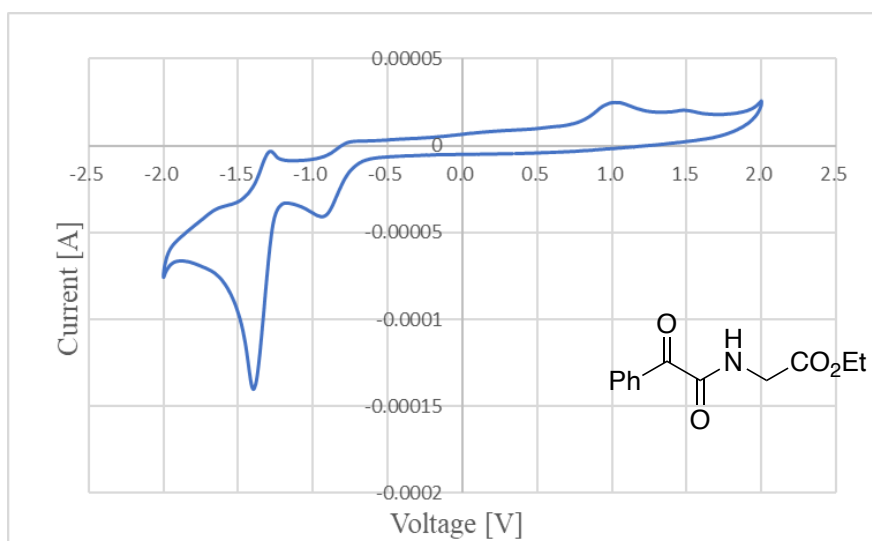


Figure S2-4. Cyclic voltammogram of **5a**

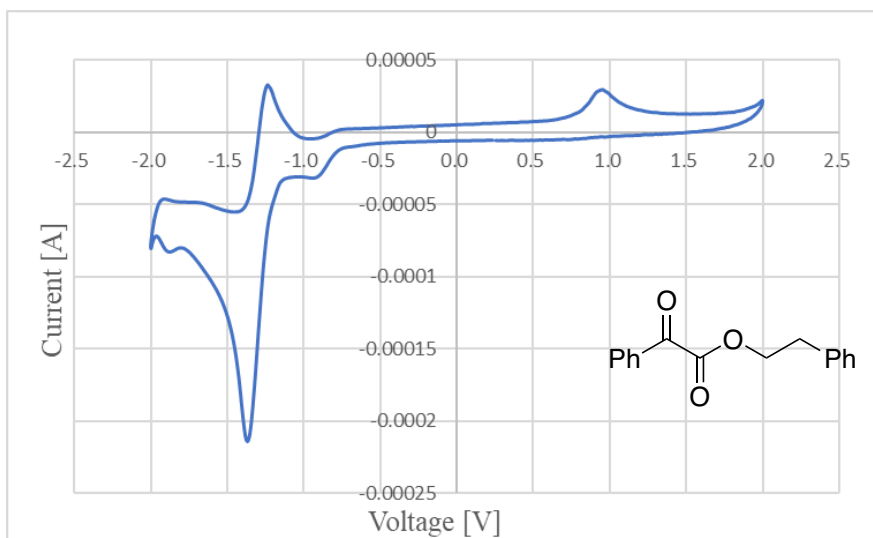


Figure S2-5. Cyclic voltammogram of **2A**

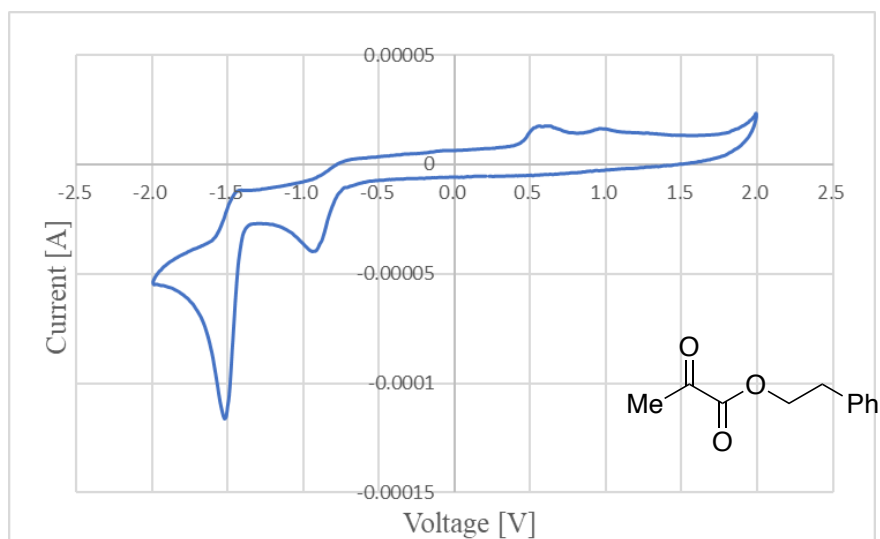


Figure S2-6. Cyclic voltammogram of **2B**

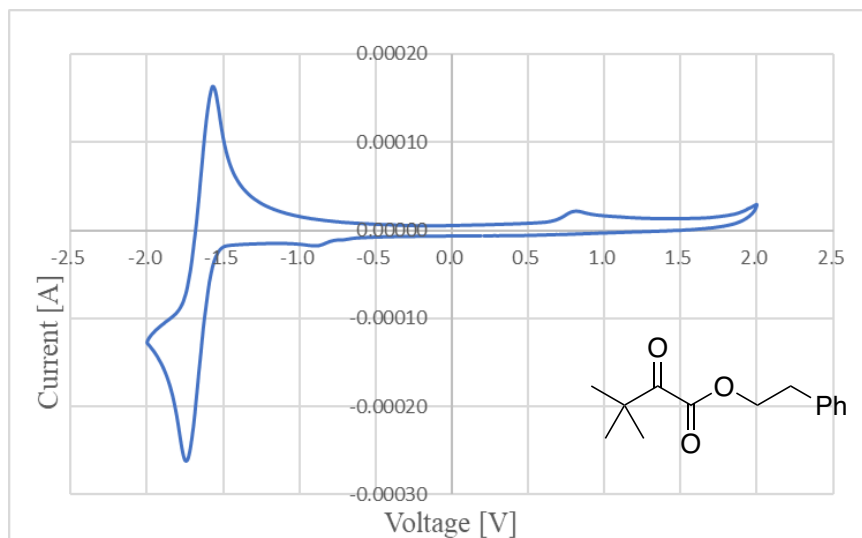


Figure S2-7. Cyclic voltammogram of **2C**

13. Calculation of Radical Stabilization Energys (RSEs)

The density functional theory (DFT) calculation was conducted using the Gaussian 09 program¹⁷. Geometry optimizations were conducted using DFT method with UB3LYP functional¹⁸. The usual 6-31+G(d) basis sets were used for all atoms¹⁹. We carried out vibrational frequency calculations with CBS-QB3²⁰ to obtain thermal corrections to enthalpies (H) at 0 K. Energies were adjusted by adding a scaled (by 0.9806²¹)

The BDE values of C–H bonds in substrates were calculated according to the following equation.

$$\text{BDE (C–H)} = \Delta H_{\text{C radical}} + \Delta H_{\text{H radical}} - \Delta H_{\text{C–H}}$$

The RSEs of ketyl radicals from α -ketocarboxyls were calculated according to the following equation²².

$$\text{RSE} = \text{BDE (CH}_4\text{)} - \text{BDE (CHX}_3\text{)}$$

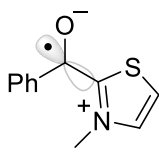
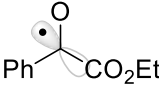
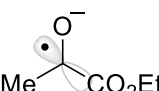
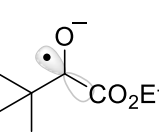
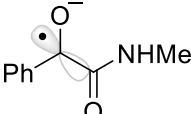
radicals	$\Delta H_{\text{C radical}}$ (Hartree)	$\Delta H_{\text{H radical}}$ (Hartree)	$\Delta H_{\text{C-H}}$ (Hartree)	BDE (C-H) (kcal/mol)	RSE (kcal/mol)
(a) 	-39.051594	-0.492414	-39.703674	100.2	0
(b) 	-934.796303	-0.492414	-935.346914	36.5	63.7
(c) 	-600.891986	-0.492414	-601.448541	40.3	59.9
(d) 	-412.863760	-0.492414	-413.430649	46.7	53.5
(e) 	-528.468643	-0.492414	-529.040794	50.0	50.2
(f) 	-542.853553	-0.492414	-543.420381	46.7	53.5

Figure S2-8. RSEs of ketyl radicals from α -ketocarboxyls

Optimization structure of H radical

H	2.67543529	2.35363551	-0.84625388
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Optimization structure of (a)

C	1.68316840	0.91230550	0.00000000
H	2.67632020	1.31048825	0.00000000
H	0.84175612	1.57330882	0.00000000
H	1.53142888	-0.14688056	0.00000000

Optimization structure of (a) C-H

C	0.38532110	0.30275229	0.00000000
H	0.74197552	-0.70605771	0.00000000
H	0.74199394	0.80715048	0.87365150

H	0.74199394	0.80715048	-0.87365150
H	-0.68467890	0.30276547	0.00000000

Optimization structure of (b)

C	-3.43003822	-3.77090747	0.00125800
C	-2.03487822	-3.77090747	0.00125800
C	-1.33734022	-2.56315647	0.00125800
C	-2.03499422	-1.35464747	0.00005900
C	-3.42981922	-1.35472547	-0.00042000
C	-4.12742022	-2.56293147	0.00057600
H	-3.97979722	-4.72322447	0.00170800
H	-1.48537022	-4.72342047	0.00257300
H	-0.23766022	-2.56307647	0.00189200
H	-3.97994122	-0.40244447	-0.00137300
H	-5.22702422	-2.56274847	0.00039600
C	-1.26499856	-0.02096607	-0.00073530
C	-0.99321791	0.45191434	1.43944504
S	-1.19912901	2.03877408	1.92485501
C	-0.40581244	0.40976004	3.68622312
C	-0.73009806	1.73535385	3.50101535
H	-0.07105012	-0.03324767	4.62592172
H	-0.69530120	2.51003365	4.26445869
N	-0.56052020	-0.34283863	2.47766075
C	0.21706933	-1.17299325	3.40884163
H	1.14715076	-0.69037684	3.62547479
H	-0.33567841	-1.30544025	4.31538877
H	0.40573618	-2.12742487	2.96345965
O	-0.85809191	0.68207506	-1.17762108

Optimization structure of (b) C-H

C	-3.43003822	-3.77090747	0.00125800
C	-2.03487822	-3.77090747	0.00125800
C	-1.33734022	-2.56315647	0.00125800
C	-2.03499422	-1.35464747	0.00005900
C	-3.42981922	-1.35472547	-0.00042000
C	-4.12742022	-2.56293147	0.00057600

H	-3.97979722	-4.72322447	0.00170800
H	-1.48537022	-4.72342047	0.00257300
H	-0.23766022	-2.56307647	0.00189200
H	-3.97994122	-0.40244447	-0.00137300
H	-5.22702422	-2.56274847	0.00039600
C	-1.26499856	-0.02096607	-0.00073530
H	-1.87409473	0.73307068	-0.55611443
O	-0.03840331	-0.21403867	-0.71002159
C	-0.99321791	0.45191434	1.43944504
S	-1.19912901	2.03877408	1.92485501
C	-0.40581244	0.40976004	3.68622312
C	-0.73009806	1.73535385	3.50101535
H	-0.07105012	-0.03324767	4.62592172
H	-0.69530120	2.51003365	4.26445869
N	-0.56052020	-0.34283863	2.47766075
C	0.21706933	-1.17299325	3.40884163
H	1.14715076	-0.69037684	3.62547479
H	-0.33567841	-1.30544025	4.31538877
H	0.40573618	-2.12742487	2.96345965

Optimization structure of (c)

C	-4.93396565	-3.01126015	0.00125800
C	-3.53880565	-3.01126015	0.00125800
C	-2.84126765	-1.80350915	0.00125800
C	-3.53892165	-0.59500015	0.00005900
C	-4.93374665	-0.59507815	-0.00042000
C	-5.63134765	-1.80328415	0.00057600
H	-5.48372465	-3.96357715	0.00170800
H	-2.98929765	-3.96377315	0.00257300
H	-2.98872165	0.35714285	0.00000000
H	-5.48386865	0.35720285	-0.00137300
H	-6.73095165	-1.80310115	0.00039600
C	-1.30126791	-1.80339712	0.00214586
O	-0.50476007	-0.61576281	0.00227428
C	-0.71693348	-3.22823140	0.00287963
O	-0.65460886	-4.05822703	0.90885132
O	-0.20387033	-3.57485330	-1.20460927

C	0.32784749	-4.90168443	-1.16343497
C	1.23408377	-5.14670507	-2.33367031
H	-0.52736644	-5.62043333	-1.16840383
H	0.88204942	-5.02563524	-0.20140647
H	1.64970694	-6.18305427	-2.30185545
H	0.67954075	-5.02258696	-3.29551980
H	2.08907043	-4.42764583	-2.32856296

Optimization structure of (c) C-H

C	-3.55246982	-2.57346649	1.18634586
C	-2.15730982	-2.57346649	1.18634586
C	-1.45977182	-1.36571549	1.18634586
C	-2.15742582	-0.15720649	1.18514686
C	-3.55225082	-0.15728449	1.18466786
C	-4.24985182	-1.36549049	1.18566386
H	-4.10222882	-3.52578349	1.18679586
H	-1.60780182	-3.52597949	1.18766086
H	-1.60722582	0.79493651	1.18508786
H	-4.10237282	0.79499651	1.18371486
H	-5.34945582	-1.36530749	1.18548386
C	0.08022792	-1.36560346	1.18723372
H	0.43667412	-2.24535702	1.68107558
O	0.55641286	-0.20634477	1.87590431
C	0.59439642	-1.34773655	-0.26428670
O	0.31374025	-0.59333387	-1.19470086
O	1.49318550	-2.33566598	-0.50425260
C	1.94604302	-2.28576696	-1.85973412
C	3.13653376	-3.19014063	-2.05036783
H	2.21156439	-1.22884149	-2.10440801
H	1.10453196	-2.59735383	-2.52471747
H	3.95402252	-2.83294330	-1.45958683
H	2.88250365	-4.18345215	-1.74426176
H	3.41826309	-3.19608584	-3.08259515

Optimization structure of (d)

C	0.35028092	-0.50760092	0.00006701
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C	0.58116853	-1.39532298	-1.18711054
H	-0.13772086	-2.25029223	-1.18741080
H	0.44612272	-0.82561776	-2.13857062
H	1.61792651	-1.81128723	-1.17365303
O	-0.91626707	0.13164306	0.17929675
C	1.47725058	-0.28477475	1.02568287
O	2.37924618	0.55170485	1.04204203
O	1.42404105	-1.17307383	2.05013564
C	2.48447944	-0.93398129	2.97922401
C	2.41568647	-1.90179595	4.12349337
H	2.39691740	0.11785449	3.34527035
H	3.45464978	-1.03409094	2.43447636
H	3.24392998	-1.71540700	4.84947292
H	1.44534045	-1.80143799	4.66795143
H	2.50303303	-2.95355934	3.75710722

Optimization structure of (d) C-H

C	-0.98205927	0.14703551	0.00000000
H	-0.62540484	-0.86177449	0.00000000
H	-0.62538643	0.65143370	0.87365150
H	-0.62538643	0.65143370	-0.87365150
C	-2.52205927	0.14705448	0.00000000
C	-3.18628017	-1.24233497	-0.00274822
O	-2.67852255	-2.36293269	-0.00492809
O	-4.54107504	-1.16525811	-0.00271303
C	-5.11960756	-2.47300174	-0.00530576
C	-6.61758904	-2.39053091	-0.00495307
H	-4.75347184	-3.01812846	0.89846249
H	-4.75363853	-3.01448986	-0.91131885
H	-7.06991885	-3.41188680	-0.00703794
H	-6.98317710	-1.84890877	0.90117525
H	-6.98341370	-1.84513889	-0.90871981
O	-2.96858687	0.85316996	1.16056625
H	-2.85617429	0.67883784	-0.86629880

Optimization structure of (e)

C	-2.26718601	2.03166773	-0.02273351
O	-3.11304945	2.45925673	0.80506674
O	-1.88943106	2.80837873	-1.06936201
C	-2.57303989	4.06397559	-1.03687365
C	-1.99232151	5.01056504	-2.04557808
H	-2.48446824	4.48269642	-0.00496112
H	-3.65450418	3.87780986	-1.24610973
H	-2.52609064	5.99150312	-2.02056856
H	-0.91082535	5.19642535	-1.83605551
H	-2.08082169	4.59146035	-3.07736945
C	-1.66074057	0.62692977	0.15200975
C	-2.76674312	-0.41823127	0.38864609
C	-3.31097926	-0.22619809	1.78840757
C	-3.85514065	-0.20062457	-0.64106669
C	-2.15863252	-1.79656244	0.23789759
H	-2.49949382	-0.36274296	2.54293038
H	-3.73492869	0.80023746	1.90305357
H	-4.11861011	-0.96771527	2.00002305
H	-3.44358816	-0.31777174	-1.67226772
H	-4.67891604	-0.94176447	-0.50309077
H	-4.28333761	0.82578159	-0.54306752
H	-2.93108864	-2.58585148	0.40312352
H	-1.73609488	-1.92482384	-0.78751301
H	-1.33908654	-1.94315595	0.98176049
O	-0.26213463	0.33325288	0.10145988

Optimization structure of (e) C-H

C	-1.55294948	0.66731493	-0.01997059
C	-2.54435009	-0.51112677	-0.01990358
C	-3.40179347	-0.41125093	1.22396843
C	-3.39903352	-0.41389562	-1.26582999
C	-1.75054246	-1.80038429	-0.01768652
H	-2.76487806	-0.45803380	2.13972381
H	-3.96548856	0.55241152	1.23098854
H	-4.13695882	-1.25089931	1.26163719

H	-2.76012665	-0.46202175	-2.18013650
H	-4.13372728	-1.25397538	-1.30354800
H	-3.96318623	0.54948112	-1.27598160
H	-2.43553043	-2.68228920	-0.01700451
H	-1.10088551	-1.85826387	-0.92380557
H	-1.10223446	-1.85595855	0.88955409
H	-0.93337933	0.59881402	-0.88964896
O	-0.72828195	0.57872277	1.14492206
C	-2.26718601	2.03166773	-0.02273351
O	-3.09682159	2.49290896	0.75990506
O	-1.88943106	2.80837873	-1.06936201
C	-2.57303989	4.06397559	-1.03687365
C	-1.99232151	5.01056504	-2.04557808
H	-2.48446824	4.48269642	-0.00496112
H	-3.65450418	3.87780986	-1.24610973
H	-2.52609064	5.99150312	-2.02056856
H	-0.91082535	5.19642535	-1.83605551
H	-2.08082169	4.59146035	-3.07736945

Optimization structure of (f)

C	-2.01628761	1.96201626	0.03354147
C	-2.39252369	2.54914711	-1.17515217
C	-2.38461052	2.55486900	1.24118416
C	-3.13618344	3.72905890	-1.17546949
H	-2.10234622	2.08159180	-2.12724754
C	-3.12934022	3.73460936	1.24069707
H	-2.08823869	2.09238934	2.19394359
C	-3.50496400	4.32174148	0.03250388
H	-3.43313124	4.19177611	-2.12781217
H	-3.41975989	4.20169791	2.19285973
H	-4.09165687	5.25175981	0.03203630
C	-1.19448793	0.65961658	0.03412610
C	-0.84454821	0.09442479	-1.35501048
O	-1.11911458	0.52107891	-2.47578761
N	-0.02390375	-1.20572606	-1.26697394
H	-0.54000012	-1.95447345	-1.68293292
O	-0.78364834	0.01774356	1.24413018

C	1.24865526	-1.03129860	-1.98186459
H	1.87840041	-0.36394868	-1.43144192
H	1.05929809	-0.62360905	-2.95286052
H	1.73455171	-1.97937388	-2.08165391

Optimization structure of (f) C-H

C	1.07619861	0.80837537	1.77605491
C	1.24434849	2.19355999	1.76171133
C	1.37247851	0.08190965	2.92931238
C	1.70931440	2.85129573	2.90031228
H	1.01051525	2.76632026	0.85255557
C	1.83663965	0.74011517	4.06849182
H	1.24006905	-1.00978948	2.94093022
C	2.00519397	2.12464630	4.05396185
H	1.84157422	3.94291406	2.88942447
H	2.06996037	0.16722590	4.97760587
H	2.37134444	2.64345879	4.95168690
C	0.56285639	0.08241910	0.51864994
H	-0.12040074	0.77253171	-0.03304078
O	-0.19303188	-1.05871514	0.93258901
C	1.74219728	-0.34303830	-0.37563249
O	2.76263457	-0.97047711	-0.09529323
N	1.57130859	0.09331610	-1.76893501
H	2.45264325	0.39175052	-2.13524922
C	1.05975659	-1.02551797	-2.57356218
H	1.75468365	-1.83830611	-2.53679518
H	0.11659341	-1.34465597	-2.18177889
H	0.93563853	-0.70798124	-3.58779348

14. Stern-Volmer Quenching Experiments

In a glovebox, to a screw-top 1.0 cm quartz cuvette was added 500 μL of a 40 μM solution of 4CzIPN in degassed DMSO and 500 μL of cesium carboxylate **1a'** or α -ketoester **2a** (quencher) of appropriate concentration in degassed DMSO (quencher concentration = 2 mM, 4 mM, 8 mM, 16 mM, 32 mM). Raw fluorescence intensity was measured at $\lambda = 554$ nm after excitation at $\lambda = 435$ nm in the quartz cuvette.

第二章 実験項 参考文献

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第三章 光駆動型ラジカル極性交差機構を活用した核酸リン原子の第三級アルキル化反応

第一節 着想背景および作業仮説

核酸医薬品は、従来の低分子医薬品や抗体医薬品では標的困難な分子を認識できると同時に、標的分子に対する高い特異性を有するため、創薬研究において注目されている。¹ この核酸医薬品は、糖骨格・核酸塩基・ホスホジエステル基から構成されるヌクレオチドが、十から数十個繋がったオリゴヌクレオチドである。天然型のオリゴヌクレオチドは体内での核酸分解酵素による易分解性の問題があるため、多くの核酸医薬品は化学修飾が施された非天然型のオリゴヌクレオチド構造を有する。² 中でも、ホスホジエステル骨格の化学修飾は、代謝安定性や薬物動態に影響するため重要である。³ 現在承認されている核酸医薬品に活用されているホスホジエステル化学修飾核酸として、ホスホロチオエート修飾核酸やモルフォリノ核酸（ホスホロジアミダート）、チオホスホロアミダート修飾核酸が開発されている（**Figure 3-1**）。⁴

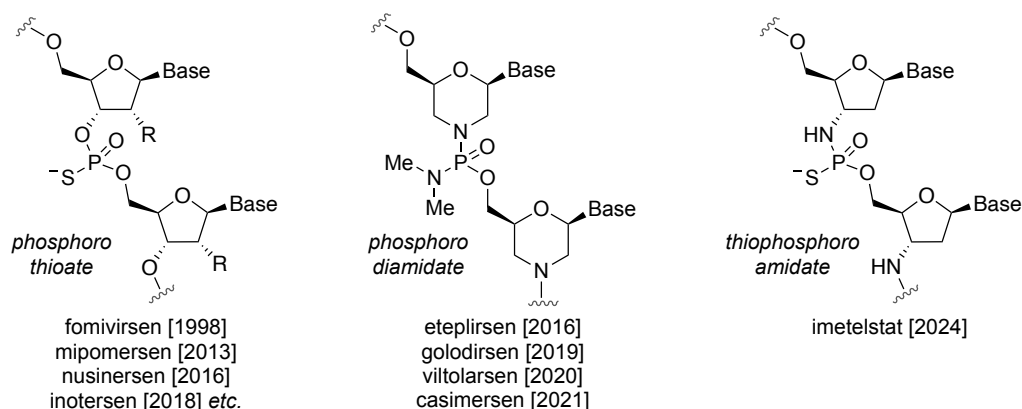


Figure 3-1. ホスホジエステル化学修飾核酸

中でも、電荷中性のホスホジエステル化学修飾核酸は、負電荷を有する化学修飾核酸では問題であった毒性を回避しつつ、高い代謝安定性を維持することができるため注目されている。ホスホジエステル基の非架橋酸素原子をアルキル基に置換したアルキルホスホン酸ジエステル修飾核酸は、電荷中性の化学修飾核酸であり、高い代謝安定性を示しつつも毒性が低いことが報告されている。⁵ しかし、従来の合成法では、リン原子に導入できる置換基が、メチル基や第一級あるいは第二級の嵩の小さなアルキル基に制限されていた（**Figure 3-2**）。これらは塩基性条件に不安定であるため、オリゴヌクレオチド合成時の加水分解の課題があった。そのため、リン中心に嵩高い第三級アルキル基を導入することができれば、高い化学的安定性を有する堅牢な電荷中性ホスホジエステル構造となり、新たな核酸医薬品の創出に繋がることが期待される。

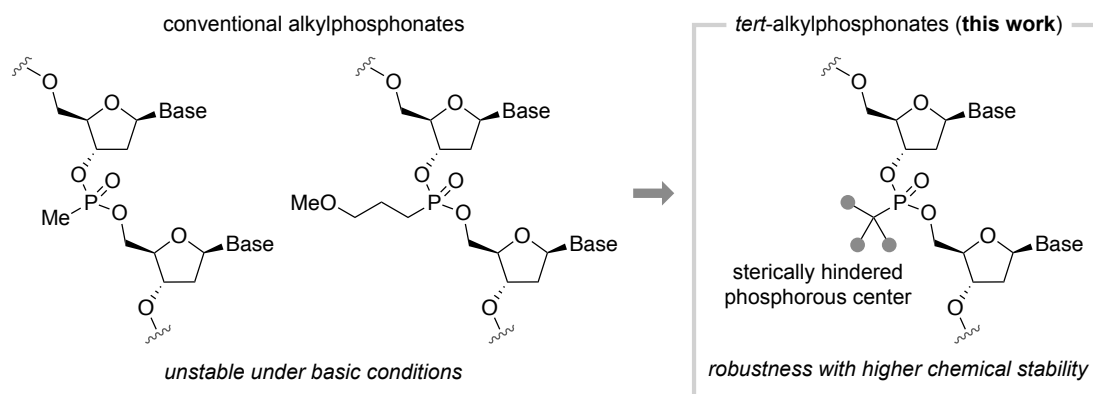


Figure 3-2. アルキルホスホン酸ジエステル修飾核酸

嵩高い $C(sp^3)$ -ヘテロ原子結合形成の強力な手法として、カルボカチオンを経る S_N1 反応がある。⁶ しかし、従来の手法では、カルボカチオンを発生させるために強酸を用いる必要があり、官能基許容性の問題があった。⁷ 一方で、近年では光化学的および電気化学的な手法により、強酸を用いずに穏和な条件下でカルボカチオンを生成することが可能となり、様々なヘテロ原子求核剤との反応による $C(sp^3)$ -ヘテロ原子結合形成が達成されている。⁸

著者の所属研究室では、光駆動型ラジカル-極性交差機構 (RPC: radical-polar crossover) を活用することで、強酸を用いずにカルボカチオン等価体を触媒的に発生させ、様々な求核剤と反応させる手法を開発に成功している。⁹ 具体的には、可視光とフェノチアジン型光酸化還元触媒 (PTH) を利用することで、種々のヘテロ原子求核剤と脂肪族カルボン酸誘導体であるレドックス活性エステルとの脱炭酸クロスカップリング反応が進行することを見出している (**Figure 3-3**)。この反応では、可視光照射下 PTH からレドックス活性エステルへの一電子移動が起こり、脱炭酸を伴って PTH ラジカルカチオンとアルキルラジカルが生成する。生じたアルキルラジカルと PTH ラジカルカチオンがカップリングすることで、アルキルスルホニウムを形成する。このアルキルスルホニウムがカルボカチオン等価体として、ヘテロ原子求核剤と反応を起こす。本 RPC 機構を活用することで、強酸を用いずにカルボカチオン等価体を発生させることができるため、高い官能基許容性を示し、高度に官能基化された分子を一挙に構築することが可能である。

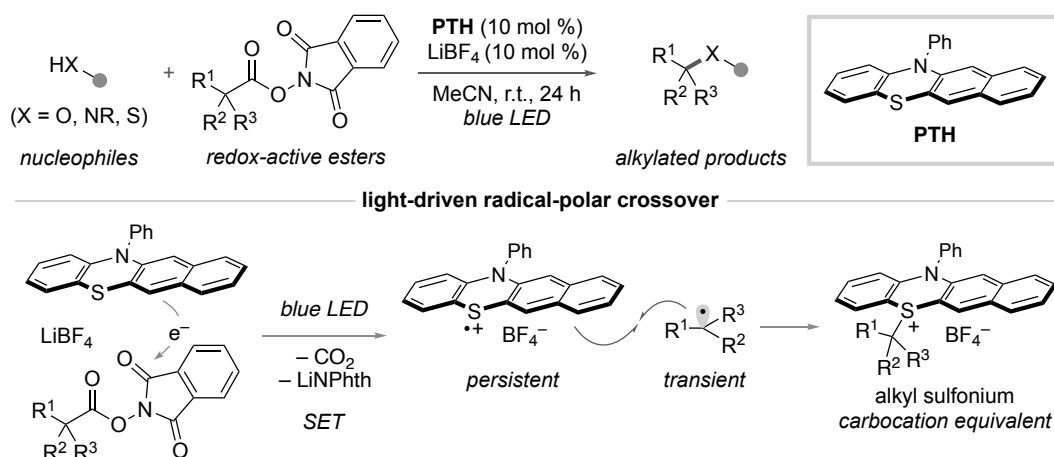


Figure 3-3. 有機分子触媒によるヘテロ原子求核剤と脂肪族カルボン酸誘導体の脱炭酸クロスカップリング反応

以上の背景を踏まえて、光駆動型ラジカル-極性交差機構で発生したカルボカチオン等価体を活用することで、核酸リン原子の第三級アルキル化反応に応用できると考えた。すなわち、PTH と脂肪族カルボン酸誘導体であるレドックス活性エステルを用いた二つのデオキシヌクレオシド構造と脱離基を有する亜リン酸エステルの Michaelis-Arbuzov 型アルキル化反応を着想した (**Figure 3-4**)。本反応は、1) ラジカル-極性交差機構で形成したカルボカチオン等価体への核酸リン原子の求核攻撃、2) 生成したホスホニウムからのβ-脱離、を経て進行すると想定した。¹⁰

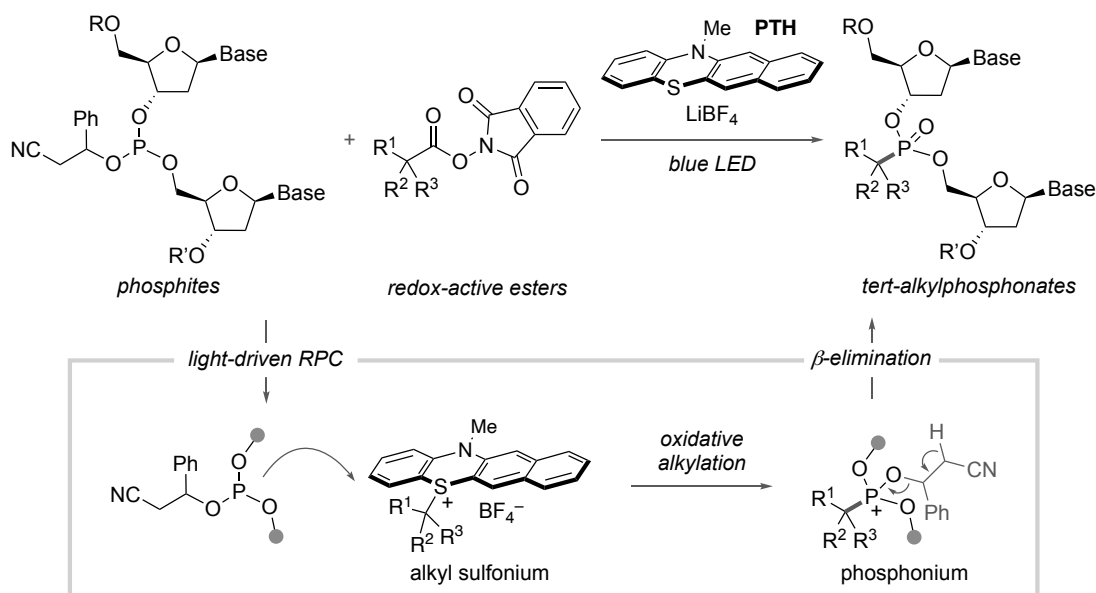


Figure 3-4. 光駆動型ラジカル-極性交差機構を活用した第三級アルキルホスホン酸ジエステル合成

最近、光化学的または電気化学的な手法によって発生させたアルキルラジカルやカルボカチオンといった反応性中間体と亜リン酸エステルとの反応によるアルキルホスホン酸ジエステル合成が数例報告されている。^{8b,11} しかし、これらの反応では、適用できる亜リン酸エステルが亜リン酸トリエチルのような単純な基質に限定されることが多く、複雑な核酸リン原子の化学修飾への適用例はない。

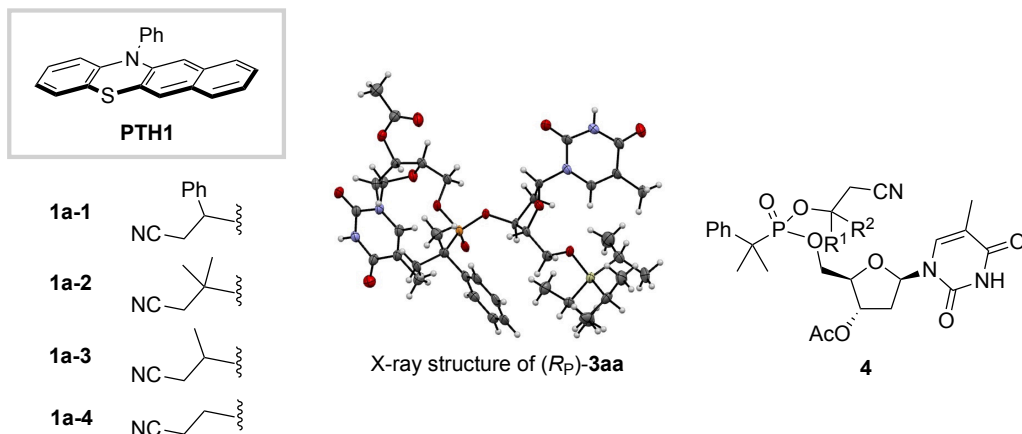
第二節 脱離基の検討

上記の作業仮説に基づき、*N*-フェニルベンゾ[*b*]フェノチアジン (PTH1) およびテトラフルオロホウ酸リチウム存在下、アルキル源として 2-フェニルイソ酪酸誘導体 (2a) を用いて、亜リン酸エステル **1a** の脱炭酸型アルキル化反応における脱離基の検討を行った (Table 3-1)。化学量論量の PTH1 およびテトラフルオロホウ酸リチウム存在下、二つのチミジン構造と脱離基として 2-シアノ-1-フェニルエチル基を有する亜リン酸エステル (**1a-1**) と **2a** をアセトニトリルとジクロロメタンの混合溶媒中 18 時間可視光照射したところ、C(sp³)-P 結合形成反応が進行し、目的のアルキルホスホン酸ジエステル **3aa** を良好な収率で与えた (entry 1)。**3aa** はジアステレオマー比が 1:1 の立体異性体の混合物であり、シリカゲルカラムクロマトグラフィーを用いて分離した後、ジアステレオマーの 1 つの構造を X 線結晶構造解析によって決定した。触媒量の PTH1 を用いた場合では、収率が低下した (entry 2)。脱離基に 2-シアノ-1,1-ジメチルエチル基¹² を有する亜リン酸エステル (**1a-2**) を用いた場合でも、良好な収率で **3aa** を与えた (entry 3)。一方で、2-シアノ-1-メチルエチル基 (**1a-3**) や 2-シアノエチル基 (**1a-4**) を脱離基に用いた場合では、所望の生成物 **3aa** ではなく副生成物 **4** の生成が確認された (entries 4 and 5)。この副生成物は、**1a** とカルボカチオンの反応により形成したホスホニウム中間体において、脱離基の α -シアノ位ではなくリボース分子の 2' 位での脱プロトン化が進行することで生じたと考えられる。¹³ そのため、フェニル基 (**1a-1**) または 1,1-ジメチル (**1a-2**) 基を有する脱離基は、 α -シアノ位での優先的な脱プロトン化に効果的であったことが示唆された。

Table 3-1. 脱離基の検討^a

entry	phosphite substrate	yield (%) of 3aa ^b
1	1a-1 : R ¹ = Ph, R ² = H	71

2 ^c	1a-1 : R ¹ = Ph, R ² = H	20
3	1a-2 : R ¹ , R ² = Me	68
4	1a-3 : R ¹ = Me, R ² = H	trace
5	1a-4 : R ¹ , R ² = H	trace



^aEach reaction was carried out with **1** (0.05 mmol), **2a** (0.15 mmol), **PTH1** (0.05 mmol) and LiBF₄ (0.05 mmol) in MeCN (0.3 mL) and DCM (0.2 mL) at 10 °C under blue LED irradiation for 18 h. ^b¹H NMR yields. ^c**PTH1** (10 mol %) was used.

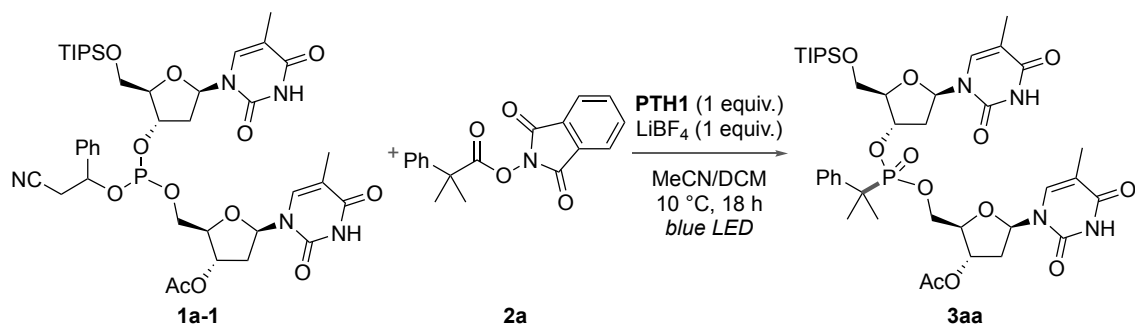
第三節 反応条件の最適化および基質適用範囲の検討

続いて、基質として亜リン酸エステル **1a-1** を用いて、脂肪族カルボン酸誘導体 **2a** との脱炭酸型クロスカップリングにおける反応条件の最適化を行った (Table 3-2)。PTH の窒素原子上の置換基を検討したところ、**PTH1** を用いた際と比較して、*N*-メチルベンゾ[b]フェノチアジン (**PTH2**) は同程度の収率で **3aa** を与えた一方で、*N*-H ベンゾ[b]フェノチアジン (**PTH3**) では収率が著しく減少した (entries 1-3)。*N*-フェニルフェノチアジン (**PTH4**) を用いた場合では目的物が全く得られなかったことから、本反応においてベンゾ[b]フェノチアジン骨格が重要であることが示唆された (entry 4)。

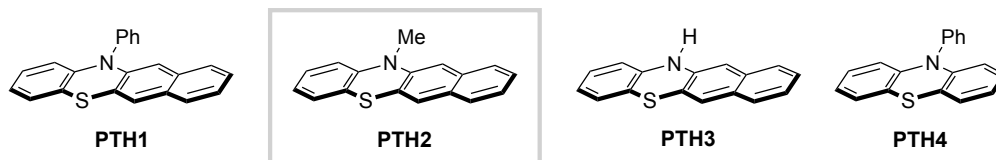
PTH1 とは対照的に **PTH2** は遷移金属触媒によるアミノ化を必要とせずに合成できるため、酸化還元メディエーターとして **PTH2** を用いて、様々な添加剤や溶媒の効果を調査した。テトラフルオロホウ酸リチウムを加えない場合や他の添加剤としてヘキサフルオロリン酸リチウムやテトラフルオロホウ酸ナトリウムを用いた場合では、目的のアルキルホスホン酸ジエステル体 **3aa** は得られなかった (entries 5-7)。これらの結果から、本反応においてリチウムカチオンとテトラフルオロホウ酸イオンが重要であることが示された。アセトニトリルやジクロロメタンを単独溶媒として用いた場合、**1a-1** の酸化的アルキル化反応は進行したが、**3aa** の収率は低下した (entries 8 and 9)。他の溶媒として、高極性溶媒であるジメチルホルムアミドを用いると目的物は全く得られず、極性の低いテトラヒドロフランを用いると収率は大きく低下した (entries 10 and 11)。反応

温度を 10 °C から 0 °C へと下げた場合や 20 °C や 40 °C へと上げた場合では、収率が低下した (entries 12–14)。

Table 3-2. 反応条件の最適化 ^a



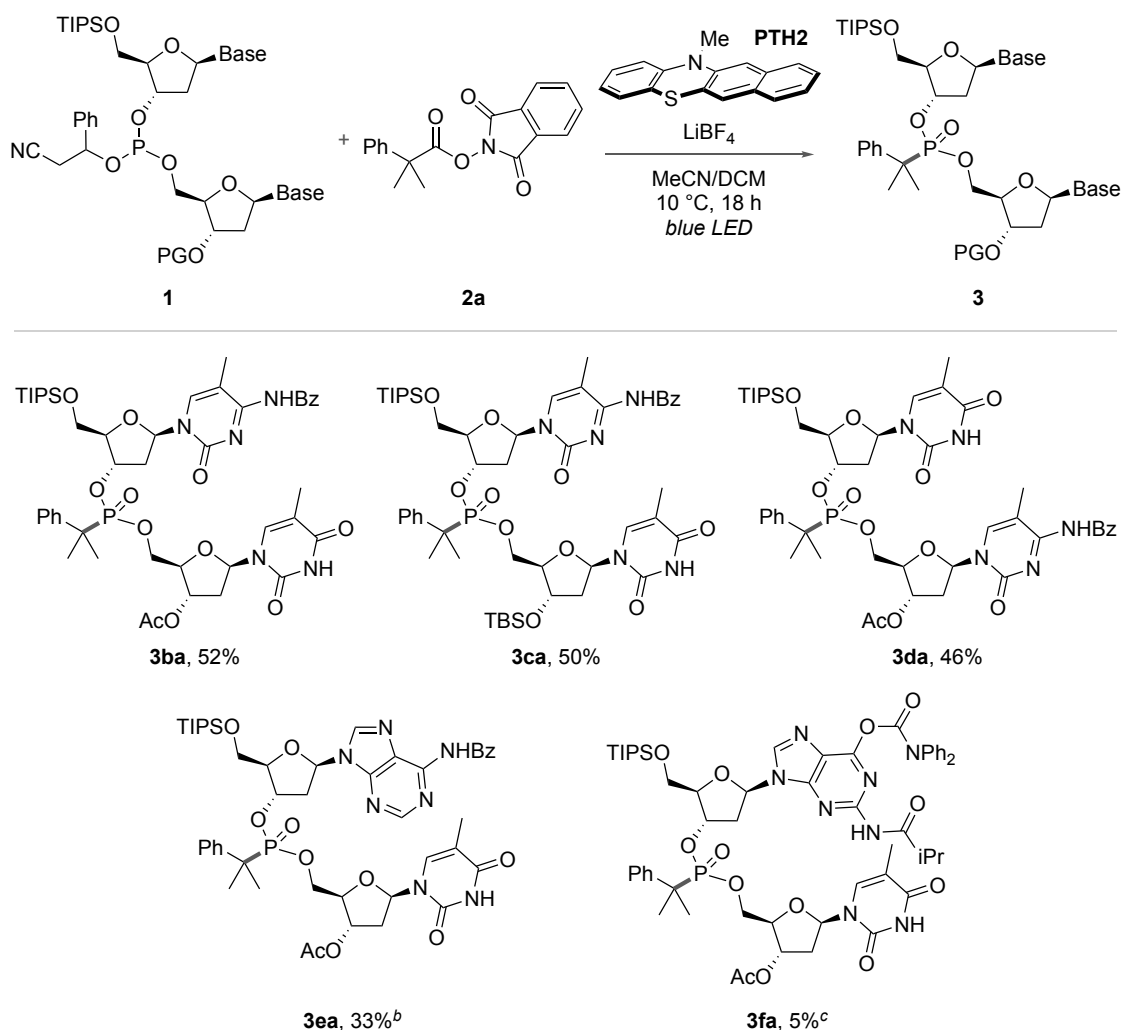
entry	change from standard conditions	yield (%) of 3aa ^b
1	none	71
2	PTH2 instead of PTH1	74 (70)
3	PTH3 instead of PTH1	37
4	PTH4 instead of PTH1	0
5 ^c	without LiBF ₄	0
6 ^c	LiPF ₆ instead of LiBF ₄	trace
7 ^c	NaBF ₄ instead of LiBF ₄	0
8 ^c	MeCN instead of MeCN/DCM	45
9 ^c	DCM instead of MeCN/DCM	53
10 ^c	DMF instead of MeCN/DCM	0
11 ^c	THF instead of MeCN/DCM	39
12 ^c	0 °C instead of 10 °C	31
13 ^c	20 °C instead of 10 °C	69
14 ^c	40 °C instead of 10 °C	65



^aEach reaction was carried out with **1a-1** (0.05 mmol), **2a** (0.15 mmol), **PTH1** (0.05 mmol) and LiBF₄ (0.05 mmol) in MeCN (0.3 mL) and DCM (0.2 mL) at 10 °C under blue LED irradiation for 18 h. ^b¹H NMR yields. The number in parentheses is the isolated yield. ^c**PTH2** (1.0 equiv.) was used.

得られた最適反応条件を用いて、基質の検討を行った。まず、カップリングパートナーとして 2-フェニルイソ酪酸誘導体 (**2a**) を用い、亜リン酸エステル **1** の適用範囲を調べた (Table 3-3)。チミジンだけでなく、シチジン (**3ba–3da**) やデオキシアデノシン (**3ea**)、デオキシグアノシン (**3fa**) が許容され、対応する第三級アルキルホスホン酸ジエステル体を与えた。**3ea** と **3fa** の収率が低下した原因として、プリン塩基の求核的な N7 位のアルキル化や酸化電位の低さが考えられる。¹⁴ 3'-OH の保護基として *tert*-ブチルジメチルシリル基を有する亜リン酸エステルを用いた場合でも、問題なく反応が進行した (**3ca**)。

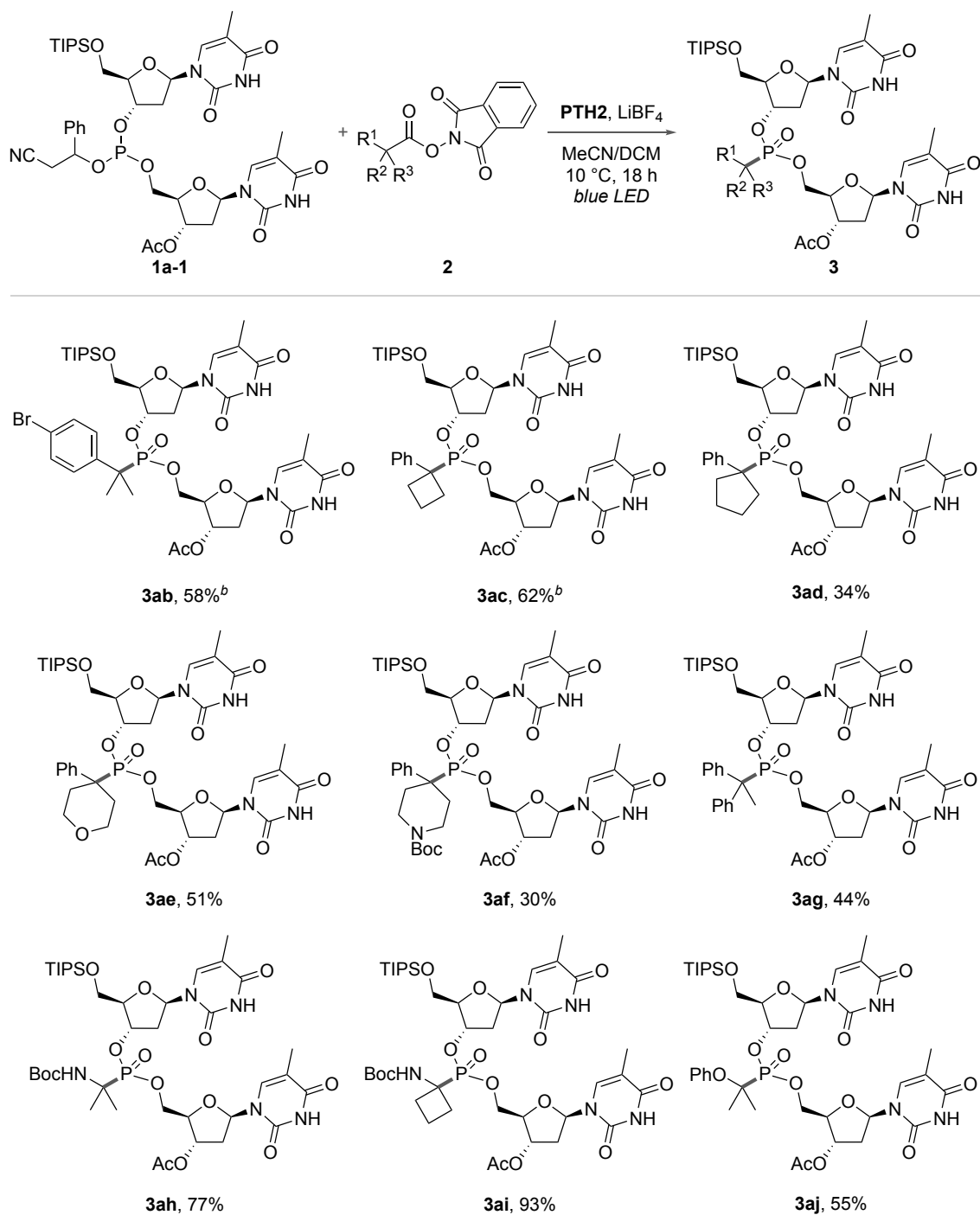
Table 3-3. 亜リン酸エステルの検討^a



^aEach reaction was carried out with **1** (0.05 mmol), **2a** (0.15 mmol), **PTH2** (0.05 mmol) and LiBF_4 (0.05 mmol) in MeCN (0.3 mL) and DCM (0.2 mL) at 10 °C under blue LED irradiation for 18 h. ^b **PTH2** (1.5 equiv.), LiBF_4 (1.5 equiv.) and RAE (5.0 equiv.) were used ^c**PTH2** (2.0 equiv.), LiBF_4 (2.0 equiv.) and RAE (5.0 equiv.) were used.

続いて、求核剤として **1a-1** を用いて、脂肪族カルボン酸誘導体 **2** の適用範囲を検討した (**Table 3-4**)。遷移金属触媒では反応点となり得る C(sp²)-Br 結合を有する脂肪族カルボン酸誘導体の適用が可能であった (**3ab**)。また、様々な環状炭素骨格を有する脂肪族カルボン酸誘導体を適用でき、対応するアルキルホスホン酸ジエステル体を良好な収率で与えた (**3ac-3af**)。さらに、より嵩高いジフェニルメチル基をリン中心に導入することも可能であった (**3ag**)。本反応は、ベンジル位だけでなく、窒素原子や酸素原子などのヘテロ原子のα位でも問題なく進行した (**3ah-3aj**)。

Table 3-4. 脂肪族カルボン酸誘導体の検討^a



^aEach reaction was carried out with **1** (0.05 mmol), **2a** (0.15 mmol), **PTH2** (0.05 mmol) and **LiBF₄** (0.05 mmol) in **MeCN** (0.3 mL) and **DCM** (0.2 mL) at 10 °C under blue LED irradiation for 18 h.

^bEach reaction was carried out at 20 °C.

第四節 反応機構解析

本反応の反応機構を明らかにすべく、いくつかの機構実験を行った (**Figure 3-5**)。まず、テトラフルオロホウ酸リチウムの存在下で **PTH2** とレドックス活性エステル **2a** の化学量論的な反応を行い、鍵となるアルキルスルホニウム中間体を観察した。4 時間可視光照射した後に、エレクトロスプレー法によって反応溶液を分析したところ、対応するアルキルスルホニウムの形成を確認できた。しかし、核磁気共鳴分光法による解析やアルキルスルホニウムを単離することはできなかった。

これらの機構実験において、4 時間の可視光照射後も **2a** のほとんどが未反応で回収された。一方で、亜リン酸エステル **1a-1** を一当量加え同じ条件下で反応させた場合では、**2a** の変換率が 96% まで上昇した。この結果から、**1a-1** がレドックス活性エステルの変換に影響を与えることが示唆された。また、一当量のチミンを添加した場合でも **2a** の変換率が上昇した。ブレンステッド酸は、光酸化還元触媒からレドックス活性エステルへの一電子移動に関与し、アルキルラジカルの発生を促進することが知られている。^{9c,9g,15} 以上のことから、本反応において、**1a-1** のチミン部分の N-H 基がブレンステッド酸として働くことで、レドックス活性エステル **2a** の効率的な変換に寄与していると考えられる。

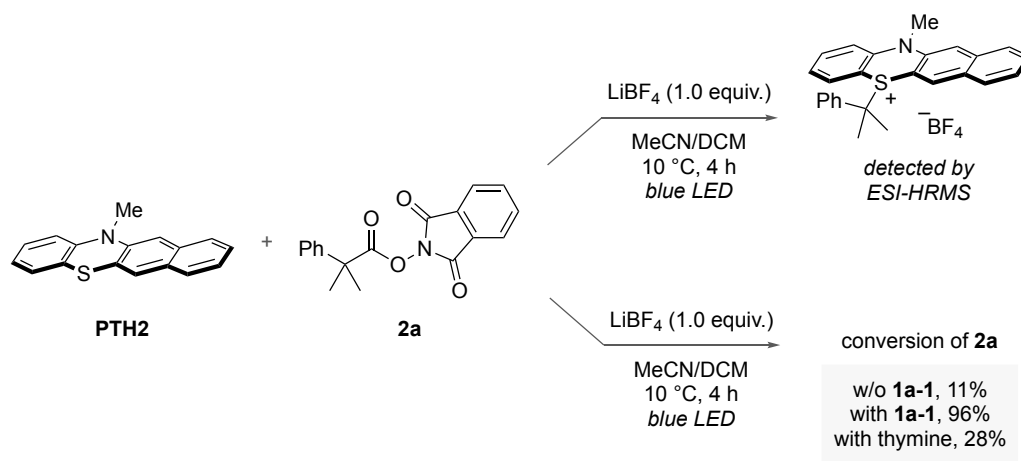


Figure 3-5. 機構実験

続いて、他のカルボカチオン発生法との比較を行った (**Figure 3-6**)。まず、Aggarwal らによって報告された有機光酸化触媒的なカルボカチオン発生条件^{11a}で、**1a-1** の酸化アルキル化を検討したが、目的の **3aa** は全く得られなかった。これは、添加剤として加えているトリフルオロ酢酸によって **1a-1** が分解したことが原因だと考えられる。他にも、ルイス酸を用いたアルコールからのカルボカチオン発生法を用いた検討も行った。¹⁶ ルイス酸として触媒量のトリフルオロメタンスルホン酸トリメチルシリルや化学量論量のヨウ化亜鉛、基質として亜リン酸エステル **1a-1** および 2-フェニル-2-プロパノール (**5a**) を用い、トルエン溶媒中加熱条件下で反応させた。しかし、**3aa** は得られず、複雑な混合物を与える結果となった。これらの結果から、穏和な条件でカルボカチ

オンを発生できる本反応の有用性が示された。

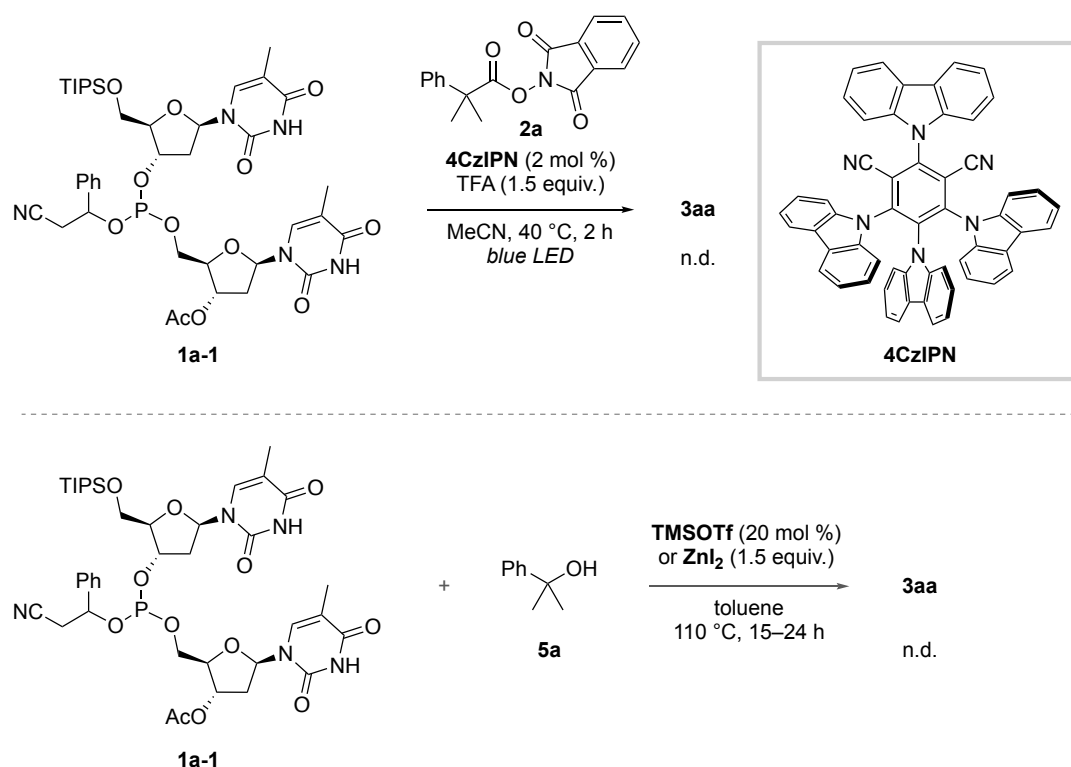


Figure 3-6. 他のカルボカチオン発生法を用いた検討

第五節 オリゴヌクレオチド合成

本手法により構築した第三級アルキルホスホン酸ジエステル構造を導入したオリゴヌクレオチドの合成を試みた。まず、第三級アルキルホスホン酸ジエステル **3aa** のジアステレオマーをそれぞれ単離し、対応するホスホロアミダイト **3aa-3** への誘導化を行った (Figure 3-7)。アンモニア/メチルアミン溶液による 3'-O-アセチル基の脱保護と続くテトラブチルアンモニウムフルオリド (TBAF) による 5'-O-トリイソプロピルシリル基の脱保護を行い、対応するジオール体 **3aa-1** を得た。次に、得られた **3aa-1** をピリジン溶媒中室温下で 4,4'-ジメトキシトリチルクロリド (DMTrCl) と反応させることで、5'-O-DMTr 体 **3aa-2** を合成した。最後に、**3aa-2** とクロロホスホロアミダイト試薬との反応により、目的のホスホロアミダイト体 **3aa-3** へと誘導した。これらの誘導化の際に用いた塩基性条件や TBAF 条件において、第三級アルキルホスホン酸ジエステル構造の分解などは確認されなかったことから、本化学構造の堅牢性が示された。

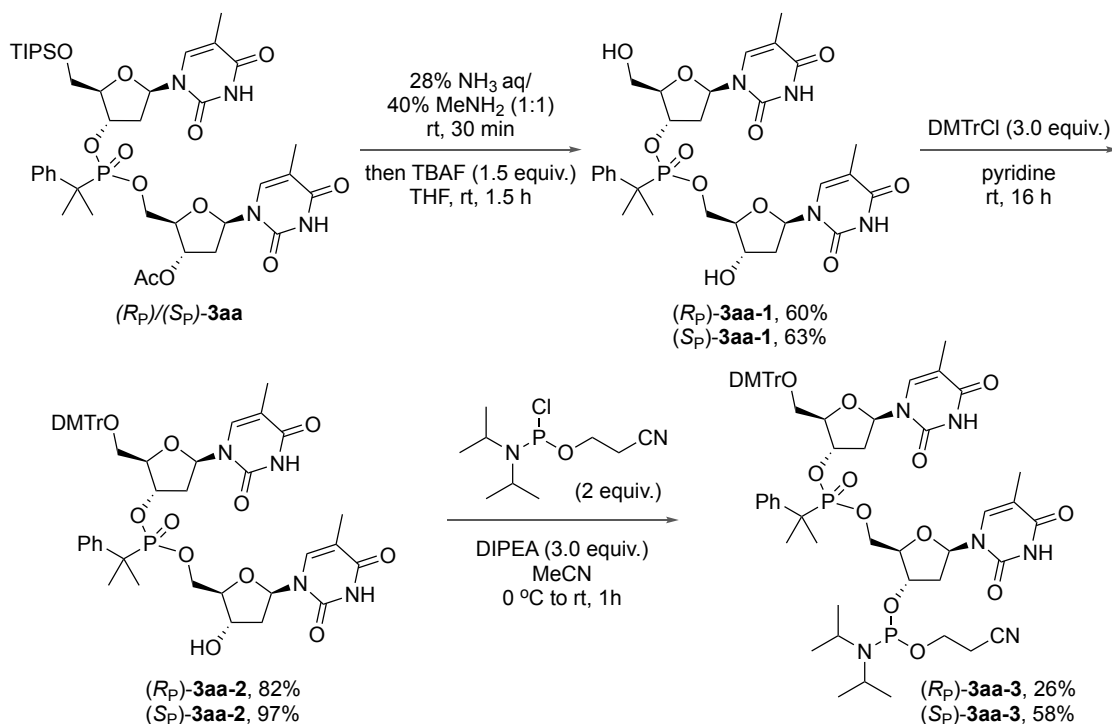


Figure 3-7. 第三級アルキルホスホン酸ジエステルからホスホロアミダイトへの誘導化

合成したホスホロアミダイト (R_P)-**3aa-3** および 5'-*O*-DMTr-チミジン (dT) 由来のホスホロアミダイト **6a** を用い、ホスホロアミダイト法¹⁷による自動固相合成¹⁸を行うことで、第三級アルキルホスホン酸ジエステル構造を有するオリゴヌクレオチド (**Oligo-1**) を合成した (**Figure 3-8**)。ホスホロアミダイト法とは、ホスホロアミダイトと 5'-OH のカップリング、リン中心の酸化、DMTr 基の脱保護のサイクルを目的の鎖長になるまで繰り返し、その後固相担体から切り出すことで、目的のオリゴヌクレオチドを合成する手法である。

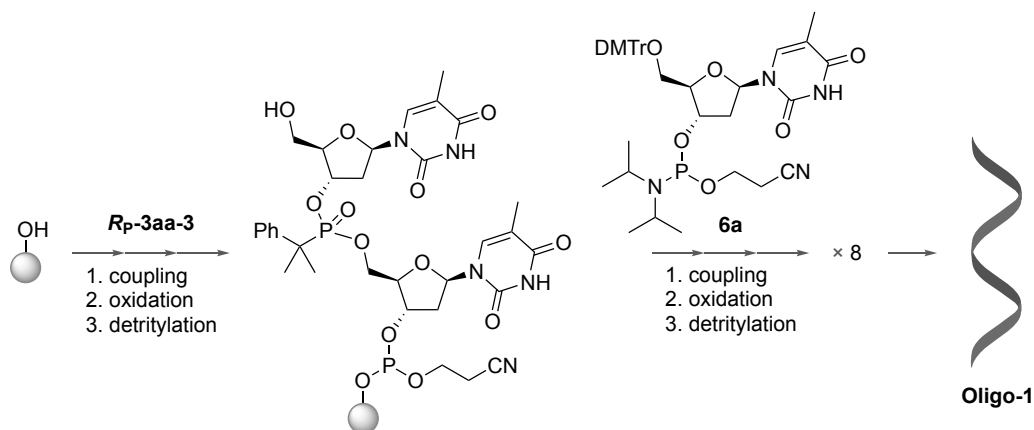


Figure 3-8. 自動固相合成法によるオリゴヌクレオチドの合成

同様の手法により、他のオリゴヌクレオチド (**Oligo-2–Oligo-8**) を合成し、逆相液体クロマトグラフィーにおける保持時間を比較した (**Figure 3-9**)。第三級アルキルホスホン酸ジエステル構造を有するオリゴヌクレオチド (**Oligo-1–Oligo-5**) は、天然型のホスホジエステル結合のみからなる **Oligo-6** と同等度の収率で合成することが可能であった。一方で、逆相液体クロマトグラフィーによる分析では、**Oligo-1–Oligo-5** は、天然型の **Oligo-6** より全体的に保持時間が長くなり、第三級アルキルホスホン酸ジエステル骨格の導入により疎水性が向上することが示唆された。また、 S_P 型は R_P 型よりも保持時間が長く、より疎水性であることが示された (**Oligo-1 vs Oligo-2 / Oligo-3 vs Oligo-4**)。 **Oligo-1–Oligo-5** は、他の電荷中性の化学修飾核酸 (**Oligo-7 and Oligo-8**) と比較しても、より長い保持時間を示した。

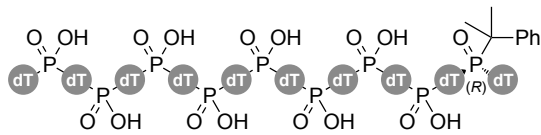
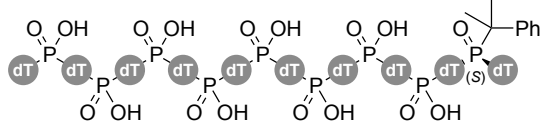
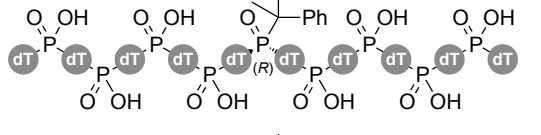
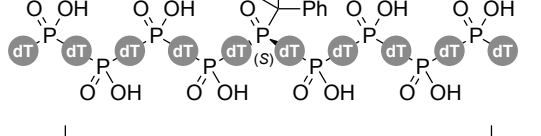
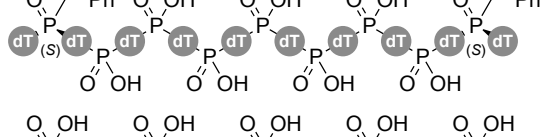
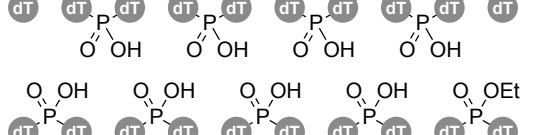
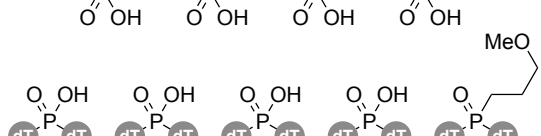
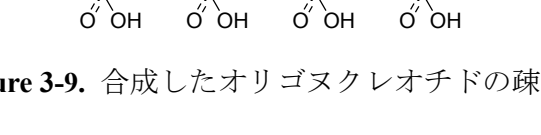
	oligonucleotides	retention time (min)
Oligo-1		3.09
Oligo-2		3.14
Oligo-3		2.80
Oligo-4		2.83
Oligo-5		3.66
Oligo-6		2.04
Oligo-7		2.63
Oligo-8		2.68

Figure 3-9. 合成したオリゴヌクレオチドの疎水性の比較

第六節 結論

光駆動型ラジカル-極性交差機構で発生したカルボカチオン等価体を活用することで、核酸リン原子の第三級アルキル化反応の開発に成功した。本反応は、1) ラジカル-極性交差機構機構で形成したカルボカチオン等価体への核酸リン原子の求核攻撃、2) 生成したホスホニウムからの β -脱離、を経て進行する。本手法により、従来法では達成が困難な嵩高い第三級アルキルホスホン酸ジエステルを構築できる。また、オリゴヌクレオチドへの第三級アルキルホスホン酸ジエステル構造の導入を実証し、その過程において本化学構造の堅牢性が示された。

第三章 参考文献

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第三章 実験項

1. Instrumentation and Chemicals

NMR spectra were recorded on a Bruker AVANCE NEO 400N spectrometer, operating at 400 MHz for ^1H NMR, 100.6 MHz for ^{13}C NMR, and 162 MHz for ^{31}P NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si and the residual solvent resonances, respectively. Chemical shifts were reported in δ ppm. Mass spectra were obtained with Bruker Impact HD mass spectrometer (ESI). TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60F₂₅₄. Silica gel (Wakosil[®] 60, 64~210 μm) was used for column chromatography. Biotage Selekt was used for purification. Gilson GX-281 was used as a Preparative HPLC. The column was YMCActus Triart C18 (50×20 mmI.D., 5 μm) with a flow rate of 25 mL/min at room temperature. Melting points were measured on a Stanford Research Systems MPA100. Kessil A160WE 40W Tuna Blue (highest blue and intensity setting) was used as a light source. Techno Sigma UCR-150N was used as a cryocooler. TEKNOS MG9 was used as a fan.

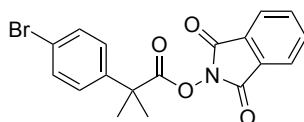
For Prep-HPLC, Waters MS-trigger HPLC systems equipped with YMC-Actus Triart C18 (30 mm ID × 100 mm L, 5 μm) column and Waters Acquity QDa MS detector were used. The eluent was 10mM NH_4HCO_3 aq./MeCN. GeneDesign ns8-II oligosynthesizer was used for the automated solid-support synthesis of oligonucleotides. Oligonucleotides were analyzed for characterization by a Waters Xevo G2-XS Qtof UPLC-MS system (ESI-Qtof) with a ACQUITY UPLC OST C18 (1.7 μm , 2.1 x 50 mm) column. The eluent was 240 mM hexafluoroisopropanol/7 mM triethylamine aqueous solution containing 5% MeOH and the methanolic solution (100% MeOH). For distillation of volatile components, a Thermo Scientific SAVANT SPD2010 SpeedVac Concentrator was used. Quantification of oligonucleotides was conducted based on UV absorbance measurement on Unchained Labs LUNATIC.

All reactions were carried out under nitrogen atmosphere. Materials were obtained from commercial suppliers listed as below and stored under nitrogen and used as received or prepared according to standard procedures unless otherwise noted. **PTH1** and **PTH3** were prepared by the reported procedure.¹ **PTH2** was prepared by the methylation of benzo[*b*]phenothiazine with iodomethane.² **PTH4** was prepared by the reported procedure.³ LiBF_4 , NaBF_4 and LiPF_6 were purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. MeCN, DCM, DMF, THF and toluene were purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. Alcohol **S1-1** was prepared by the reported procedure.⁴ Alcohol **S1-2** was prepared by the reported procedure.⁵ Alcohol **S1-3** was prepared by the reported procedure.⁶ Phosphordiamidite **S2-3** was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Redox-active esters **2a-2k** were prepared according to the

reported procedure.⁷ Thymine was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. 4CzIPN was prepared by the reported procedure.⁸ Trifluoroacetic acid (TFA) was purchased from Nacalai Tesque Inc., stored under nitrogen, and used as received. 2-Phenyl-2-propanol (**5a**) was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was purchased from Tokyo Chemical Industry Co., zinc iodide (ZnI₂) was purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. Phosphites **1g** and **1h** were purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received.

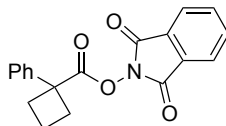
2. Characterization Data for Redox-Active Esters

1,3-Dioxoisindolin-2-yl 2-(4-Bromophenyl)-2-methylpropanoate (**2b**)



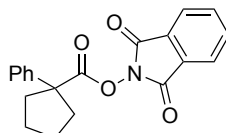
White solid. **M.p.** 125–127 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.88–7.85 (m, 2H), 7.80–7.76 (m, 2H), 7.56–7.52 (m, 2H), 7.39–7.35 (m, 2H), 1.76 (s, 6H). ¹³C NMR (100.6 MHz, CDCl₃) δ 172.7, 161.9, 141.6, 134.7, 131.8, 128.9, 127.6, 123.9, 121.5, 46.0, 26.7. **HRMS–ESI** (*m/z*): [M+H]⁺ calcd for C₁₈H₁₅BrNO₄, 388.0179; found, 388.0187.

1,3-Dioxoisindolin-2-yl 1-Phenylcyclobutane-1-carboxylate (**2c**)



White solid. **M.p.** 93–96 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.86–7.84 (m, 2H), 7.77–7.75 (m, 2H), 7.45–7.40 (m, 4H), 7.32 (m, 1H), 3.11–3.04 (m, 2H), 2.74–2.67 (m, 2H), 2.25 (m, 1H), 2.01 (m, 1H). ¹³C NMR (100.6 MHz, CDCl₃) δ 172.2, 161.9, 141.1, 134.6, 129.0, 128.6, 127.4, 126.4, 123.8, 50.9, 32.6, 16.8. **HRMS–ESI** (*m/z*): [M+NH₄]⁺ calcd for C₁₉H₁₉N₂O₄, 339.1339; found, 339.1337.

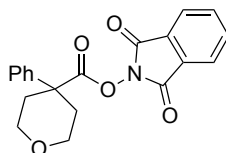
1,3-Dioxoisindolin-2-yl 1-Phenylcyclopentane-1-carboxylate (**2d**)



White solid. **M.p.** 84–87 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.85–7.83 (m, 2H), 7.77–7.75 (m, 2H), 7.50–7.48 (m, 2H), 7.42–7.39 (m, 2H), 7.33 (m, 1H), 2.82–2.76 (m, 2H), 2.17–2.10 (m, 2H), 1.95–1.84 (m, 4H). ¹³C NMR (100.6 MHz, CDCl₃) δ 172.6, 162.0, 141.1, 134.6, 129.0, 128.6,

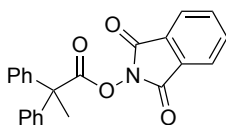
127.4, 126.8, 123.8, 58.0, 37.1, 23.8. **HRMS–ESI** (m/z): $[M+NH_4]^+$ calcd for $C_{20}H_{21}N_2O_4$, 353.1496; found, 353.1501.

1,3-Dioxoisindolin-2-yl 4-Phenyltetrahydro-2H-pyran-4-carboxylate (2e)



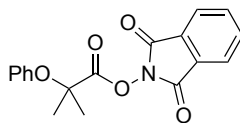
White solid. **M.p.** 122–124 °C. **1H NMR** (400 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2H), 7.79–7.77 (m, 2H), 7.53–7.51 (m, 2H), 7.47–7.43 (m, 2H), 7.37 (m, 1H), 4.07–4.02 (m, 2H), 3.88–3.81 (m, 2H), 2.65–2.61 (m, 2H), 2.21–2.14 (m, 2H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.0, 161.8, 140.7, 134.8, 129.0, 128.9, 128.0, 125.8, 123.9, 65.3, 48.9, 34.8. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{20}H_{18}NO_5$, 352.1179; found, 352.1175.

1,3-Dioxoisindolin-2-yl 2,2-Diphenylpropanoate (2g)



White solid. **M.p.** 114–118 °C. **1H NMR** (400 MHz, $CDCl_3$) δ 7.88–7.86 (m, 2H), 7.78–7.76 (m, 2H), 7.44–7.30 (m, 10H), 2.17 (s, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.9, 161.9, 142.3, 134.7, 129.0, 128.4, 128.0, 127.5, 123.9, 55.8, 27.1. **HRMS–ESI** (m/z): $[M+NH_4]^+$ calcd for $C_{23}H_{21}N_2O_4$, 389.1496; found, 389.1506.

1,3-Dioxoisindolin-2-yl 2-Methyl-2-phenoxypropanoate (2j)



White solid. **M.p.** 74–77 °C. **1H NMR** (400 MHz, $CDCl_3$) δ 7.92–7.89 (m, 2H), 7.81–7.79 (m, 2H), 7.35–7.31 (m, 2H), 7.11–7.06 (m, 3H), 1.79 (s, 6H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.9, 161.8, 154.6, 134.8, 129.4, 128.9, 124.0, 123.2, 120.2, 78.6, 25.7. **HRMS–ESI** (m/z): $[M+NH_4]^+$ calcd for $C_{18}H_{19}N_2O_5$, 343.1288; found, 343.1287.

3. General Procedure for Synthesis of Phosphites

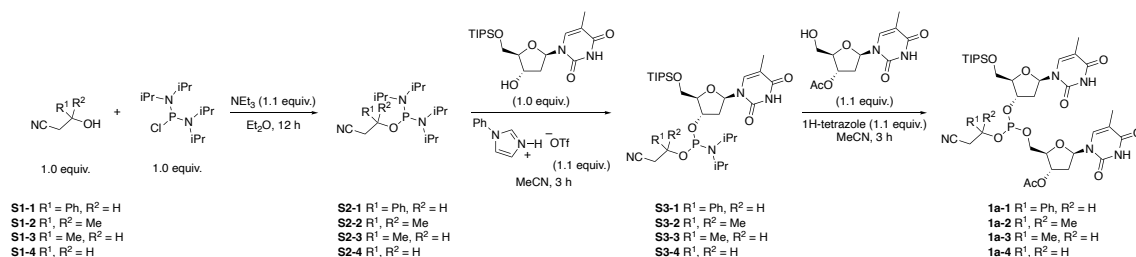


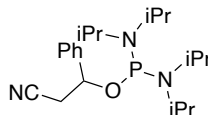
Figure S3-1. Synthesis of phosphites

Synthesis of 1a-1 as a representative (Figure S3-1). Phosphordiamidite **S2-1** was prepared according to the literature.⁹ To a solution of 5'-*O*-TIPS thymidine (1.0 g, 2.5 mmol) and phosphordiamidite **S2-1** (0.94 g, 2.5 mmol) in MeCN (20 mL), 1-phenyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (0.81 g, 2.75 mmol) was added. The reaction mixture was stirred for 3 h at room temperature under a nitrogen atmosphere. After the solvent was removed under reduced pressure, purification by flash column chromatography on silica gel (Biotage Selekt, 95:5–70:30, hexane/EtOAc) gave the phosphoramidite **S3-1** as a white amorphous solid (1.23 g, 1.82 mmol, 73%).

To a solution of phosphoramidite **S3-1** (1.22 g, 1.82 mmol) and 3'-*O*-Ac thymidine (0.57 g, 2.0 mmol) in MeCN (7 mL), 1*H*-tetrazole (0.14 g, 2.0 mmol) was added. The reaction mixture was stirred for 3 h at room temperature under a nitrogen atmosphere. After the filtrate was concentrated under reduced pressure, purification by flash column chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) gave the phosphite **1a-1** (1.37 g, 1.60 mmol, 88%) as a white amorphous solid.

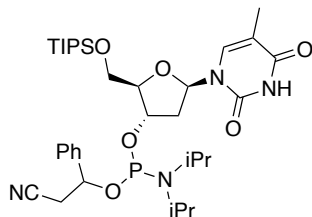
4. Characterization Data for Phosphites and the Synthetic Intermediates

3- $\{[\text{Bis}(\text{diisopropylamino})\text{phosphaneyl}]\text{oxy}\}$ -3-phenylpropanenitrile (**S2-1**)



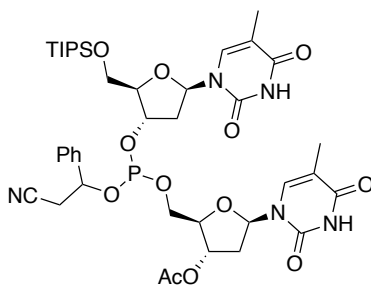
S2-1 was purified by flash chromatography on silica gel (70:29:1, hexane/EtOAc/NEt₃) (Figure S3-1; 10 mmol scale; 3.24 g, 8.58 mmol, 86% isolated yield). White solid. The spectrum data of **S2-1** was consistent with the literature.⁹

Phosphoramidite (S3-1)



S3-1 was purified by flash chromatography on silica gel (Biotage Selekt, 95:5–70:30, hexane/EtOAc) (Figure S3-1; 2.5 mmol scale; 1.23 g, 1.82 mmol, 73% isolated yield). The ratio (2:2:1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.21 (brs, 1H), 7.48–7.31 (m, 6H), 6.37 (m, 0.33H), 6.15 (m, 0.67H), 5.00 (m, 1H), 4.65 (m, 0.33H), 4.40 (m, 0.67H), 4.11 (m, 0.33H), 4.01–3.87 (m, 1.33H), 3.81–3.51 (m, 3.34H), 2.82–2.75 (m, 2H), 2.47 (m, 0.33H), 2.27 (m, 0.33H), 2.15 (m, 0.67H), 1.96–1.81 (m, 3.67H), 1.28–0.96 (m, 33H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 163.6, 150.3, 150.2, 150.1, 140.1, 140.1, 139.9, 135.4, 135.4, 135.3, 128.7, 128.7, 128.6, 128.6, 126.1, 126.1, 126.1, 126.0, 116.9, 116.8, 116.8, 111.0, 110.8, 110.8, 110.7, 86.8, 86.6, 86.6, 86.4, 86.4, 84.7, 84.6, 84.5, 73.7, 73.5, 73.3, 72.2, 72.0, 71.2, 71.0, 63.4, 63.3, 63.2, 43.5, 43.4, 43.3, 43.2, 40.1, 40.0, 39.9, 39.8, 39.8, 28.4, 28.4, 28.3, 28.3, 24.7, 24.6, 24.6, 24.6, 24.5, 24.5, 24.4, 24.2, 24.1, 24.0, 18.0, 18.0, 12.3, 12.3, 11.8, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 149.8, 149.6, 148.3, 147.7. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{34}\text{H}_{55}\text{N}_4\text{NaO}_6\text{PSi}$, 697.3521; found, 697.3526.

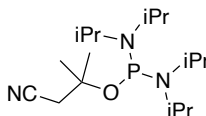
Phosphite (1a-1)



1a-1 was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (Figure S3-1; 1.82 mmol scale; 1.37 g, 1.60 mmol, 88% isolated yield). The ratio (1.3:1.2:1.1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 9.09–8.90 (m, 2H), 7.52–7.28 (m, 7H), 6.34–6.21 (m, 2H), 5.40 (m, 1H), 5.19 (m, 1H), 4.83 (m, 1H), 4.17–3.53 (m, 6H), 2.94–2.75 (m, 2H), 2.43–2.04 (m, 7H), 1.99–1.88 (m, 6H), 1.14–1.05 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.7, 170.5, 170.4, 170.4, 163.7, 163.6, 150.3, 150.2, 139.3, 139.2, 138.9, 138.7, 136.2, 135.3, 135.2, 135.1, 135.0, 134.9, 129.4, 129.3, 129.3, 129.2, 129.1, 125.9, 125.8, 116.7, 116.6, 116.6,

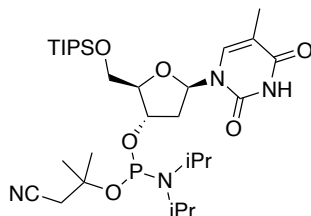
116.5, 111.6, 111.4, 111.4, 111.3, 111.1, 111.0, 111.0, 86.3, 85.9, 85.0, 84.7, 84.6, 84.5, 84.4, 83.4, 83.3, 83.2, 74.7, 74.4, 74.2, 74.1, 73.9, 73.8, 73.5, 73.4, 71.6, 71.6, 71.5, 71.4, 71.0, 70.9, 70.7, 70.7, 63.1, 63.0, 63.0, 62.6, 62.4, 62.3, 62.1, 40.0, 39.9, 39.7, 37.3, 37.2, 37.2, 37.1, 37.0, 28.1, 27.9, 21.0, 20.9, 18.0, 12.6, 12.6, 12.3, 11.8, 11.8 (only observed peaks). **³¹P NMR** (162 MHz, CDCl₃) δ 140.0, 139.9, 139.9, 139.2. **HRMS–ESI** (m/z): [M+NH₄]⁺ calcd for C₄₀H₆₀N₆O₁₂PSi, 875.3771; found, 875.3772.

3-**{[Bis(diisopropylamino)phosphaneyl]oxy}**-3-methylbutanenitrile (S2-2)



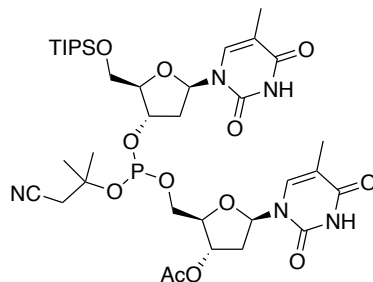
S2-2 was purified by flash chromatography on silica gel (70:29:1, hexane/EtOAc/NEt₃) (Figure S3-1; 3.3 mmol scale; 789 mg, 2.4 mmol, 73% isolated yield). White solid. **M.p.** 57–59 °C. **¹H NMR** (400 MHz, CDCl₃) δ 3.62–3.53 (m, 4H), 2.59 (s, 2H), 1.51 (s, 6H), 1.20–1.16 (m, 24H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 118.1, 74.2 (d, J_{C-P} = 17.4 Hz), 45.0 (d, J_{C-P} = 13.4 Hz), 32.9 (d, J_{C-P} = 4.9 Hz), 28.1 (d, J_{C-P} = 10.2 Hz), 24.4 (d, J_{C-P} = 5.7 Hz), 24.0 (d, J_{C-P} = 8.4 Hz). **³¹P NMR** (162 MHz, CDCl₃) δ 99.6. **HRMS–ESI** (m/z): [M+H]⁺ calcd for C₁₇H₃₇N₃OP, 330.2669; found, 330.2675.

Phosphoramidite (S3-2)



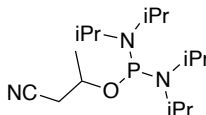
S3-2 was purified by flash chromatography on silica gel (Biotage Selekt, 93:7–65:35, hexane/EtOAc) (Figure S3-1; 1.5 mmol scale; 621 mg, 0.99 mmol, 66% isolated yield). The ratio (1.2:1) of diastereomers was determined by ³¹P-NMR analysis. White amorphous solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.89 (brs, 1H), 7.45 (s, 1H), 6.34 (m, 1H), 4.54 (m, 1H), 4.13 (m, 1H), 4.00–3.85 (m, 2H), 3.67–3.58 (m, 2H), 2.66–2.40 (m, 3H), 2.07 (m, 1H), 1.90 (s, 3H), 1.52–1.50 (m, 6H), 1.22–1.09 (m, 33H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 163.8, 163.8, 150.3, 150.2, 135.3, 135.3, 117.4, 117.4, 110.8, 110.8, 86.9, 86.8, 86.6, 86.5, 84.9, 84.7, 74.1, 74.0, 74.0, 73.9, 73.0, 72.9, 72.8, 72.7, 63.5, 63.5, 43.3, 43.2, 40.1, 40.0, 39.8, 39.8, 32.9, 32.9, 32.9, 32.8, 28.4, 28.4, 28.3, 28.3, 24.5, 24.4, 24.4, 24.3, 24.3, 24.2, 24.1, 18.0, 18.0, 12.3, 11.8, 11.8 (only observed peaks). **³¹P NMR** (162 MHz, CDCl₃) δ 139.5, 139.4. **HRMS–ESI** (m/z): [M+H]⁺ calcd for C₃₀H₅₆N₄O₆PSi, 627.3701; found, 627.3710.

Phosphite (1a-2)



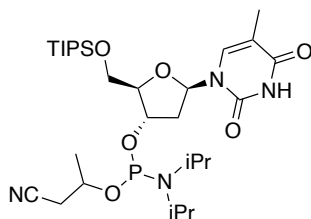
1a-2 was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (Figure S3-1; 0.6 mmol scale; 389 mg, 0.48 mmol, 80% isolated yield). The ratio (1.2:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.15–8.08 (m, 2H), 7.44–7.38 (m, 2H), 6.37–6.30 (m, 2H), 5.28 (m, 1H), 4.95 (m, 1H), 4.27–3.94 (m, 6H), 2.65–2.64 (m, 2H), 2.48–2.37 (m, 2H), 2.25–2.11 (m, 5H), 1.94–1.90 (m, 6H), 1.60–1.56 (m, 6H), 1.17–1.09 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 170.4, 163.7, 163.5, 150.4, 150.3, 135.2, 135.1, 134.9, 116.8, 116.7, 111.5, 111.4, 111.1, 111.0, 86.4, 86.4, 86.3, 84.6, 84.6, 84.5, 83.4, 83.3, 83.3, 75.7, 75.6, 75.5, 75.4, 74.2, 73.8, 73.5, 73.4, 73.1, 73.0, 63.2, 63.2, 61.4, 61.1, 40.0, 39.8, 37.3, 37.3, 32.9, 32.9, 30.9, 28.9, 28.8, 28.8, 28.7, 28.6, 20.9, 20.9, 18.0, 18.0, 12.6, 12.6, 12.3, 12.3, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 135.0, 134.6. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{57}\text{N}_5\text{O}_{12}\text{PSi}$, 810.3505; found, 810.3497.

3-[[Bis(diisopropylamino)phosphaneyl]oxy]butanenitrile (S2-3)



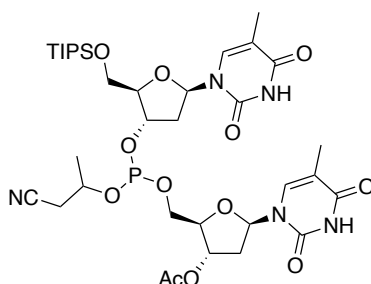
S2-3 was purified by flash chromatography on silica gel (70:29:1, hexane/EtOAc/ NEt_3) (Figure S3-1; 4 mmol scale; 505 mg, 1.6 mmol, 40% isolated yield). White solid. **M.p.** 41–45 °C. ^1H NMR (400 MHz, CDCl_3) δ 4.00 (m, 1H), 3.58–3.48 (m, 4H), 2.64–2.54 (m, 2H), 1.38 (d, J = 6.4 Hz, 3H), 1.19–1.16 (m, 24H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 117.6, 65.4, 65.2, 44.8, 44.6, 44.5, 26.6, 26.5, 24.4, 24.3, 24.2, 24.1, 24.1, 21.6, 21.6 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 113.2. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{35}\text{N}_3\text{OP}$, 316.2512; found, 316.2513.

Phosphoramidite (S3-3)



S3-3 was purified by flash chromatography on silica gel (Biotage Selekt, 93:7–55:45, hexane/EtOAc) (Figure S3-1; 1 mmol scale; 251 mg, 0.41 mmol, 41% isolated yield). The ratio (1.3:1.2:1.1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (brs, 1H), 7.45 (m, 1H), 6.33 (m, 1H), 4.58 (m, 1H), 4.18–4.07 (m, 2H), 4.00–3.86 (m, 2H), 3.66–3.57 (m, 2H), 2.66–2.38 (m, 3H), 2.10 (m, 1H), 1.91 (s, 3H), 1.41–1.36 (m, 3H), 1.22–1.09 (m, 33H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 163.6, 150.2, 150.2, 150.1, 135.4, 135.4, 135.3, 135.3, 117.1, 117.1, 117.1, 117.0, 110.9, 110.8, 110.8, 87.0, 87.0, 86.8, 86.8, 86.5, 86.5, 86.4, 84.8, 84.8, 84.6, 84.5, 73.5, 73.4, 73.3, 73.3, 73.2, 73.2, 66.2, 66.0, 65.9, 65.7, 65.6, 65.6, 65.4, 65.4, 63.5, 63.4, 63.3, 43.3, 43.3, 43.2, 43.2, 43.2, 43.1, 40.1, 40.1, 40.1, 40.0, 39.9, 39.9, 26.9, 26.8, 26.8, 26.8, 26.7, 26.7, 24.6, 24.5, 24.5, 24.5, 24.4, 24.4, 24.3, 22.0, 21.9, 21.9, 21.9, 18.0, 18.0, 18.0, 12.3, 12.3, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 147.4, 147.2, 147.1, 146.8. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{53}\text{N}_4\text{NaO}_6\text{PSi}$, 635.3364; found, 635.3361.

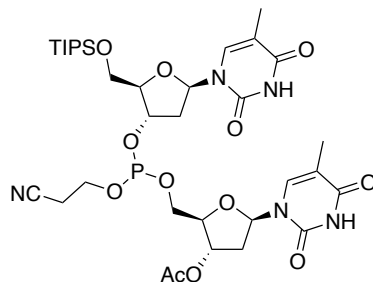
Phosphite (1a-3)



1a-3 was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (Figure S3-1; 0.4 mmol scale; 305 mg, 0.38 mmol, 96% isolated yield). The ratio (1.1:1:1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.66–8.53 (m, 2H), 7.43–7.39 (m, 2H), 6.36–6.29 (m, 2H), 5.28 (m, 1H), 4.96 (m, 1H), 4.54 (m, 1H), 4.40–4.08 (m, 4H), 3.98–3.93 (m, 2H), 2.70–2.55 (m, 2H), 2.51–2.38 (m, 2H), 2.28–2.11 (m, 5H), 1.96–1.91 (m, 6H), 1.53–1.40 (m, 3H), 1.21–1.09 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 170.5, 163.7, 163.6, 150.4, 150.3, 135.2, 135.2, 135.1, 134.9, 134.9, 134.9, 116.8, 116.7, 116.6, 116.6, 111.6, 111.6, 111.5, 111.3, 111.1, 86.4, 86.4, 86.4, 86.3, 86.3, 84.7, 84.6, 84.6, 84.5, 83.4, 83.3, 83.3, 83.2, 74.2, 74.1, 74.1, 74.0, 73.9, 73.8,

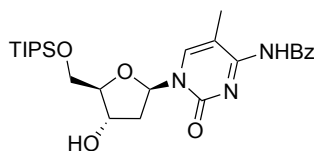
73.7, 73.5, 73.4, 73.3, 66.5, 66.4, 66.3, 66.2, 66.1, 66.1, 65.9, 63.4, 63.2, 62.1, 62.1, 62.0, 61.9, 61.8, 61.8, 61.7, 40.0, 40.0, 39.9, 39.9, 39.8, 39.8, 37.3, 37.2, 37.2, 27.0, 26.9, 26.9, 26.9, 26.8, 22.4, 22.4, 22.3, 22.3, 22.2, 20.9, 20.9, 20.8, 18.0, 18.0, 12.7, 12.6, 12.3, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 139.7, 139.2, 139.1, 139.0. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{35}\text{H}_{54}\text{N}_5\text{NaO}_{12}\text{PSi}$, 818.3168; found, 818.3167.

Phosphite (1a-4)



1a-4 was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (Figure S3-1; 0.6 mmol scale; 403 mg, 0.52 mmol, 86% isolated yield). The ratio (1.1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.64 (brs, 2H), 7.42–7.38 (m, 2H), 6.36–6.29 (m, 2H), 5.29 (m, 1H), 4.95 (m, 1H), 4.20–4.04 (m, 6H), 3.98–3.91 (m, 2H), 2.71–2.68 (m, 2H), 2.49–2.39 (m, 2H), 2.27–2.11 (m, 5H), 1.94–1.91 (m, 6H), 1.19–1.08 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.7, 170.6, 170.5, 163.8, 163.7, 150.4, 150.3, 136.3, 135.3, 135.2, 135.0, 135.0, 117.2, 117.1, 111.6, 111.5, 111.4, 111.2, 111.2, 86.4, 86.4, 86.3, 86.0, 85.0, 84.8, 84.7, 84.6, 84.5, 83.4, 83.4, 83.3, 83.3, 74.7, 74.2, 74.1, 74.0, 73.8, 73.7, 63.1, 62.6, 62.3, 62.2, 62.2, 58.0, 57.8, 57.5, 57.4, 40.0, 39.9, 37.3, 37.2, 37.2, 21.0, 20.9, 20.4, 20.3, 20.3, 18.0, 18.0, 12.6, 12.6, 12.6, 12.3, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 139.7, 139.3. HRMS–ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{34}\text{H}_{56}\text{N}_6\text{O}_{12}\text{PSi}$, 799.3458; found, 799.3459.

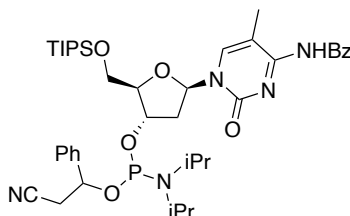
N-Benzoyl-5'-*O*-TIPS-5-methyl-2'-deoxycytidine



***N*-Benzoyl-5'-*O*-TIPS-5-methyl-2'-deoxycytidine** was prepared according to the reported procedure⁹ and purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:45:5, hexane/EtOAc/MeOH) (3 mmol scale; 948 mg, 1.89 mmol, 63% isolated yield). White solid. **M.p.** 113–117 °C. ^1H NMR (400 MHz, CDCl_3) δ 13.3 (brs, 1H), 8.31 (d, J = 7.6 Hz, 2H), 7.65 (s, 1H), 7.52 (m, 1H), 7.46–7.42 (m, 2H), 6.39 (t, J = 6.8 Hz, 1H), 4.58 (m, 1H), 4.06–3.95 (m, 3H), 2.45

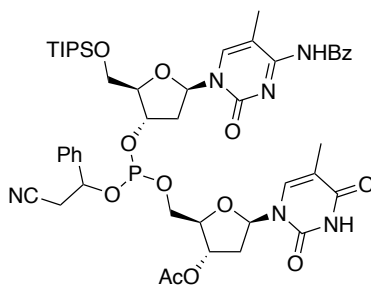
(m, 1H), 2.20–2.10 (m, 5H), 1.20–1.11 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 179.6, 159.7, 147.9, 137.2, 136.5, 132.4, 129.9, 128.1, 111.7, 87.1, 85.4, 72.1, 63.6, 41.4, 18.0, 13.5, 11.8. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{40}\text{N}_3\text{O}_5\text{Si}$, 502.2732; found, 502.2734.

***N*-Benzoyl-5'-*O*-TIPS-5-methyl-2'-deoxycytidine Phosphoramidite**



***N*-Benzoyl-5'-*O*-TIPS-5-methyl-2'-deoxycytidine Phosphoramidite** was purified by flash chromatography on silica gel (Biotage Selekt, 100:0–80:20, hexane/EtOAc) (1.5 mmol scale; 840 mg, 1.08 mmol, 72% isolated yield). The ratio (2.2:1.8:1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 13.29 (brs, 1H), 8.33–8.30 (m, 2H), 7.69–7.31 (m, 9H), 6.39 (m, 0.34H), 6.15 (m, 0.66H), 5.02 (m, 1H), 4.66 (m, 0.34H), 4.40 (m, 0.66H), 4.20–3.51 (m, 5H), 2.84–2.72 (m, 2H), 2.54 (m, 0.34H), 2.38–2.07 (m, 4H), 1.90 (m, 0.66H), 1.28–0.96 (m, 33H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 179.6, 159.8, 159.7, 147.7, 147.7, 140.1, 140.1, 140.1, 140.0, 139.8, 137.2, 136.7, 136.6, 136.5, 132.3, 129.9, 128.7, 128.7, 128.1, 126.1, 126.1, 126.1, 126.0, 116.9, 116.8, 116.8, 116.8, 111.6, 111.5, 87.1, 86.9, 86.9, 86.7, 86.6, 85.5, 85.4, 85.2, 73.8, 73.7, 73.6, 73.5, 73.3, 72.3, 72.2, 72.0, 71.9, 71.2, 71.2, 71.0, 63.4, 63.3, 63.3, 63.1, 43.6, 43.6, 43.5, 43.4, 43.4, 43.2, 40.3, 40.3, 40.2, 40.1, 28.5, 28.4, 28.3, 28.3, 24.7, 24.6, 24.6, 24.5, 24.5, 24.1, 24.1, 24.0, 18.0, 18.0, 13.4, 11.9, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 149.8, 149.8, 148.3, 147.9. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{41}\text{H}_{61}\text{N}_5\text{O}_6\text{PSi}$, 778.4123; found, 778.4122.

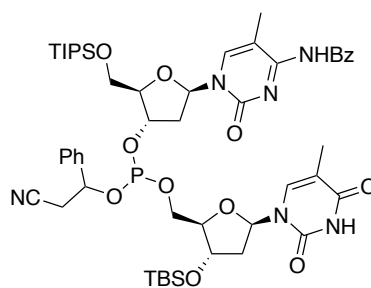
Phosphite (1b)



1b was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (0.48 mmol scale; 300 mg, 0.31 mmol, 65% isolated yield). The ratio (1.1:1.1:1:1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 13.30 (brs, 1H), 8.33–8.30 (m, 3H), 7.61–7.28 (m, 10H), 6.35–6.22

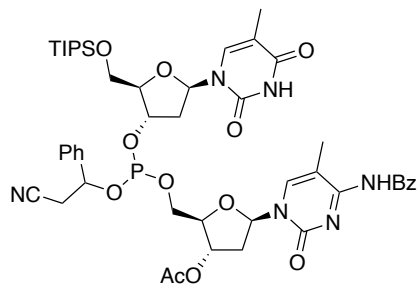
(m, 2H), 5.43 (m, 1H), 5.21 (m, 1H), 4.86 (m, 1H), 4.18–3.56 (m, 6H), 2.94–2.75 (m, 2H), 2.48–1.78 (m, 13H), 1.25–1.06 (m, 21H). ¹³C NMR (100.6 MHz, CDCl₃) δ 170.4, 170.4, 170.4, 163.2, 163.2, 159.6, 150.1, 150.1, 147.8, 147.8, 139.3, 139.2, 138.8, 138.7, 137.1, 136.2, 136.1, 136.1, 135.3, 135.1, 135.0, 135.0, 132.4, 129.9, 129.4, 129.4, 129.3, 129.2, 129.1, 128.1, 125.9, 125.8, 125.8, 116.7, 116.6, 116.6, 116.5, 111.9, 111.8, 111.8, 111.5, 111.4, 111.4, 111.3, 86.6, 86.6, 86.2, 85.2, 85.1, 85.0, 84.7, 84.6, 84.5, 84.5, 83.3, 83.3, 83.2, 83.2, 74.5, 74.2, 74.2, 74.1, 74.0, 73.3, 71.8, 71.6, 71.4, 71.0, 70.9, 70.7, 63.1, 63.0, 62.5, 62.5, 62.1, 40.3, 40.1, 37.3, 37.2, 37.1, 37.0, 28.1, 27.9, 20.9, 20.9, 18.0, 13.4, 12.6, 12.6, 11.8, 11.8 (only observed peaks). ³¹P NMR (162 MHz, CDCl₃) δ 139.9, 139.8, 139.7, 139.2. HRMS–ESI (*m/z*): [M+H]⁺ calcd for C₄₇H₆₂N₆O₁₂PSi, 961.3927; found, 961.3930.

Phosphite (1c)



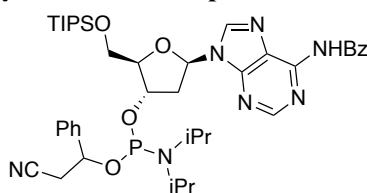
1c was purified by flash chromatography on silica gel (Biotage Selekt, 98:2–80:20, DCM/EtOAc) (0.63 mmol scale; 267 mg, 0.26 mmol, 41% isolated yield). The ratio (1.3:1.2:1.1:1) of diastereomers was determined by ³¹P-NMR analysis. White amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 13.29 (brs, 1H), 8.32–8.30 (m, 2H), 8.07 (m, 1H), 7.59–7.51 (m, 2H), 7.46–7.20 (m, 8H), 6.31–6.16 (m, 2H), 5.39 (m, 1H), 4.85 (m, 1H), 4.38–3.54 (m, 7H), 2.92–2.74 (m, 2H), 2.46–1.74 (m, 10H), 1.18–1.07 (m, 21H), 0.90–0.88 (m, 9H), 0.09–0.08 (m, 6H). ¹³C NMR (100.6 MHz, CDCl₃) δ 179.5, 163.6, 159.6, 150.2, 150.1, 147.8, 139.4, 139.2, 138.9, 138.7, 137.1, 136.1, 135.8, 135.6, 132.4, 129.8, 129.3, 129.3, 129.2, 129.0, 128.1, 125.8, 125.7, 116.6, 116.6, 116.5, 116.4, 111.8, 111.8, 111.7, 111.0, 110.9, 110.9, 110.9, 86.7, 86.6, 86.6, 86.6, 86.3, 86.3, 85.7, 85.7, 85.6, 85.6, 85.5, 85.4, 85.4, 85.2, 85.1, 85.0, 85.0, 85.0, 84.9, 74.3, 74.1, 74.1, 73.9, 73.6, 73.5, 73.1, 73.0, 71.9, 71.6, 71.5, 71.4, 71.4, 71.4, 71.3, 70.7, 70.6, 70.3, 70.3, 63.0, 63.0, 62.9, 62.4, 62.3, 62.1, 62.1, 61.8, 61.7, 61.6, 61.5, 40.4, 40.3, 40.2, 40.0, 28.2, 27.9, 27.8, 25.6, 18.0, 17.8, 13.4, 13.3, 12.6, 12.5, 11.8, 11.7, –4.7, –4.7, –4.7, –4.8 (only observed peaks). ³¹P NMR (162 MHz, CDCl₃) δ 139.7, 139.6, 139.4, 139.1. HRMS–ESI (*m/z*): [M+H]⁺ calcd for C₅₁H₇₄N₆O₁₁PSi₂, 1033.4686; found, 1033.4683.

Phosphite (1d)



1d was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (0.8 mmol scale; 431 mg, 0.45 mmol, 56% isolated yield). The ratio (1.1:1.1:1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 13.25 (brs, 1H), 8.62 (m, 1H), 8.33–8.31 (m, 2H), 7.59–7.34 (m, 10H), 6.36–6.23 (m, 2H), 5.43 (m, 1H), 5.18 (m, 1H), 4.86 (m, 1H), 4.19–3.57 (m, 6H), 2.95–2.75 (m, 2H), 2.45–1.74 (m, 13H), 1.16–1.04 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 179.7, 179.7, 170.4, 170.4, 170.3, 163.4, 159.4, 159.4, 150.2, 150.1, 147.9, 139.2, 138.8, 138.8, 137.0, 136.3, 136.3, 136.2, 136.2, 136.1, 136.0, 135.0, 135.0, 134.9, 132.5, 129.9, 129.4, 129.4, 129.3, 129.2, 129.1, 129.1, 128.1, 126.0, 125.8, 125.8, 116.7, 116.6, 116.5, 112.4, 112.3, 112.2, 112.1, 111.1, 111.0, 111.0, 111.0, 86.3, 86.3, 86.0, 85.9, 85.2, 85.1, 85.0, 84.9, 84.5, 84.4, 84.4, 83.6, 83.5, 83.5, 83.4, 83.4, 74.4, 74.3, 74.2, 74.1, 74.1, 74.0, 73.8, 73.5, 73.4, 71.6, 71.6, 71.5, 71.0, 70.9, 70.9, 70.8, 63.1, 63.1, 63.0, 62.6, 62.5, 62.5, 62.4, 62.3, 62.2, 62.1, 62.0, 40.0, 39.8, 39.7, 39.7, 37.6, 37.5, 37.4, 37.3, 28.1, 27.9, 27.9, 20.9, 20.9, 18.0, 13.7, 12.3, 11.8, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 140.3, 140.0, 139.7, 139.2. HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{47}\text{H}_{62}\text{N}_6\text{O}_{12}\text{PSi}$, 961.3927; found, 961.3925.

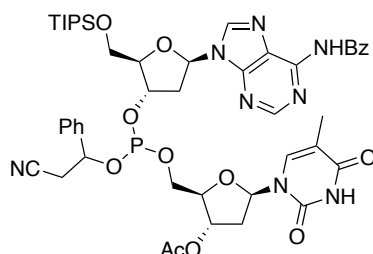
*N*⁶-Benzoyl-5'-*O*-TIPS-2'-deoxyadenosine Phosphoramidite



*N*⁶-Benzoyl-5'-*O*-TIPS-2'-deoxyadenosine Phosphoramidite was purified by flash chromatography on silica gel (Biotage Selekt, 88:12–45:55, hexane/EtOAc) (3.33 mmol scale; 1.32 g, 1.67 mmol, 50% isolated yield). The ratio (2.3:2.3:1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 9.00 (m, 1H), 8.82 (m, 1H), 8.34 (s, 0.15H), 8.32 (s, 0.15H), 8.26 (s, 0.35H), 8.17 (s, 0.35H), 8.04–8.01 (m, 2H), 7.63–7.51 (m, 3H), 7.42–7.24 (m, 5H), 6.58 (m, 0.3H), 6.31 (m, 0.35H), 6.18 (m, 0.35H), 5.04 (m, 1H), 4.84 (m, 0.3H), 4.59 (m, 0.7H), 4.27 (m, 0.3H), 4.07–3.85 (m, 2H), 3.80–3.55 (m, 2.7H), 2.86–2.70 (m, 2.65H), 2.54 (m, 1H), 2.28 (m, 0.35H), 1.30–0.97 (m, 33H). ^{13}C NMR (100.6 MHz,

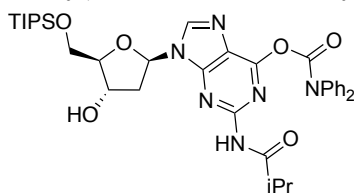
CDCl₃) δ 164.6, 152.6, 152.5, 152.5, 151.5, 151.5, 151.4, 151.4, 149.4, 149.4, 149.3, 141.5, 141.4, 141.3, 140.2, 140.2, 140.2, 139.9, 139.9, 139.9, 133.8, 133.7, 132.7, 128.8, 128.7, 128.6, 127.8, 126.1, 126.1, 126.0, 123.3, 123.2, 123.2, 123.2, 116.9, 116.8, 116.8, 116.7, 87.4, 87.4, 87.1, 87.1, 87.0, 86.9, 84.6, 84.5, 84.5, 73.9, 73.7, 73.6, 73.5, 73.4, 73.3, 73.2, 73.1, 72.3, 72.1, 72.1, 71.9, 71.4, 71.3, 71.2, 71.1, 63.3, 63.3, 63.1, 53.4, 43.6, 43.5, 43.4, 43.3, 43.2, 43.2, 40.1, 40.0, 40.0, 39.9, 39.5, 39.5, 28.4, 28.4, 28.3, 24.7, 24.6, 24.6, 24.5, 24.5, 24.5, 24.2, 24.1, 24.1, 24.0, 17.9, 17.9, 11.8, 11.8 (only observed peaks). ³¹P NMR (162 MHz, CDCl₃) δ 150.3, 149.2, 148.4, 147.6. HRMS–ESI (*m/z*): [M+H]⁺ calcd for C₄₁H₅₉N₇O₅PSi, 788.4079; found, 788.4083.

Phosphite (1e)



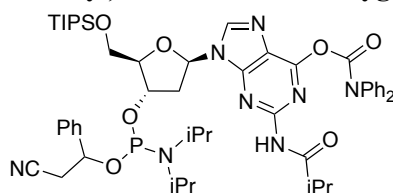
1e was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (1.67 mmol scale; 1.06 g, 1.09 mmol, 65% isolated yield). The ratio (1.4:1.4:1.2:1) of diastereomers was determined by ³¹P-NMR analysis. White amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 9.31–8.79 (m, 3H), 8.26 (m, 1H), 8.06–8.04 (m, 2H), 7.63–7.50 (m, 3H), 7.43–7.31 (m, 6H), 6.47–6.22 (m, 2H), 5.52–4.93 (m, 3H), 4.28–4.08 (m, 3H), 4.04–3.61 (m, 3H), 2.96–2.60 (m, 4H), 2.49–2.05 (m, 5H), 1.95–1.87 (m, 3H), 1.14–1.02 (m, 21H). ¹³C NMR (100.6 MHz, CDCl₃) δ 170.6, 170.5, 170.4, 170.4, 164.8, 163.4, 152.5, 151.6, 150.2, 149.6, 141.6, 141.5, 141.2, 141.0, 139.2, 139.2, 138.9, 138.8, 136.2, 135.2, 135.1, 135.0, 133.6, 132.7, 129.4, 129.4, 129.3, 129.1, 129.1, 128.9, 128.8, 128.0, 125.8, 125.7, 125.5, 123.4, 123.4, 116.7, 116.6, 116.6, 116.5, 111.5, 111.4, 111.4, 86.9, 86.9, 86.8, 86.8, 86.8, 85.9, 85.0, 84.8, 84.7, 84.6, 84.6, 84.3, 83.5, 83.5, 83.4, 83.4, 83.3, 83.3, 74.7, 74.4, 74.3, 74.3, 74.2, 74.2, 74.1, 73.9, 73.7, 71.8, 71.6, 71.5, 71.3, 71.2, 70.2, 63.0, 62.9, 62.9, 62.6, 62.5, 62.4, 62.3, 62.3, 62.2, 62.2, 40.0, 40.0, 39.4, 39.1, 39.1, 37.3, 37.2, 37.2, 37.0, 28.2, 28.1, 28.0, 28.0, 28.0, 21.0, 20.9, 20.9, 18.0, 18.0, 12.6, 12.6, 12.5, 11.8, 11.8 (only observed peaks). ³¹P NMR (162 MHz, CDCl₃) δ 140.8, 140.0, 139.8, 139.0. HRMS–ESI (*m/z*): [M+H]⁺ calcd for C₄₇H₆₀N₈O₁₁PSi, 971.3883; found, 971.3892.

***N*²-Isobutyryl-*O*⁶-(diphenylcarbamoyl)-5'-*O*-TIPS-2'-deoxyguanosine**



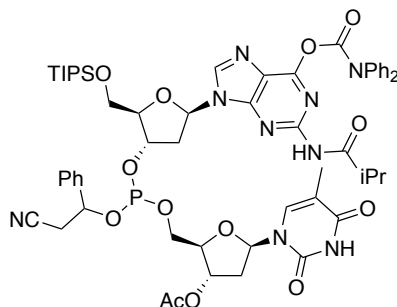
***N*²-Isobutyryl-*O*⁶-(diphenylcarbamoyl)-5'-*O*-TIPS-2'-deoxyguanosine** was prepared according to the reported procedure¹⁰ and purified by flash chromatography on silica gel (Biotage Selekt, 90:10–67:33, DCM/EtOAc) (2.84 mmol scale; 1.39 g, 2.02 mmol, 71% isolated yield). White solid. **M.p.** 123–127 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.27 (m, 1H), 8.03 (m, 1H), 7.44–7.34 (m, 8H), 7.26–7.23 (m, 2H), 6.63 (m, 1H), 4.80 (m, 1H), 4.14 (m, 1H), 3.99–3.91 (m, 2H), 2.85 (brs, 1H), 2.67–2.59 (m, 2H), 1.64 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 6H), 1.18–1.05 (m, 21H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 175.3, 155.8, 154.7, 151.5, 150.4, 142.8, 141.7, 129.1, 127.1, 121.3, 88.2, 84.6, 72.4, 64.2, 41.7, 36.3, 19.3, 18.0, 11.9. **HRMS–ESI** (*m/z*): [M+H]⁺ calcd for C₃₆H₄₉N₆O₆Si, 689.3477; found, 689.3475.

***N*²-Isobutyryl-*O*⁶-(diphenylcarbamoyl)-5'-*O*-TIPS-2'-deoxyguanosine Phosphoramidite**



***N*²-Isobutyryl-*O*⁶-(diphenylcarbamoyl)-5'-*O*-TIPS-2'-deoxyguanosine Phosphoramidite** was purified by flash chromatography on silica gel (Biotage Selekt, 93:7–66:34, hexane/EtOAc) (1 mmol scale; 676 mg, 0.7 mmol, 70% isolated yield). The ratio (2.1:1.9:1:1) of diastereomers was determined by ³¹P-NMR analysis. White amorphous solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.18 (m, 1H), 7.94 (m, 1H), 7.43–7.22 (m, 15H), 6.47 (m, 0.34H), 6.16 (m, 0.66H), 5.03 (m, 1H), 4.80 (m, 0.34H), 4.54 (m, 0.66H), 4.23 (m, 0.34H), 4.02–3.57 (m, 4.66H), 3.07 (m, 1H), 2.88–2.29 (m, 4H), 1.29–0.97 (m, 39H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 175.9, 175.5, 156.0, 155.9, 155.9, 154.5, 154.4, 154.4, 151.9, 151.9, 151.8, 150.4, 150.3, 142.3, 142.2, 142.2, 141.7, 140.1, 139.9, 129.0, 128.6, 128.6, 128.5, 126.8, 126.1, 126.1, 126.0, 126.0, 121.3, 121.2, 121.1, 116.9, 116.8, 116.7, 87.4, 87.4, 87.2, 87.1, 87.0, 87.0, 87.0, 86.9, 84.5, 84.3, 73.9, 73.7, 73.5, 73.4, 73.3, 73.2, 73.1, 72.9, 72.0, 72.0, 71.8, 71.8, 71.3, 71.2, 71.1, 71.0, 63.4, 63.0, 43.6, 43.5, 43.4, 43.3, 43.3, 43.2, 43.1, 40.2, 40.0, 39.6, 39.6, 35.6, 35.3, 28.4, 28.4, 28.3, 28.2, 24.6, 24.6, 24.5, 24.4, 24.1, 24.0, 24.0, 19.2, 19.1, 17.9, 11.8, 11.8 (only observed peaks). **³¹P NMR** (162 MHz, CDCl₃) δ 150.1, 149.2, 148.6, 147.7. **HRMS–ESI** (*m/z*): [M+H]⁺ calcd for C₅₁H₇₀N₈O₇PSi, 965.4869; found, 965.4866.

Phosphite (1f)



1f was purified by flash chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/EtOAc/MeOH) (0.6 mmol scale; 641 mg, 0.56 mmol, 93% isolated yield). The ratio (1.2:1.1:1:1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.83 (m, 1H), 8.29 (m, 1H), 8.16 (m, 1H), 7.50–7.24 (m, 16H), 6.35–6.24 (m, 2H), 5.50–4.93 (m, 3H), 4.25–3.59 (m, 6H), 2.94–2.57 (m, 4H), 2.50–2.29 (m, 2H), 2.24–2.04 (m, 4H), 1.97–1.88 (m, 3H), 1.26–1.24 (m, 6H), 1.09–1.00 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 175.4, 175.3, 170.6, 170.5, 170.4, 170.4, 163.5, 156.0, 154.5, 152.0, 151.9, 150.4, 150.2, 142.5, 142.3, 142.2, 141.7, 139.2, 139.0, 138.8, 136.2, 135.4, 135.3, 135.3, 129.3, 129.3, 129.2, 129.1, 129.0, 127.1, 125.9, 125.8, 121.4, 121.4, 121.3, 116.6, 116.6, 116.5, 111.4, 111.3, 111.3, 111.3, 86.9, 86.8, 86.6, 85.8, 85.0, 84.9, 84.9, 84.7, 84.6, 84.5, 84.4, 84.3, 84.2, 83.6, 83.5, 83.3, 83.3, 74.7, 74.4, 74.3, 74.3, 74.2, 74.1, 73.6, 71.7, 71.5, 71.3, 71.0, 70.8, 70.7, 63.2, 63.0, 62.5, 62.5, 62.3, 62.1, 40.0, 39.9, 39.5, 39.4, 37.3, 37.2, 37.1, 37.0, 36.0, 28.1, 27.9, 21.0, 20.9, 19.3, 17.9, 12.6, 12.5, 11.8, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 141.0, 140.5, 139.8, 139.1. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{57}\text{H}_{71}\text{N}_9\text{O}_{13}\text{PSi}$, 1148.4673; found, 1148.4672.

5. General Procedure for Synthesis of *tert*-Alkylphosphonate Oligonucleotides

The reaction in Table 3-2, entry 2 is representative. In a glovebox, to an oven-dried vial with a stirring bar was added PTH2 (13.2 mg, 0.05 mmol), phosphite **1a-1** (42.9 mg, 0.05 mmol), redox-active ester **2a** (46.4 mg, 0.15 mmol) and LiBF_4 (4.7 mg, 0.05 mmol). Then, MeCN (300 μL) and DCM (200 μL) were added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with UC reactor to keep the temperature at 10 $^\circ\text{C}$ (Figure S3-2). After 18 h, the solvents were removed under reduced pressure. The crude material was then purified by flash column chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) to give the alkylated product **3aa** (29.6 mg, 0.035 mmol, 70% isolated yield) as a white amorphous solid.

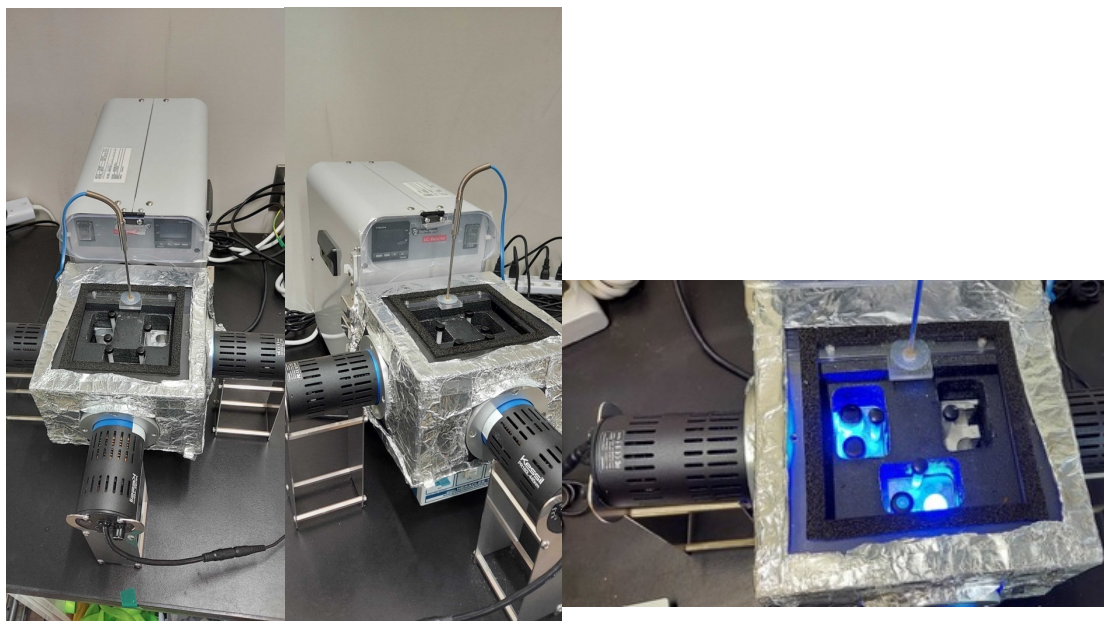
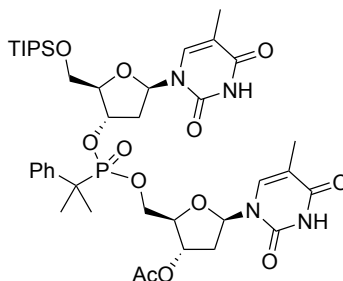


Figure S3-2. Light set up

6. Characterization Data for Alkylated Products

tert-Alkylphosphonate **3aa**



The product **3aa** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-2, entry 2; 29.6 mg, 0.035 mmol, 70% isolated yield). The ratio (before isolation: 1.2:1 → after isolation: 1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 9.07–8.98 (m, 2H), 7.55–7.23 (m, 7H), 6.29–6.24 (m, 2H), 5.14 (m, 1H), 4.86 (t, J = 5.8 Hz, 0.5H), 4.60 (t, J = 6.0 Hz, 0.5H), 4.26–4.11 (m, 3.5H), 3.87 (m, 1H), 3.71 (m, 1H), 3.39 (m, 0.5H), 2.45–2.34 (m, 1.5H), 2.10–1.85 (m, 11.5H), 1.70–1.65 (m, 6H), 1.10–1.03 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 170.3, 163.6, 163.5, 150.3, 140.2, 140.2, 140.0, 139.9, 135.1, 134.8, 134.6, 128.4, 128.4, 128.4, 127.7, 127.7, 127.6, 127.5, 127.4, 127.4, 127.4, 111.6, 111.5, 111.2, 86.8, 86.8, 85.6, 85.6, 84.7, 84.7, 84.3, 83.0, 82.9, 82.8, 82.7, 78.5, 78.5, 78.4, 78.3, 73.9, 73.9, 65.6, 65.5, 64.8, 64.8, 63.2, 40.1, 40.1, 39.9, 39.0, 38.9, 38.8, 38.7, 37.2, 37.2, 24.5, 24.5, 24.1, 24.1, 23.7, 23.7, 23.5, 23.5, 20.8, 18.0, 18.0, 18.0, 12.6, 12.3, 12.3, 12.2, 11.7, 11.7 (only observed peaks). ^{31}P NMR (162

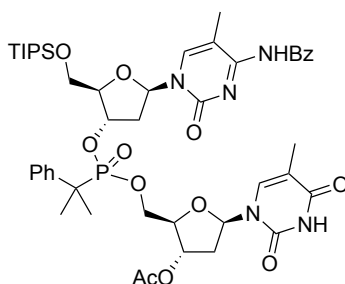
MHz, CDCl₃) δ 34.6, 33.5. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for C₄₀H₆₀N₄O₁₂PSi, 847.3709; found, 847.3710.

The separation of the diastereomers of **3aa**.

The crude residue of **3aa** (from 20 $\times$ 0.05 mmol scale) was purified with column chromatography (silica gel, hexane/EtOAc/MeOH = 50:50:0 to 42.5:42.5:15), and then the fractions containing the diastereomers mixture were collected and further purified by preparative HPLC (Reverse phase, C18 column, 10mM NH₄HCO₃ aq./MeCN = 30/70 to 15/85) to obtain 200 mg (0.24 mmol) of (**R_P**)-**3aa** and 250 mg (0.30 mmol) of (**S_P**)-**3aa**.

50 mg of the single diastereomer [identified as (**R_P**)-**3aa**] was weighed out and transferred to a clean glass tube. About 1 mL of acetonitrile was added to the tube and the mixture was heated until the solid dissolved completely. To the solution was added water (2~3 mL) quietly and the solution was allowed to cool slowly to room temperature. The solution was then placed in the fridge to further promote crystal formation. The crystals were collected using a filtration apparatus and washed with a small amount of water. The crystals were then dried in vacuo.

tert-Alkylphosphonate **3ba**



The product **3ba** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-3; 24.7 mg, 0.026 mmol, 52% isolated yield). The ratio (before isolation: 1.2:1) of diastereomers was determined by ³¹P-NMR analysis. The diastereomers **3ba-d1** and **3ba-d2** were separated and data were measured respectively.

3ba-d1

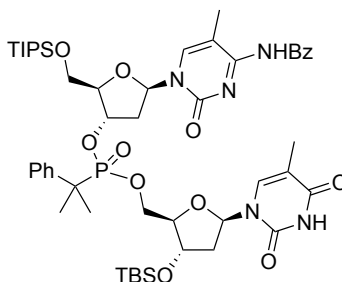
White amorphous solid. **¹H NMR** (400 MHz, CDCl₃) δ 13.29 (brs, 1H), 8.32–8.30 (m, 2H), 8.15 (brs, 1H), 7.56–7.51 (m, 4H), 7.46–7.42 (m, 2H), 7.36–7.32 (m, 2H), 7.27–7.24 (m, 2H), 6.30–6.24 (m, 2H), 5.14 (m, 1H), 4.61 (t, J = 6.0 Hz, 1H), 4.25 (m, 1H), 4.15–4.13 (m, 2H), 4.07 (m, 1H), 3.92–3.86 (m, 2H), 2.37 (m, 1H), 2.17 (m, 1H), 2.10–2.07 (m, 6H), 1.99 (d, J = 1.2 Hz, 3H), 1.93–1.84 (m, 2H), 1.70–1.65 (m, 6H), 1.14–1.03 (m, 21H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 170.3, 163.0, 159.6, 149.9, 147.8, 140.0, 139.9, 137.1, 136.0, 134.6, 132.5, 129.9, 128.5, 128.5, 128.1, 127.6, 127.6, 127.5, 112.0, 111.6, 87.2, 85.0, 84.8, 82.8, 82.8, 78.6, 78.5, 73.9, 64.9, 64.8,

63.3, 40.1, 39.4, 39.3, 38.8, 37.2, 24.2, 24.1, 23.7, 23.7, 20.9, 18.0, 18.0, 13.4, 12.6, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 34.7. HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{47}\text{H}_{65}\text{N}_5\text{O}_{12}\text{PSi}$, 950.4131; found, 950.4128.

3ba-d2

White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 13.29 (brs, 1H), 8.32–8.29 (m, 2H), 8.13 (m, 1H), 7.57–7.42 (m, 7H), 7.37–7.34 (m, 2H), 7.28 (m, 1H), 6.29–6.22 (m, 2H), 5.14 (m, 1H), 4.89 (t, $J = 6.4$ Hz, 1H), 4.25–4.08 (m, 3H), 3.75–3.72 (m, 2H), 3.41 (m, 1H), 2.53 (dd, $J = 13.6, 4.8$ Hz, 1H), 2.38 (m, 1H), 2.10–2.03 (m, 7H), 1.99 (d, $J = 1.2$ Hz, 3H), 1.85 (m, 1H), 1.69–1.64 (m, 6H), 1.13–1.04 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 163.2, 159.6, 149.9, 147.9, 140.2, 137.1, 136.0, 135.1, 132.5, 129.9, 128.4, 128.4, 128.1, 127.7, 127.7, 127.4, 127.4, 112.0, 111.5, 86.0, 85.9, 84.9, 84.8, 83.0, 83.0, 78.5, 78.4, 73.8, 65.5, 65.4, 63.3, 40.3, 40.3, 40.1, 38.8, 37.2, 24.5, 24.5, 23.6, 23.5, 20.9, 18.0, 13.4, 12.3, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 33.6. HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{47}\text{H}_{65}\text{N}_5\text{O}_{12}\text{PSi}$, 950.4131; found, 950.4131.

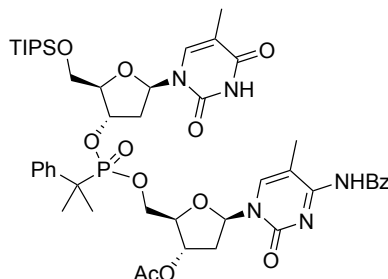
tert-Alkylphosphonate 3ca



The product **3ca** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-3; 25.6 mg, 0.025 mmol, 50% isolated yield). The ratio (before isolation: 1.1:1→after isolation: 1.3:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 13.30 (brs, 1H), 8.37–8.30 (m, 3H), 7.58–7.22 (m, 10H), 6.30–6.17 (m, 2H), 4.88 (t, $J = 6.0$ Hz, 0.43H), 4.63 (t, $J = 6.0$ Hz, 0.57H), 4.24 (m, 1H), 4.12–3.88 (m, 4.57H), 3.76 (m, 1H), 3.49 (m, 0.43H), 2.50 (m, 0.43H), 2.22–1.77 (m, 9.57H), 1.70–1.64 (m, 6H), 1.11–1.05 (m, 21H), 0.89 (s, 9H), 0.08–0.07 (m, 6H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 179.6, 163.4, 163.3, 159.6, 149.9, 147.8, 140.4, 140.1, 140.0, 137.1, 136.0, 135.7, 135.1, 132.5, 129.9, 128.4, 128.4, 128.4, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 112.0, 112.0, 111.2, 111.1, 87.2, 86.1, 85.4, 85.3, 85.3, 85.1, 85.0, 78.3, 78.3, 78.0, 77.9, 71.8, 71.6, 65.5, 65.4, 64.4, 64.3, 63.3, 63.2, 40.6, 40.5, 40.3, 40.2, 40.1, 39.4, 39.3, 38.8, 38.7, 25.7, 24.2, 24.1, 24.0, 23.8, 23.6, 18.0, 18.0, 18.0, 17.9, 13.4, 13.4, 12.6, 12.3, 11.8, 11.7, –4.7, –4.8, –4.9 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 34.7, 33.2. HRMS-ESI (m/z):

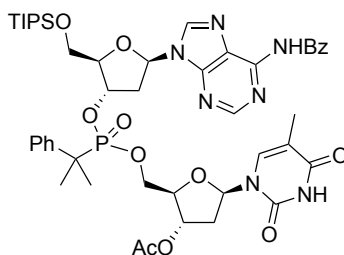
$[M+H]^+$ calcd for $C_{51}H_{77}N_5O_{11}PSi_2$, 1022.4890; found, 1022.4885.

tert-Alkylphosphonate **3da**



The product **3da** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-3; 21.9 mg, 0.023 mmol, 46% isolated yield). The ratio (before isolation: 1.1:1→after isolation: 1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. 1H NMR (400 MHz, $CDCl_3$) δ 13.29 (brs, 1H), 8.42–8.32 (m, 3H), 7.72–7.25 (m, 10H), 6.30–6.24 (m, 2H), 5.14 (m, 1H), 4.89 (t, J = 6.0 Hz, 0.5H), 4.66 (t, J = 6.0 Hz, 0.5H), 4.28–4.08 (m, 3.5H), 3.88 (m, 1H), 3.72 (m, 1H), 3.42 (m, 0.5H), 2.47–2.42 (m, 1.5H), 2.18–2.17 (m, 3H), 2.12–2.04 (m, 4H), 1.91–1.81 (m, 4.5H), 1.71–1.65 (m, 6H), 1.10–1.04 (m, 21H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.7, 170.5, 170.3, 163.3, 159.6, 159.4, 150.1, 147.8, 140.2, 140.2, 140.0, 139.9, 137.1, 137.0, 136.3, 135.6, 134.8, 134.8, 132.6, 132.5, 129.9, 128.5, 128.4, 128.4, 128.1, 128.1, 127.7, 127.7, 127.6, 127.5, 127.4, 112.5, 112.4, 111.2, 86.9, 85.7, 85.6, 85.3, 85.2, 84.4, 84.3, 83.3, 83.2, 83.1, 83.0, 78.5, 78.4, 78.3, 73.9, 65.4, 65.4, 64.8, 64.7, 63.3, 40.1, 40.1, 39.9, 39.1, 39.0, 38.8, 38.8, 37.5, 37.5, 24.5, 24.5, 24.1, 24.1, 23.7, 23.6, 20.8, 18.0, 18.0, 18.0, 13.7, 13.4, 12.3, 12.2, 11.8, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.7, 33.7. HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{47}H_{65}N_5O_{12}PSi$, 950.4131; found, 950.4133.

tert-Alkylphosphonate **3ea**



The product **3ea** was purified by flash chromatography on silica gel (50:50:0–50:42:8, hexane/EtOAc/MeOH) (Table 3-3; 15.8 mg, 0.017 mmol, 33% isolated yield). The ratio (before isolation: 1.1:1) of diastereomers was determined by ^{31}P -NMR analysis. The diastereomers **3ea-d1** and **3ea-d2** were separated and data were measured respectively.

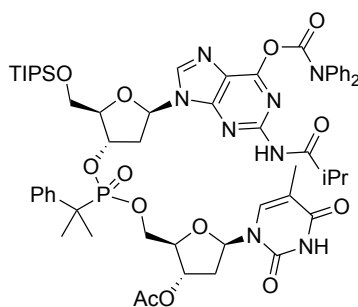
3fa-d1

White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 9.08 (brs, 1H), 8.81 (s, 1H), 8.69 (brs, 1H), 8.28 (s, 1H), 8.03 (d, $J = 7.2$ Hz, 2H), 7.62–7.28 (m, 9H), 6.51 (m, 1H), 6.18 (m, 1H), 5.12–5.08 (m, 2H), 4.24–4.12 (m, 3H), 3.94 (s, 1H), 3.79 (m, 1H), 3.50 (m, 1H), 2.81–2.71 (m, 2H), 2.32 (m, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.80–1.68 (m, 7H), 1.12–1.03 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 163.3, 150.0, 140.4, 140.3, 135.3, 133.6, 132.8, 132.8, 128.8, 128.5, 128.5, 128.0, 127.7, 127.6, 127.4, 127.4, 111.5, 86.4, 86.4, 85.2, 84.3, 83.2, 83.2, 78.6, 78.6, 74.0, 63.3, 40.2, 37.0, 29.7, 29.6, 24.6, 24.5, 23.7, 23.6, 20.9, 18.0, 12.4, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 33.8. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{47}\text{H}_{63}\text{N}_7\text{O}_{11}\text{PSi}$, 960.4087; found, 960.4096.

3fa-d2

White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 9.00 (brs, 1H), 8.82 (s, 1H), 8.25 (brs, 1H), 8.21 (s, 1H), 8.03 (d, $J = 7.2$ Hz, 2H), 7.64–7.51 (m, 5H), 7.37–7.33 (m, 2H), 7.28–7.22 (m, 2H), 6.37 (m, 1H), 6.27 (m, 1H), 5.16 (m, 1H), 4.87 (t, $J = 6.0$ Hz, 1H), 4.33–4.24 (m, 2H), 4.17–4.11 (m, 2H), 3.93–3.84 (m, 2H), 2.55 (m, 1H), 2.39 (m, 1H), 2.21 (m, 1H), 2.11 (s, 3H), 2.00–1.91 (m, 4H), 1.73–1.69 (m, 6H), 1.14–1.02 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.3, 163.1, 149.9, 141.1, 134.7, 132.8, 128.9, 128.5, 128.5, 127.9, 127.6, 127.6, 127.5, 111.6, 87.2, 84.9, 84.2, 82.9, 82.8, 78.6, 78.5, 73.9, 64.9, 63.2, 40.1, 39.2, 39.2, 38.8, 37.2, 24.3, 24.3, 23.7, 23.6, 20.9, 18.0, 12.7, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 34.3. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{47}\text{H}_{63}\text{N}_7\text{O}_{11}\text{PSi}$, 960.4087; found, 960.4088.

tert-Alkylphosphonate 3fa



The product **3fa** (from total 0.45 mmol scale synthesis) was purified with column chromatography (silica gel, hexane/EtOAc/MeOH = 50:50:0 to 50:40:10), and then the fractions containing the product were collected and further purified by preparative HPLC (30:70–0:100, 10mM NH_4HCO_3 in $\text{H}_2\text{O}/\text{MeCN}$) (Table 3-3; 25.6 mg, 0.023 mmol, 5% isolated yield). The ratio (before isolation: 1.1:1) of diastereomers was determined by ^{31}P -NMR analysis. The diastereomers **3fa-d1** and **3fa-d2** were separated and data were measured respectively.

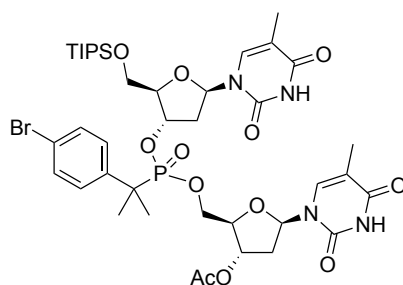
3fa-d1

Off-white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.36–8.26 (m, 2H), 8.12 (s, 1H), 7.59–7.21 (m, 16H), 6.29–6.25 (m, 2H), 5.18 (m, 1H), 4.86 (t, J = 6.0 Hz, 1H), 4.32–4.12 (m, 4H), 3.90–3.82 (m, 2H), 2.38 (m, 1H), 2.20–2.08 (m, 6H), 2.01–1.95 (m, 4H), 1.72–1.68 (m, 6H), 1.27 (d, J = 6.8 Hz, 6H), 1.05–1.00 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.3, 163.3, 156.0, 154.6, 152.1, 150.4, 150.0, 142.0, 140.1, 140.0, 134.8, 129.1, 128.5, 128.4, 127.6, 127.6, 127.5, 126.8, 121.2, 111.5, 87.3, 84.7, 83.9, 82.7, 82.7, 78.5, 78.4, 73.8, 64.9, 64.8, 63.2, 40.1, 39.3, 39.3, 38.8, 37.2, 36.0, 24.3, 24.3, 23.6, 23.6, 20.9, 19.3, 18.0, 18.0, 12.7, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 34.6. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{57}\text{H}_{74}\text{N}_8\text{O}_{13}\text{PSi}$, 1137.4877; found, 1137.4885.

3fa-d2

Off-white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.41–8.24 (m, 2H), 8.17 (s, 1H), 7.58–7.24 (m, 16H), 6.42 (m, 1H), 6.16 (dd J = 8.8, 5.2 Hz, 1H), 5.13 (m, 1H), 5.03 (m, 1H), 4.26–4.12 (m, 3H), 3.89 (m, 1H), 3.74 (m, 1H), 3.49 (m, 1H), 2.77–2.67 (m, 2H), 2.31 (m, 1H), 2.12–2.06 (m, 4H), 2.00–1.99 (m, 3H), 1.81 (m, 1H), 1.71–1.67 (m, 6H), 1.25 (d, J = 6.8 Hz, 6H), 1.05–1.02 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 163.4, 156.0, 154.6, 152.1, 150.4, 149.9, 142.1, 141.8, 140.4, 140.4, 135.5, 129.2, 128.4, 128.4, 127.7, 127.6, 127.4, 121.3, 111.4, 86.3, 86.3, 85.2, 84.2, 83.1, 83.0, 78.6, 78.6, 73.9, 65.6, 65.5, 63.3, 40.2, 38.9, 37.0, 24.5, 24.5, 23.7, 23.6, 20.8, 19.3, 19.3, 18.0, 12.3, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 33.5. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{57}\text{H}_{74}\text{N}_8\text{O}_{13}\text{PSi}$, 1137.4877; found, 1137.4891.

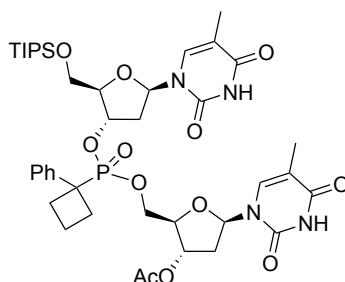
tert-Alkylphosphonate 3ab



The product **3ab** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 26.9 mg, 0.029 mmol, 58% isolated yield). The ratio (before isolation: 1.2:1 $\rightarrow$ after isolation: 1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.93–8.86 (m, 2H), 7.49–7.24 (m, 6H), 6.29–6.24 (m, 2H), 5.15 (m, 1H), 4.86 (t, J = 6.0 Hz, 0.5H), 4.57 (t, J = 5.8 Hz, 0.5H), 4.28–4.09 (m, 3.5H), 3.91–3.72 (m, 2H), 3.38 (m, 0.5H), 2.47–2.38 (m, 1.5H), 2.11–1.88 (m, 11.5H), 1.66–1.61 (m, 6H), 1.15–1.00 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.7, 170.5, 170.3, 163.6,

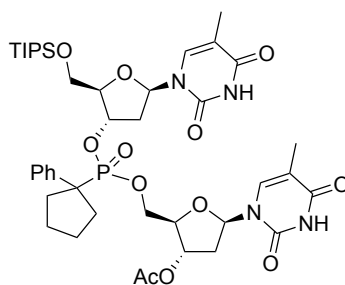
163.5, 150.5, 150.3, 150.2, 139.4, 139.4, 139.1, 139.1, 136.1, 135.1, 134.8, 134.7, 134.6, 131.5, 131.5, 131.4, 129.6, 129.5, 129.5, 129.4, 121.8, 121.7, 121.7, 121.6, 111.7, 111.6, 111.4, 111.3, 111.3, 86.9, 85.9, 85.6, 85.6, 85.0, 84.9, 84.3, 84.3, 82.9, 82.9, 82.7, 82.7, 78.8, 78.7, 78.5, 78.4, 74.7, 73.7, 65.8, 65.7, 64.9, 64.9, 63.2, 62.6, 40.0, 39.9, 39.0, 39.0, 38.7, 38.6, 37.2, 24.5, 24.4, 24.1, 24.1, 23.5, 23.5, 23.5, 23.4, 21.0, 20.8, 18.0, 12.6, 12.6, 12.4, 12.3, 11.8, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 33.7, 32.7. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{40}\text{H}_{59}\text{BrN}_4\text{O}_{12}\text{PSi}$, 925.2814; found, 925.2816.

tert-Alkylphosphonate **3ac**



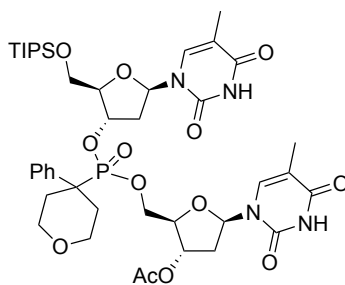
The product **3ac** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 26.6 mg, 0.031 mmol, 62% isolated yield). The ratio (crude 1.1:1→isolated 1.1:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.94–8.82 (m, 2H), 7.49–7.16 (m, 7H), 6.32–6.23 (m, 2H), 5.18 (m, 1H), 4.95 (t, J = 5.8 Hz, 0.48H), 4.69 (t, J = 6.0 Hz, 0.52H), 4.33–4.08 (m, 3.52H), 3.91–3.79 (m, 2H), 3.62 (m, 0.48H), 2.95–2.88 (m, 2H), 2.68–2.56 (m, 2H), 2.50–2.23 (m, 3H), 2.11–1.89 (m, 12H), 1.15–1.03 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.4, 170.4, 163.5, 163.4, 150.2, 141.6, 141.6, 141.5, 141.5, 135.1, 134.8, 134.8, 134.5, 128.3, 128.2, 128.2, 127.5, 127.5, 127.5, 127.5, 126.9, 111.8, 111.6, 111.2, 111.2, 86.7, 85.8, 85.7, 84.7, 84.6, 84.4, 84.3, 83.0, 82.9, 82.7, 82.7, 78.3, 78.2, 78.2, 73.7, 73.7, 65.8, 65.8, 65.1, 65.1, 63.4, 63.2, 45.7, 45.6, 44.3, 44.2, 39.8, 39.3, 39.3, 37.2, 37.1, 30.9, 30.8, 30.5, 30.5, 30.5, 30.4, 29.7, 20.9, 18.0, 18.0, 18.0, 17.2, 17.2, 12.6, 12.3, 12.3, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 31.9, 30.8. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{41}\text{H}_{60}\text{N}_4\text{O}_{12}\text{PSi}$, 859.3709; found, 859.3714.

tert-Alkylphosphonate **3ad**



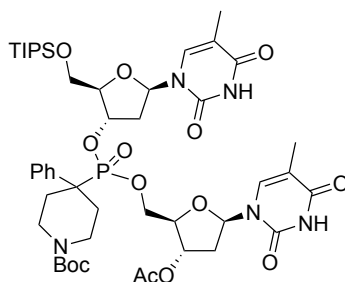
The product **3ad** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 14.8 mg, 0.017 mmol, 34% isolated yield). The ratio (before isolation: 1.2:1→after isolation: 1.2:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.63–8.51 (m, 2H), 7.49–7.15 (m, 7H), 6.28–6.20 (m, 2H), 5.12 (m, 1H), 4.90 (t, J = 5.6 Hz, 0.45H), 4.65 (t, J = 5.8 Hz, 0.55H), 4.24–4.04 (m, 3.55H), 3.88–3.76 (m, 2H), 3.56 (m, 0.45H), 2.46–1.83 (m, 21H), 1.14–1.03 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.4, 170.3, 163.4, 150.1, 139.3, 135.2, 134.8, 134.6, 128.5, 128.3, 127.3, 111.7, 111.5, 111.2, 86.7, 85.7, 84.8, 84.6, 84.3, 82.7, 78.2, 78.1, 73.8, 73.7, 65.6, 65.0, 64.9, 63.4, 63.3, 51.9, 51.9, 50.5, 39.8, 39.2, 39.2, 37.1, 35.1, 35.0, 34.2, 34.1, 24.2, 24.2, 20.9, 18.0, 18.0, 18.0, 12.6, 12.3, 12.3, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 34.2, 33.1. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{42}\text{H}_{62}\text{N}_4\text{O}_{12}\text{PSi}$, 873.3866; found, 873.3863.

tert-Alkylphosphonate **3ae**



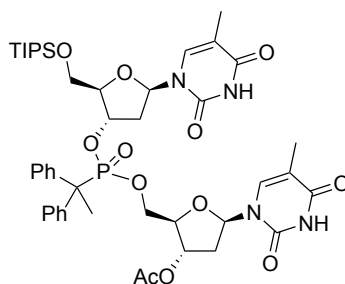
The product **3ae** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 22.7 mg, 0.026 mmol, 51% isolated yield). The ratio (crude 1.2:1→isolated 1.2:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.69–8.51 (m, 2H), 7.48–7.22 (m, 7H), 6.28–6.20 (m, 2H), 5.16 (m, 1H), 4.84 (t, J = 6.0 Hz, 0.43H), 4.45 (t, J = 5.6 Hz, 0.57H), 4.26–4.05 (m, 3.57H), 3.86–3.74 (m, 4H), 3.54–3.50 (m, 1.43H), 3.40 (m, 1H), 2.46–2.34 (m, 5H), 2.11–1.80 (m, 12H), 1.13–1.02 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.4, 170.4, 163.4, 163.3, 163.2, 150.2, 150.1, 135.3, 134.8, 134.4, 129.3, 129.3, 129.2, 129.2, 129.0, 128.9, 127.7, 127.7, 127.6, 111.7, 111.6, 111.2, 86.9, 85.6, 85.5, 85.0, 84.3, 84.3, 82.9, 82.8, 82.7, 82.6, 78.8, 78.7, 78.4, 73.7, 73.6, 65.1, 65.0, 63.3, 63.2, 62.9, 62.8, 62.7, 43.1, 41.7, 39.9, 39.0, 37.1, 37.1, 30.5, 29.7, 29.6, 20.8, 18.0, 18.0, 18.0, 12.6, 12.3, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 30.2, 29.1. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{42}\text{H}_{62}\text{N}_4\text{O}_{13}\text{PSi}$, 889.3815; found, 889.3814.

tert-Alkylphosphonate **3af**



The product **3af** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 14.8 mg, 0.015 mmol, 30% isolated yield). The ratio (crude 1.3:1→isolated 2.2:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.39–8.20 (m, 2H), 7.47–7.17 (m, 7H), 6.27–6.16 (m, 2H), 5.13 (m, 1H), 4.84 (m, 0.31H), 4.44 (m, 0.69H), 4.22–3.53 (m, 10H), 2.84–2.74 (m, 2H), 2.54–2.32 (m, 4H), 2.11–2.07 (m, 5H), 1.96–1.88 (m, 6H), 1.43–1.42 (m, 9H), 1.10–1.02 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.4, 170.3, 163.2, 163.2, 163.1, 154.8, 150.0, 149.9, 135.5, 134.8, 129.3, 129.3, 129.2, 129.2, 129.0, 129.0, 128.9, 128.9, 127.8, 127.7, 111.7, 111.5, 111.2, 86.9, 85.3, 84.3, 82.7, 79.9, 77.7, 73.5, 70.5, 63.2, 37.0, 37.0, 29.7, 28.4, 28.3, 20.8, 18.0, 18.0, 18.0, 12.6, 12.3, 12.3, 11.8, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 30.6, 29.5. HRMS–ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{47}\text{H}_{74}\text{N}_6\text{O}_{14}\text{PSi}$, 1005.4764; found, 1005.4765.

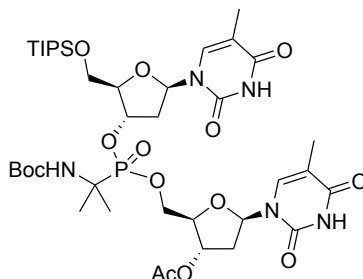
tert-Alkylphosphonate **3ag**



The product **3ag** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 20.0 mg, 0.022 mmol, 44% isolated yield). The ratio (crude 1.2:1→isolated 1.2:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.48–8.38 (m, 2H), 7.52–7.07 (m, 12H), 6.27–6.20 (m, 2H), 5.19 (m, 0.55H), 5.06 (m, 0.45H), 4.93 (t, $J = 6.0$ Hz, 0.45H), 4.42 (m, 1H), 4.27 (m, 0.55H), 4.17–4.11 (m, 2.55H), 3.87 (m, 1H), 3.63 (m, 0.55H), 3.50 (s, 0.45H), 3.29 (m, 0.45H), 2.50 (m, 0.45H), 2.30 (m, 1H), 2.10–2.02 (m, 6H), 1.97–1.69 (m, 8.55H), 1.12–1.03 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.6, 170.3, 163.5, 163.5, 163.4, 163.3, 150.2, 150.2, 142.7, 142.7, 142.5, 142.5, 140.8, 140.8, 140.3, 140.3, 134.9, 134.8, 134.5, 129.2, 129.1, 129.0, 129.0, 128.5, 128.4, 128.3, 128.2, 127.5, 127.2, 111.7, 111.6, 111.2, 111.2, 87.1, 85.3, 85.3, 84.6, 84.5, 84.3, 83.0, 82.9,

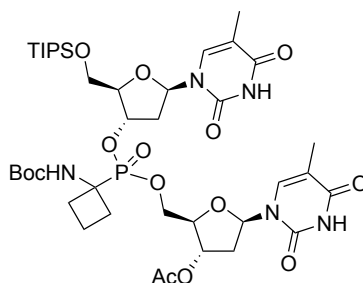
82.7, 82.6, 79.2, 79.2, 79.2, 79.1, 74.0, 74.0, 65.8, 65.7, 65.1, 65.0, 63.3, 63.2, 51.0, 50.9, 49.6, 49.6, 40.0, 38.8, 38.7, 37.0, 29.7, 25.1, 25.0, 20.8, 18.0, 18.0, 18.0, 18.0, 12.5, 12.3, 12.2, 12.1, 11.8, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 31.1, 30.0. HRMS–ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{45}\text{H}_{65}\text{N}_5\text{O}_{12}\text{PSi}$, 926.4131; found, 926.4140.

tert-Alkylphosphonate **3ah**



The product **3ah** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 34.1 mg, 0.039 mmol, 77% isolated yield). The ratio (crude 1:1→isolated 1:1) of diastereomers was determined by ^{31}P -NMR analysis. Off-white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.46–8.32 (m, 2H), 7.62 (s, 0.5H), 7.45–7.36 (m, 1.5H), 6.38–6.27 (m, 2H), 5.27–5.17 (m, 2H), 4.89 (d, J = 4.4 Hz, 0.5H), 4.76 (d, J = 4.0 Hz, 0.5H), 4.41–4.19 (m, 4H), 4.03–3.94 (m, 2H), 2.58 (m, 1H), 2.44 (m, 1H), 2.30–2.10 (m, 5H), 1.95–1.91 (m, 6H), 1.63–1.55 (m, 6H), 1.42–1.41 (m, 9H), 1.17–1.08 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 170.3, 163.8, 163.7, 163.6, 154.2, 154.2, 154.1, 150.5, 150.4, 150.4, 150.4, 135.4, 134.9, 134.9, 111.8, 111.7, 111.2, 111.2, 86.7, 85.8, 85.7, 85.0, 84.7, 84.4, 82.9, 82.8, 82.7, 82.7, 79.9, 79.8, 78.6, 78.5, 78.3, 78.3, 73.9, 73.8, 66.2, 66.1, 65.3, 65.3, 63.4, 63.3, 52.8, 52.8, 51.3, 51.2, 39.8, 39.3, 39.2, 37.0, 36.8, 28.3, 23.8, 23.8, 23.5, 23.3, 20.8, 18.0, 12.4, 12.3, 12.2, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 30.0, 29.2. HRMS–ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{39}\text{H}_{68}\text{N}_6\text{O}_{14}\text{PSi}$, 903.4295; found, 903.4296.

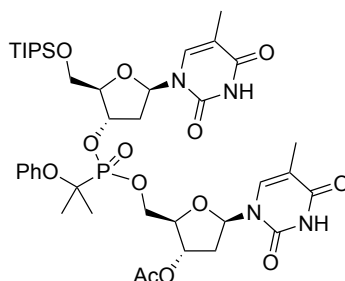
tert-Alkylphosphonate **3ai**



The product **3ai** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 41.8 mg, 0.047 mmol, 93% isolated yield). The ratio (crude 1.2:1→isolated 1.1:1) of diastereomers was determined by ^{31}P -NMR analysis. Off-white

amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.47–8.37 (m, 2H), 7.62 (s, 0.48H), 7.46–7.35 (m, 1.52H), 6.38–6.25 (m, 2H), 5.26–5.21 (m, 2H), 5.10 (s, 0.52H), 4.92 (s, 0.48H), 4.39–4.18 (m, 4H), 4.05–3.93 (m, 2H), 2.63–2.10 (m, 13H), 1.96–1.91 (m, 6H), 1.42 (s, 9H), 1.19–1.08 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.4, 170.3, 163.7, 163.7, 163.6, 153.9, 153.8, 150.5, 150.4, 150.3, 135.4, 135.2, 134.9, 111.7, 111.6, 111.2, 111.2, 86.6, 85.9, 85.9, 85.2, 84.8, 84.4, 84.4, 82.9, 82.9, 82.8, 82.8, 80.0, 80.0, 78.5, 78.4, 78.3, 73.9, 66.0, 65.9, 65.4, 65.3, 63.5, 63.4, 54.2, 54.1, 52.7, 52.5, 39.8, 39.4, 39.4, 37.0, 36.7, 29.9, 29.7, 29.4, 28.3, 28.3, 20.9, 18.0, 16.4, 12.5, 12.3, 11.8 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 27.5, 26.7. HRMS–ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{40}\text{H}_{68}\text{N}_6\text{O}_{14}\text{PSi}$, 915.4295; found, 915.4298.

tert-Alkylphosphonate **3aj**



The product **3aj** was purified by flash chromatography on silica gel (80:20:0–50:45:5, hexane/EtOAc/MeOH) (Table 3-4; 23.7 mg, 0.028 mmol, 55% isolated yield). The ratio (crude 1.2:1→isolated 1.2:1) of diastereomers was determined by ^{31}P -NMR analysis. White amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.58–8.33 (m, 2H), 7.58 (m, 0.45H), 7.44 (m, 1H), 7.38 (m, 0.55H), 7.31–7.27 (m, 2H), 7.17–7.05 (m, 3H), 6.41–6.29 (m, 2H), 5.36–5.29 (m, 2H), 4.52–4.31 (m, 3H), 4.22 (s, 1H), 4.05–3.81 (m, 2H), 2.59 (m, 1H), 2.44 (m, 1H), 2.25–2.10 (m, 5H), 1.94–1.90 (m, 6H), 1.58–1.44 (m, 6H), 1.14–1.01 (m, 21H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 170.5, 170.4, 163.4, 163.3, 153.1, 153.0, 153.0, 152.9, 150.2, 150.2, 135.2, 134.8, 134.8, 129.2, 124.9, 124.2, 111.8, 111.7, 111.3, 111.2, 86.7, 86.7, 86.0, 86.0, 84.8, 84.7, 84.5, 84.3, 83.0, 82.9, 82.8, 82.7, 79.7, 79.6, 78.8, 78.8, 78.7, 78.0, 77.8, 74.0, 73.9, 66.2, 66.1, 65.7, 65.6, 63.5, 63.4, 40.0, 39.5, 39.4, 37.2, 37.0, 29.7, 29.6, 23.8, 23.8, 23.3, 23.3, 22.6, 22.6, 22.2, 22.2, 20.9, 20.8, 18.0, 17.9, 12.4, 12.3, 11.8, 11.7 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 25.9, 25.3. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{40}\text{H}_{60}\text{N}_4\text{O}_{13}\text{PSi}$, 863.3658; found, 863.3659.

7. X-ray Structure of (*R_p*)-**3aa**

Details of the crystal data and a summary of the intensity data collection parameters for (*R_p*)-**3aa** are listed in Table S3-1. A suitable crystal obtained by recrystallization from acetonitrile and water was mounted with mineral oil on a MiTeGen MicroMounts and transferred to the goniometer of the kappa goniometer of a RIGAKU XtaLAB Synergy-S system with 1.2 kW MicroMax-007HF microfocus rotating anode (Graphite-monochromated Mo K α radiation (λ = 0.71073 Å)) and HyPix-6000HE hybrid photon-counting detector. Cell parameters were determined and refined, and raw frame data were integrated using CrysAlis^{Pro} (Agilent Technologies, 2010) and a multi-scan absorption correction using SCALE3 ABSPACK was applied. The structures were solved by direct methods with SHELXT¹¹ and refined by full-matrix least-squares techniques against F^2 (SHELXL-2018/3)¹² by using Olex2 software package.¹³ The intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to 1.5 times the U_{eq} of their pivot atoms for terminal sp^3 carbon atoms and 1.2 times for all other carbon atoms. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. CCDC 2263561 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

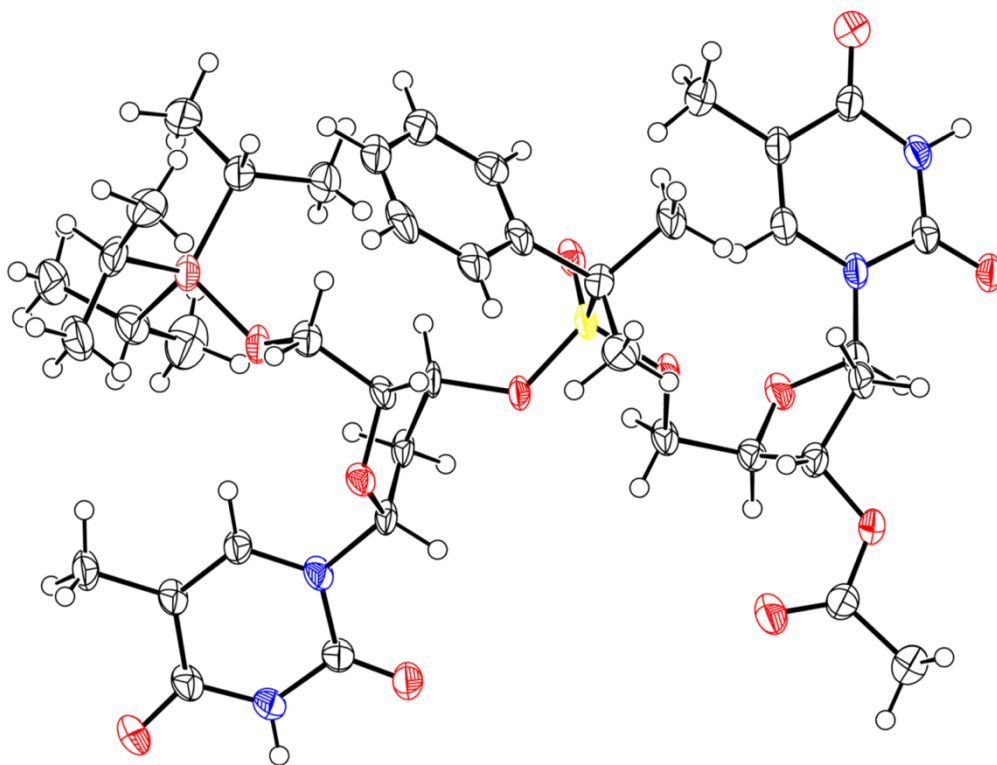


Table S3-1. Crystallographic data and structure refinement details of (*R*_p)-**3aa**

	(<i>R</i> _p)- 3aa
CCDC No.	2263561
formula	C ₄₀ H ₅₉ N ₄ O ₁₂ PSi
fw	846.97
<i>T</i> (K)	123(2)
λ (Å)	0.71073
cryst syst	orthorhombic
space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> (Å)	9.8268(2)
<i>b</i> (Å)	13.5743(4)
<i>c</i> (Å)	32.2626(14)
α (deg)	90
β (deg)	90
γ (deg)	90
<i>V</i> (Å ³)	4303.6(2)
<i>Z</i>	4
<i>D</i> _{calc} (g·cm ⁻³)	1.307
μ (mm ⁻¹)	0.157
F(000)	1808
cryst size (mm ³)	0.2 × 0.04 × 0.01
2 θ range (deg)	5.12 to 54.97
reflns collected	22102
indep reflns/ <i>R</i> _{int}	9462 / 0.0632
params	534
GOF on <i>F</i> ²	1.050
<i>R</i> ₁ , <i>wR</i> ₂ [<i>I</i> > 2 σ (<i>I</i>)]	0.0692, 0.1709
<i>R</i> ₁ , <i>wR</i> ₂ (all data)	0.0909, 0.1798
Flack parameter	-0.11(8)

8. Derivatization of *tert*-Alkylphosphonates to the Phosphoramidites

Procedure for synthesis of (*S_P*)-3aa-3 and (*R_P*)-3aa-3

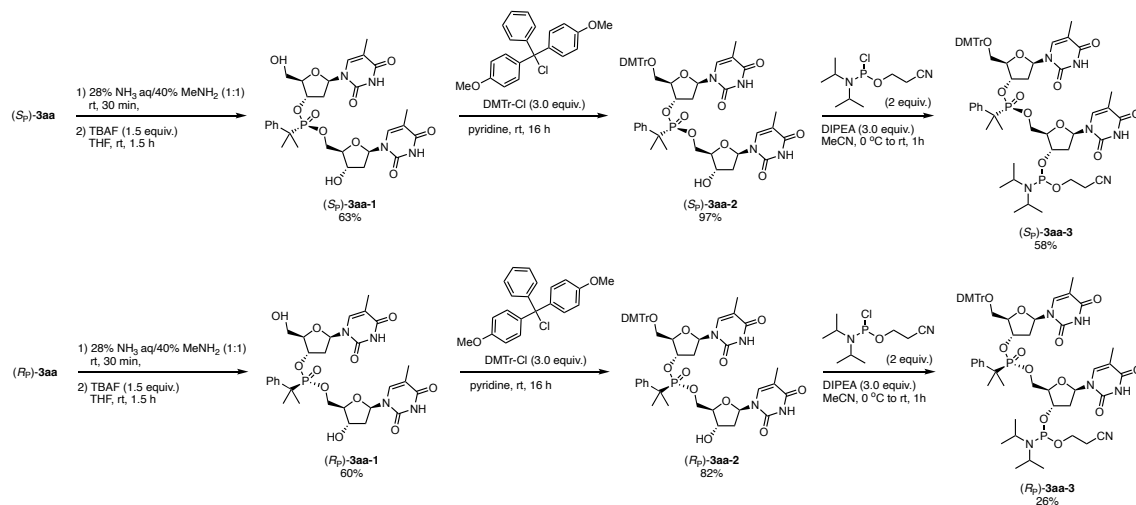


Figure S3-3. Derivatization of *tert*-alkylphosphonates to the phosphoramidites

Deprotection. (*S_P*)-**3aa** (250 mg, 0.30 mmol) was dissolved in ammonia solution (28% NH_3 aq.: 40% MeNH_2 aq. = 1:1). Stirred for 30 min, the reaction mixture was evaporated to remove solvents and reactants. The residue was used for the desilylation without further purification. The residue was dissolved in THF (0.7 mL) and the THF solution of tetrabutylammonium fluoride (0.44 mL, 0.44 mmol) was added to the solution. The reaction mixture was stirred for 90 min and then was evaporated. The crude mixture was purified by silica-gel column chromatography (silica gel, hexane/EtOAc = 50:50 to EtOAc only, then EtOAc/MeOH = 100:0 to 90:10) to obtain (*S_P*)-**3aa-1** (120 mg, 0.19 mmol, 63%). (*R_P*)-**3aa-1** was synthesized using the same protocol (46 mg, 0.07 mmol, 60% from 0.12 mmol scale synthesis).

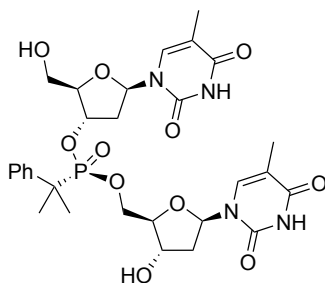
DMTr protection. To a solution of (*S_P*)-**3aa-1** (120 mg, 0.19 mmol) in dry pyridine (2.0 mL) was added 4,4'-{chloro(phenyl)methylene}bis(methoxybenzene) (190 mg, 0.56 mmol) at room temperature. After stirring for 16 hours under a dry atmosphere, the reaction was quenched with MeOH (1 mL) and then the solvent was evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 20:80 to EtOAc only, then EtOAc/MeOH = 100:0 to 90:10) to give (*S_P*)-**3aa-2** (170 mg, 0.18 mmol, 97 %) as amorphous solid. (*R_P*)-**3aa-2** was synthesized using the same protocol (42 mg, 0.044 mmol, 82% from 0.05 mmol scale synthesis).

Phosphoramidation. To a solution of (*S_P*)-**3aa-2** (160 mg, 0.17 mmol) in dry MeCN (4.0 mL) was added DIPEA (0.10 mL, 0.59 mmol) and 3-[(chloro(diisopropylamino)phosphanyl)oxy]propanenitrile (0.094 mL, 0.34 mmol) at 0 °C.

Cooling bath was removed and the mixture was allowed to be stirred at room temperature under dry nitrogen for 1 h. The reaction mixture was washed with hexane (5mL). The resulting oil was purified by column chromatography (silica gel, pre-wetted with hexane/EtOAc/triethylamine = 25:74:1, eluted with hexane/EtOAc = 25:75 to EtOAc only) to give (*S_P*)-**3aa-3** (110 mg, 0.098 mmol, 58%) as a colorless amorphous solid. (*R_P*)-**3aa-3** was synthesized using the same protocol, but the further purification with column chromatography (silica gel, pre-wetted with hexane/EtOAc/triethylamine = 25:74:1, eluted with hexane/EtOAc = 25:75 to EtOAc only) was required to result in lower yield. (12 mg, 0.04 mmol, 26% from 0.04 mmol scale synthesis).

9. Characterization Data for Phosphoramidites

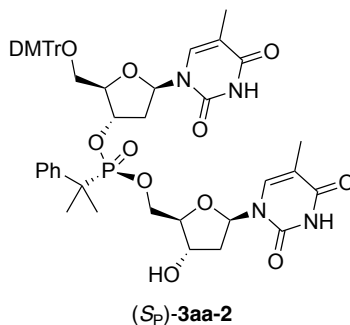
(*S_P*)-**3aa-1**



(*S_P*)-**3aa-1**

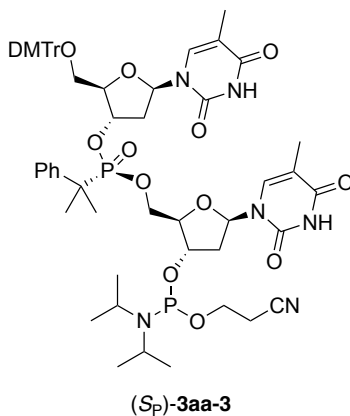
Colorless amorphous solid. The sample contains inseparable impurities. **¹H NMR** (400 MHz, CD₃OD) δ 7.76 (m, 1H), 7.58–7.56 (m, 2H), 7.37–7.34 (m, 3H), 7.25 (m, 1H), 6.23–6.17 (m, 2H), 4.86 (m, 1H), 4.28 (m, 1H), 4.18–4.05 (m, 3H), 3.99 (m, 1H), 3.69–3.68 (m, 2H), 2.22 (m, 1H), 2.11–2.04 (m, 3H), 1.89–1.85 (m, 6H), 1.70–1.65 (m, 6H). **¹³C NMR** (100.6 MHz, CD₃OD) δ 166.3, 166.3, 152.3, 152.2, 141.5 (d, J_{C-P} = 5.1 Hz), 137.8, 137.5, 129.5 ($\times 2C$) (d, J_{C-P} = 2.8 Hz), 128.9 ($\times 2C$) (d, J_{C-P} = 5.4 Hz), 128.4 (d, J_{C-P} = 2.8 Hz), 111.9, 111.8, 87.4 (d, J_{C-P} = 3.5 Hz), 86.5, 86.2 (d, J_{C-P} = 6.5 Hz), 85.9, 79.1 (d, J_{C-P} = 7.6 Hz), 71.8, 67.3 (d, J_{C-P} = 7.8 Hz), 62.4, 40.4 (d, J_{C-P} = 135.8 Hz), 40.4, 39.3 (d, J_{C-P} = 4.6 Hz), 24.4 (d, J_{C-P} = 3.8 Hz), 24.1 (d, J_{C-P} = 4.1 Hz), 12.7, 12.4. **³¹P NMR** (162 MHz, CD₃OD) δ 33.7. **HRMS–ESI** (m/z): [M+H]⁺ calcd for C₂₉H₃₈N₄O₁₁P, 649.2269; found, 649.2288.

(S_P)-3aa-2



Colorless amorphous solid. **¹H NMR** (400 MHz, CDCl₃) δ 9.09–8.98 (m, 2H), 7.58–7.56 (m, 2H), 7.39–7.19 (m, 13H), 7.08 (s, 1H), 6.84–6.82 (m, 4H), 6.30 (m, 1H), 6.13 (m, 1H), 4.81 (m, 1H), 4.19 (m, 1H), 4.12 (m, 1H), 3.99 (m, 1H), 3.85–3.78 (m, 8H), 3.42–3.34 (m, 3H), 2.28 (s, 1H), 2.10–2.08 (m, 2H), 1.95–1.89 (m, 4H), 1.69–1.65 (m, 6H), 1.38 (s, 3H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 163.6, 158.7, 158.7, 150.4, 150.1, 144.1, 139.9, 139.9, 135.3, 135.2, 135.1, 135.0, 130.1, 128.5, 128.5, 128.1, 128.0, 127.7, 127.7, 127.6, 127.5, 127.2, 113.3, 111.6, 111.1, 87.1, 85.0, 85.0, 84.8, 84.6, 84.2, 77.8, 77.7, 77.2, 70.5, 64.8, 63.1, 55.3, 40.0, 39.6, 38.7, 38.7, 38.7, 24.0, 24.0, 23.7, 23.7, 12.6, 11.6 (only observed peaks). **³¹P NMR** (162 MHz, CDCl₃) δ 34.7. **HRMS–ESI** (*m/z*): [M+NH₄]⁺ calcd for C₅₀H₅₉N₅O₁₃P, 968.3842; found, 968.3840.

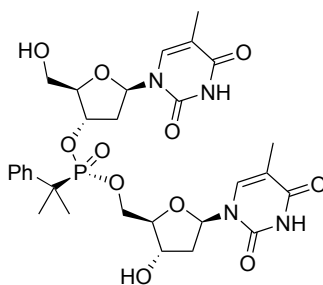
(S_P)-3aa-3



Colorless amorphous solid. **¹H NMR** (400 MHz, CDCl₃) δ 8.45 (brs, 2H), 7.58–7.56 (m, 2H), 7.39–7.11 (m, 14H), 6.83–6.81 (m, 4H), 6.29 (m, 1H), 6.19 (m, 1H), 4.82 (m, 1H), 4.36 (m, 1H), 4.11–4.03 (m, 3H), 3.93–3.57 (m, 11H), 3.35–3.30 (m, 2H), 2.65–2.60 (m, 2H), 2.38 (m, 1H), 2.07–2.00 (m, 2H), 1.92–1.80 (m, 4H), 1.70–1.65 (m, 6H), 1.34–1.17 (m, 15H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 163.4, 163.3, 158.7, 158.7, 150.1, 150.0, 149.9, 144.1, 144.0, 140.2, 140.1, 140.1, 140.1, 135.2, 135.2, 135.1, 135.1, 134.9, 134.9, 130.1, 128.5, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 127.2, 117.6, 113.3, 111.5, 111.3, 111.2, 87.1, 85.2, 85.0, 84.9, 84.3, 84.0, 83.9, 77.9, 77.9,

77.2, 73.2, 73.0, 72.9, 72.7, 64.6, 64.5, 64.5, 63.1, 63.1, 58.2, 58.1, 58.0, 57.9, 55.3, 43.4, 43.3, 40.0, 39.3, 39.2, 38.8, 38.7, 30.9, 24.6, 24.5, 24.5, 24.2, 24.2, 23.7, 23.6, 23.5, 23.5, 20.5, 20.4, 20.3, 20.3, 12.6, 12.5, 11.5 (only observed peaks). **³¹P NMR** (162 MHz, CDCl₃) δ 149.3, 149.1, 34.4, 34.4. **HRMS–ESI** (m/z): [M+NH₄]⁺ calcd for C₅₉H₇₆N₇O₁₄P₂, 1168.4920; found, 1168.4934.

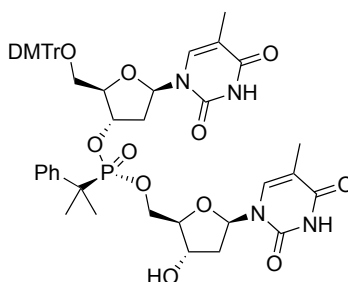
(*R_P*)-3aa-1



(*R_P*)-3aa-1

Colorless amorphous solid. The sample contains inseparable impurities. **¹H NMR** (400 MHz, CD₃OD) δ 7.74 (m, 1H), 7.58–7.56 (m, 2H), 7.49 (m, 1H), 7.37–7.35 (m, 2H), 7.28 (m, 1H), 6.24–6.19 (m, 2H), 4.85 (m, 1H), 4.26 (m, 1H), 4.13 (m, 1H), 4.04 (m, 1H), 3.96 (m, 1H), 3.82 (m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 2.38 (m, 1H), 2.23–2.10 (m, 3H), 1.88–1.84 (m, 6H), 1.69–1.65 (m, 6H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 166.3, 166.3, 152.3, 152.2, 141.6 (d, J_{C-P} = 5.1 Hz), 137.7 ($\times 2C$), 129.4 ($\times 2C$) (d, J_{C-P} = 2.7 Hz), 128.9 ($\times 2C$) (d, J_{C-P} = 5.4 Hz), 128.4 (d, J_{C-P} = 3.0 Hz), 111.9, 111.9, 87.1 (d, J_{C-P} = 6.0 Hz), 86.5, 86.2 (d, J_{C-P} = 5.2 Hz), 86.0, 79.4 (d, J_{C-P} = 7.6 Hz), 71.6, 68.0 (d, J_{C-P} = 7.8 Hz), 62.5, 40.5 (d, J_{C-P} = 136.0 Hz), 40.5, 40.2 (d, J_{C-P} = 2.1 Hz), 24.4 (d, J_{C-P} = 3.7 Hz), 24.1 (d, J_{C-P} = 3.9 Hz), 12.5, 12.5. **³¹P NMR** (162 MHz, CD₃OD) δ 33.3. **HRMS–ESI** (m/z): [M+H]⁺ calcd for C₂₉H₃₈N₄O₁₁P, 649.2269; found, 649.2286.

(*R_P*)-3aa-2

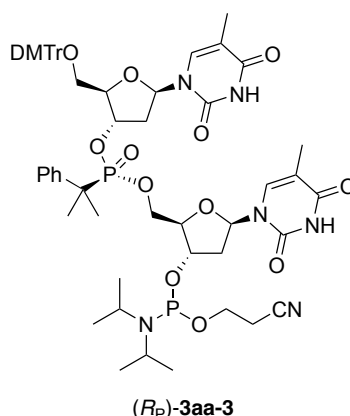


(*R_P*)-3aa-2

Pale yellow amorphous solid. **¹H NMR** (400 MHz, CDCl₃) δ 9.62 (brs, 1H), 9.21 (brs, 1H), 7.52–7.45 (m, 3H), 7.30–7.16 (m, 12H), 7.06 (m, 1H), 6.85–6.83 (m, 4H), 6.34 (m, 1H), 6.21 (m, 1H), 4.66 (m, 1H), 4.44 (m, 1H), 4.25 (m, 1H), 4.12–3.99 (m, 3H), 3.81–3.79 (m, 7H), 3.26 (m, 1H), 2.78 (m, 1H), 2.54 (m, 1H), 2.44–2.29 (m, 2H), 2.08 (m, 1H), 1.93 (s, 3H), 1.64–1.57 (m,

6H), 1.29 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 163.7, 163.5, 163.5, 158.8, 158.8, 151.1, 150.3, 143.8, 140.0, 139.9, 135.6, 135.1, 135.0, 134.9, 130.1, 128.3, 128.3, 128.2, 128.0, 127.5, 127.4, 127.4, 127.3, 127.3, 113.3, 112.2, 111.1, 87.3, 85.3, 84.8, 84.7, 84.4, 84.3, 84.3, 79.7, 79.7, 77.2, 70.8, 65.4, 65.3, 63.3, 55.3, 40.3, 40.2, 39.0, 24.4, 24.4, 23.4, 23.4, 12.5, 11.5 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 34.0. HRMS-ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{50}\text{H}_{59}\text{N}_5\text{O}_{13}\text{P}$, 968.3842; found, 968.3841.

(*R*_P)-3aa-3



Colorless amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.44–8.40 (m, 2H), 7.48–7.10 (m, 16H), 6.85–6.82 (m, 4H), 6.36 (m, 1H), 6.19 (m, 1H), 4.90 (m, 1H), 4.45 (m, 1H), 4.21–4.06 (m, 3H), 3.86–3.59 (m, 11H), 3.26 (m, 1H), 2.87 (m, 1H), 2.65–2.62 (m, 2H), 2.51–2.34 (m, 3H), 2.01–1.88 (m, 4H), 1.62–1.56 (m, 6H), 1.30–1.18 (m, 15H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 163.5, 163.3, 158.8, 150.2, 150.2, 150.0, 143.9, 140.3, 140.2, 136.0, 135.8, 135.3, 135.3, 135.1, 134.9, 130.1, 128.3, 128.3, 128.2, 128.0, 127.6, 127.5, 127.5, 127.5, 127.3, 117.8, 113.1, 111.6, 111.2, 111.1, 87.2, 85.7, 84.5, 84.4, 84.2, 78.7, 78.6, 78.4, 77.2, 73.2, 65.5, 63.3, 58.1, 57.9, 55.3, 43.4, 43.4, 43.3, 43.2, 40.2, 40.2, 39.8, 39.4, 39.4, 39.1, 38.8, 38.8, 24.6, 24.5, 24.5, 24.4, 23.6, 20.5, 20.4, 20.4, 20.4, 12.3, 11.5, 11.4 (only observed peaks). ^{31}P NMR (162 MHz, CDCl_3) δ 149.3, 148.9, 33.4, 33.3. HRMS-ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{59}\text{H}_{76}\text{N}_7\text{O}_{14}\text{P}_2$, 1168.4920; found, 1168.4943.

10. Procedure for Automated Solid-Support Synthesis of Oligonucleotides

The automated solid-support synthesis of oligonucleotides were performed on nS8-II (GeneDesign). The detailed protocol for nS8-II was given in the table below. All the oligonucleotides were synthesized using low-loaded UnylinkerTM universal solid support (0.5 μmol , 42.6 $\mu\text{mol/g}$, ChemGenes, N-4000-10). After the synthetic cycle, the solid support was dried with an argon gas flush and placed into a 2 mL microtube. 500 μL of ammonia methyl amine (AMA) solution (28% NH_3 aq./ 40% MeNH_2 aq. = 1/1) was added to the tube and the support was

treated for 30 minutes at 58 °C. The remaining ammonia and MeNH₂ was evaporated and purified with the cartridge purification system (Glen-PakTM DNA Purification Cartridge, #60-5200, according to the manual provided) to afford aqueous solution containing the purified oligonucleotide. UV absorbance of the solution was measured and then the sample was lyophilized to afford a white powder. Yield was calculated based on absorbance of 260 nm, in which the molar absorption coefficient of the oligonucleotides (**Oligo-1-8**) was calculated from the known 260 nm absorption coefficient of thymine in aqueous media.

Synthesis cycle for oligonucleotides (0.5 umol scale)

Step	Reaction	Reagent	Volume (1CV = 500 uL)	Reaction time
1	Detritylation	Dichloroacetic Acid-Toluene (3:97)	2 CV (incubation twice)	90 sec (60 + 30 seq) 4 min for
2	Coupling	Activator solution: 0.1M Amidite solution = 40:60	12 eq.	(R_P/S_P)-3aa-3 1 min for dT amidite
3	Oxidation	Iodine Solution (abt. 0.05mol/L)] [Pyridine:Water(9:1)	1 CV (incubation)	30 sec
4	Capping	1-Methylimidazole- Acetonitrile (2:8) + Acetic Anhydride-2,6-Lutidine- Acetonitrile (2:3:5)	1 CV (incubation)	90 sec

Note: Before starting the coupling cycle, conduct deblocking of DMTr group on solid-support sufficiently in order to prevent generation of -1nt oligomer byproduct. The dimer amidite (**(R_P/S_P)-3aa-3**) was dehydrated by azeotropic distillation and dried in vacuo with P₂O₅ before use.

UPLC-MS's LC charts and ESI-QTOF MS spectra of oligonucleotides

Analysis conditions with Waters UPLC MS systems

System	Waters, UPLC Xevo G2-XS QTof
column	ACQUITY UPLC OST C18 Column, 1.7 μm, 2.1 x 50 mm
Buffer	A···240 mM HFIP, 7 mM TEA (5% MeOH) B···240 mM HFIP, 7 mM TEA (100% MeOH)
Gradient	10 to 80 for 6min
Flow rate	0.2 ml/min

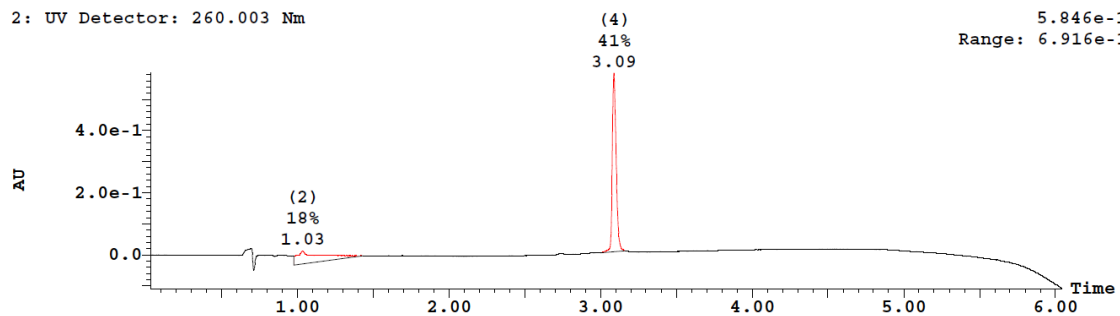
Column oven temperature 60 °C

Detector UV 260 nm

Oligo-1 (R_p)-TTTTTTTTT_{Alk}T

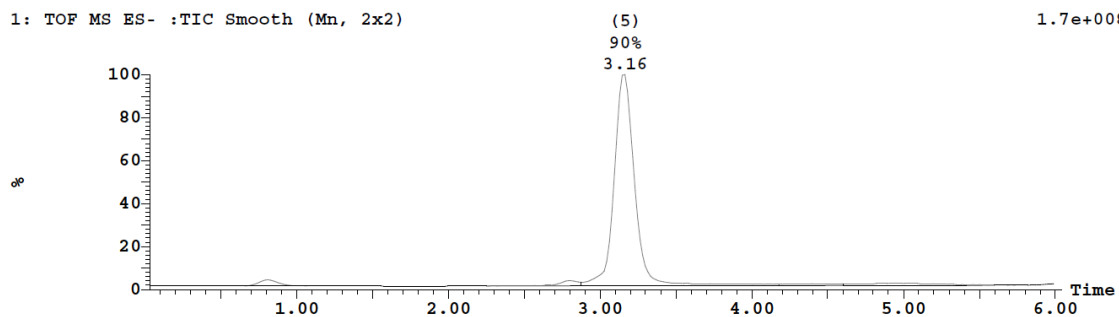
2: UV Detector: 260.003 Nm

5.846e-1
Range: 6.916e-1



1: TOF MS ES- :TIC Smooth (Mn, 2x2)

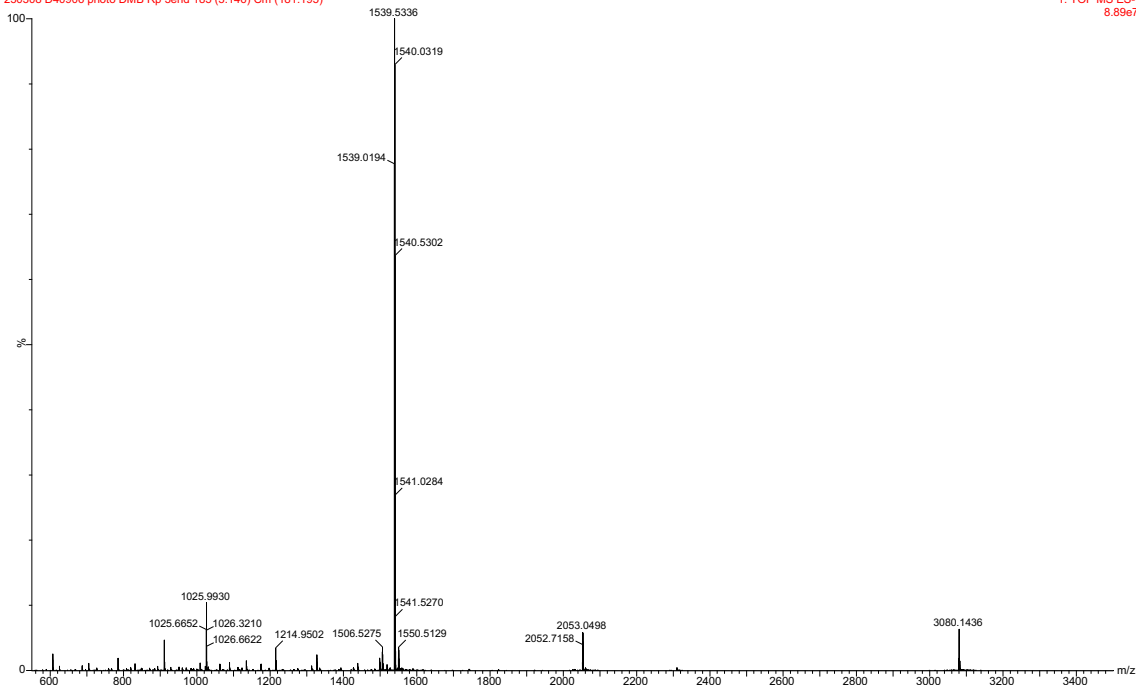
1.7e+008



10-80

230308 D40906 photo DMB Rp 3end 185 (3.146) Cm (181:195)

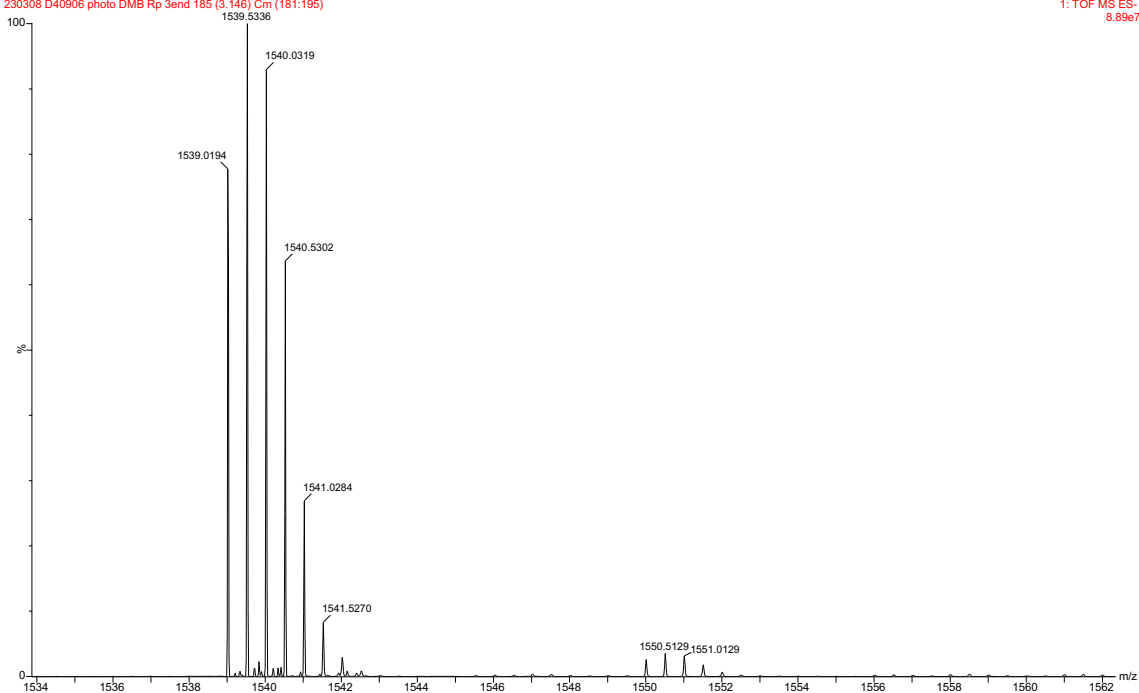
1: TOF MS ES-
6.89e7



10-80

230308 D40906 photo DMB Rp 3end 185 (3.146) Cm (181:195)

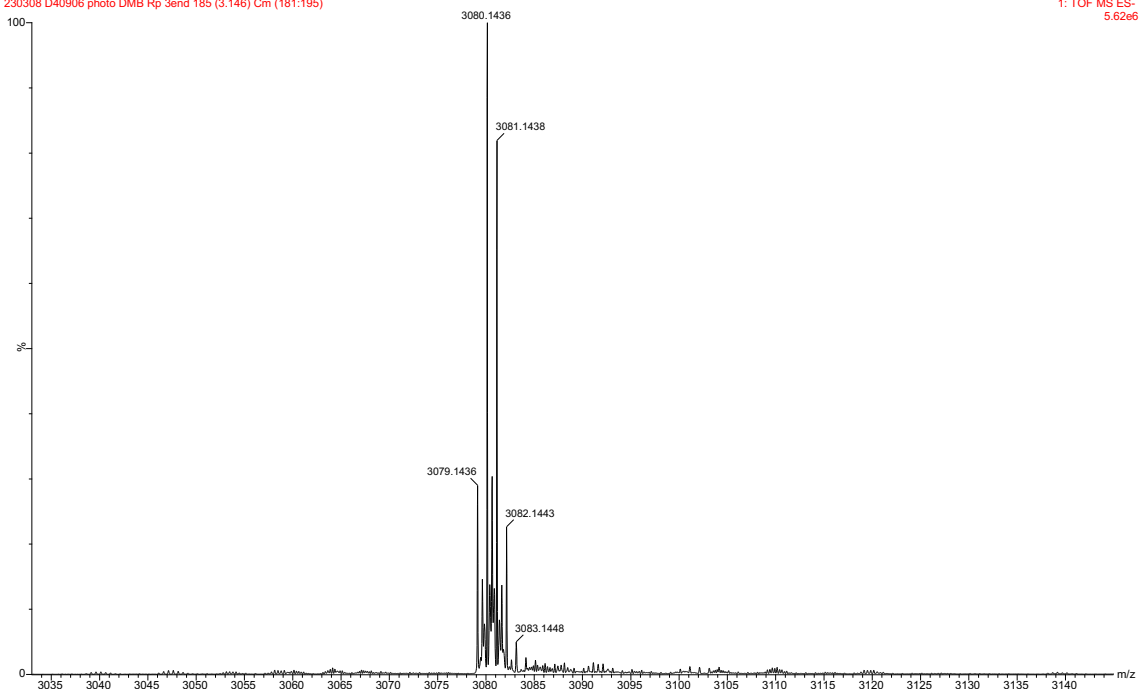
1: TOF MS ES-
8.89e7



10-80

230308 D40906 photo DMB Rp 3end 185 (3.146) Cm (181:195)

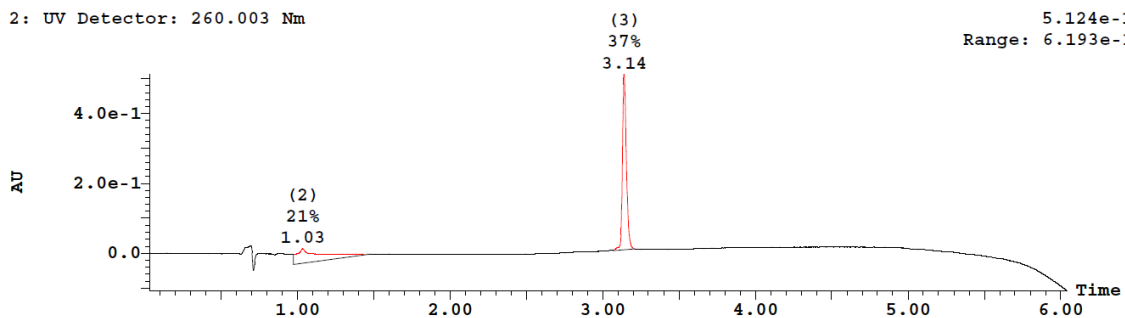
1: TOF MS ES-
5.62e6



Oligo-2 (S_P)-TTTTTTTTT_{Alk}T

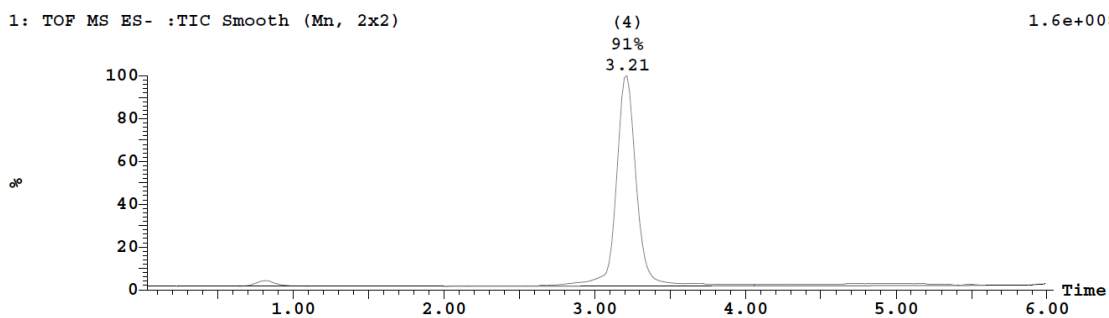
2: UV Detector: 260.003 Nm

5.124e-1
Range: 6.193e-1



1: TOF MS ES- :TIC Smooth (Mn, 2x2)

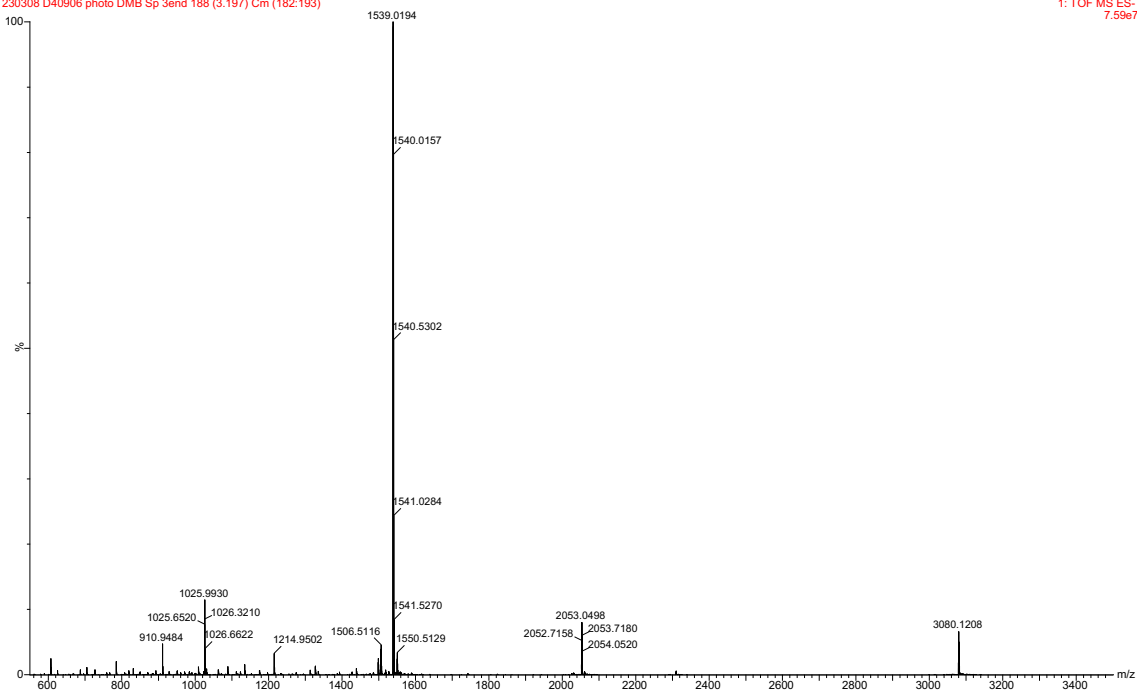
1.6e+008



10-80

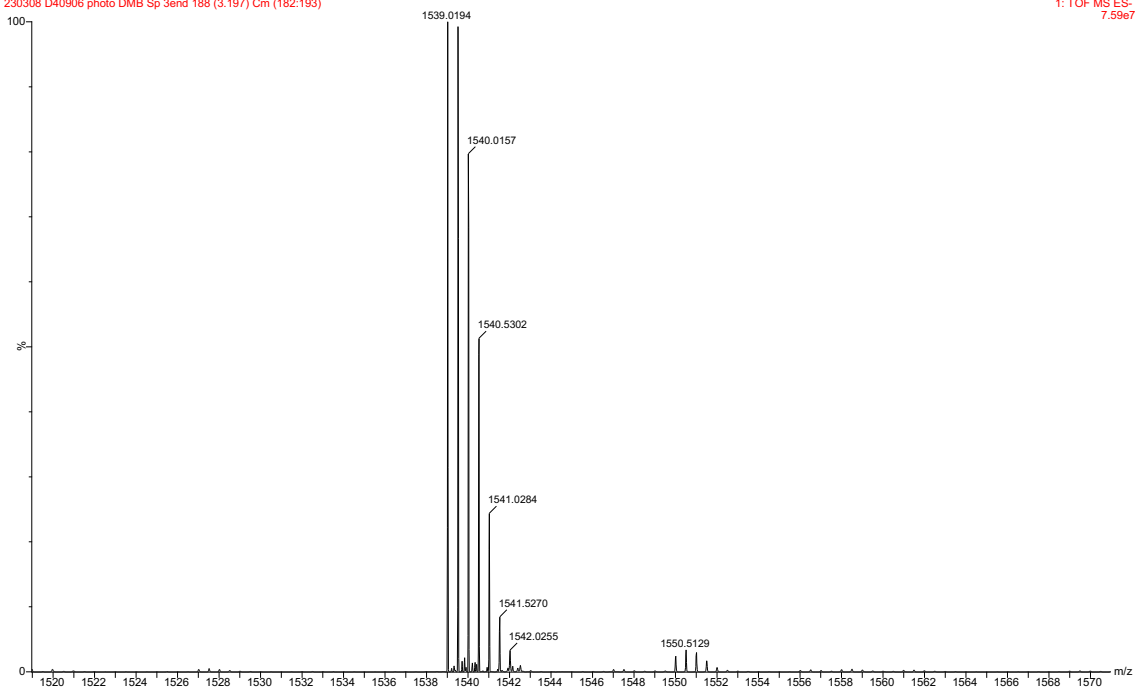
230308 D40906 photo DMB Sp 3end 188 (3.197) Cm (182:193)

1: TOF MS ES-
7.59e7



10-80

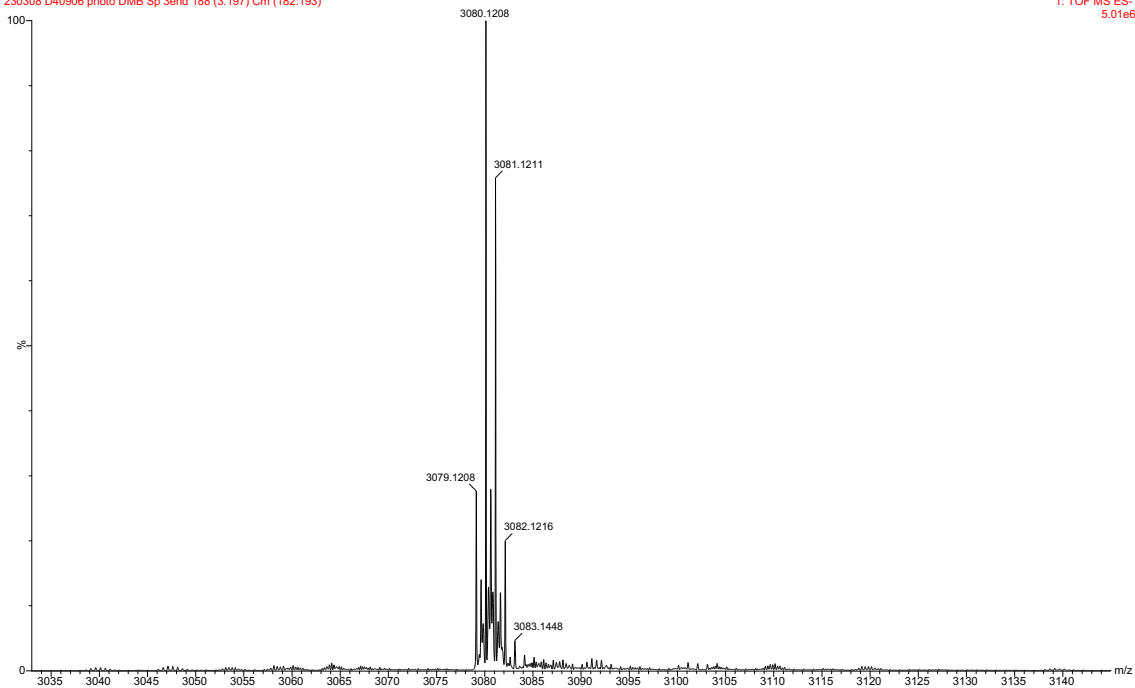
230308 D40906 photo DMB Sp 3end 188 (3.197) Cm (182:193)



1: TOF MS ES-
7.59e7

10-80

230308 D40906 photo DMB Sp 3end 188 (3.197) Cm (182:193)

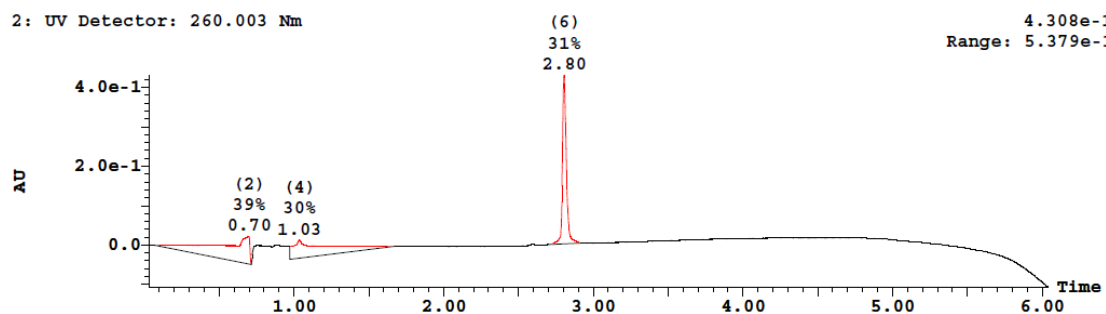


1: TOF MS ES-
5.01e6

Oligo-3 (R_p)-TTTTT_{Alk}TTTTT

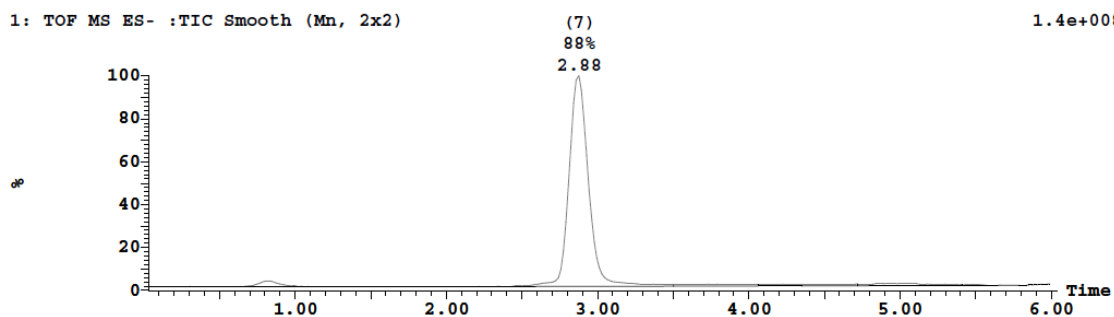
2: UV Detector: 260.003 Nm

4.308e-1
Range: 5.379e-1



1: TOF MS ES- :TIC Smooth (Mn, 2x2)

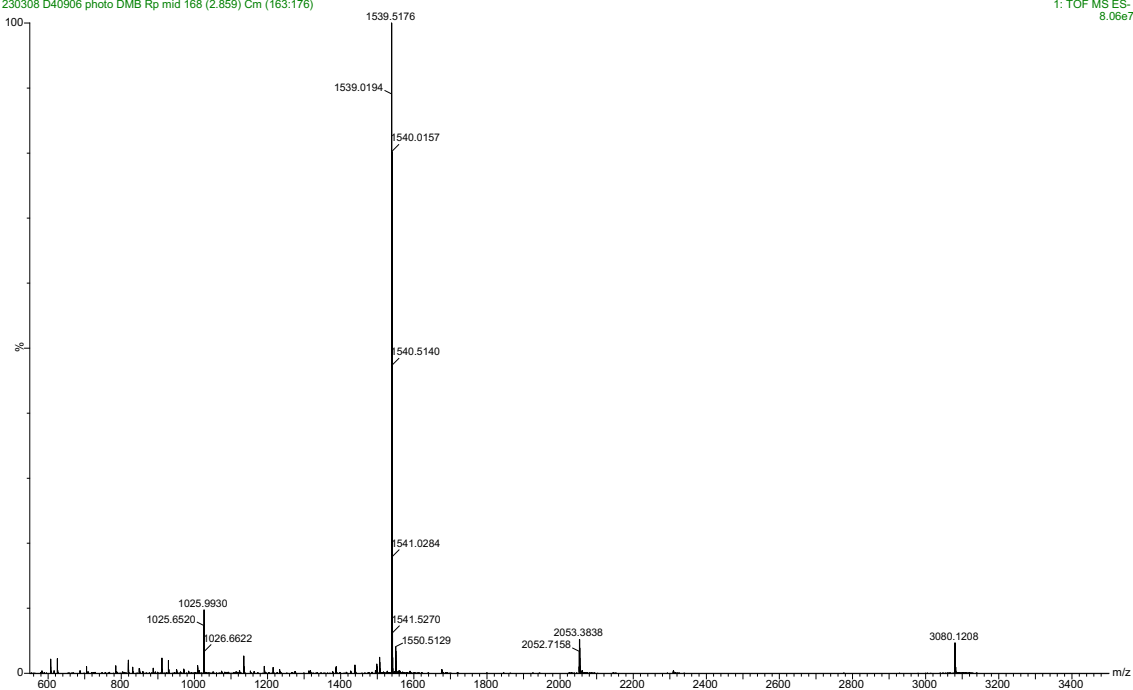
1.4e+008



10-80

230308 D40906 photo DMB Rp mid 168 (2.859) Cm (163:176)

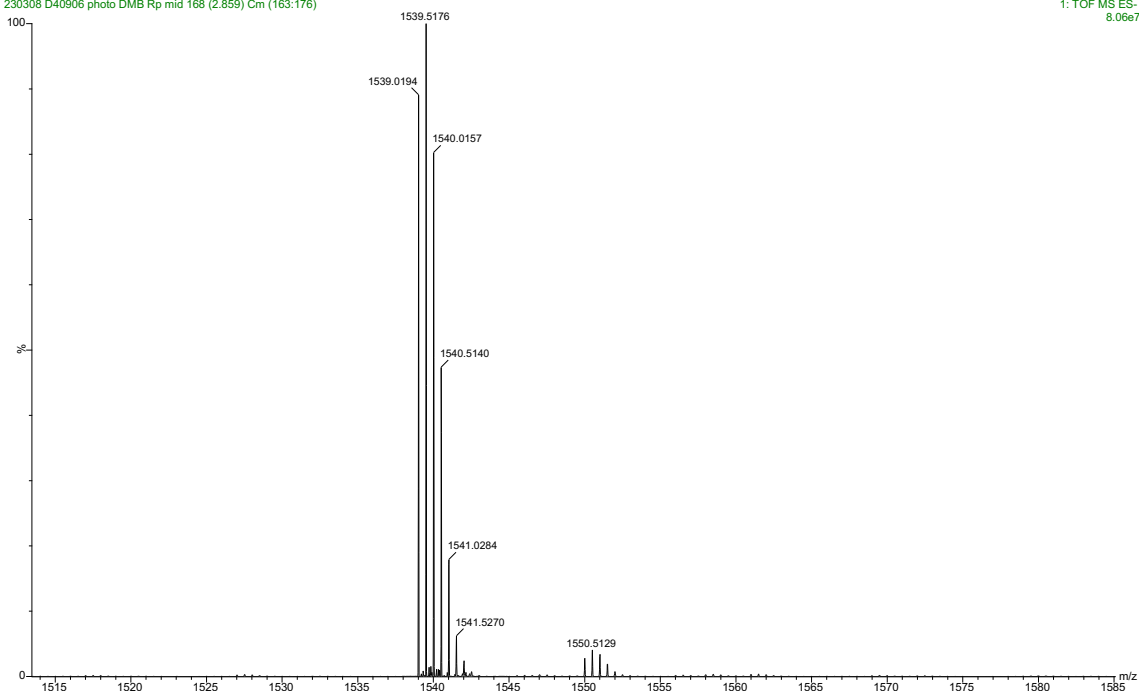
1: TOF MS ES-
8.06e7



10-80

230308 D40906 photo DMB Rp mid 168 (2.859) Cm (163:176)

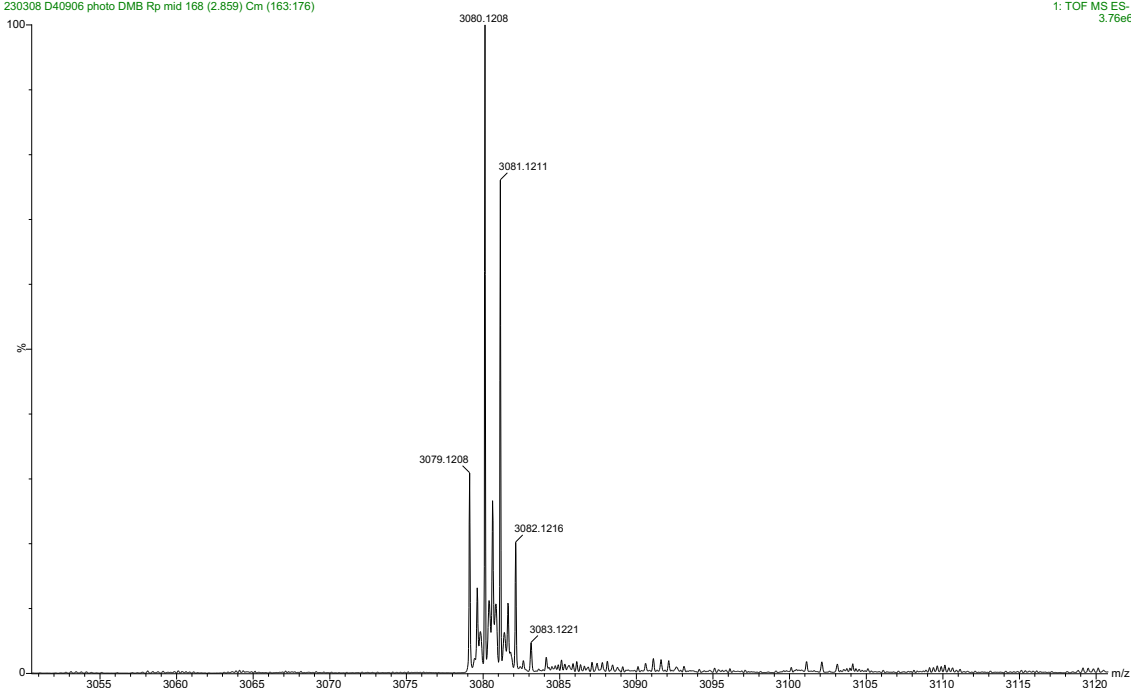
1: TOF MS ES-
8.06e7



10-80

230308 D40906 photo DMB Rp mid 168 (2.859) Cm (163:176)

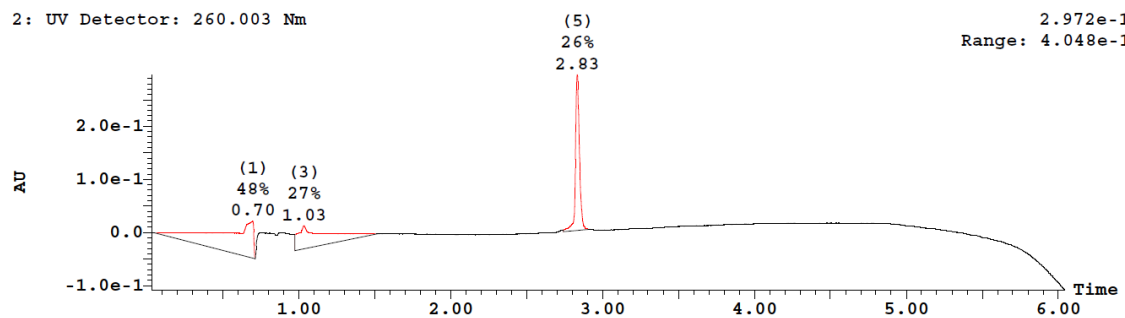
1: TOF MS ES-
3.76e6



Oligo-4 (S_P)-TTTTT_{Alk}TTTTT

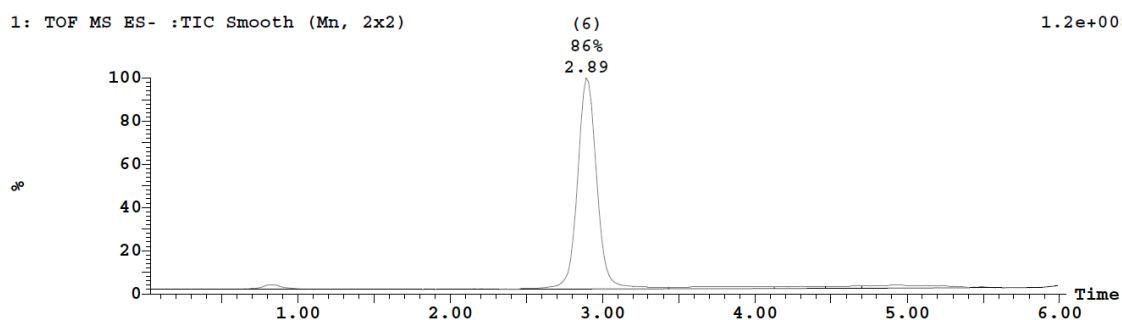
2: UV Detector: 260.003 Nm

2.972e-1
Range: 4.048e-1



1: TOF MS ES- :TIC Smooth (Mn, 2x2)

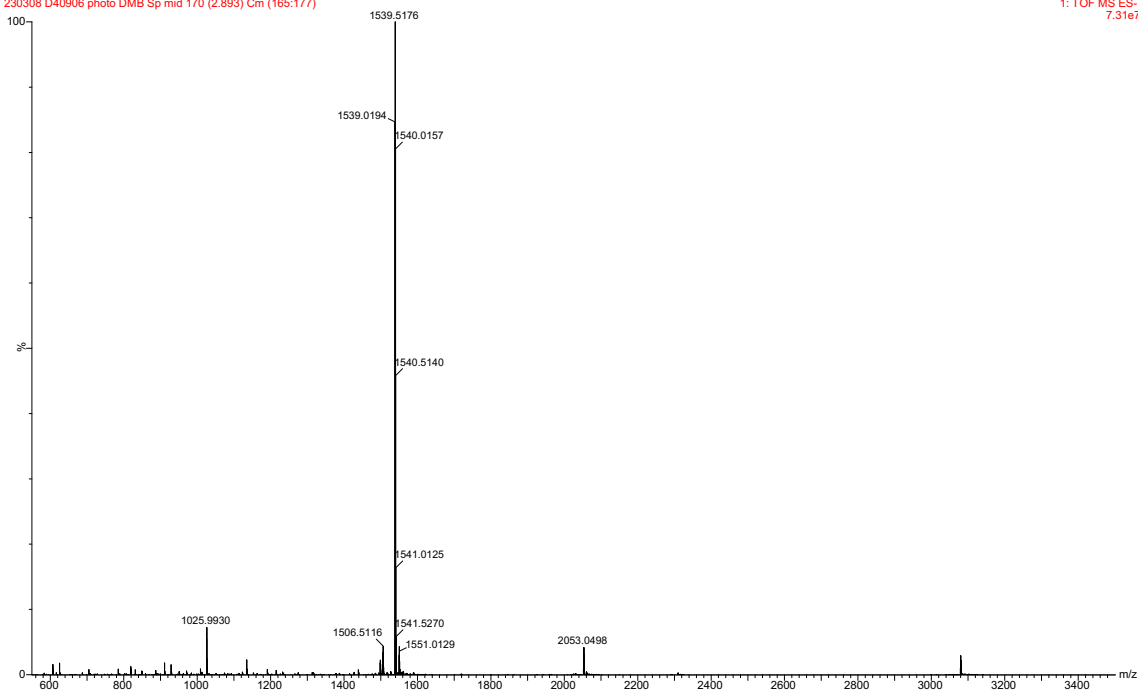
1.2e+008



10-80

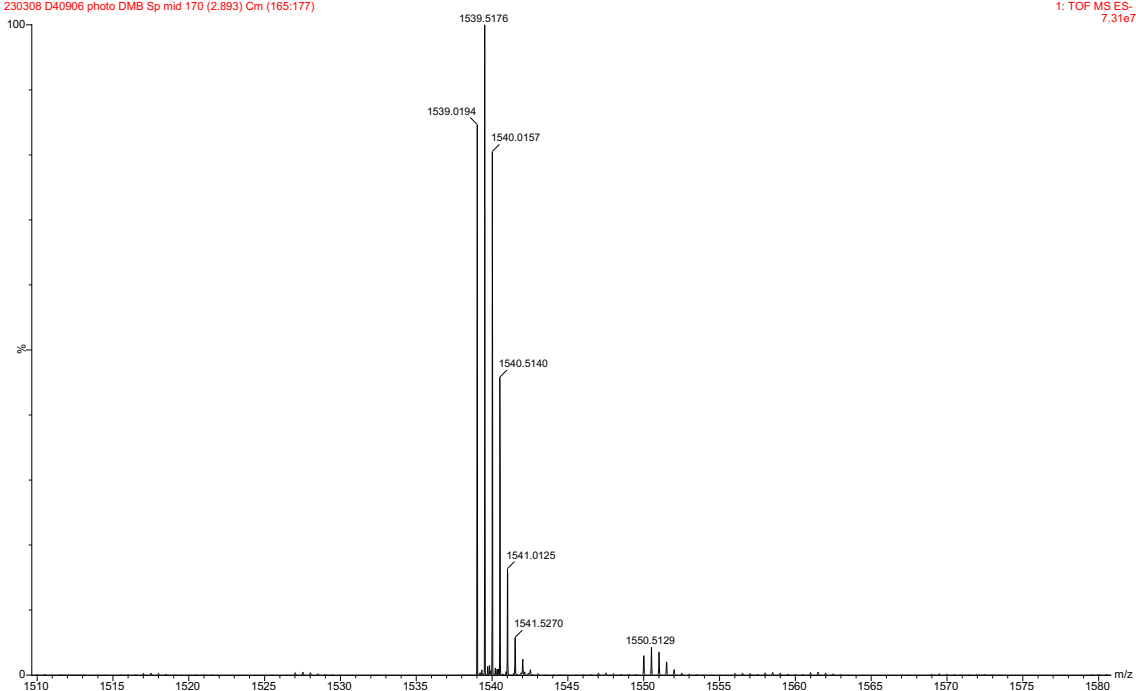
230308 D40906 photo DMB Sp mid 170 (2.893) Cm (165.177)

1: TOF MS ES-
7.31e7



10-80

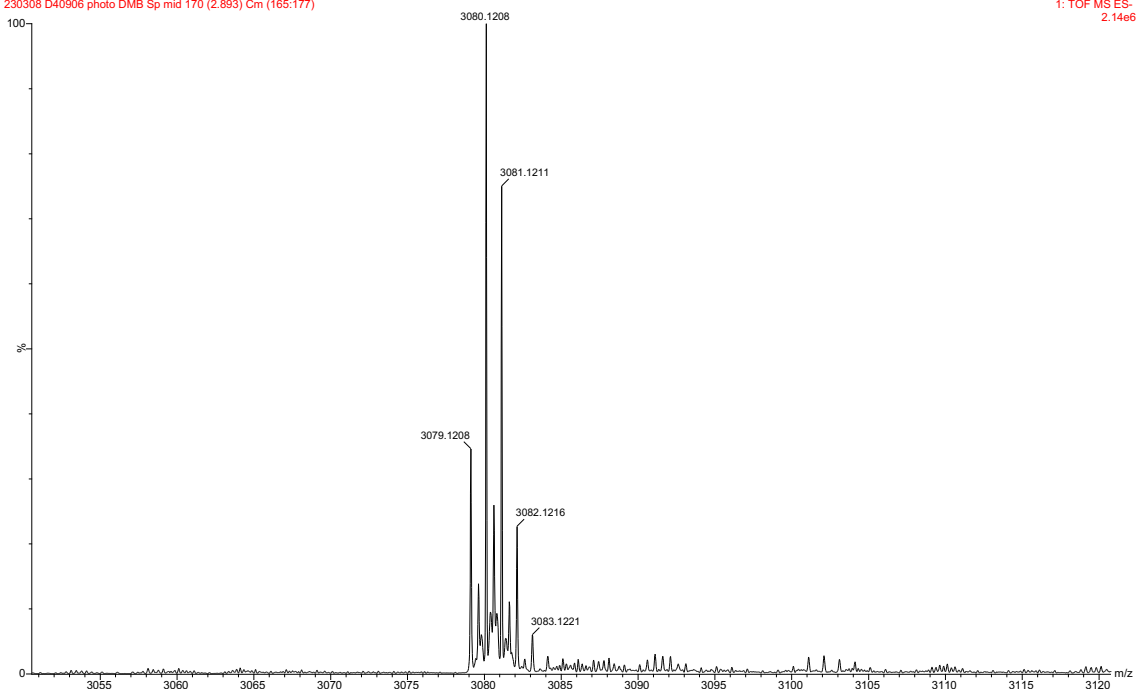
230308 D40906 photo DMB Sp mid 170 (2.893) Cm (165:177)



1: TOF MS ES-
7.31e7

10-80

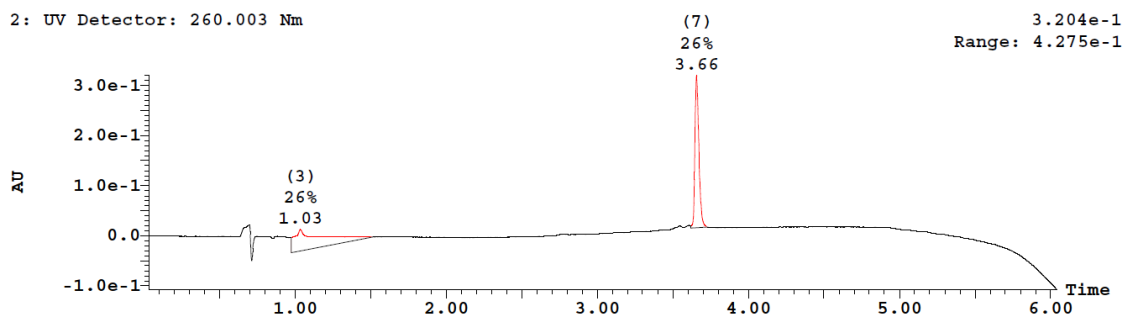
230308 D40906 photo DMB Sp mid 170 (2.893) Cm (165:177)



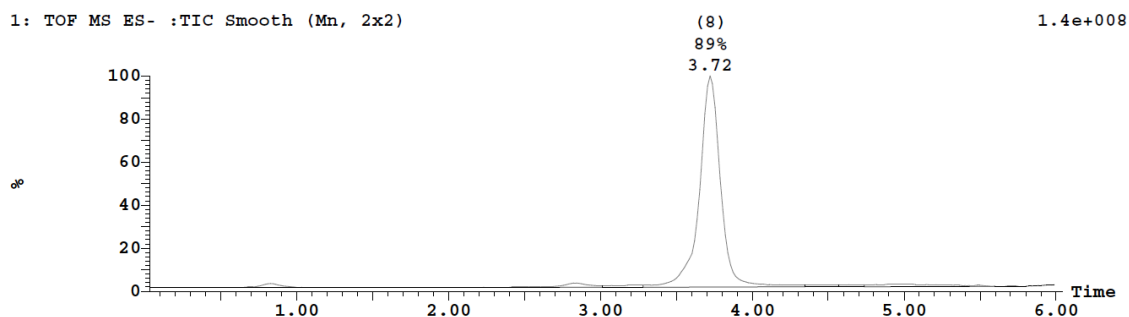
1: TOF MS ES-
2.14e6

Oligo-5 (*S_P*,*S_P*)-T_{Alk}TTTTTTTTT_{Alk}T

2: UV Detector: 260.003 Nm

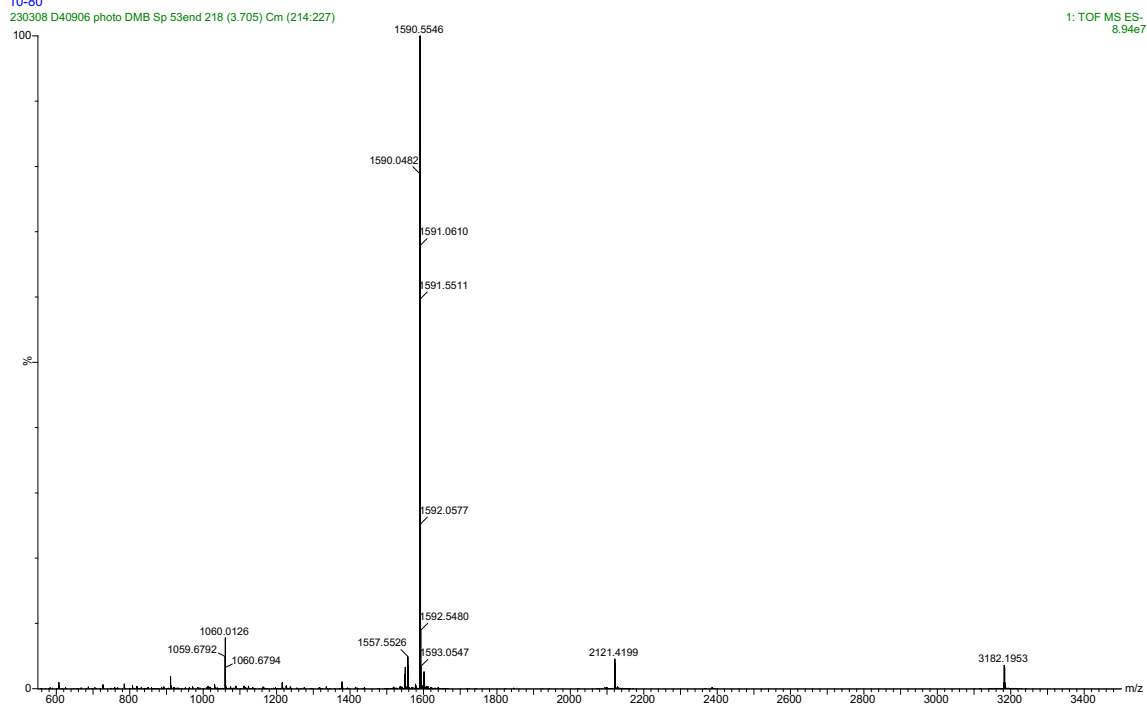


1: TOF MS ES- :TIC Smooth (Mn, 2x2)



10-80

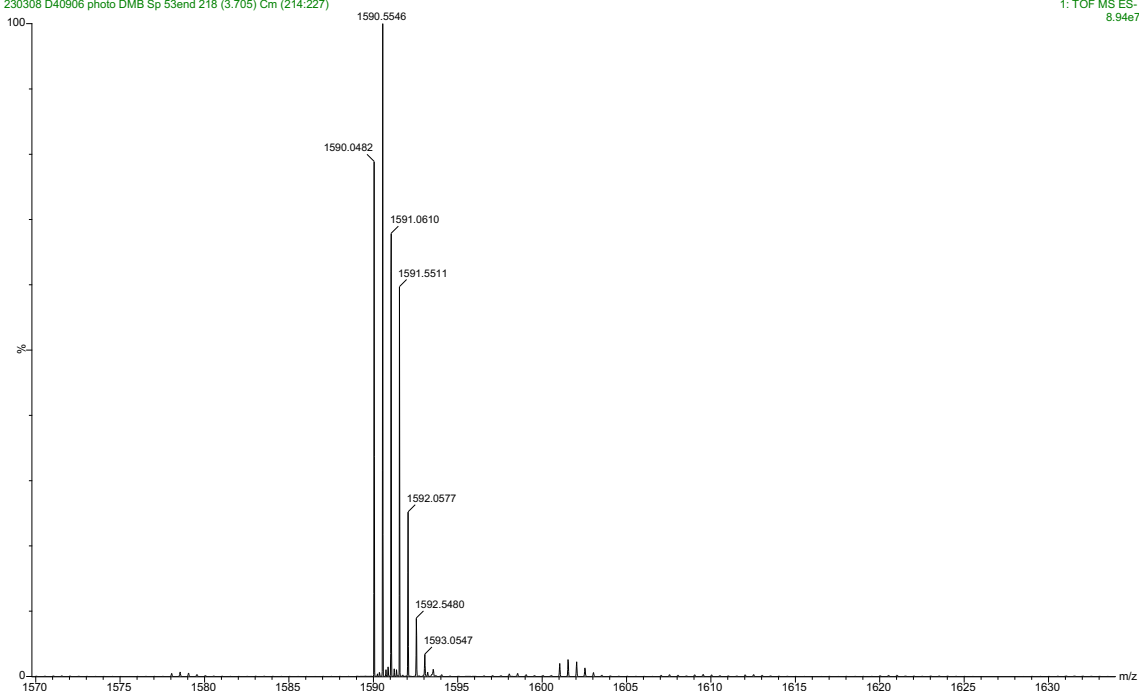
230308 D40906 photo DMB Sp 53end 218 (3.705) Cm (214:227)



10-80

230308 D40906 photo DMB Sp 53end 218 (3.705) Cm (214:227)

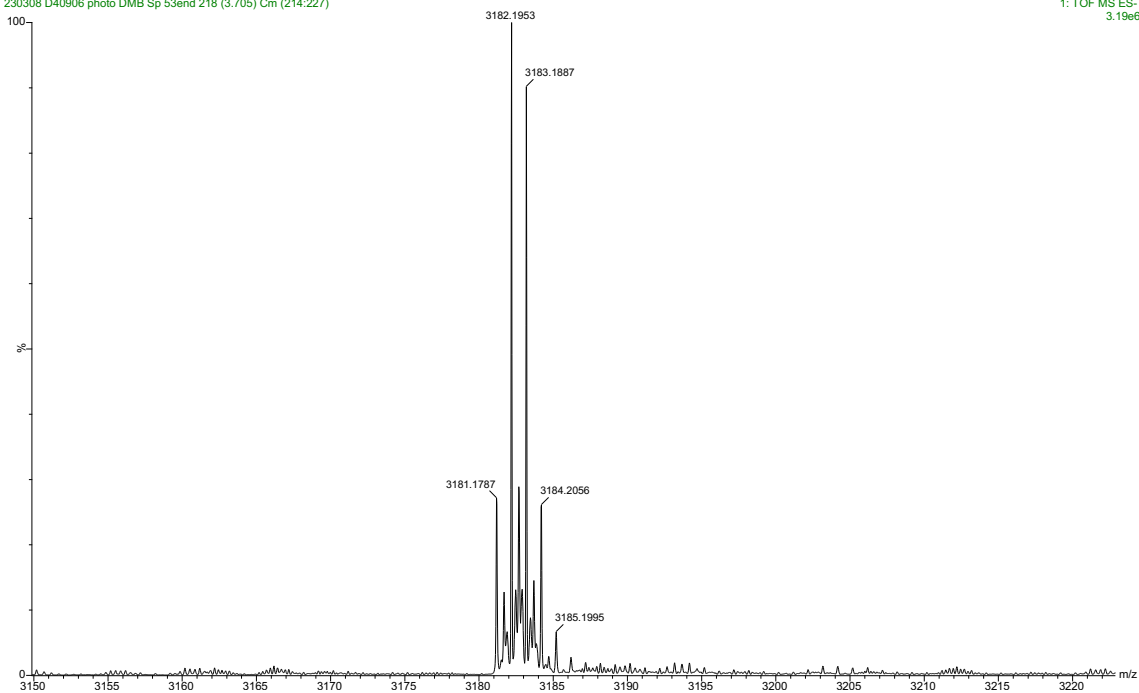
1: TOF MS ES-
8.94e7



10-80

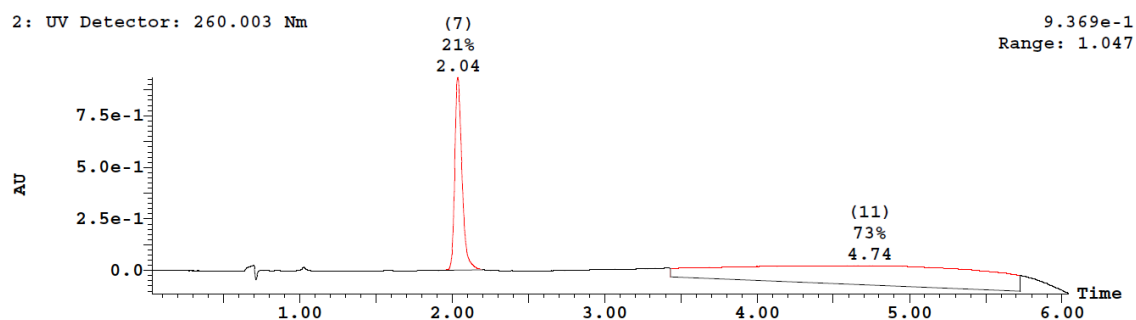
230308 D40906 photo DMB Sp 53end 218 (3.705) Cm (214:227)

1: TOF MS ES-
3.19e6

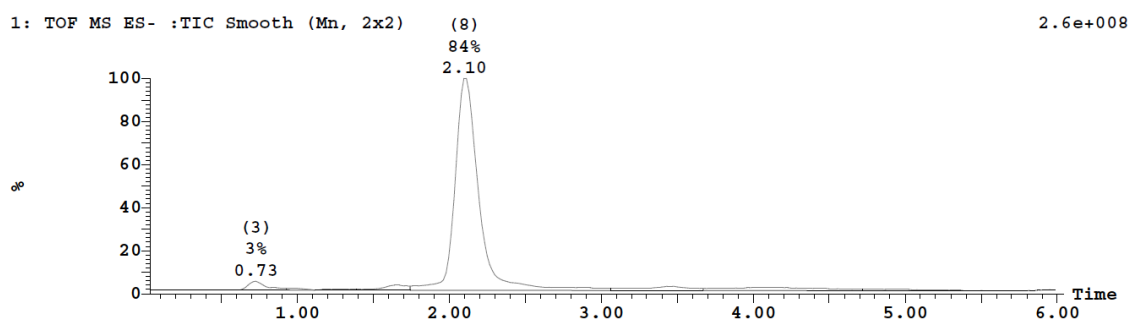


Oligo-6 TTTTTTTTTT

2: UV Detector: 260.003 Nm

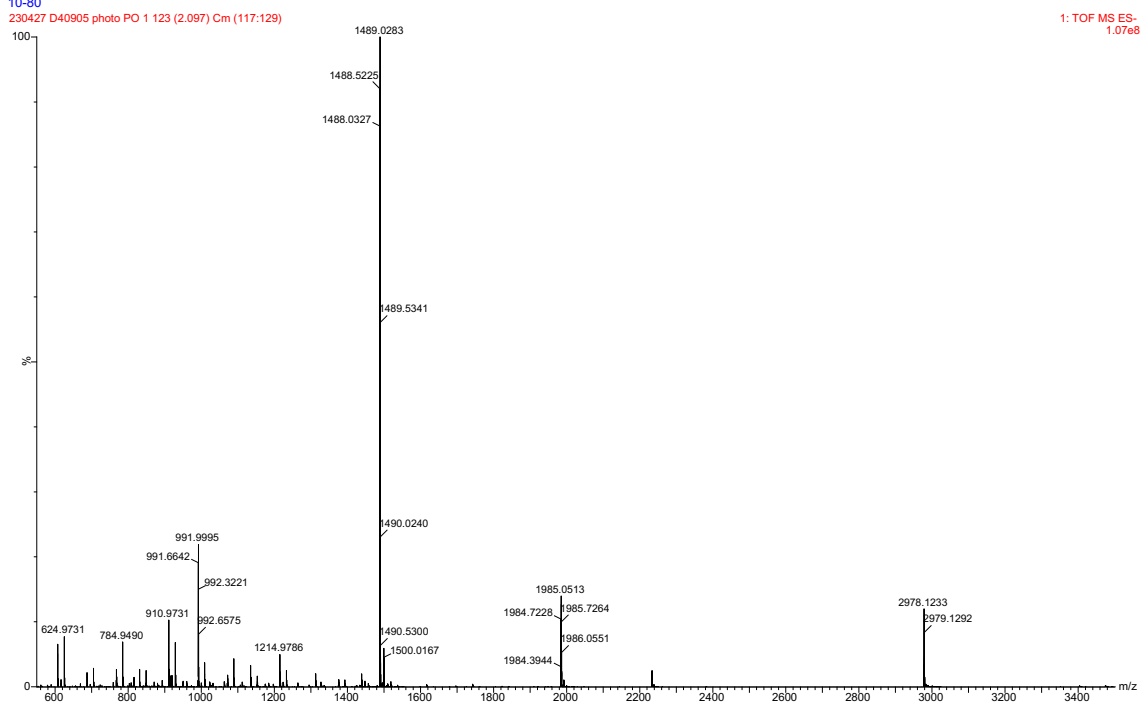


1: TOF MS ES- :TIC Smooth (Mn, 2x2)



10-80

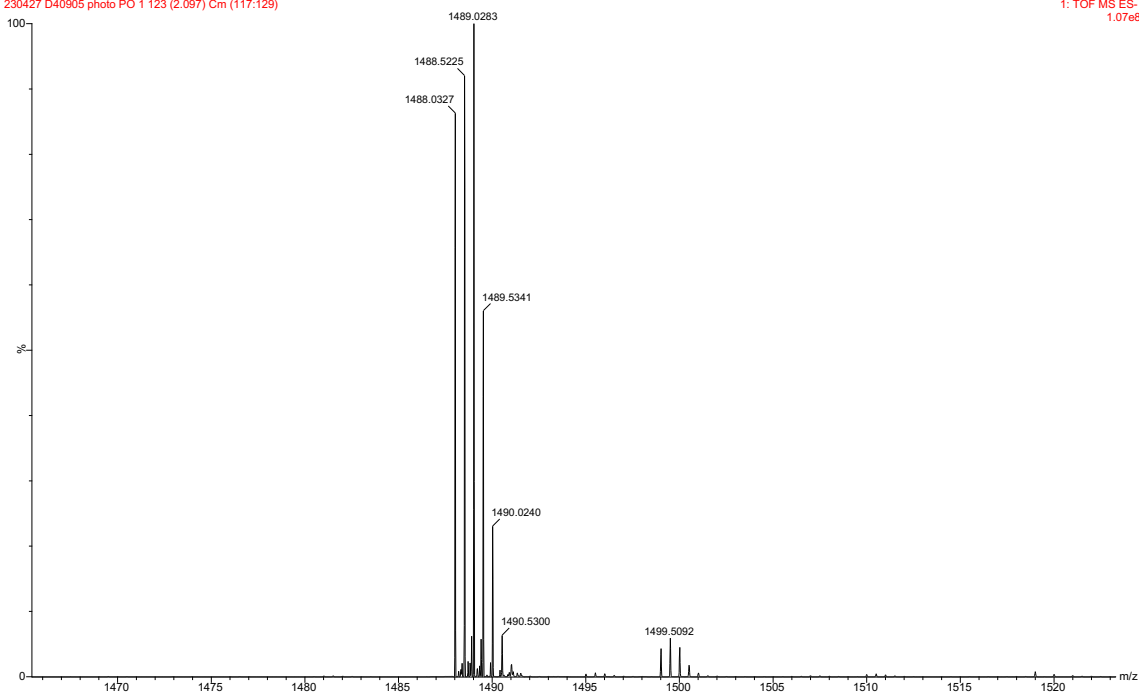
230427 D40905 photo PO 1 123 (2.097) Cm (117:129)



10-80

230427 D40905 photo PO 1 123 (2.097) Cm (117:129)

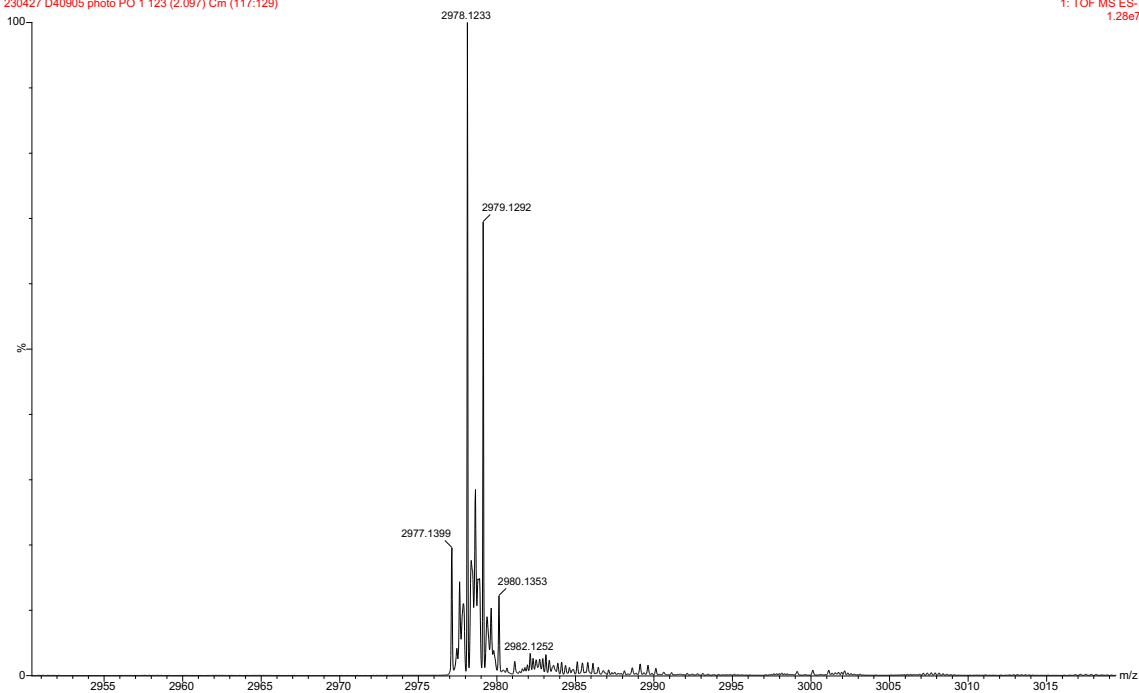
1: TOF MS ES-
1.07e8



10-80

230427 D40905 photo PO 1 123 (2.097) Cm (117:129)

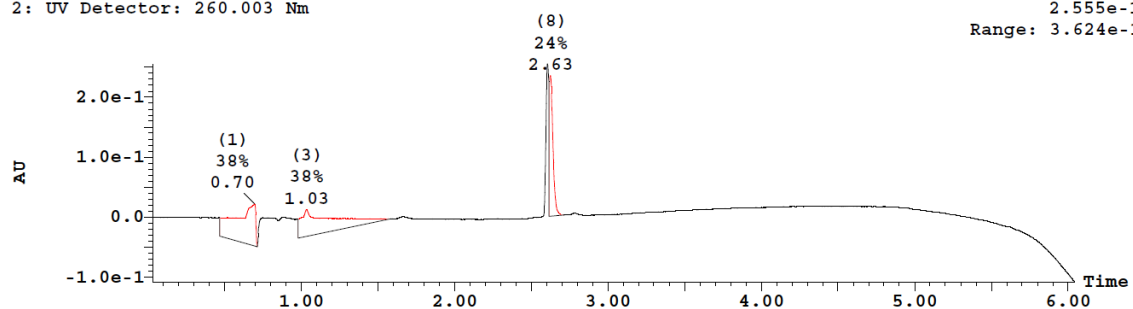
1: TOF MS ES-
1.28e7



Oligo-7 TTTTTTTTTT_{OE}T

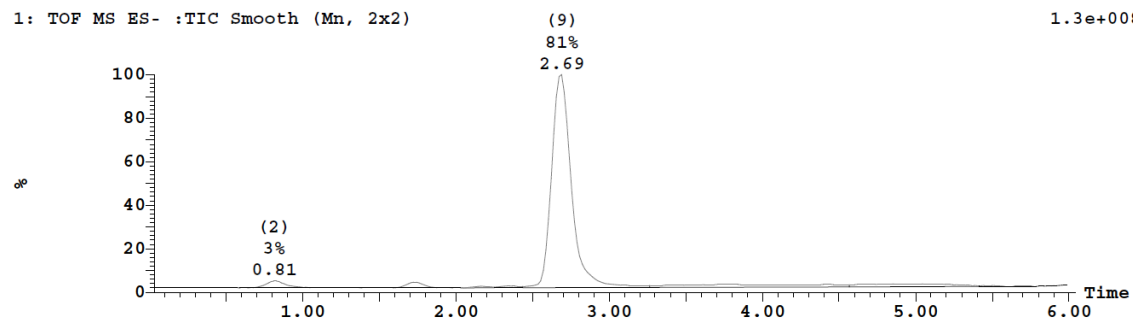
2: UV Detector: 260.003 Nm

2.555e-1
Range: 3.624e-1



1: TOF MS ES- :TIC Smooth (Mn, 2x2)

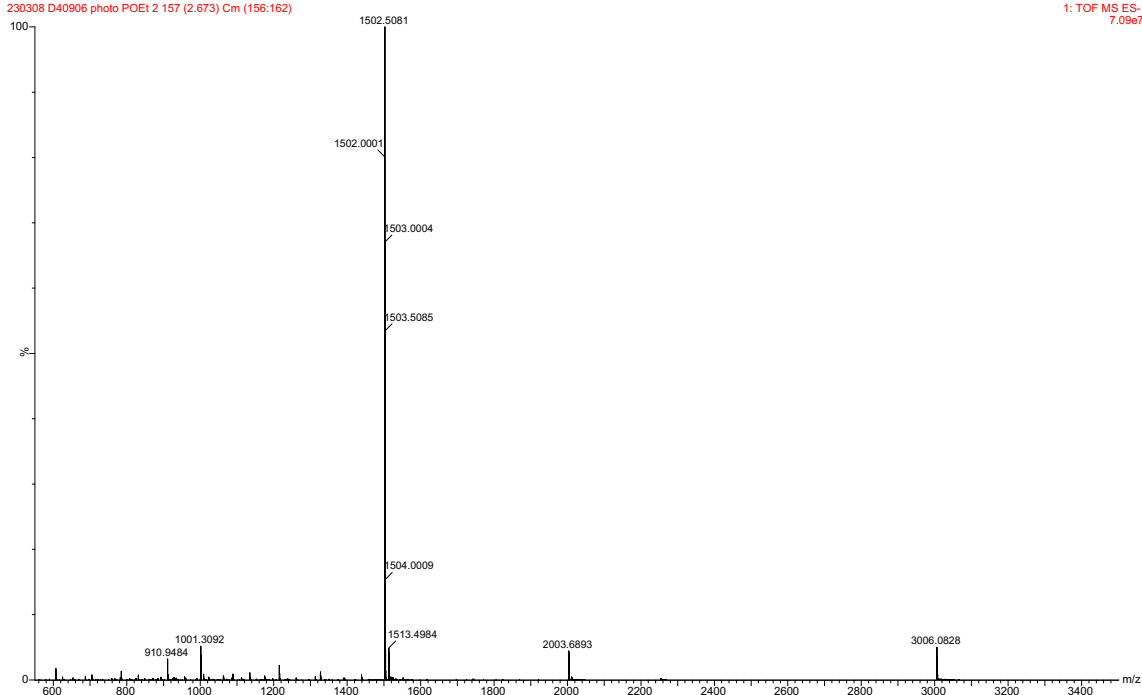
1.3e+008



10-80

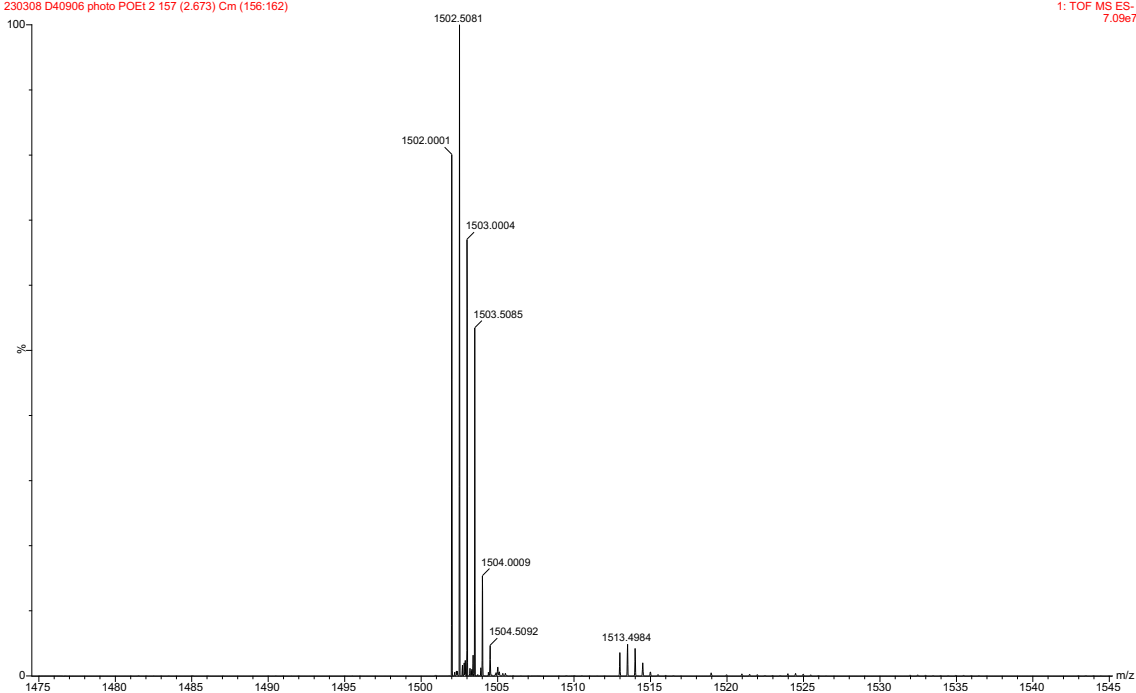
230308 D40906 photo POEt 2 157 (2.673) Cm (156:162)

1: TOF MS ES-
7.09e7



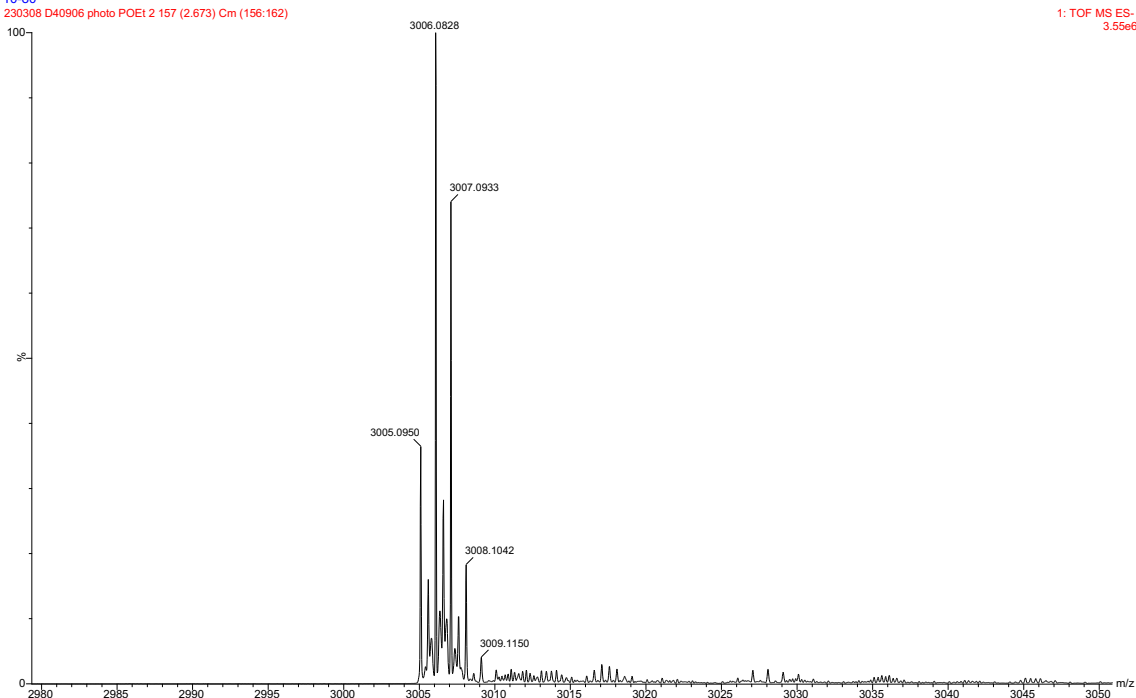
10-80

230308 D40906 photo POEt 2 157 (2.673) Cm (156:162)



10-80

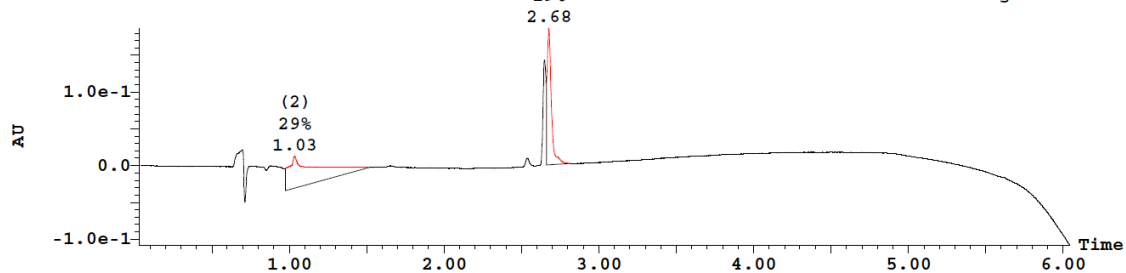
230308 D40906 photo POEt 2 157 (2.673) Cm (156:162)



Oligo-8 TTTTTTTTTT_{MOP}T

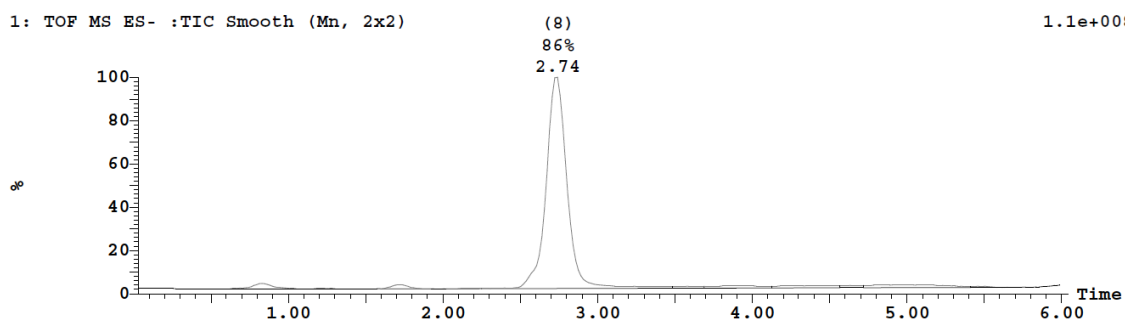
2: UV Detector: 260.003 Nm

1.87e-1
Range: 2.945e-1



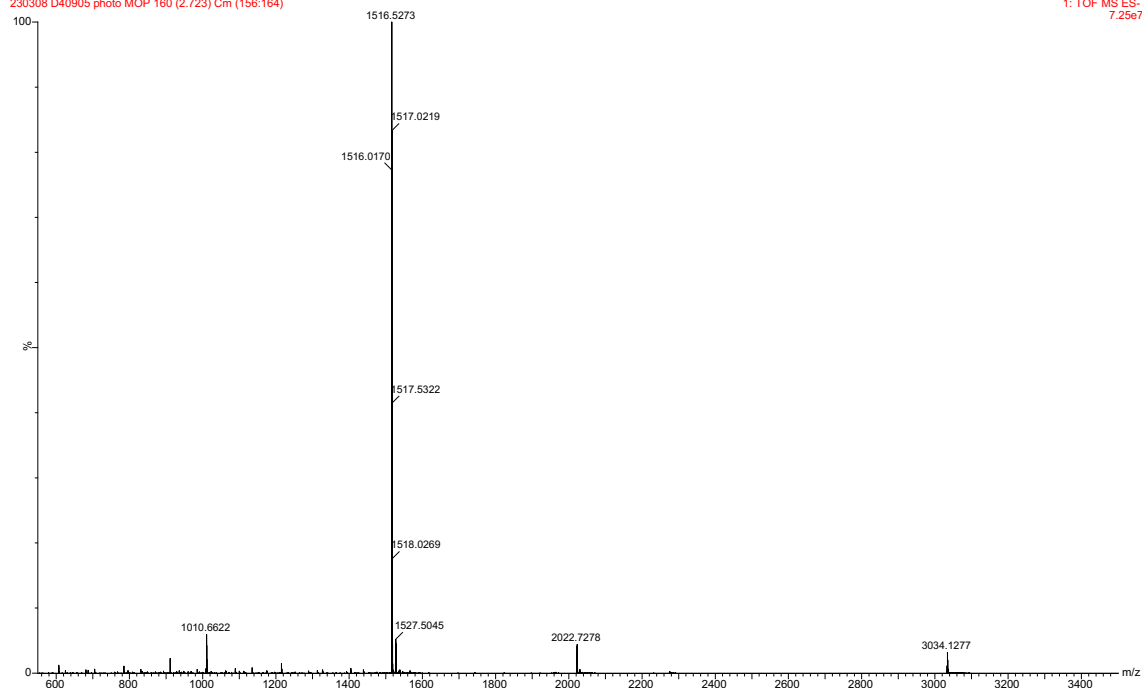
1: TOF MS ES- :TIC Smooth (Mn, 2x2)

1.1e+008



10-80

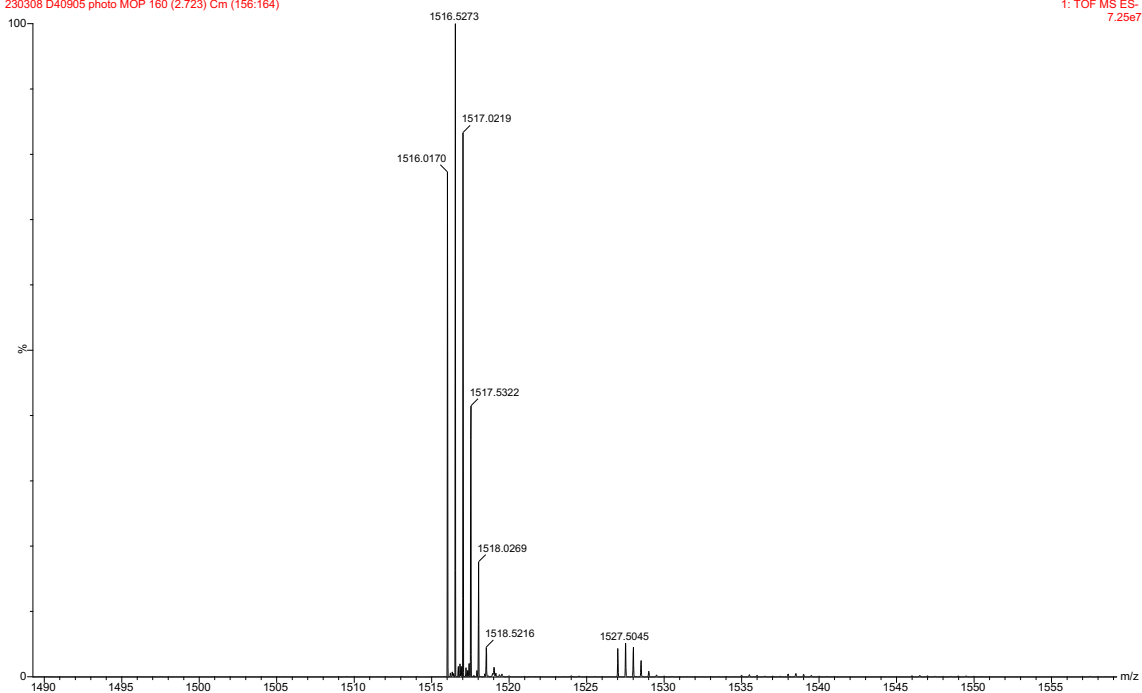
230308 D40905 photo MOP 160 (2.723) Cm (156:164)



1: TOF MS ES-
7.25e7

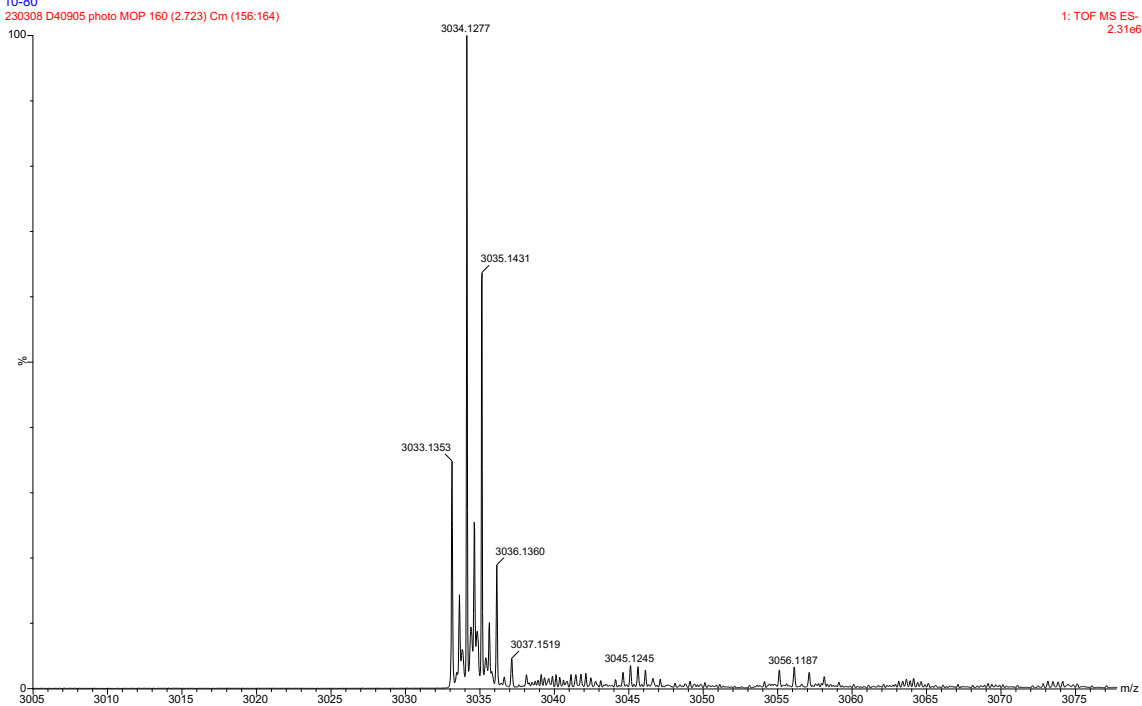
10-80

230308 D40905 photo MOP 160 (2.723) Cm (156:164)



10-80

230308 D40905 photo MOP 160 (2.723) Cm (156:164)



Synthesized oligonucleotides	MW: M-H (calcd)	MW: M-H (obsd)	crude yield (%)	retention time on LC (min)
Oligo-1 (R_P)-TTTTTTTT _{Alk} T	3079.58	3079.14	35	3.09
Oligo-2 (S_P)-TTTTTTTT _{Alk} T	3079.58	3079.12	43	3.14
Oligo-3 (R_P)-TTTT _{Alk} TTTT	3079.58	3079.12	47	2.80
Oligo-4 (S_P)-TTTT _{Alk} TTTT	3079.58	3079.12	31	2.83
Oligo-5 (S_P, S_P)-T _{Alk} TTTTTTTT _{Alk} T	3181.66	3181.18	32	3.66
Oligo-6 TTTTTTTTT	2977.50	2977.14	52	2.04
Oligo-7 TTTTTTTTT _{OEt} T	3005.53	3005.10	25	2.63*
Oligo-8 TTTTTTTTT _{MOP} T	3033.56	3033.14	37	2.68*

* LC diagram showed shouldered peaks in these compounds. MS spectra of each compound was the same, suggesting that they are diastereomers with a different stereo configuration around backbone phosphorous atom.

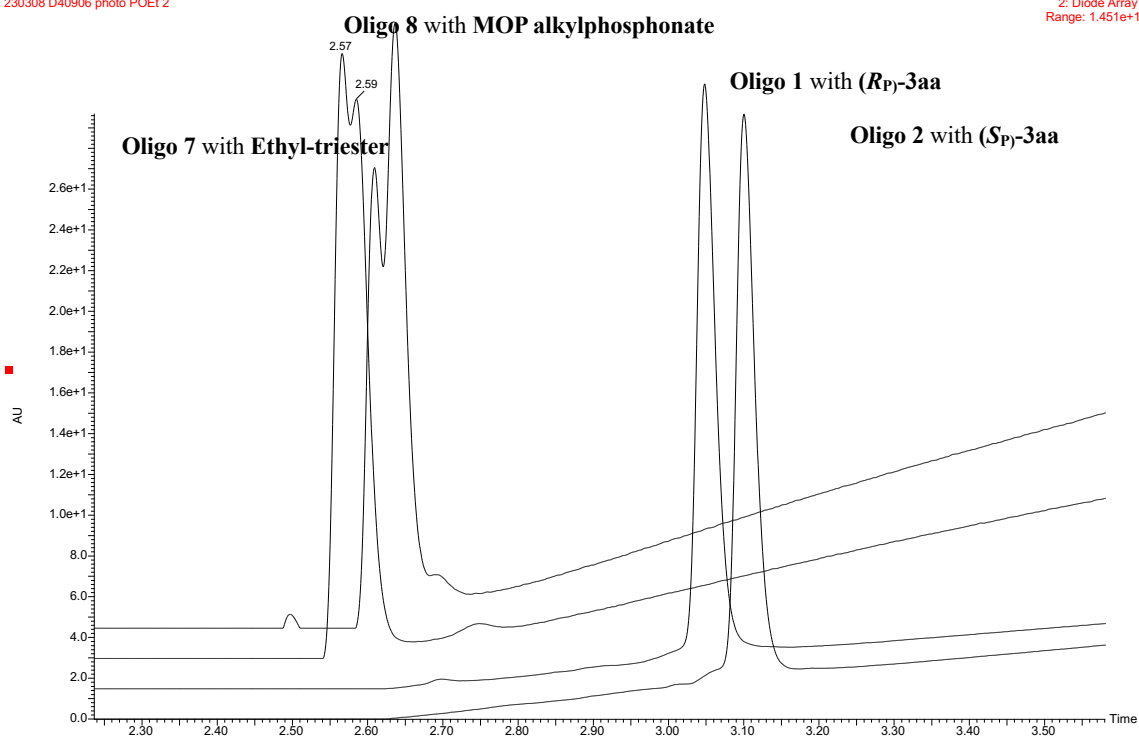
Figure S3-4. Summary of Yields and Retention Time of Oligo-1-8

Comparison between other charge-neutral backbonemodified Oligos (Oligo1,2 vs. Oligo-7,8)

Retention time (lipophilicity) of **Oligo-1** and **Oligo-2** was increased compared to the ethyl-triester- and MOP-modified oligos (**Oligo-7** and **8**), and the retention time gap due to the difference between the S_P and R_P configurations was also expanded. The influence of chirality on global hydrophilicity/hydrophobicity seemed to be increased due to its large size, which may also contribute to protein binding profiles and lead to eutomer/distomer differences as a pharmaceutical.

10-80
230308 D40906 photo POEt 2

2: Diode Array
Range: 1.451e+1



11. Detection of Alkylsulfonium

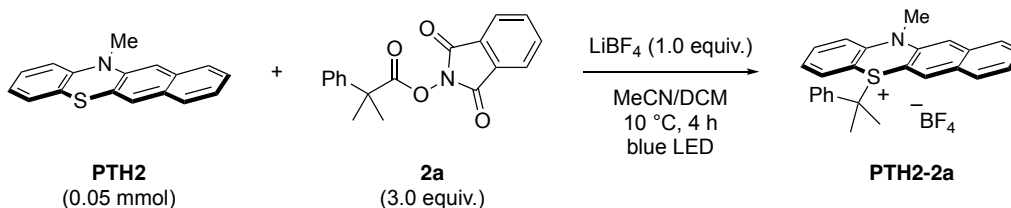


Figure S3-5. Detection of Alkylsulfonium

In a glovebox, to an oven-dried vial equipped with a stirring bar was added **PTH2** (13.2 mg, 0.05 mmol), redox-active ester **2a** (46.4 mg, 0.15 mmol) and LiBF_4 (4.7 mg, 0.15 mmol). Then, MeCN (300 μL) and DCM (200 μL) were added to the reaction mixture. After sealing the vial with a cap and removed from the glove box, the reaction was stirred and irradiated with a 34W blue LED with a cooling UC reactor to keep the temperature at 10 $^\circ\text{C}$ (Figure S3-2). After 4 h, the reaction solution was directly used for MS analysis (HRMS–ESI). **PTH2-2a**: HRMS–ESI (m/z): $[\text{M}-\text{BF}_4]^+$ calcd for $\text{C}_{26}\text{H}_{24}\text{NS}$, 382.1624; found, 382.1614.

12. Effects of Additives on Conversion of Redox-Active Esters

In a glovebox, to an oven-dried vial with a stirring bar was added **PTH2** (13.2 mg, 0.05 mmol), phosphite **1a** (42.9 mg, 0.05 mmol), redox-active ester **2a** (46.4 mg, 0.15 mmol), LiBF_4 (4.7 mg, 0.15 mmol) and thymine (6.3 mg, 0.05 mmol). Then, MeCN (300 μL) and DCM (200 μL) were added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with a cooling UC reactor to keep the temperature at 10 $^\circ\text{C}$ (Figure S3-2). After 4 h, the solvents were removed under reduced pressure and the residue was analyzed by ^1H NMR. The increase in conversion of **2a** to 28% was observed with the addition of thymine compared to without thymine (11%).

13. Comparison with Other Carbocation Methods

Comparison with Aggarwal's Method. Tertiary alkylation of phosphite **1a-1** was conducted with reference to the reported procedure.¹⁴ In a glovebox, to an oven-dried vial with a stirring bar was added photoredox catalyst 4CzIPN (0.79 mg, 0.001 mmol), phosphite **1a-1** (42.9 mg, 0.05 mmol) and redox-active ester **2a** (46.4 mg, 0.15 mmol). Then, MeCN (500 μL) and TFA (5.7 μL , 0.075 mmol) were added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED (3 cm away) with a cooling fan to keep the temperature around 40 $^\circ\text{C}$. After 2 h, the solvents were removed under reduced pressure and the residue was analyzed by ^1H NMR. However, the desired product **3aa** was not obtained, and the decomposition products of **1a-1** were observed.

Comparison with methods using Lewis acid. Tertiary alkylation of phosphite **1a-1** was conducted with reference to the reported procedure.^{15,16} In a glovebox, to an oven-dried vial with a stirring bar was added phosphite **1a-1** (42.9 mg, 0.05 mmol) and 2-phenyl-2-propanol (**5a**) (20.4 mg, 0.15 mmol). Then, toluene (500 μ L) and Lewis acid TMSOTf (1.81 μ L, 0.01 mmol) or ZnI₂ (23.9 mg, 0.075 mmol) were added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred at 110 °C. After 15–24 h, the solvents were removed under reduced pressure and the residue was analyzed by ¹H NMR. However, the desired product **3aa** was not obtained, giving a complex mixture.

14. The Effects of Chiral Leaving Groups

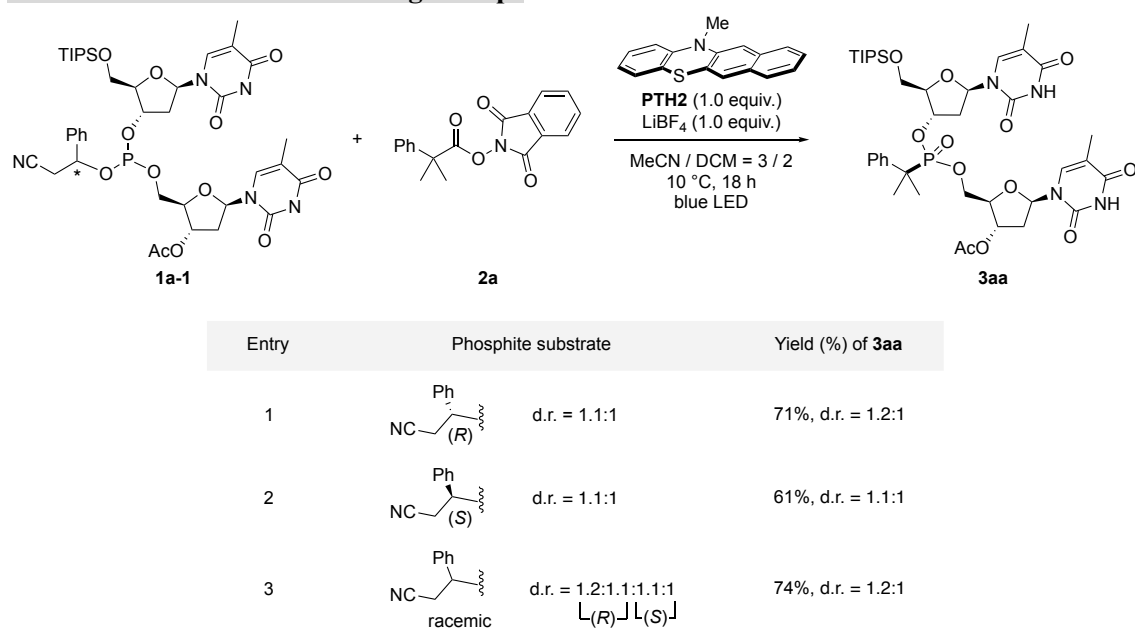


Figure S3-6. The Effects of Chiral Leaving Groups

Chiral alcohols were prepared from chiral styrene oxide.¹⁷ Phosphite (*R*)/(*S*)-**1a-1** having chiral leaving groups were synthesized by the above mentioned procedure (Figure S3-1). In a glovebox, to an oven-dried vial with a stirring bar was added **PTH2** (13.2 mg, 0.05 mmol), phosphite (*R*)-**1a-1** or (*S*)-**1a-1** (42.9 mg, 0.05 mmol), redox-active ester **2a** (46.4 mg, 0.15 mmol) and LiBF₄ (4.7 mg, 0.05 mmol). Then, MeCN (300 μ L) and DCM (200 μ L) were added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with a cooling UC reactor to keep the temperature at 10 °C (Figure S3-2). After 18 h, the solvents were removed under reduced pressure and the yield was determined by ¹H NMR analysis. The effect of the chiral leaving group on this reaction was investigated, but no significant difference in the yield and the ratio of diastereomers of the alkylated product **3aa** was observed.

15. Examination of Catalytic Reactions

When simple phosphite **1g** was used as a nucleophile, oxidative alkylation proceeded catalytically with high efficiency (Figure S3-7A). On the other hand, when *H*-phosphonate **1h** was used as a nucleophile instead of phosphite, no alkylated product was obtained (Figure S3-7B).

Procedure. In a glovebox, to an oven-dried vial with a stirring bar was added **PTH1** (3.3 mg, 0.01 mmol), trihexyl phosphite **1g** (74.3 μ L, 0.2 mmol) or dibutyl phosphite **1h** (39.2 μ L, 0.2 mmol), redox-active ester **2a** (92.8 mg, 0.3 mmol), LiBF₄ (0.9 mg, 0.01 mmol) and DCM (600 μ L). After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with a cooling fan to keep the temperature around 40 °C. After 16 h, the solvents were removed under reduced pressure and the residue was analyzed by ¹H NMR.

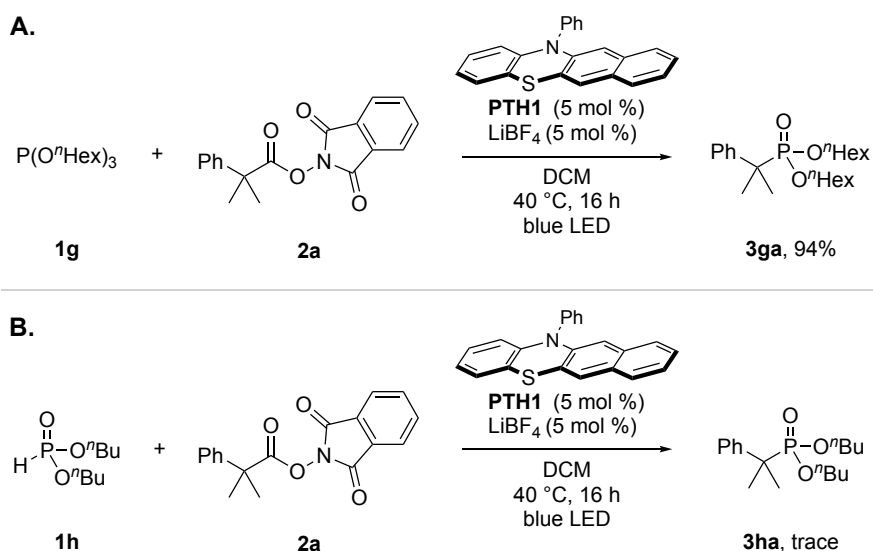


Figure S3-7. Examination of Catalytic Reactions

16. Examination of the Addition of Trapping Reagent for Carbocation

PTH-catalytic reactions were investigated by adding a stoichiometric amount of sulfilimine, used in the stabilized cation pool method,¹⁸ as a trapping reagent for the carbocation, but the yield was not improved (Figure S3-8).

Procedure. In a glovebox, to an oven-dried vial with a stirring bar was added **PTH1** (1.63 mg, 0.005 mmol), phosphite **1a-1** (42.9 mg, 0.05 mmol), redox-active ester **2a** (46.4 mg, 0.15 mmol) or **2k** (37.1 mg, 0.15 mmol), LiBF₄ (0.47 mg, 0.005 mmol) and sulfilimine (17.8 mg, 0.05 mmol). Then, MeCN (300 μ L) and DCM (200 μ L) were added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with a cooling UC reactor to keep the temperature at 10 °C (Figure S3-2). After 18 h, the solvents were removed under reduced pressure and the residue was analyzed by ¹H NMR.

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第四章 イミダゾリウムホスホナイトを用いたアルキルリン(V)化合物の合成

第一節 着想背景および作業仮説

有機リン化合物は、医薬品、農薬、材料など幅広い分野で利用されている重要な化合物群である。¹ 特にアルキルリン(V)化合物は、医薬品のビルディングブロックとして注目されており、リン(V)上のヘテロ原子置換基は、化学的および物理的特性に大きな影響を与えることが知られている (**Figure 4-1**)。² 例えば、二つのエステル基を持つアルキルホスホン酸ジエステル構造は、第三章で示したように核酸医薬品の化学修飾されたホスホジエステルバックボーンとして注目されている。³ また、ホスホン酸ジエステルの P-O 結合の一つを P-N 結合に置き換えたホスホナミデートは、テノホビルアラフェナミドに代表される ProTide 技術というプロドラッグ法で活用されている。⁴ さらに、P-F 結合を有するフルオロホスフェートは、メチルアラキドニルフルオロホスフェートに代表されるように、セリンヒドロラーゼおよびセリンプロテアーゼの阻害剤として機能する。⁵ このようにアルキルリン(V)化合物の重要性は明らかであり、リン(V)中心に様々なアルキルやヘテロ原子の置換基を容易に導入できる新たな合成法の開発が強く望まれている。

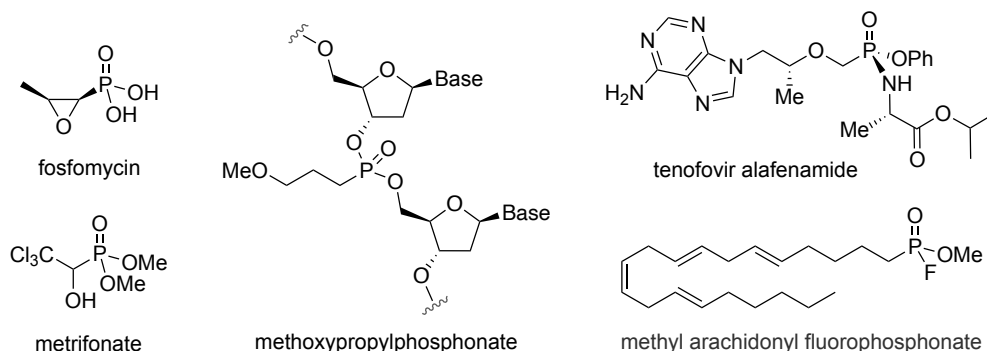


Figure 4-1. 代表的なアルキルリン(V)化合物

アルキルリン(V)化合物の従来の合成法として、1) 亜リン酸エステルとハロゲン化アルキルを用いた Michaelis-Arbuzov 反応、2) *H*-ホスホネートのアルキル化反応、3) 有機金属試薬と求電子的なリン(V)試薬を用いた $S_NP(V)$ 反応、などがある。⁶ しかし、これらの手法によって構築できるリン(V)構造は、ほとんどが対称的なアルキルホスホン酸ジエステル体である (**Figure 4-2**)。アルキルホスホン酸ジエステルに対するヘテロ原子求核剤の $S_NP(V)$ 反応は一般に遅いため、直接的なリン(V)上のヘテロ置換基変換は困難である。そのため、非対称なアルキルホスホン酸ジエステルやホスホナミデート、フルオロホスホネートおよびその他の誘導体化には、塩化オキサリルやトリフルオロメタンスルホン酸無水物、ジアリールヨードニウム塩などの活性化試薬が必要であった。⁷

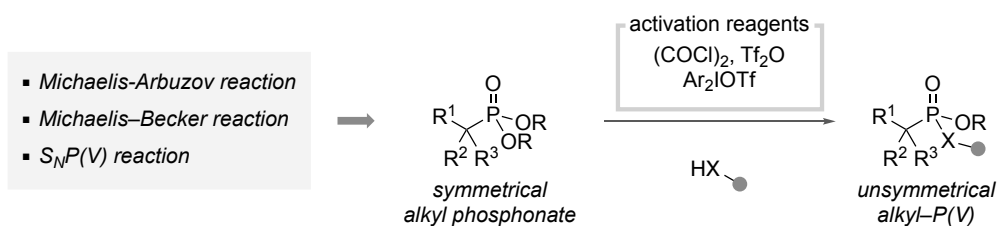


Figure 4-2. 非対称なアルキルリン(V)化合物の合成法

C(sp³)-P 結合形成の強力な手法として、近年ラジカルホスホリル化反応が注目されている。⁸ Bentrude らは、リン(III)試薬と C(sp²)またはヘテロ原子ラジカルを反応させると、ホスホラニルラジカル中間体が形成され、この中間体から β-開裂が進行することで、様々なリン(V)化合物が得られることを報告している。⁹ しかし、アルキルラジカルの場合、鍵となるホスホラニルラジカルにおいて出発物質が再生される α-開裂が優勢的に起きてしまう。そのため、Aggarwal、¹⁰ MacMillan、¹¹ Li、¹² らは、生成系への β-開裂を促進する離脱基を持つリン(III)試薬を設計することで、この問題を解決している (Figure 4-3)。他の C(sp³)-P 結合形成法として、特殊なリン(III)試薬を用いたラジカルの捕捉やラジカル置換反応、^{13,14} リンラジカルのアルケンへの付加、^{8a-8f, 15} 遷移金属触媒的なカップリング反応、¹⁶ ラジカル-極性交差機構を経た S_N1 型の反応¹⁷ なども開発されている。しかし、ほとんどの反応において、生成物はアルキルホスホン酸ジエステル体であり、直接的な S_NP(V)反応による置換基変換は困難である。また、リン中心に導入可能な第三級アルキル骨格は、アダマンチル基あるいはシクロプロピル基のような小さな環状骨格を有するアルキル基に限定されていた。

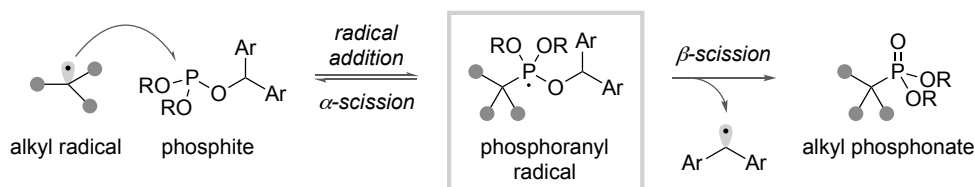


Figure 4-3. リン(III)試薬へのアルキルラジカルの付加による C(sp³)-P 結合形成法

イミダゾリウム置換基は、隣接するヘテロ原子ラジカルを安定化できることが知られている。¹⁸ そのため、リン中心へのアルキルラジカルの付加により生じるホスホラニルラジカル中間体を安定化できると考えられる。また、N-ヘテロ環状カルベン触媒反応で利用されているように、優れた脱離基として働き、多様な求核剤との S_NP(V)反応が期待される。¹⁹ 以上の背景を踏まえて、二官能基性リン(III)試薬としてイミダゾリウムホスホナイト²⁰を用いた、アルキルリン(V)化合物の新たな合成法を着想した (Figure 4-4)。すなわち、アルキル基とヘテロ原子置換基を、それぞれ一電子的な過程と二電子的な過程によってリン(V)中心に順次導入することで、従来法では達成困難な嵩高い非対称アルキルリン(V)構造を効率的に構築できると考えた。

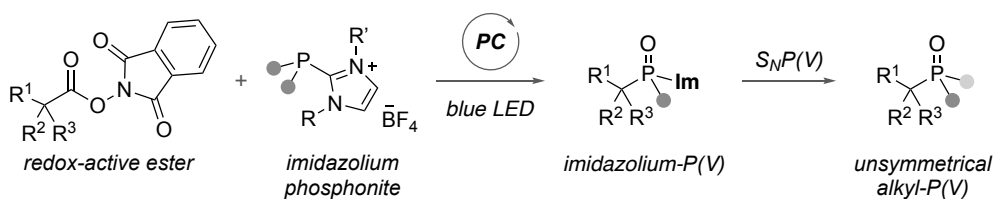


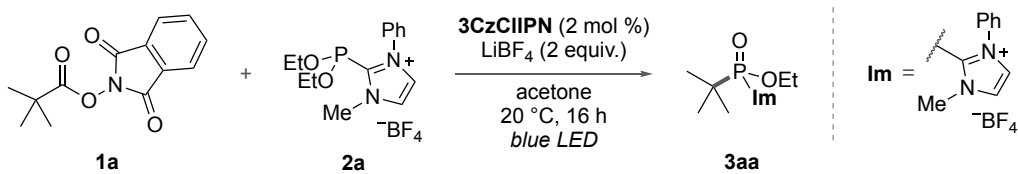
Figure 4-4. イミダゾリウムホスホナイトを用いた
非対称アルキルリン(V)化合物の合成

第二節 反応条件の最適化

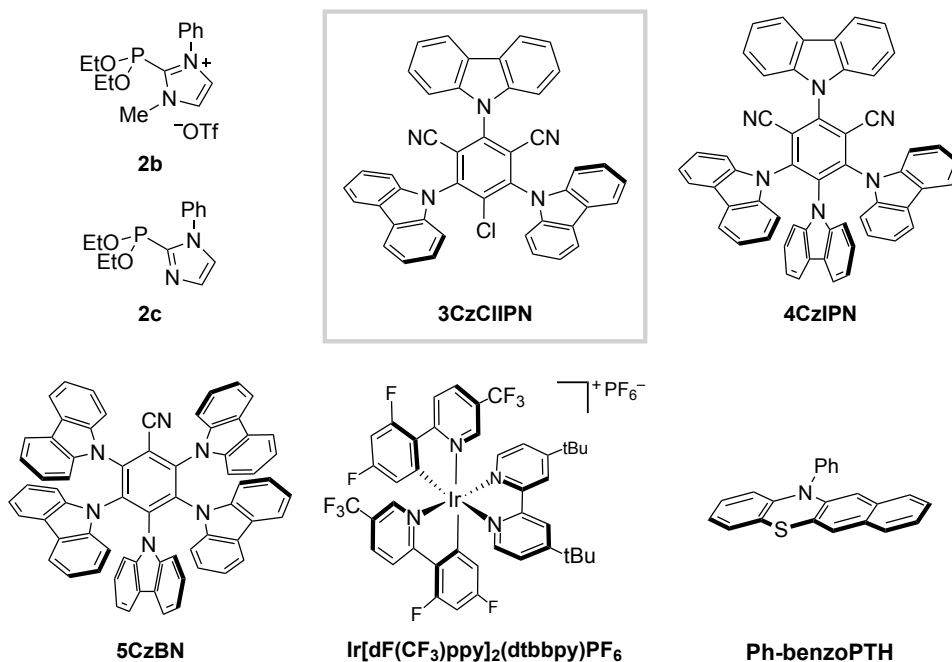
上記の作業仮説を検証するため、まず、光酸化還元触媒とピバル酸誘導体 (**1a**) を用い、リン(III)試薬 **2** の酸化的なアルキル化反応を検討した (Table 4-1)。光酸化還元触媒である 2,4,6-tri(9H-carbazol-9-yl)-5-chloroisophthalonitrile (3CzClIPN)²¹ および添加剤であるテトラフルオロホウ酸リチウム (LiBF₄) 存在下、基質として **1a** と *N*-メチル-*N*-フェニルイミダゾリウムテトラフルオロボレート (Im) 構造を有するホスホナイト (**2a**) を用い、アセトン中青色 LED 照射下で反応させたところ、脱炭酸型クロスカップリングが進行し、所望のアルキル化体 **3aa** を高収率で与えた (entry 1)。イミダゾリウムのカウンターアニオンとしてトリフルオロメタンスルホン酸イオンを有するホスホナイト **2b** を用いた場合でも反応は進行したが、**3aa** の収率がわずかに低下した (entry 2)。一方で、電荷中性のホスホナイト **2c** を用いると、目的物は全く得られなかった (entry 3)。これらの結果から、リン(III)試薬のカチオン性置換基の重要性が示された。

次に、レドックス活性エステル **1a** とリン(III)試薬 **2a** の脱炭酸型クロスカップリング反応における光酸化還元触媒や添加剤、溶媒の影響を検討した。他のカルバゾール系光酸化還元触媒²¹ や、3CzClIPN と同程度の酸化還元電位を持つ Ir 型光酸化還元触媒 (Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆)²² を用いた場合でも、良好な収率で目的物 **3aa** を与えた (entries 4–6)。一方で、*N*-フェニルベンゾ[*b*]フェノチアジン (Ph-benzpPTH)²³ を用いた場合では、目的のアルキル化体 **3aa** はほとんど得られなかった (entry 7)。Ph-benzpPTH は、同様の反応条件下でラジカル-極性交差機構 (RPC: radical-polar crossover) によってカルボカチオンを発生できることが知られている。^{17b,24} これらのことから、本反応では、RPC により発生したカルボカチオンに対するリン(III)試薬 **2a** の求核攻撃という二電子的な過程を経て進行していないことが示唆された。添加剤である LiBF₄ を触媒量に減らした場合や他の添加剤を用いた場合では、**3aa** の収率は低下した (entries 8–11)。また、溶媒としてアセトニトリルやジクロロメタンなどの他の極性溶媒を用いると、**3aa** の収率は中程度になった (entries 12 and 13)。対照実験の結果から、本反応において光酸化還元触媒や LiBF₄、可視光照射の要素が重要であることが示された (entries 14–16)。反応時間を 32 時間に延ばすことで、1 mmol へのスケールアップが可能であった (entry 17)。

Table 4-1. 反応条件の最適化 ^a



entry	change from standard conditions	yield of 3aa (%) ^b
1	none	94 (85)
2 ^c	2b instead of 2a	68 (58)
3	2c instead of 2a	0
4	4CzIPN instead of 3CzCIIPN	85
5	5CzBN instead of 3CzCIIPN	82
6	Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆ instead of 3CzCIIPN	79
7	Ph-benzoPTH instead of 3CzCIIPN	8
8	LiBF ₄ (10 mol %)	44
9	NaBF ₄ instead of LiBF ₄	50
10	TFA instead of LiBF ₄	34
11	2,4,6-collidine•HBF ₄ instead of LiBF ₄	60
12	MeCN instead of acetone	53
13	DCM instead of acetone	48
14	w/o 3CzCIIPN	17
15	w/o LiBF ₄	32
16	w/o blue LED	0
17 ^d	1 mmol scale	76



^aReaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), 3CzCIIPN (0.004 mmol), LiBF₄ (0.4 mmol), acetone (0.6 mL), 20 °C, 16 h under blue LED irradiation. ^b¹H NMR yield based on **2a**. Yield of the isolated product is in parentheses. ^cLiOTf (0.4 mmol) instead of LiBF₄ (0.4 mmol) ^d32 h.

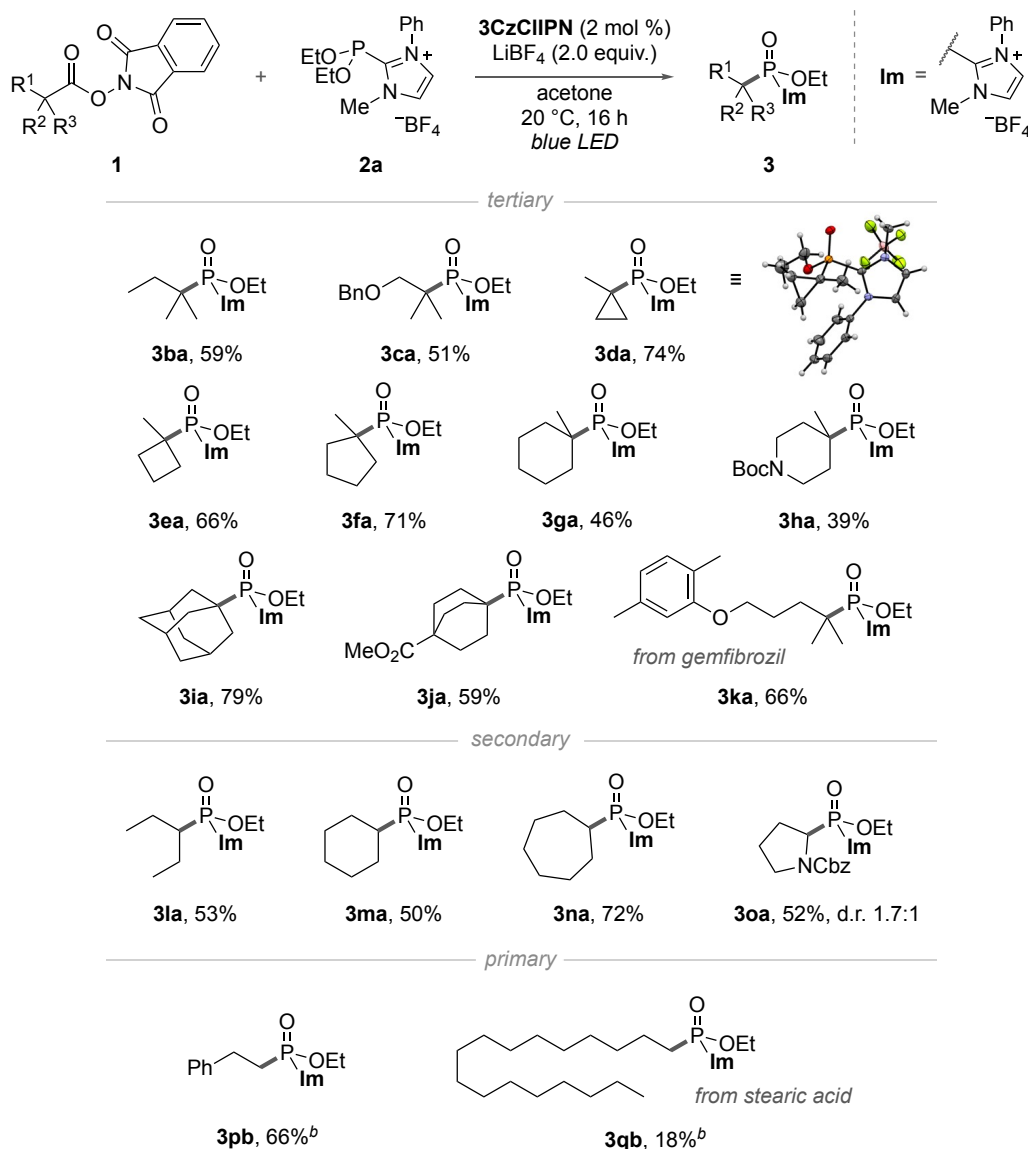
第三節 基質適用範囲の検討および生成物の誘導化

最適化された反応条件を基に、リン(III)試薬として **2a** を用いて脂肪族カルボン酸誘導体 **1** の適用範囲を検討した (Table 4-2)。単純なアルキル基またはβ-ベンジルオキシ基を有する非環状第三級脂肪族カルボン酸誘導体の適用が可能であった (**3ba** and **3ca**)。また、多様な環状炭素骨格を有する第三級アルキル基をリン中心へ導入することができ、対応するアルキル化体を良好な収率で与えた (**3da–3ga**)。3da の構造は、X 線結晶構造解析により同定された。ピペリジン環、アダマンチル基、ビスクロ[2.2.2]オクチル基を含む第三級アルキル基をリン中心へ導入することも可能であった (**3ha–3ja**)。また、医薬品であるゲムフィブロジルのカルボン酸部位をホスフィネート構造に変換することもできた (**3ka**)。

本光酸化還元触媒系では、第一級および第二級脂肪族カルボン酸誘導体も許容された。リン中心への非環状あるいは環状の第二級アルキル基の導入が可能であり、対応するアルキル化体を良好な収率で与えた (**3la–3na**)。本手法により、α-アミノ酸を創薬化学的に重要なα-アミノホスフィネートに変換することができた (**3oa**)。²⁵ 第一級アルキルカルボン酸誘導体の場合、**3** の代わりに P-F 結合を有するフルオロホスフィネート体が得られた。これは、第一級アルキル基の立体障害が小さいことから、カウンターアニオンであるテトラフルオロボウ酸イオンのフッ素原子との置換反応が進行することで生成したと考えられる。そこで、この副反応を避けるために、リン(III)試薬としてカウンターアニオンにトリフルオロメタンスルホン酸イオンを有する **2b** および添加剤として

トリフルオロメタンスルホン酸リチウムを用いたところ、対応するアルキル化体を良好な収率で得ることができた (**3pb**)。ステアリン酸由来のレドックス活性エステルも許容され、リン脂質に類似した構造を構築できた (**3qb**)。

Table 4-2. 脂肪族カルボン酸誘導体の検討 ^a

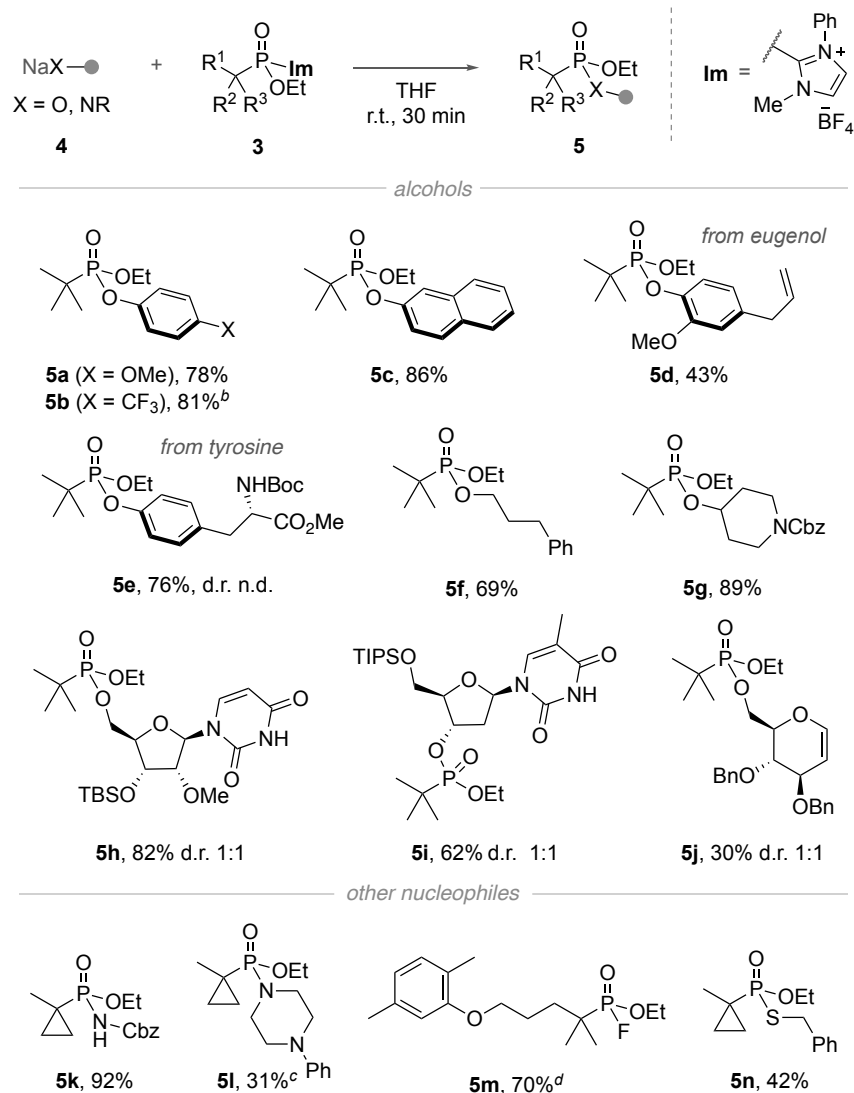


^aReaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), 3CzClIPN (0.004 mmol), LiBF₄ (0.4 mmol), acetone (0.6 mL), 20 °C, 16 h under blue LED irradiation. ^b**1** (0.4 mmol), **2b** (0.2 mmol), 3CzClIPN (0.004 mmol), LiPF₆ (0.4 mmol), acetone (0.6 mL), 20 °C, 16 h under blue LED irradiation.

Jacobsen らの報告 ²⁶ に基づき、単離したイミダゾリウムホスフィナート **3** と様々なヘテロ原子求核剤との S_NP(V)反応を検討した (Table 4-3)。ベンゼン環のパラ位に電子

供与性基または電子求引性基を持つフェノールの適用が可能であり、対応するホスホン酸ジエステル体を高収率で与えた (**5a** and **5b**)。π 共役系が広がった 2-ナフトールも許容された (**5c**)。生理活性物質であるオイゲノールやα-アミノ酸であるチロシンなどの複雑なフェノール類の適用も可能であった (**5d** and **5e**)。また、第一級や第二級の脂肪族アルコールも $S_NP(V)$ 反応に適用できた (**5f** and **5g**)。さらに、複雑なデオキシヌクレオシドや *D*-グルカルに第三級アルキルリン(V)構造を導入することも可能であった (**5h–5j**)。アルコール以外のヘテロ原子求核剤として、カルバミン酸ベンジルや環状アミンといった窒素求核剤の適用も可能であり、対応するホスホナミデート体を良好な収率で与えた (**5k** and **5l**)。また、テトラブチルアンモニウムフルオリドとの反応により、さらなる変換が可能なフルオロホスフェートへと誘導することができた (**5m**)。²⁷ さらに、チオベンジルアルコールのような硫黄求核剤も適用できた (**5n**)。

Table 4-3. イミダゾリウムホスフィナートのアルキルリン(V)化合物への誘導化^a



^aReaction conditions: **3** (0.1 mmol), **4** (0.2 mmol), room temperature, 30 min. ^b4 h. ^cReaction

conditions: **3** (0.1 mmol), lithium amide **4** (0.15 mmol), THF (1.0 mL), room temperature, 30 min.

^dReaction conditions: **3ka** (0.05 mmol), TBAF (0.1 mmol), THF (0.125 mL), room temperature, 30 min.

第四節 応用

本反応の有用性を拡大するために、いくつかの応用的な検討を行った。まず、イミダゾリウムホスホナイトの酸化的なアルキル化反応と続く求核置換反応をワンポットで行った (**Figure 4-5**)。標準条件下でレドックス活性エステル **1a** とイミダゾリウムホスホナイト **2a** を反応させた後に、溶媒をテトラヒドロフランへと置換し、三当量の *p*-メトキシフェノキシドを加えた。その後、室温下で 2 時間反応させたところ、対応する非対称なアルキルホスホン酸ジエステル体 **5a** を良好な収率で得ることができた。



Figure 4-5. ワンポット合成

次に、イミダゾリウムホスフィネート **3aa** のサイクリックボルタンメトリーを測定したところ、その還元電位は $E_{\text{red}} = -1.76 \text{ V}$ (vs SCE in MeCN) であることが示された。この結果から、**3aa** の一電子還元によりリンラジカルを発生でき、新たな分子変換に応用できる可能性が示唆された。そこで、光酸化還元触媒によるイミダゾリウムホスフィネート **3aa** とアルケンの P-C 結合形成反応を検討した (**Figure 4-6**)。この反応では、まず可視光により励起された光酸化還元触媒から **3aa** への一電子移動によってリンラジカル **A** が生成する。次に、このリンラジカル **A** がアルケン **6** に付加することで、炭素ラジカル **B** が生じる。その後、炭素ラジカル **B** は光酸化還元触媒によって一電子酸化され、カルボカチオン **C** となり、脱プロトン化を経てアルケニル化体 **7** が生成する。実際に、励起状態で高い還元力を持つ tris(2-phenylpyridinato)iridium(III) ($\text{Ir}(\text{ppy})_3$, $E_{\text{ox}}^* = -1.73 \text{ V vs SCE in MeCN}$)²⁸ 存在下、基質としてイミダゾリウムホスフィネート **3aa** と *p*-メトキシスチレン (**6a**) を用い、ジメチルアセトアミド溶媒中で 16 時間青色 LED を照射したところ、目的の P-C 結合形成体を高収率で得ることができた (**7a**)。アルケンとして α -メチルスチレンを用いた場合、アルケニル化体ではなくアリル化体が主生成物として得られた (**7b**)。脂肪族アルケンを用いた場合、Hantzsch エステルを加えることで、*tert*-ブチル基と 4-フェニルブチル基の二つのアルキル置換基を有するホスフィネートを合成することができた (**7c**)。この場合、リンラジカル **A** のアルケンへの付加によって生じる炭素ラジカル **B** と Hantzsch エステルラジカルカチオンとの水素原子移動を経て目的物が生成したと考えられる。²⁹

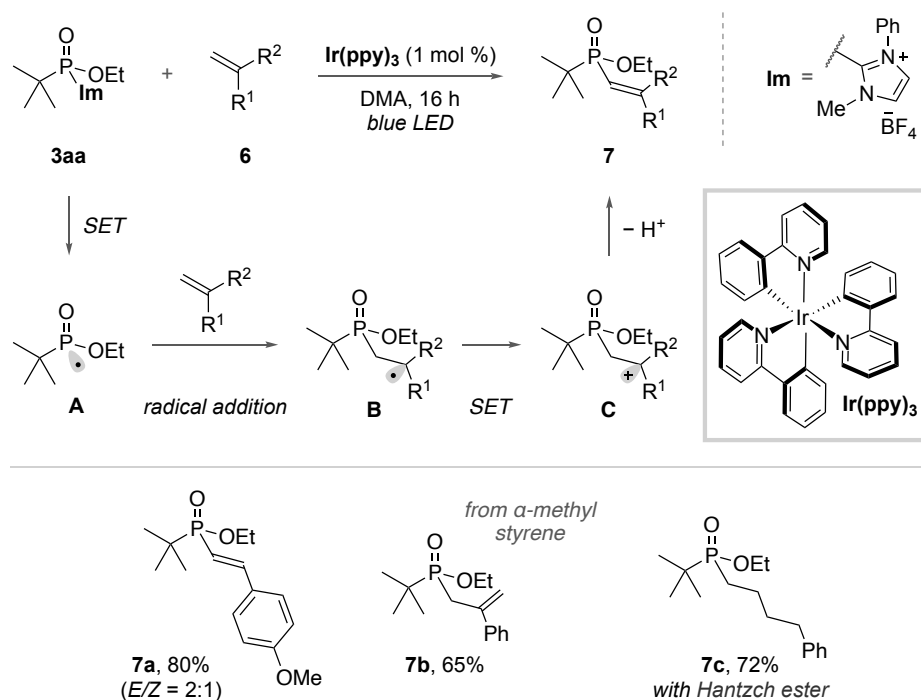


Figure 4-6. 光酸化還元触媒によるイミダゾリウムホスフィネートとアルケンを用いた P-C 結合形成反応

第五節 反応機構解析

量子化学計算を用いて、イミダゾリウムホスホナイト **P-1** と Aggarwal らによって開発されたリン(III)試薬 **P-2**¹⁰ の第三級アルキルラジカルに対する反応性を比較した (Figure 4-7)。その結果、*tert*-ブチルラジカルの場合、両 P(III)試薬への付加における活性化エネルギーは同等であることが示された (TS-1 vs TS-2)。一方で、**P-1** は **P-2** よりもラジカル付加体であるホスホニルラジカル中間体を熱力学的に 9.0 kcal/mol 安定化することが明らかとなった (Int-1 vs Int-2)。この熱力学的な安定化が第三級アルキルラジカルの効率的な捕捉に寄与していると考えられる。

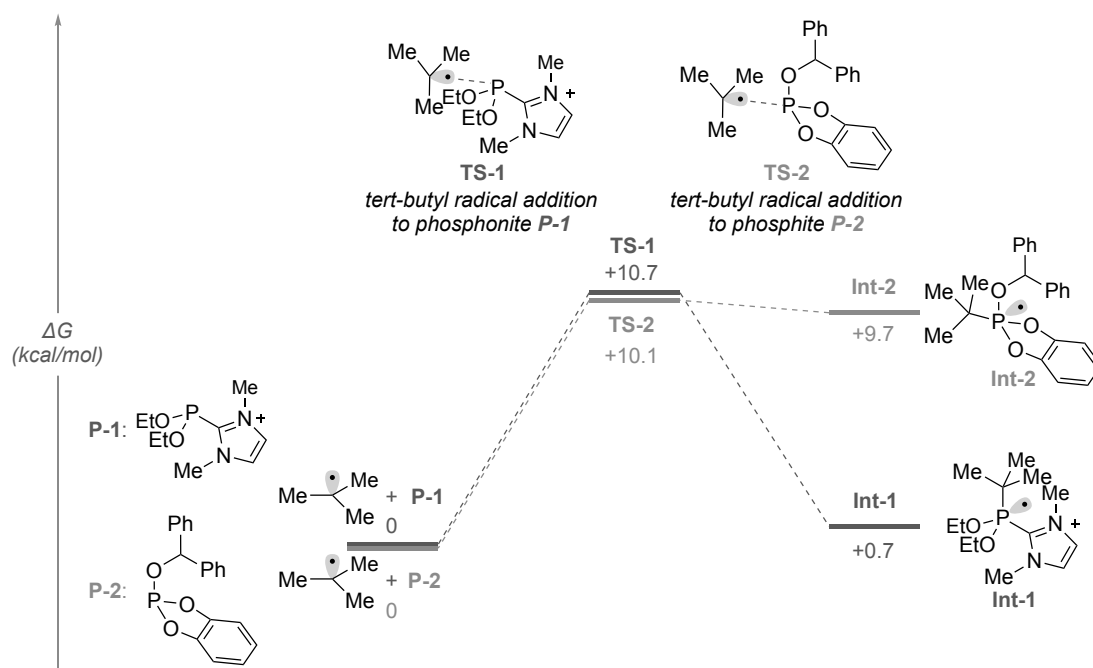


Figure 4-7. 第三級アルキルラジカルに対するリン(III)試薬の反応性の比較

第六節 推定反応機構

本反応の推定反応機構を以下に示す (Figure 4-8)。まず、可視光によって励起された光酸化還元触媒から脂肪族カルボン酸誘導体 **1** への一電子移動が進行することで、脱炭酸を経てアルキルラジカル **A** が発生する。生じたアルキルラジカル **A** がイミダゾウムホスホナイト **2** に付加し、安定化されたホスホラニルラジカル中間体 **B** を生成する。その後、ラジカルカチオン状態の光酸化還元触媒により **B** が一電子酸化されることで、^{13f,30} ホスホニウム **C** が形成されると共に基底状態の光酸化還元触媒が再生する。このホスホニウム **C** のエチル基部位の β -脱離によって、アルキル化体 **3** が生成すると考えられる。

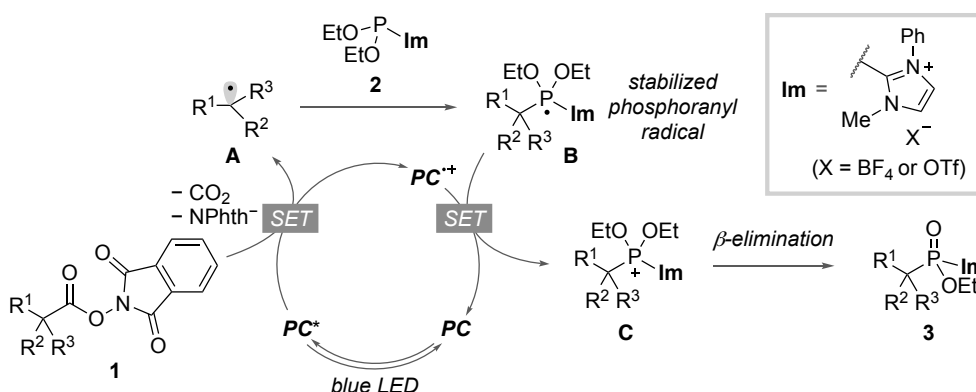


Figure 4-8. 推定反応機構

第六節 結論

二官能性リン(III)試薬であるイミダゾリウムホスホナイトを用いることで、リン中心に様々なアルキル基とヘテロ原子を一挙に導入する手法の開発に成功した。本反応では、1) 有機光酸化還元触媒と脂肪族カルボン酸誘導体を用いたイミダゾリウムホスホナイトの脱炭酸型アルキル化反応による $C(sp^3)$ -P 結合形成、2) $S_NP(V)$ 反応によるリン(V)-ヘテロ原子結合形成、という二段階の過程を経る。本手法により、従来法では達成困難な複雑かつ嵩高い非対称なアルキルリン(V)化合物を効率的に構築できる。

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第四章 実験項

1. Instrumentation and Chemicals

NMR spectra were recorded on a Bruker AVANCE NEO 400N spectrometer, operating at 400 MHz for ^1H NMR, 100.6 MHz for ^{13}C NMR, 376.5 MHz for ^{19}F NMR, and 162 MHz for ^{31}P NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si and the residual solvent resonances, respectively. Chemical shifts were reported in δ ppm. Mass spectra were obtained with Bruker Impact HD mass spectrometer (ESI). TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60F₂₅₄. Silica gel (Wakosil® 60, 64~210 μm) was used for column chromatography. Biotage Selekt was used for purification. IR spectra were measured with a ATR Accessory (QATR-S) for the Shimadzu IRSpirit FT-IR Spectrometer. Melting points were measured on a Stanford Research Systems MPA100. Kessil A160WE 40W Tuna Blue (highest blue and intensity setting) was used as a light source. Techno Sigma UCR-150N was used as a cryocooler. TEKNOS MG9 was used as a fan. Single-crystal X-ray diffraction data were collected on a Bruker Single Crystal CCD X-ray Diffractometer (SMART APEX II).

All reactions were carried out under nitrogen atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. 3CzClIPN, 4CzIPN, and 5CzBN were prepared by the reported procedure.^{1,2} $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ and $\text{Ir}(\text{ppy})_3$ were purchased from Merck Sigma–Aldrich Japan Inc., stored under nitrogen, and used as received. Ph-benzoPTH was prepared by the reported procedure.³ Lithium tetrafluoroborate, lithium trifluoromethanesulfonate, and sodium tetrafluoroborate were purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Trifluoroacetic acid was purchased from Nacalai Tesque Inc., stored under nitrogen, and used as received. 2,4,6-Collidine· HBF_4 was prepared by the reported procedure.⁴ Acetone, acetonitrile, dichloromethane, dimethylacetamide, and tetrahydrofuran were purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. Sodium hydride (60% dispersion in Paraffin Liquid) was purchased from Nacalai Tesque Inc., stored under nitrogen, and used as received. Redox-active esters **1a–q** were prepared according to the reported procedure.^{5–14} Phosphonites **2b** and **2c** were prepared by the reported procedure.¹⁵ Nucleophiles **4a–g**, **4l**, **4n** were purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Nucleosides **4h** and **4i** were prepared according to the reported procedure.^{16,17} 3,4-Di-*O*-benzyl-D-glucal (**4j**) was prepared by the reported procedure.¹⁸ Benzyl carbamate (**4k**) was purchased from FUJIFILM Wako Pure Chemical Co., stored under nitrogen, and used as received. Tetrabutylammonium fluoride (*ca.* 1 mol/L in tetrahydrofuran) was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. *n*-Butyllithium (1.51 M in hexane) was purchased from Kanto Chemical Co., stored under nitrogen,

and used as received. Styrenes **6a** and **6b** were purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used after filtration through a short pad of alumina. 4-Phenyl-1-butene (**6c**) was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received. Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester) was purchased from Tokyo Chemical Industry Co., stored under nitrogen, and used as received.

2. General Procedure for Synthesis of Imidazolium Phosphonites

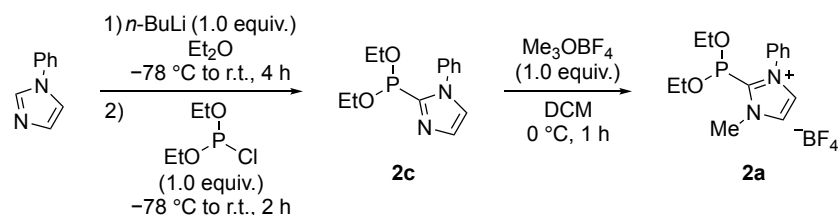
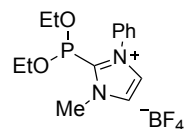


Figure S4-1. Synthesis of imidazolium phosphonites

Phosphonite **2c** was prepared according to the literature.¹⁵ To a solution of **2c** (2.11 g, 8.0 mmol) in DCM (50 mL), trimethyloxonium tetrafluoroborate (1.18 g, 8.0 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at 0 °C. After removing the solvent under reduced pressure, the product was washed three times with Et₂O in a glove box, yielding imidazolium phosphonite **2a** as a white solid (2.72 g, 7.44 mmol, 93%).

3. Characterization Data for Phosphonites

2-(Diethoxyphosphaneyl)-1-methyl-3-phenyl-1H-imidazolium Tetrafluoroborate (**2a**)



White solid. **M.p.** 36–41 °C. **IR** (neat) 694, 763, 924, 1010, 1047, 1241, 1387, 1498, 1596, 2982 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.77 (d, J = 1.6 Hz, 1H), 7.60–7.55 (m, 3H), 7.50–7.47 (m, 3H), 4.19 (s, 3H), 4.03–3.85 (m, 4H), 1.25 (t, J = 7.2 Hz, 6H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 146.6 (d, J_{C-P} = 69.6 Hz), 135.0 (d, J_{C-P} = 2.0 Hz), 131.0, 129.9, 127.0, 126.4 (d, J_{C-P} = 3.4 Hz), 124.7, 66.0 (d, J_{C-P} = 20.0 Hz), 37.6 (d, J_{C-P} = 2.2 Hz), 16.8 (d, J_{C-P} = 6.2 Hz). **³¹P NMR** (162 MHz, CDCl₃) δ 143.7. **HRMS–ESI** (m/z): [M–BF₄]⁺ calcd for C₁₄H₂₀N₂O₂P, 279.1257; found, 279.1255.

4. General Procedure for Synthesis of Alkyl Imidazolium Phosphinates

The reaction conditions for oxidative alkylation of **2a (procedure A).** In a glovebox, to an oven-dried vial with a stirring bar was added 3CzClIPN (2.63 mg, 0.004 mmol), redox-active

ester **1** (0.4 mmol), phosphonite **2a** (73.2 mg, 0.2 mmol), and LiBF₄ (37.5 mg, 0.4 mmol). Then, acetone (600 μ L) was added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with UC reactor to keep the temperature at 20 °C (Figure S4-2). After 16 h, the solvent was removed under reduced pressure. The crude material was then purified by flash column chromatography on silica gel to give the alkylated product **3**.

1 mmol scale reaction. In a glovebox, to an oven-dried vial with a stirring bar was added 3CzClIPN (13.2 mg, 0.02 mmol), redox-active ester **1a** (0.49 g, 2.0 mmol), phosphonite **2a** (0.37 g, 1.0 mmol), and LiBF₄ (0.19 g, 2.0 mmol). Then, acetone (3 mL) was added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with UC reactor to keep the temperature at 20 °C (Figure S4-2). After 32 h, the solvent was removed under reduced pressure to give the alkylated product **3aa** (76% ¹H NMR yield).

The reaction conditions for oxidative alkylation of 2b (procedure B). In a glovebox, to an oven-dried vial with a stirring bar was added 3CzClIPN (2.63 mg, 0.004 mmol), redox-active ester **1** (0.4 mmol), phosphonite **2b** (85.7 mg, 0.2 mmol), and LiOTf (62.4 mg, 0.4 mmol). Then, acetone (600 μ L) was added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with UC reactor to keep the temperature at 20 °C (Figure S4-2). After 16 h, the solvent was removed under reduced pressure. The crude material was then purified by flash column chromatography on silica gel to give the alkylated product **3**.

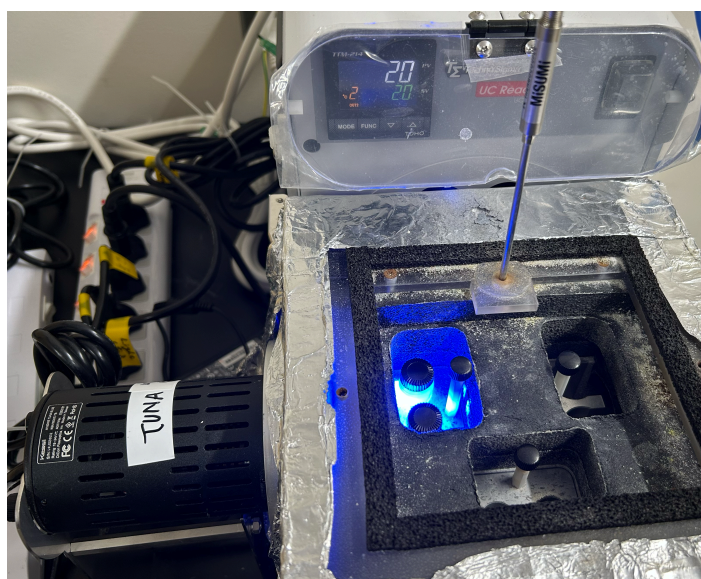
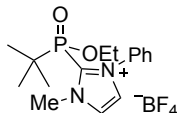


Figure S4-2. Light set-up using UC reactor as a cryocooler

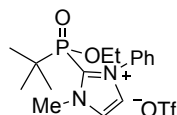
5. Characterization Data for Alkyl Imidazolium Phosphinates

2-[*tert*-Butyl(ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3aa)



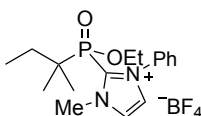
The reaction was carried out according to **procedure A**. The product **3aa** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–90:0, DCM/MeOH) (Table 4-1, entry 1; 67.0 mg, 0.170 mmol, 85% isolated yield). Off-white solid. **M.p.** 43–48 °C. **IR** (neat) 748, 1005, 1021, 1050, 1165, 1212, 1241, 1379, 1498, 2360 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.93 (m, 1H), 7.61–7.50 (m, 6H), 4.41 (m, 1H), 4.33 (s, 3H), 4.06 (m, 1H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.13 (d, $J = 18.8$ Hz, 9H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 137.2 (d, $J_{\text{C-P}} = 100.4$ Hz), 135.7, 131.1, 128.8, 128.4 (d, $J_{\text{C-P}} = 4.0$ Hz), 128.2 (d, $J_{\text{C-P}} = 3.8$ Hz), 127.4, 64.3 (d, $J_{\text{C-P}} = 8.0$ Hz), 38.9, 35.2 (d, $J_{\text{C-P}} = 109.2$ Hz), 23.3, 16.1 (d, $J_{\text{C-P}} = 5.0$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 37.5. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2\text{P}$; 307.1570, found 307.1571.

2-[*tert*-Butyl(ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Trifluoromethanesulfonate (3ab)



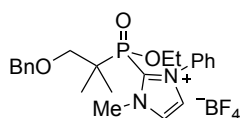
The reaction was carried out according to **procedure B**. The product **3ab** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–90:10, DCM/MeOH) (Table 4-1, entry 2; 52.9 mg, 0.116 mmol, 58% isolated yield). Pale yellow oil. **IR** (neat) 636, 770, 964, 1008, 1030, 1151, 1224, 1258, 1380, 1498 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 8.01 (s, 1H), 7.62–7.51 (m, 6H), 4.45–4.35 (m, 4H), 4.05 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 18.8$ Hz, 9H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 137.5 (d, $J_{\text{C-P}} = 99.6$ Hz), 135.7, 131.2, 128.9, 128.6 (d, $J_{\text{C-P}} = 4.0$ Hz), 128.3 (d, $J_{\text{C-P}} = 3.8$ Hz), 127.4, 120.6 (q, $J_{\text{C-F}} = 320.4$ Hz), 64.4 (d, $J_{\text{C-P}} = 8.0$ Hz), 39.2, 35.4 (d, $J_{\text{C-P}} = 108.6$ Hz), 23.4, 16.2 (d, $J_{\text{C-P}} = 5.0$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 37.7. **HRMS–ESI** (m/z): $[\text{M-OTf}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2\text{P}$; 307.1570, found 307.1573.

2-[Ethoxy(*tert*-pentyl)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3ba)



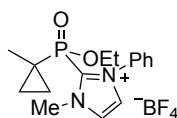
The reaction was carried out according to **procedure A**. The product **3ba** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–92:8, DCM/MeOH) (Table 4-2; 48.2 mg, 0.118 mmol, 59% isolated yield). Pale yellow oil. **IR** (neat) 547, 698, 771, 964, 1014, 1054, 1165, 1240, 1472, 1498 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.96 (s, 1H), 7.61–7.49 (m, 6H), 4.42 (m, 1H), 4.33 (s, 3H), 4.11 (m, 1H), 1.54–1.45 (m, 2H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.09–1.02 (m, 6H), 0.85 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 137.5 (d, $J_{\text{C-P}} = 98.4$ Hz), 135.8, 131.2, 128.9, 128.6 (d, $J_{\text{C-P}} = 4.0$ Hz), 128.3 (d, $J_{\text{C-P}} = 4.0$ Hz), 127.5, 64.3 (d, $J_{\text{C-P}} = 8.0$ Hz), 39.1, 38.5 (d, $J_{\text{C-P}} = 107.6$ Hz), 27.6, 19.8, 19.6, 16.2 (d, $J_{\text{C-P}} = 5.6$ Hz), 7.1 (d, $J_{\text{C-P}} = 11.2$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 38.1. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_2\text{P}$; 321.1726, found 321.1731.

2-[[1-(Benzyloxy)-2-methylpropan-2-yl](ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3ca)



The reaction was carried out according to **procedure A**. The product **3ca** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–90:10, DCM/MeOH) (Table 4-2; 51.0 mg, 0.102 mmol, 51% isolated yield). Pale yellow oil. **IR** (neat) 697, 748, 1011, 1051, 1165, 1238, 1385, 1458, 1474, 1498 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.60–7.48 (m, 4H), 7.43–7.32 (m, 5H), 7.24 (m, 1H), 7.18–7.16 (m, 2H), 4.42–4.36 (m, 3H), 4.16–4.13 (m, 4H), 3.58–3.37 (m, 2H), 1.29 (t, $J = 6.4$ Hz, 3H), 1.12–1.04 (m, 6H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 138.3 (d, $J_{\text{C-P}} = 110.4$ Hz), 136.6, 135.7, 131.1, 128.9, 128.7, 128.4, 128.0, 127.8 (d, $J_{\text{C-P}} = 4.4$ Hz), 127.4, 127.2 (d, $J_{\text{C-P}} = 4.0$ Hz), 74.4, 74.1, 64.5 (d, $J_{\text{C-P}} = 7.6$ Hz), 41.3 (d, $J_{\text{C-P}} = 109.6$ Hz), 39.1, 19.7, 19.4, 16.1 (d, $J_{\text{C-P}} = 6.0$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 33.5. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_3\text{P}$; 413.1989, found 413.1989.

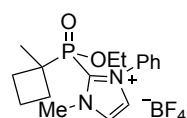
2-[Ethoxy(1-methylcyclopropyl)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3da)



The reaction was carried out according to **procedure A**. The product **3da** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–95:5, DCM/MeOH) (Table 4-2; 58.0 mg, 0.148 mmol, 74% isolated yield). Off-white solid. **M.p.** 118–123 $^{\circ}\text{C}$. **IR** (neat) 701, 778, 823, 961, 1013, 1171, 1222, 1245, 1386, 1498 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.89 (m, 1H),

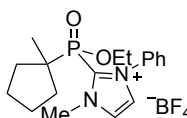
7.63–7.53 (m, 6H), 4.36 (s, 3H), 4.26 (m, 1H), 4.10 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.15 (d, $J = 16.4$ Hz, 3H), 0.94–0.77 (m, 2H), 0.67 (m, 1H), 0.56 (m, 1H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.0 (d, $J_{\text{C-P}} = 125.8$ Hz), 135.5, 131.4, 129.4, 128.4 (d, $J_{\text{C-P}} = 5.0$ Hz), 127.4 (d, $J_{\text{C-P}} = 4.2$ Hz), 127.1, 64.0 (d, $J_{\text{C-P}} = 6.6$ Hz), 39.1, 17.3 (d, $J_{\text{C-P}} = 9.0$ Hz), 16.0 (d, $J_{\text{C-P}} = 6.0$ Hz), 13.4 (d, $J_{\text{C-P}} = 156.0$ Hz), 13.3 (d, $J_{\text{C-P}} = 3.0$ Hz), 12.5 (d, $J_{\text{C-P}} = 1.8$ Hz). ^{31}P NMR (162 MHz, CDCl_3) δ 29.3. HRMS–ESI (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2\text{P}$; 305.1413, found 305.1413.

2-[Ethoxy(1-methylcyclobutyl)phosphoryl]-1-methyl-3-phenyl-1H-imidazolium Tetrafluoroborate (3ea)



The reaction was carried out according to **procedure A**. The product **3ea** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–95:5, DCM/MeOH) (Table 4-2; 53.6 mg, 0.132 mmol, 66% isolated yield). Pale yellow oil. IR (neat) 544, 697, 750, 1011, 1050, 1165, 1232, 1379, 1459, 1500 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.88 (m, 1H), 7.61–7.48 (m, 6H), 4.39 (m, 1H), 4.31 (s, 3H), 4.08 (m, 1H), 2.45 (m, 1H), 2.27–2.09 (m, 2H), 1.88–1.69 (m, 2H), 1.51 (m, 1H), 1.39–1.29 (m, 6H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 137.8 (d, $J_{\text{C-P}} = 102.6$ Hz), 135.4, 131.4, 129.3, 128.5 (d, $J_{\text{C-P}} = 4.2$ Hz), 127.7 (d, $J_{\text{C-P}} = 4.0$ Hz), 127.1, 64.2 (d, $J_{\text{C-P}} = 7.8$ Hz), 38.9, 38.7 (d, $J_{\text{C-P}} = 110.2$ Hz), 28.2 (d, $J_{\text{C-P}} = 5.0$ Hz), 28.2 (d, $J_{\text{C-P}} = 5.0$ Hz), 20.1 (d, $J_{\text{C-P}} = 4.4$ Hz), 16.2 (d, $J_{\text{C-P}} = 5.0$ Hz), 16.1 (d, $J_{\text{C-P}} = 17.2$ Hz). ^{31}P NMR (162 MHz, CDCl_3) δ 31.5. HRMS–ESI (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2\text{P}$; 319.1570, found 319.1569.

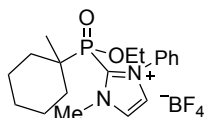
2-[Ethoxy(1-methylcyclopentyl)phosphoryl]-1-methyl-3-phenyl-1H-imidazolium Tetrafluoroborate (3fa)



The reaction was carried out according to **procedure A**. The product **3fa** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–95:5, DCM/MeOH) (Table 4-2; 59.7 mg, 0.142 mmol, 71% isolated yield). Pale yellow oil. IR (neat) 547, 697, 766, 1008, 1050, 1165, 1238, 1379, 1459, 1498 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.94 (s, 1H), 7.60–7.50 (m, 6H), 4.45–4.34 (m, 4H), 4.08 (m, 1H), 1.88–1.64 (m, 6H), 1.47–1.37 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 20.8$ Hz, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.1 (d, $J_{\text{C-P}} = 101.6$ Hz), 135.7, 131.2, 129.0, 128.5 (d, $J_{\text{C-P}} = 4.0$ Hz), 128.1 (d, $J_{\text{C-P}} = 3.8$ Hz), 127.4, 64.2 (d, $J_{\text{C-P}} = 8.0$ Hz), 44.9 (d, $J_{\text{C-P}} = 112.6$ Hz), 39.1, 33.9 ($\times 2\text{C}$), 24.3 (d, $J_{\text{C-P}} = 4.0$ Hz), 24.2 (d, $J_{\text{C-P}} = 3.6$ Hz), 20.8 (d, $J_{\text{C-P}}$

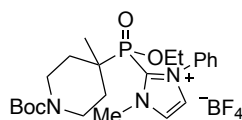
$\text{P} = 2.0 \text{ Hz}$), 16.2 (d, $J_{\text{C-P}} = 5.4 \text{ Hz}$). ^{31}P NMR (162 MHz, CDCl_3) δ 36.6. HRMS–ESI (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2\text{P}$; 333.1726, found 333.1727.

2-[Ethoxy(1-methylcyclohexyl)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3ga)



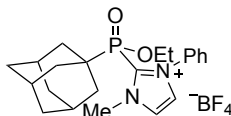
The reaction was carried out according to **procedure A**. The product **3ga** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–95:5, DCM/MeOH) (Table 4-2; 39.9 mg, 0.092 mmol, 46% isolated yield). Pale yellow oil. IR (neat) 553, 697, 961, 1011, 1050, 1237, 1382, 1469, 1498, 2934 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.96 (s, 1H), 7.61–7.52 (m, 6H), 4.46–4.33 (m, 4H), 4.08 (m, 1H), 1.63–1.38 (m, 9H), 1.31 (t, $J = 6.8 \text{ Hz}$, 3H), 1.18–1.11 (m, 4H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 137.6 (d, $J_{\text{C-P}} = 97.6 \text{ Hz}$), 135.8, 131.2, 128.9, 128.5 (d, $J_{\text{C-P}} = 3.0 \text{ Hz}$), 128.3 (d, $J_{\text{C-P}} = 4.0 \text{ Hz}$), 127.5, 64.3 (d, $J_{\text{C-P}} = 8.0 \text{ Hz}$), 39.2, 38.8 (d, $J_{\text{C-P}} = 109.6 \text{ Hz}$), 29.2, 29.0, 24.9, 19.8 (d, $J_{\text{C-P}} = 10.0 \text{ Hz}$), 19.7 (d, $J_{\text{C-P}} = 10.4 \text{ Hz}$), 16.3, 16.3 (d, $J_{\text{C-P}} = 5.4 \text{ Hz}$). ^{31}P NMR (162 MHz, CDCl_3) δ 37.2. HRMS–ESI (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2\text{P}$; 347.1883, found 347.1882.

2-[[1-(*tert*-Butoxycarbonyl)-4-methylpiperidin-4-yl](ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3ha)



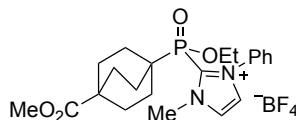
The reaction was carried out according to **procedure A**. The product **3ha** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–95:5, DCM/MeOH) (Table 4-2; 41.8 mg, 0.078 mmol, 39% isolated yield). Pale yellow oil. IR (neat) 546, 698, 767, 1014, 1057, 1153, 1244, 1367, 1498, 1686 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.96 (s, 1H), 7.61–7.52 (m, 6H), 4.46–4.34 (m, 4H), 4.10 (m, 1H), 3.89–3.82 (m, 2H), 2.94–2.93 (m, 2H), 1.75–1.65 (m, 4H), 1.43 (s, 9H), 1.31 (t, $J = 6.4 \text{ Hz}$, 3H), 1.21 (d, $J = 21.2 \text{ Hz}$, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 154.5, 137.1 (d, $J_{\text{C-P}} = 102.6 \text{ Hz}$), 135.6, 131.4, 129.0, 128.7, 128.5 (d, $J_{\text{C-P}} = 3.0 \text{ Hz}$), 127.5, 80.0, 64.7 (d, $J_{\text{C-P}} = 8.0 \text{ Hz}$), 39.2, 37.5 (d, $J_{\text{C-P}} = 112.6 \text{ Hz}$), 28.7, 28.5, 28.4, 16.3 (d, $J_{\text{C-P}} = 6.0 \text{ Hz}$), 15.7. ^{31}P NMR (162 MHz, CDCl_3) δ 35.0. HRMS–ESI (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{23}\text{H}_{35}\text{N}_3\text{O}_4\text{P}$; 448.2360, found 448.2362.

**2-[(Adamantan-1-yl)(ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium
Tetrafluoroborate (3ia)**



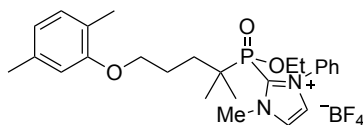
The reaction was carried out according to **procedure A**. The product **3ia** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–95:5, DCM/MeOH) (Table 4-2; 74.6 mg, 0.158 mmol, 79% isolated yield). Pale yellow oil. **IR** (neat) 552, 754, 974, 1015, 1054, 1165, 1238, 1456, 1498, 2910 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.96 (s, 1H), 7.60–7.52 (m, 6H), 4.40–4.33 (m, 4H), 4.02 (m, 1H), 2.03 (s, 3H), 1.74–1.67 (m, 12H), 1.29 (t, $J = 6.8$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 137.4 (d, $J_{\text{C-P}} = 98.6$ Hz), 135.8, 131.2, 128.9, 128.6 (d, $J_{\text{C-P}} = 4.0$ Hz), 128.3 (d, $J_{\text{C-P}} = 4.0$ Hz), 127.4, 64.1 (d, $J_{\text{C-P}} = 8.0$ Hz), 39.1, 38.2 (d, $J_{\text{C-P}} = 112.6$ Hz), 35.8 (d, $J_{\text{C-P}} = 1.2$ Hz), 33.9 (d, $J_{\text{C-P}} = 3.0$ Hz), 26.7 (d, $J_{\text{C-P}} = 12.4$ Hz), 16.2 (d, $J_{\text{C-P}} = 5.4$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 33.2. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2\text{P}$; 385.2039, found 385.2038.

**2-{Ethoxy[4-(methoxycarbonyl)bicyclo[2.2.2]octan-1-yl]phosphoryl}-1-methyl-3-phenyl-
1*H*-imidazolium Tetrafluoroborate (3ja)**



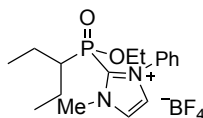
The reaction was carried out according to **procedure A**. The product **3ja** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–92:8, DCM/MeOH) (Table 4-2; 59.5 mg, 0.118 mmol, 59% isolated yield). Off-white solid. **M.p.** 62–67 °C. **IR** (neat) 556, 698, 768, 1017, 1054, 1166, 1240, 1458, 1498, 1725 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.95 (s, 1H), 7.61–7.52 (m, 6H), 4.42–4.30 (m, 4H), 4.03 (m, 1H), 3.62 (s, 3H), 1.80–1.66 (m, 12H), 1.28 (t, $J = 6.8$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 176.8, 137.1 (d, $J_{\text{C-P}} = 105.2$ Hz), 135.7, 131.2, 128.9, 128.6 (d, $J_{\text{C-P}} = 4.0$ Hz), 128.3 (d, $J_{\text{C-P}} = 3.8$ Hz), 127.4, 64.3 (d, $J_{\text{C-P}} = 7.8$ Hz), 51.9, 39.1, 37.9, 35.7 (d, $J_{\text{C-P}} = 120.8$ Hz), 26.7 (d, $J_{\text{C-P}} = 14.0$ Hz), 23.4, 16.3 (d, $J_{\text{C-P}} = 5.2$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 34.8. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_4\text{P}$; 417.1938, found 417.1934.

2-[[5-(2,5-Dimethylphenoxy)-2-methylpentan-2-yl](ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3ka)



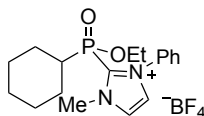
The reaction was carried out according to **procedure A**. The product **3ka** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–90:10, DCM/MeOH) (Table 4-2; 71.6 mg, 0.132 mmol, 66% isolated yield). White solid. **M.p.** 49–54 °C. **IR** (neat) 552, 666, 695, 747, 1013, 1051, 1129, 1159, 1238, 1498 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.94 (s, 1H), 7.52–7.48 (m, 4H), 7.41–7.37 (m, 2H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 7.2 Hz, 1H), 6.60 (s, 1H), 4.42 (m, 1H), 4.31 (s, 3H), 4.11 (m, 1H), 3.89 (t, *J* = 5.6 Hz, 2H), 2.31 (s, 3H), 2.08 (s, 3H), 1.78–1.70 (m, 2H), 1.64–1.57 (m, 2H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.17–1.09 (m, 6H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 156.6, 137.3 (d, *J*_{C-P} = 99.6 Hz), 136.6, 135.7, 131.1, 130.3, 128.8, 128.6 (d, *J*_{C-P} = 4.0 Hz), 128.3 (d, *J*_{C-P} = 4.0 Hz), 127.5, 123.2, 120.8, 111.8, 67.2, 64.4 (d, *J*_{C-P} = 8.0 Hz), 39.1, 38.1 (d, *J*_{C-P} = 107.6 Hz), 31.6, 22.8 (d, *J*_{C-P} = 11.2 Hz), 21.3, 20.1, 16.2 (d, *J*_{C-P} = 6.0 Hz), 15.7. **³¹P NMR** (162 MHz, CDCl₃) δ 37.5. **HRMS–ESI** (*m/z*): [M–BF₄]⁺ calcd for C₂₆H₃₆N₂O₃P; 455.2458, found 455.2460.

2-[Ethoxy(pentan-3-yl)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3la)



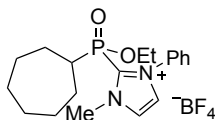
The reaction was carried out according to **procedure A**. The product **3la** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–90:10, DCM/MeOH) (Table 4-2; 43.3 mg, 0.106 mmol, 53% isolated yield). Off-white solid. **M.p.** 115–120 °C. **IR** (neat) 520, 557, 698, 768, 964, 974, 1017, 1053, 1240, 1500 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.87 (s, 1H), 7.67–7.50 (m, 6H), 4.40–4.32 (m, 4H), 4.08 (m, 1H), 1.73–1.43 (m, 5H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.91–0.86 (m, 6H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 137.8 (d, *J*_{C-P} = 104.8 Hz), 135.2, 131.6, 129.7, 128.5 (d, *J*_{C-P} = 4.0 Hz), 127.2 (d, *J*_{C-P} = 4.0 Hz), 126.7, 63.9 (d, *J*_{C-P} = 8.0 Hz), 41.5 (d, *J*_{C-P} = 107.8 Hz), 38.8, 19.1, 18.2 (d, *J*_{C-P} = 5.0 Hz), 16.1 (d, *J*_{C-P} = 6.4 Hz), 11.9 (d, *J*_{C-P} = 8.0 Hz), 11.0 (d, *J*_{C-P} = 13.2 Hz). **³¹P NMR** (162 MHz, CDCl₃) δ 33.1. **HRMS–ESI** (*m/z*): [M–BF₄]⁺ calcd for C₁₇H₂₆N₂O₂P; 321.1726, found 321.1718.

2-[Cyclohexyl(ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3ma)



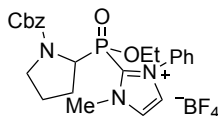
The reaction was carried out according to **procedure A**. The product **3ma** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–92:8, DCM/MeOH) (Table 4-2; 42.0 mg, 0.100 mmol, 50% isolated yield). Pale yellow oil. **IR** (neat) 567, 698, 773, 1020, 1056, 1166, 1241, 1452, 1500, 2932 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 7.89 (m, 1H), 7.68–7.50 (m, 6H), 4.35–4.29 (m, 4H), 4.04 (m, 1H), 1.80–1.65 (m, 4H), 1.50–1.37 (m, 4H), 1.27–1.15 (m, 6H). **¹³C NMR** (100.6 MHz, CDCl_3) δ 137.6 (d, $J_{\text{C-P}} = 105.6$ Hz), 135.2, 131.6, 129.8, 128.5 (d, $J_{\text{C-P}} = 4.0$ Hz), 127.2 (d, $J_{\text{C-P}} = 4.0$ Hz), 126.5, 64.0 (d, $J_{\text{C-P}} = 8.0$ Hz), 38.9, 38.5 (d, $J_{\text{C-P}} = 111.6$ Hz), 25.5, 25.4, 25.2 (d, $J_{\text{C-P}} = 2.0$ Hz), 24.0, 23.1 (d, $J_{\text{C-P}} = 5.4$ Hz), 16.1 (d, $J_{\text{C-P}} = 6.4$ Hz). **³¹P NMR** (162 MHz, CDCl_3) δ 31.1. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2\text{P}$; 333.1726, found 333.1729.

2-[Cycloheptyl(ethoxy)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3na)



The reaction was carried out according to **procedure A**. The product **3na** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–92:8, DCM/MeOH) (Table 4-2; 62.5 mg, 0.144 mmol, 72% isolated yield). Pale yellow oil. **IR** (neat) 559, 697, 768, 1011, 1050, 1166, 1240, 1382, 1459, 1500 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 7.89 (s, 1H), 7.67–7.50 (m, 6H), 4.39–4.31 (m, 4H), 4.08 (m, 1H), 1.84–1.74 (m, 3H), 1.59–1.25 (m, 13H). **¹³C NMR** (100.6 MHz, CDCl_3) δ 137.6 (d, $J_{\text{C-P}} = 106.6$ Hz), 135.1, 131.7, 129.7, 128.6 (d, $J_{\text{C-P}} = 4.0$ Hz), 127.2 (d, $J_{\text{C-P}} = 3.6$ Hz), 126.6, 64.1 (d, $J_{\text{C-P}} = 8.0$ Hz), 39.2 (d, $J_{\text{C-P}} = 106.6$ Hz), 38.8, 27.9, 27.6, 27.2 (d, $J_{\text{C-P}} = 17.2$ Hz), 26.9 (d, $J_{\text{C-P}} = 19.0$ Hz), 25.6, 24.7 (d, $J_{\text{C-P}} = 5.0$ Hz), 16.2 (d, $J_{\text{C-P}} = 6.2$ Hz). **³¹P NMR** (162 MHz, CDCl_3) δ 33.0. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2\text{P}$; 347.1883, found 347.1881.

2-({1-[(Benzyloxy)carbonyl]pyrrolidin-2-yl}(ethoxy)phosphoryl)-1-methyl-3-phenyl-1*H*-imidazolium Tetrafluoroborate (3oa)



The reaction was carried out according to **procedure A**. The product **3oa** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–90:10, DCM/MeOH) (Table 4-2; 56.3 mg, 0.104 mmol, 52% isolated yield). The diastereomeric ratio (1.7:1) was determined by ^{31}P NMR.

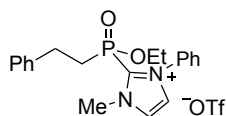
3oa-major

Pale yellow oil. **IR** (neat) 556, 701, 768, 1054, 1172, 1247, 1357, 1406, 1500, 1696 cm^{-1} . ^1H **NMR** (400 MHz, CDCl_3) δ 7.67–7.50 (m, 6H), 7.42–7.31 (m, 6H), 5.11 (d, $J = 12.0$ Hz, 1H), 4.92 (d, $J = 12.0$ Hz, 1H), 4.30 (m, 1H), 4.12 (m, 1H), 3.92–3.83 (m, 4H), 3.61–3.47 (m, 2H), 2.30–2.04 (m, 3H), 1.95 (m, 1H), 1.11 (t, $J = 6.8$ Hz, 3H). ^{13}C **NMR** (100.6 MHz, CDCl_3) δ 155.6, 137.0 (d, $J_{\text{C-P}} = 120.0$ Hz), 135.9, 135.8, 131.3, 129.6, 128.8, 128.7 ($\times 2$ C), 127.9 (d, $J_{\text{C-P}} = 5.0$ Hz), 127.1 (d, $J_{\text{C-P}} = 4.0$ Hz), 126.5, 67.9, 64.9 (d, $J_{\text{C-P}} = 8.0$ Hz), 57.7 (d, $J_{\text{C-P}} = 134.2$ Hz), 47.4, 38.0, 25.6, 24.9, 15.9 (d, $J_{\text{C-P}} = 6.0$ Hz). ^{31}P **NMR** (162 MHz, CDCl_3) δ 19.3. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_4\text{P}$; 454.1890, found 454.1889.

3oa-minor

Pale yellow oil. **IR** (neat) 557, 698, 768, 1053, 1242, 1357, 1405, 1456, 1500, 1698 cm^{-1} . ^1H **NMR** (400 MHz, CDCl_3) δ 7.60–7.50 (m, 5H), 7.44–7.33 (m, 7H), 5.12 (d, $J = 12.0$ Hz, 1H), 4.93 (d, $J = 12.0$ Hz, 1H), 4.42–4.25 (m, 2H), 4.08 (m, 1H), 3.90 (s, 3H), 3.60–3.46 (m, 2H), 2.29–2.04 (m, 4H), 1.28 (t, $J = 7.2$ Hz, 3H). ^{13}C **NMR** (100.6 MHz, CDCl_3) δ 155.7, 137.4 (d, $J_{\text{C-P}} = 117.8$ Hz), 135.7, 135.7, 131.2, 130.6, 129.4, 128.9, 128.8, 127.8 (d, $J_{\text{C-P}} = 5.0$ Hz), 127.1 (d, $J_{\text{C-P}} = 3.0$ Hz), 126.5, 68.1, 65.4 (d, $J_{\text{C-P}} = 7.8$ Hz), 58.1 (d, $J_{\text{C-P}} = 129.8$ Hz), 47.4, 37.9, 25.3, 24.9, 16.2 (d, $J_{\text{C-P}} = 6.0$ Hz). ^{31}P **NMR** (162 MHz, CDCl_3) δ 22.1. **HRMS–ESI** (m/z): $[\text{M-BF}_4]^+$ calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_4\text{P}$; 454.1890, found 454.1893.

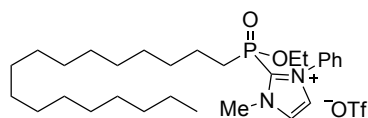
2-[Ethoxy(phenethyl)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium Trifluoromethanesulfonate (3pb)



The reaction was carried out according to **procedure B**. The product **3pb** was purified by flash

column chromatography on silica gel (Biotage Selekt, 100:0–90:10, DCM/MeOH) (Table 4-2; 66.6 mg, 0.132 mmol, 66% isolated yield). Pale yellow oil. **IR** (neat) 517, 636, 697, 754, 975, 1028, 1152, 1224, 1257, 1500 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.77 (s, 1H), 7.63 (m, 1H), 7.58–7.52 (m, 4H), 7.49 (s, 1H), 7.28–7.25 (m, 2H), 7.20 (m, 1H), 7.09 (d, $J = 7.2$ Hz, 2H), 4.34 (s, 3H), 4.20 (m, 1H), 3.94 (m, 1H), 2.99–2.81 (m, 2H), 2.27 (m, 1H), 2.10 (m, 1H), 1.15 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 138.8 (d, $J_{\text{C-P}} = 15.0$ Hz), 138.0 (d, $J_{\text{C-P}} = 116.6$ Hz), 135.1, 131.7, 129.8, 128.7, 128.1 (d, $J_{\text{C-P}} = 4.8$ Hz), 128.0, 126.9, 126.8 (d, $J_{\text{C-P}} = 4.0$ Hz), 126.7, 120.6 (q, $J_{\text{C-F}} = 320.0$ Hz), 63.9 (d, $J_{\text{C-P}} = 8.0$ Hz), 39.0, 31.8 (d, $J_{\text{C-P}} = 109.6$ Hz), 26.5 (d, $J_{\text{C-P}} = 4.0$ Hz), 15.9 (d, $J_{\text{C-P}} = 6.0$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 28.2. **HRMS–ESI** (m/z): $[\text{M-OTf}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2\text{P}$; 355.1570, found 355.1565.

**2-[Ethoxy(heptadecyl)phosphoryl]-1-methyl-3-phenyl-1*H*-imidazolium
Trifluoromethanesulfonate (3qb)**



The reaction was carried out according to **procedure B**. The product **3qb** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–92:8, DCM/MeOH) (Table 4-2; 23.0 mg, 0.036 mmol, 18% isolated yield). Pale yellow oil. **IR** (neat) 559, 636, 697, 767, 1030, 1153, 1224, 1258, 1501, 2923 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.82 (s, 1H), 7.65–7.54 (m, 6H), 4.35 (s, 3H), 4.24 (m, 1H), 3.92 (m, 1H), 1.90 (m, 1H), 1.81–1.69 (m, 2H), 1.56–1.46 (m, 2H), 1.30–1.19 (m, 30H), 0.88 (t, $J = 6.8$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 138.4 (d, $J_{\text{C-P}} = 113.8$ Hz), 135.2, 131.6, 129.8, 128.1 (d, $J_{\text{C-P}} = 4.2$ Hz), 126.8 (d, $J_{\text{C-P}} = 3.6$ Hz), 126.6, 120.6 (q, $J_{\text{C-F}} = 320.2$ Hz), 63.7 (d, $J_{\text{C-P}} = 7.4$ Hz), 38.9, 31.9, 30.4 (d, $J_{\text{C-P}} = 110.0$ Hz), 30.2 (d, $J_{\text{C-P}} = 16.8$ Hz), 29.7 ($\times 4\text{C}$), 29.6 ($\times 2\text{C}$), 29.6, 29.5, 29.3, 29.2, 28.9, 22.7, 20.4 (d, $J_{\text{C-P}} = 5.2$ Hz), 16.0 (d, $J_{\text{C-P}} = 6.0$ Hz), 14.1. **^{31}P NMR** (162 MHz, CDCl_3) δ 29.8. **HRMS–ESI** (m/z): $[\text{M-OTf}]^+$ calcd for $\text{C}_{29}\text{H}_{50}\text{N}_2\text{O}_2\text{P}$; 489.3604, found 489.3607.

6. X-ray Structure of 3da

A suitable crystal obtained by recrystallization was mounted with mineral oil on a Cargille Immersion Oil Type B and transferred to Bruker Single Crystal CCD X-ray Diffractometer (SMART APEX II) (Graphite-monochromated Mo K α radiation ($\lambda = 0.71073$ Å)). Cell parameters were determined and refined, and raw frame data were integrated using APEX 3 (Bruker) and a multi-scan absorption correction using an empirical method was applied. The structures were solved by direct methods with SHELXT and refined by full-matrix least-squares techniques against F² (SHELXL2018/3) by using Yadokari-XG software package. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre.

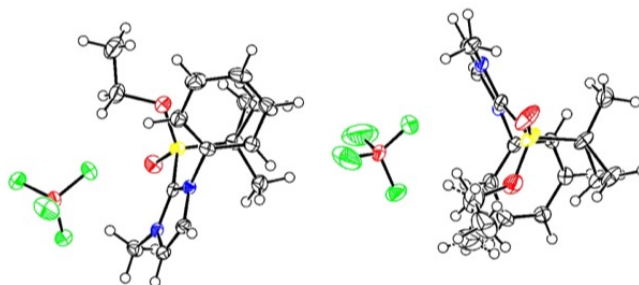


Figure S4-3. ORTEP diagram of **3da**. Ellipsoids are drawn at 50% probability. A single crystal used for the analysis was obtained by recrystallization from hexane/DCM.

Table S4-1. Crystallographic data and structure refinement details of **3da**

	3da
CCDC No.	2417872
formula	C ₃₂ H ₄₄ B ₂ F ₈ N ₄ O ₄ P ₂
fw	784.27
<i>T</i> (K)	86(2)
λ (Å)	0.71073
cryst syst	triclinic
space group	P $\bar{1}$
<i>a</i> (Å)	7.936(4)
<i>b</i> (Å)	12.536(6)
<i>c</i> (Å)	19.859(9)
α (deg)	93.626(6)
β (deg)	91.899(5)
γ (deg)	104.619(4)
<i>V</i> (Å ³)	1905.5(15)
<i>Z</i>	2
<i>D</i> _{calc} (g·cm ⁻³)	1.367
μ (mm ⁻¹)	0.194

F(000)	816
cryst size (mm ³)	0.12 × 0.27 × 0.31
2 θ range (deg)	3.37 to 50.16
reflns collected	18394
indep reflns/ R_{int}	6727 / 0.0313
params	488
GOF on F^2	1.050
R_1 , wR_2 [$I > 2\sigma(I)$]	0.0490, 0.1191
R_1 , wR_2 (all data)	0.0607, 0.1268

7. General Procedure for Synthesis of *tert*-Alkylphosphorus(V) Compounds

The reaction conditions for $S_NP(V)$ reactions with phenols (procedure C). Nucleophiles **4** (0.2 mmol) was placed in an oven-dried screw-top 4 mL vial containing a magnetic stirring bar. The vial was then introduced in the nitrogen-filled glovebox and to this was added THF (150 μ L) and NaH (60% dispersion in Paraffin Liquid, 12.0 mg, 0.3 mmol). After stirring at room temperature for 30 min, this reaction mixture was added to **3aa** (39.4 mg, 0.1 mmol) in THF (100 μ L). After stirring at room temperature for 30 min, the reaction mixture was quenched with sat. NH_4Cl aq. and extracted three times with EtOAc. After volatiles were removed under reduced pressure, purification by flash column chromatography on silica gel gave *tert*-alkylphosphorus(V) compounds **5**.

The reaction conditions for $S_NP(V)$ reactions with aliphatic alcohols (procedure D). Nucleophiles **4** (0.2 mmol) was placed in an oven-dried screw-top 4 mL vial containing a magnetic stirring bar. The vial was then introduced in the nitrogen-filled glovebox and to this was added THF (150 μ L) and NaH (60% dispersion in Paraffin Liquid, 12.0 mg, 0.3 mmol). After stirring at 40 °C for 30 min, this reaction mixture was added to **3aa** (39.4 mg, 0.1 mmol) in THF (100 μ L). After stirring at room temperature for 30 min, the reaction mixture was quenched with sat. NH_4Cl aq. and extracted three times with EtOAc. After volatiles were removed under reduced pressure, purification by flash column chromatography on silica gel gave *tert*-alkylphosphorus(V) compounds **5**.

The reaction conditions for $S_NP(V)$ reactions with nucleoside derivatives (procedure E). Nucleophiles **4** (0.2 mmol) was placed in an oven-dried screw-top 4 mL vial containing a magnetic stirring bar. The vial was then introduced in the nitrogen-filled glovebox and to this was added THF (150 μ L) and NaH (60% dispersion in Paraffin Liquid, 20.0 mg, 0.5 mmol). After stirring at 40 °C for 30 min, this reaction mixture was added to **3aa** (39.4 mg, 0.1 mmol) in THF (100 μ L). After stirring at room temperature for 30 min, the reaction mixture was quenched with sat. NH_4Cl aq. and extracted three times with EtOAc. After volatiles were removed under reduced

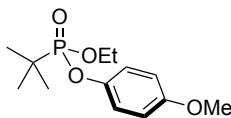
pressure, purification by flash column chromatography on silica gel gave *tert*-alkylphosphorus(V) compounds **5**.

The reaction conditions for S_NP(V) reactions with cyclic amines (procedure F). 1-Phenylpiperazine (**4l**) (22.7 μ L, 0.15 mmol) was placed in an oven-dried screw-top 4 mL vial containing a magnetic stirring bar. The vial was then introduced in the nitrogen-filled glovebox and to this was added THF (600 μ L). The vial was then removed from the glovebox, and *n*-BuLi (1.51 M in hexane, 99.3 μ L, 0.15 mmol) was added dropwise to this solution at -78°C . After stirring at -78°C for 30 min, this reaction mixture was added to **3da** (39.2 mg, 0.1 mmol) in THF (400 μ L). After stirring at room temperature for 30 min, the reaction mixture was quenched with sat. NH₄Cl aq. and extracted three times with EtOAc. After volatiles were removed under reduced pressure, purification by flash column chromatography on silica gel gave *tert*-alkylphosphorus(V) compounds **5l**.

The reaction conditions for S_NP(V) reactions with TBAF (procedure G). In a glovebox, to an oven-dried vial with a stirring bar was added **3ka** (27.1 mg, 0.005 mmol) and THF (125 μ L). Then, tetrabutylammonium fluoride solution (1 M in THF, 100 μ L, 0.1 mmol) was added to the reaction mixture. After stirring at room temperature for 30 min, the reaction mixture was quenched with sat. NH₄Cl aq. and extracted three times with EtOAc. After volatiles were removed under reduced pressure, purification by flash column chromatography on silica gel gave fluorophosphonates **5m**.

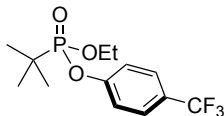
8. Characterization Data for *tert*-Alkylphosphorus Compounds

Ethyl (4-Methoxyphenyl) *tert*-Butylphosphonate (**5a**)



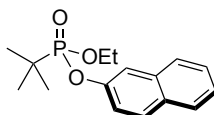
The reaction was carried out according to **procedure C**. The product **5a** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–50:50, hexane/AcOEt) (Table 4-3; 21.2 mg, 0.078 mmol, 78% isolated yield). Pale yellow oil. **IR** (neat) 659, 768, 833, 912, 1034, 1102, 1195, 1205, 1257, 1504 cm^{-1} . **¹H NMR** (400 MHz, CDCl₃) δ 7.14 (dd, J = 9.2, 1.2 Hz, 2H), 6.85–6.81 (m, 2H), 4.18–4.02 (m, 2H), 3.78 (s, 3H), 1.28 (d, J = 17.2 Hz, 9H), 1.22 (t, J = 8.0 Hz, 3H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 156.3 (d, $J_{\text{C-P}}$ = 1.4 Hz), 144.7 (d, $J_{\text{C-P}}$ = 10.2 Hz), 121.4 (d, $J_{\text{C-P}}$ = 3.8 Hz), 114.4, 62.7 (d, $J_{\text{C-P}}$ = 8.0 Hz), 55.6, 31.6 (d, $J_{\text{C-P}}$ = 142.4 Hz), 24.8 (d, $J_{\text{C-P}}$ = 2.0 Hz), 16.4 (d, $J_{\text{C-P}}$ = 6.0 Hz). **³¹P NMR** (162 MHz, CDCl₃) δ 34.4. **HRMS–ESI** (m/z): [M+H]⁺ calcd for C₁₃H₂₂O₄P; 273.1250, found 273.1245.

Ethyl [4-(Trifluoromethyl)phenyl] *tert*-Butylphosphonate (**5b**)



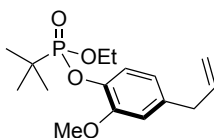
The reaction was carried out according to **procedure C**. The product **5b** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–80:20, hexane/AcOEt) (Table 4-3; 25.1 mg, 0.081 mmol, 81% isolated yield). Pale yellow oil. **IR** (neat) 722, 909, 1037, 1122, 1163, 1221, 1263, 1323, 1514, 1613 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.60 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 4.25–4.06 (m, 2H), 1.31–1.25 (m, 12H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 153.9 (d, $J_{\text{C-P}}$ = 10.6 Hz), 126.9 (q, $J_{\text{C-F}}$ = 3.6 Hz), 126.4 (q, $J_{\text{C-F}}$ = 32.2 Hz), 123.9 (q, $J_{\text{C-F}}$ = 271.6 Hz), 120.8 (d, $J_{\text{C-P}}$ = 5.0 Hz), 63.0 (d, $J_{\text{C-P}}$ = 7.8 Hz), 31.9 (d, $J_{\text{C-P}}$ = 141.8 Hz), 24.6 (d, $J_{\text{C-P}}$ = 2.2 Hz), 16.4 (d, $J_{\text{C-P}}$ = 5.6 Hz). **^{19}F NMR** (376.5 MHz, CDCl_3) δ -62.1. **^{31}P NMR** (162 MHz, CDCl_3) δ 34.9. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{19}\text{F}_3\text{O}_3\text{P}$; 311.1018, found 311.1015.

Ethyl Naphthalen-2-yl *tert*-Butylphosphonate (**5c**)



The reaction was carried out according to **procedure C**. The product **5c** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–40:60, hexane/AcOEt) (Table 4-3; 25.1 mg, 0.086 mmol, 86% isolated yield). Off-white solid. **M.p.** 57–60 °C. **IR** (neat) 748, 839, 926, 965, 1036, 1159, 1211, 1465, 1510, 1599 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.82–7.78 (m, 3H), 7.71 (s, 1H), 7.49–7.37 (m, 3H), 4.25–4.04 (m, 2H), 1.33 (d, J = 17.2 Hz, 9H), 1.23 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 148.9 (d, $J_{\text{C-P}}$ = 10.0 Hz), 133.9, 130.7, 129.5, 127.6, 127.4, 126.5, 125.1, 120.7 (d, $J_{\text{C-P}}$ = 4.0 Hz), 116.8 (d, $J_{\text{C-P}}$ = 4.0 Hz), 62.9 (d, $J_{\text{C-P}}$ = 7.6 Hz), 31.8 (d, $J_{\text{C-P}}$ = 142.8 Hz), 24.8 (d, $J_{\text{C-P}}$ = 2.0 Hz), 16.4 (d, $J_{\text{C-P}}$ = 5.6 Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 34.5. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{O}_3\text{P}$; 293.1301, found 293.1298.

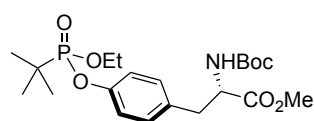
4-Allyl-2-methoxyphenyl Ethyl *tert*-Butylphosphonate (**5d**)



The reaction was carried out according to **procedure C**. The product **5d** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–40:60, hexane/AcOEt) (Table 4-3; 13.4 mg, 0.043 mmol, 43% isolated yield). Pale yellow oil. **IR** (neat) 658, 748, 915, 1036, 1126, 1152, 1211, 1258, 1270, 1510 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.22 (dd, J = 8.0, 1.2 Hz, 1H),

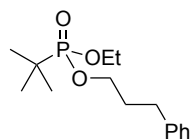
6.74–6.69 (m, 2H), 5.94 (m, 1H), 5.10–5.06 (m, 2H), 4.26–4.08 (m, 2H), 3.84 (s, 3H), 3.34 (d, J = 6.4 Hz, 2H), 1.32–1.25 (m, 12H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 150.6 (d, $J_{\text{C-P}}$ = 4.4 Hz), 138.6 (d, $J_{\text{C-P}}$ = 9.8 Hz), 137.2, 137.0, 121.6 (d, $J_{\text{C-P}}$ = 3.0 Hz), 120.6, 115.9, 112.9, 62.4 (d, $J_{\text{C-P}}$ = 8.0 Hz), 55.8, 39.9, 31.9 (d, $J_{\text{C-P}}$ = 142.8 Hz), 24.7 (d, $J_{\text{C-P}}$ = 2.4 Hz), 16.4 (d, $J_{\text{C-P}}$ = 5.8 Hz). ^{31}P NMR (162 MHz, CDCl_3) δ 34.6. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{O}_4\text{P}$; 313.1563, found 313.1560.

Methyl (S)-2-[(*tert*-Butoxycarbonyl)amino]-3-(4-{[*tert*-butyl(ethoxy)phosphoryl]oxy}phenyl)propanoate (5e)



The reaction was carried out according to **procedure C**. The product **5e** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–50:50, hexane/AcOEt) (Table 4-3; 33.7 mg, 0.076 mmol, 76% isolated yield). Off-white solid. **M.p.** 81–86 °C. **IR** (neat) 666, 753, 919, 1023, 1166, 1211, 1508, 1692, 1712, 1749 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.16 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 4.96 (d, J = 8.4 Hz, 1H), 4.56 (m, 1H), 4.21–4.02 (m, 2H), 3.71 (s, 3H), 3.11–3.00 (m, 2H), 1.43 (s, 9H), 1.30–1.21 (m, 12H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 172.2 ($\times 2\text{C}$), 155.0 ($\times 2\text{C}$), 150.2 (d, $J_{\text{C-P}}$ = 9.8 Hz) ($\times 2\text{C}$), 132.1 ($\times 2\text{C}$), 130.3 ($\times 2\text{C}$), 120.6 (d, $J_{\text{C-P}}$ = 3.0 Hz), 120.5 (d, $J_{\text{C-P}}$ = 3.6 Hz), 79.9 ($\times 2\text{C}$), 62.7 (d, $J_{\text{C-P}}$ = 7.0 Hz) ($\times 2\text{C}$), 54.3 ($\times 2\text{C}$), 52.2 ($\times 2\text{C}$), 37.5 ($\times 2\text{C}$), 31.7 (d, $J_{\text{C-P}}$ = 142.6 Hz), 31.7 (d, $J_{\text{C-P}}$ = 142.4 Hz), 28.2 ($\times 2\text{C}$), 24.7 (d, $J_{\text{C-P}}$ = 2.0 Hz) ($\times 2\text{C}$), 16.4 (d, $J_{\text{C-P}}$ = 5.4 Hz) ($\times 2\text{C}$). ^{31}P NMR (162 MHz, CDCl_3) δ 34.3. HRMS–ESI (m/z): $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{21}\text{H}_{38}\text{N}_2\text{O}_7\text{P}$; 461.2411, found 461.2408.

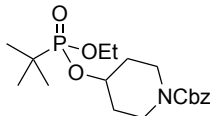
Ethyl (3-Phenylpropyl) *tert*-Butylphosphonate (5f)



The reaction was carried out according to **procedures D**. The product **5f** was purified by flash column chromatography on silica gel (Biotage Selekt, 93:7–40:60, hexane/AcOEt) (Table 4-3; 19.6 mg, 0.069 mmol, 69% isolated yield). Pale yellow oil. **IR** (neat) 699, 745, 835, 955, 1008, 1026, 1217, 1251, 1479, 2906 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.27 (m, 2H), 7.21–7.18 (m, 3H), 4.16–4.00 (m, 4H), 2.72 (t, J = 8.0 Hz, 2H), 2.02–1.95 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.19 (d, J = 16.8 Hz, 9H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 141.2, 128.4, 128.4, 125.9, 64.6 (d, $J_{\text{C-P}}$ = 8.0 Hz), 61.9 (d, $J_{\text{C-P}}$ = 7.2 Hz), 32.3 (d, $J_{\text{C-P}}$ = 5.8 Hz), 31.7, 31.3 (d, $J_{\text{C-P}}$ = 142.6 Hz), 24.8 (d, $J_{\text{C-P}}$ = 2.2 Hz), 16.6 (d, $J_{\text{C-P}}$ = 5.6 Hz). ^{31}P NMR (162 MHz, CDCl_3) δ 37.1. HRMS–ESI

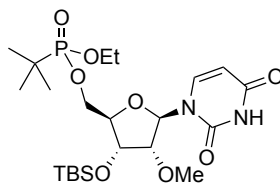
(*m/z*): [M+H]⁺ calcd for C₁₅H₂₆O₃P; 285.1614, found 285.1611.

Benzyl 4-{{*tert*-Butyl(ethoxy)phosphoryl}oxy}piperidine-1-carboxylate (5g)



The reaction was carried out according to **procedures D**. The product **5g** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–25:75, hexane/AcOEt) (Table 4-3; 34.1 mg, 0.089 mmol, 89% isolated yield). Pale yellow oil. **IR** (neat) 697, 753, 833, 875, 942, 990, 1026, 1222, 1428, 1698 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 7.37–7.32 (m, 5H), 5.13 (s, 2H), 4.63 (m, 1H), 4.15–4.05 (m, 2H), 3.75–3.69 (m, 2H), 3.43–3.37 (m, 2H), 1.89–1.74 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 16.4 Hz, 9H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 155.2, 136.7, 128.5, 128.0, 127.9, 70.9, 67.1, 61.8 (d, *J*_{C-P} = 6.4 Hz), 40.7 (d, *J*_{C-P} = 7.0 Hz), 32.4, 31.3 (d, *J*_{C-P} = 143.0 Hz), 24.7 (d, *J*_{C-P} = 2.2 Hz), 16.6 (d, *J*_{C-P} = 5.8 Hz). **³¹P NMR** (162 MHz, CDCl₃) δ 36.7. **HRMS–ESI** (*m/z*): [M+H]⁺ calcd for C₁₉H₃₁NO₅P; 384.1934, found 384.1936.

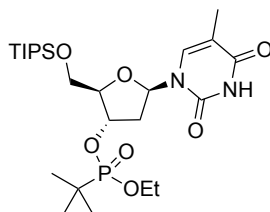
{{(2*R*,3*R*,4*R*,5*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-[2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-4-methoxytetrahydrofuran-2-yl}methyl Ethyl *tert*-Butylphosphonate (5h)



The reaction was carried out according to **procedures E**. The product **5h** was purified by flash column chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/AcOEt/MeOH) (Table 4-3; 42.7 mg, 0.082 mmol, 82% isolated yield). The diastereomeric ratio (1:1) was determined by ¹H NMR. Pale yellow oil. **IR** (neat) 751, 833, 962, 1049, 1096, 1208, 1250, 1379, 1458, 1691 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 9.13 (m, 1H), 7.86 (d, *J* = 8.0 Hz, 0.5 × 1H), 7.77 (d, *J* = 8.0 Hz, 0.5 × 1H), 5.91 (d, *J* = 2.0 Hz, 1H), 5.76 (dd, *J* = 8.0, 2.0 Hz, 0.5 × 1H), 5.70 (dd, *J* = 8.0, 2.0 Hz, 0.5 × 1H), 4.47 (m, 0.5 × 1H), 4.37 (m, 0.5 × 1H), 4.22–4.12 (m, 5H), 3.66 (m, 1H), 3.56 (s, 0.5 × 3H), 3.54 (s, 0.5 × 3H), 1.34–1.30 (m, 3H), 1.21 (d, *J* = 16.8 Hz, 9H), 0.91 (s, 0.5 × 9H), 0.91 (s, 0.5 × 9H), 0.12–0.10 (m, 6H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 163.5 (×2C), 150.2, 150.1, 139.8, 139.5, 102.3, 102.0, 88.1, 88.0, 83.6, 83.4, 82.1 (d, *J*_{C-P} = 6.2 Hz), 81.9 (d, *J*_{C-P} = 6.8 Hz), 69.2, 68.9, 63.5 (d, *J*_{C-P} = 7.0 Hz), 62.8 (d, *J*_{C-P} = 7.0 Hz), 62.8 (d, *J*_{C-P} = 7.2 Hz), 62.7 (d, *J*_{C-P} = 7.0 Hz), 58.3 (×2C), 31.7 (d, *J*_{C-P} = 141.0 Hz), 31.5 (d, *J*_{C-P} = 141.8 Hz), 25.6 (×2C), 24.7 (d, *J*_{C-P} = 2.0 Hz), 24.6 (d, *J*_{C-P} = 2.4 Hz), 18.0, 18.0, 16.6 (d, *J*_{C-P} = 6.0 Hz), 16.5 (d, *J*_{C-P} = 6.0 Hz), -4.6, -4.7, -5.0, -5.0. **³¹P NMR** (162 MHz, CDCl₃) δ 38.4, 37.9. **HRMS–**

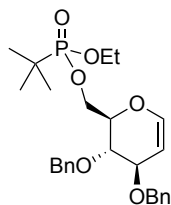
ESI (m/z): $[M+H]^+$ calcd for $C_{22}H_{42}N_2O_8PSi$; 521.2443, found 521.2442.

Ethyl ((2*R*,3*S*,5*R*)-5-[5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-2-[[triisopropylsilyl]oxy]methyl}tetrahydrofuran-3-yl) *tert*-Butylphosphonate (**5i**)



The reaction was carried out according to **procedures E**. The product **5i** was purified by flash column chromatography on silica gel (Biotage Selekt, 50:50:0–50:40:10, hexane/AcOEt/MeOH) (Table 4-3; 33.9 mg, 0.062 mmol, 62% isolated yield). The diastereomeric ratio (1:1) was determined by 1H NMR. Pale yellow oil. **IR** (neat) 664, 882, 971, 1004, 1129, 1211, 1250, 1275, 1464, 1691 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ 8.93 (m, 1H), 7.47 (d, $J = 5.6$ Hz, 1H), 6.38 (m, 1H), 5.11 (m, 1H), 4.25 (m, 0.5 $\times$ 1H), 4.21 (m, 0.5 $\times$ 1H), 4.18–4.09 (m, 2H), 4.00–3.98 (m, 2H), 2.50 (m, 1H), 2.15 (m, 1H), 1.91 (s, 3H), 1.35–1.31 (m, 3H), 1.21–1.09 (m, 30H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.6 ($\times 2C$), 150.3 ($\times 2C$), 134.9 ($\times 2C$), 111.2, 111.2, 86.6 (d, $J_{C-P} = 3.0$ Hz), 86.3 (d, $J_{C-P} = 5.0$ Hz), 84.4, 84.3, 76.0 (d, $J_{C-P} = 6.8$ Hz), 75.5 (d, $J_{C-P} = 7.0$ Hz), 63.4, 63.4, 62.4 (d, $J_{C-P} = 7.0$ Hz), 62.1 (d, $J_{C-P} = 7.0$ Hz), 39.9 (d, $J_{C-P} = 3.6$ Hz), 39.5 (d, $J_{C-P} = 5.4$ Hz), 31.4 (d, $J_{C-P} = 140.6$ Hz), 31.2 (d, $J_{C-P} = 141.0$ Hz), 24.6 (d, $J_{C-P} = 2.6$ Hz), 24.6 (d, $J_{C-P} = 2.0$ Hz), 18.0 ($\times 2C$), 16.6 (d, $J_{C-P} = 5.0$ Hz), 16.5 (d, $J_{C-P} = 6.0$ Hz), 12.3 ($\times 2C$), 11.8 ($\times 2C$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.9, 37.8. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{25}H_{48}N_2O_7PSi$; 547.2963, found 547.2961.

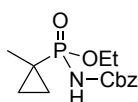
[(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-3,4-dihydro-2*H*-pyran-2-yl]methyl **Ethyl** *tert*-Butylphosphonate (**5j**)



The reaction was carried out according to **procedure D**. The product **5j** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:6–40:60, hexane/AcOEt) (Table 4-3; 14.2 mg, 0.030 mmol, 30% isolated yield). The diastereomeric ratio (1:1) was determined by ^{31}P NMR. Pale yellow oil. **IR** (neat) 697, 735, 835, 1010, 1027, 1097, 1217, 1250, 1454, 1647 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 10H), 6.40 (d, $J = 6.0$ Hz, 1H), 4.91–4.86 (m, 2H),

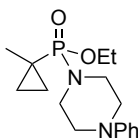
4.73–4.64 (m, 2H), 4.56 (m, 1H), 4.43–4.28 (m, 2H), 4.21 (m, 1H), 4.18–4.04 (m, 3H), 3.81 (m, 1H), 1.31–1.27 (m, 3H), 1.21–1.16 (m, 9H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 144.4, 144.4, 138.1 ($\times 2\text{C}$), 138.0, 137.9, 128.5 ($\times 2\text{C}$), 128.5 ($\times 2\text{C}$), 128.0, 127.9, 127.8, 127.8 ($\times 2\text{C}$), 127.8, 127.8, 127.7, 99.9, 99.8, 76.2 (d, $J_{\text{C-P}} = 6.0$ Hz), 76.1 (d, $J_{\text{C-P}} = 6.8$ Hz), 75.4, 75.2, 74.0, 74.0, 73.9, 73.7, 70.7, 70.6, 63.7 (d, $J_{\text{C-P}} = 7.0$ Hz), 63.7 (d, $J_{\text{C-P}} = 7.0$ Hz), 62.0, 61.9, 31.6 (d, $J_{\text{C-P}} = 142.6$ Hz), 31.5 (d, $J_{\text{C-P}} = 142.8$ Hz), 24.8, 24.7, 16.6, 16.5. ^{31}P NMR (162 MHz, CDCl_3) δ 37.5, 37.3. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{35}\text{NaO}_6\text{P}$; 497.2063, found 497.2060.

Benzyl [Ethoxy(1-methylcyclopropyl)phosphoryl]carbamate (**5k**)



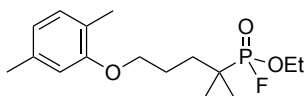
The reaction was carried out according to **procedure C**. The product **5k** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–90:10, DCM/MeOH) (Table 4-3; 27.4 mg, 0.092 mmol, 92% isolated yield). Pale yellow oil. IR (neat) 697, 840, 872, 954, 1030, 1188, 1231, 1286, 1452, 1732 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.33 (m, 5H), 6.28 (m, 1H), 5.19–5.13 (m, 2H), 4.15 (m, 1H), 4.03 (m, 1H), 1.30–1.23 (m, 7H), 1.14 (m, 1H), 0.63–0.53 (m, 2H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 153.3 (d, $J_{\text{C-P}} = 4.0$ Hz), 135.4, 128.6, 128.5, 128.3, 67.7, 61.5 (d, $J_{\text{C-P}} = 6.6$ Hz), 19.1 (d, $J_{\text{C-P}} = 6.6$ Hz), 16.1 (d, $J_{\text{C-P}} = 6.4$ Hz), 13.0 (d, $J_{\text{C-P}} = 3.0$ Hz), 11.9 (d, $J_{\text{C-P}} = 2.0$ Hz), 11.2 (d, $J_{\text{C-P}} = 181.6$ Hz). ^{31}P NMR (162 MHz, CDCl_3) δ 29.3. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{NNaO}_4\text{P}$; 320.1022, found 320.1024.

Ethyl (1-Methylcyclopropyl)(4-phenylpiperazin-1-yl)phosphinate (**5l**)



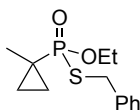
The reaction was carried out according to **procedure F**. The product **5l** was purified by flash column chromatography on silica gel (Biotage Selekt, 90:10–20:80, hexane/AcOEt) (Table 4-3; 9.6 mg, 0.031 mmol, 31% isolated yield). Pale yellow oil. IR (neat) 760, 842, 975, 1038, 1133, 1221, 1380, 1449, 1600, 2848 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.28 (m, 2H), 6.95–6.88 (m, 3H), 4.09 (m, 1H), 3.95 (m, 1H), 3.45–3.30 (m, 4H), 3.19–3.10 (m, 4H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.25 (d, $J = 13.6$ Hz, 3H), 1.11–0.96 (m, 2H), 0.58–0.47 (m, 2H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 151.5, 129.2, 120.3, 116.5, 59.9 (d, $J_{\text{C-P}} = 6.4$ Hz), 50.2 (d, $J_{\text{C-P}} = 5.0$ Hz), 44.5 (d, $J_{\text{C-P}} = 1.4$ Hz), 19.6 (d, $J_{\text{C-P}} = 6.4$ Hz), 16.3 (d, $J_{\text{C-P}} = 6.4$ Hz), 12.6 (d, $J_{\text{C-P}} = 3.2$ Hz), 10.8 (d, $J_{\text{C-P}} = 177.8$ Hz), 10.8 (d, $J_{\text{C-P}} = 2.4$ Hz). ^{31}P NMR (162 MHz, CDCl_3) δ 33.1. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_2\text{P}$; 309.1726, found 309.1724.

Ethyl [5-(2,5-Dimethylphenoxy)-2-methylpentan-2-yl]phosphonofluoridate (**5m**)



The reaction was carried out according to **procedure G**. The product **5m** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–50:50, hexane/AcOEt) (Table 4-3; 11.1 mg, 0.035 mmol, 70% isolated yield). Colorless oil. **IR** (neat) 773, 804, 846, 1034, 1130, 1158, 1265, 1278, 1472, 1510 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.01 (d, $J = 7.2$ Hz, 1H), 6.67 (d, $J = 7.2$ Hz, 1H), 6.61 (s, 1H), 4.32–4.24 (m, 2H), 3.95 (t, $J = 6.0$ Hz, 2H), 2.31 (s, 3H), 2.17 (s, 3H), 1.94–1.88 (m, 2H), 1.84–1.75 (m, 2H), 1.38 (t, $J = 6.8$ Hz, 3H), 1.31 (s, 3H), 1.26 (s, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 156.8, 136.5, 130.3, 123.5, 120.7, 111.8, 67.6, 63.2 (d, $J_{\text{C-P}} = 7.8$ Hz), 33.8, 33.7 (dd, $J_{\text{C-P, C-F}} = 140.6, 18.6$ Hz), 24.0 (d, $J_{\text{C-P}} = 7.0$ Hz), 22.0 (d, $J_{\text{C-P}} = 3.0$ Hz), 21.8 (d, $J_{\text{C-P}} = 2.8$ Hz), 21.4, 16.4 (d, $J_{\text{C-P}} = 5.0$ Hz), 15.7. **^{19}F NMR** (376.5 MHz, CDCl_3) δ -77.0 (d, $J_{\text{F-P}} = 1111.2$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 35.9 (d, $J_{\text{F-P}} = 1111.2$ Hz). **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{27}\text{FO}_3\text{P}$; 317.1676, found 317.1671.

S-Benzyl O-Ethyl (1-Methylcyclopropyl)phosphonothioate (**5n**)



The reaction was carried out according to **procedure C**. The product **5n** was purified by flash column chromatography on silica gel (Biotage Selekt, 100:0–45:55, hexane/AcOEt) (Table 4-3; 11.4 mg, 0.042 mmol, 42% isolated yield). Colorless oil. **IR** (neat) 629, 701, 768, 833, 952, 1027, 1214, 1267, 1455, 2930 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.39–7.38 (m, 2H), 7.34–7.30 (m, 2H), 7.26 (m, 1H), 4.18–3.98 (m, 4H), 1.31–1.24 (m, 6H), 1.21–0.99 (m, 2H), 0.62–0.45 (m, 2H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 138.3 (d, $J_{\text{C-P}} = 4.2$ Hz), 128.9, 128.6, 127.4, 61.6 (d, $J_{\text{C-P}} = 7.0$ Hz), 34.4 (d, $J_{\text{C-P}} = 3.0$ Hz), 19.1 (d, $J_{\text{C-P}} = 7.0$ Hz), 16.2 (d, $J_{\text{C-P}} = 150.4$ Hz), 16.2 (d, $J_{\text{C-P}} = 6.6$ Hz), 11.8 (d, $J_{\text{C-P}} = 3.4$ Hz), 11.8 (d, $J_{\text{C-P}} = 1.2$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 57.8. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2\text{PS}$; 271.0916, found 271.0914.

9. General Procedure for One-pot Reaction

In a glovebox, to an oven-dried vial with a stirring bar was added 3CzClIPN (2.63 mg, 0.004 mmol), redox-active ester **1a** (98.9 mg, 0.4 mmol), phosphonite **2a** (73.2 mg, 0.2 mmol), and LiBF_4 (37.5 mg, 0.4 mmol). Then, acetone (600 μL) was added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with UC reactor to keep the temperature at 20 $^\circ\text{C}$ (Figure S4-2). After 16 h, the solvent was

removed under reduced pressure. To this vial, a solution of *para*-methoxyphenol **4a** (74.5 mg, 0.6 mmol) and NaH (60% dispersion in Paraffin Liquid, 40.0 mg, 1.0 mmol), pre-reacted in THF (500 μ L) at room temperature for 30 min, was added under a nitrogen atmosphere. After stirring at room temperature for 2 h, the reaction mixture was quenched with sat. NH_4Cl aq. and extracted three times with EtOAc. After volatiles were removed under reduced pressure, purification by flash column chromatography on silica gel (Biotage Selekt, 95:5–40:60, hexane/EtOAc) gave *tert*-alkylphosphonates **5a** (38.1 mg, 0.140 mmol, 70% isolated yield).

10. General Procedure for P–C Bond Formation

The reaction conditions for P–C bond formation between 3aa and alkenes (procedure H). In a glovebox, to an oven-dried vial with a stirring bar was added $\text{Ir}(\text{ppy})_3$ (0.65 mg, 0.001 mmol), **3aa** (39.4 mg, 0.1 mmol), and alkenes **6** (0.15 mmol). Then, DMA (1 mL) was added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with a cooling fan to keep the temperature around 40 $^\circ\text{C}$ (Figure S4-4). After 16 h, water was added and extracted three times with AcOEt. After volatiles were removed under reduced pressure, purification by flash column chromatography on silica gel gave the P–C bond formation products **7**.

The reaction conditions for P–C bond formation between 3aa and 6c (procedure I). In a glovebox, to an oven-dried vial with a stirring bar was added $\text{Ir}(\text{ppy})_3$ (0.65 mg, 0.001 mmol), **3aa** (39.4 mg, 0.1 mmol), 4-phenyl-1-butene (**6c**) (22.5 μL , 0.15 mmol), and Hantzsch ester (50.7 mg, 0.2 mmol). Then, DMA (1 mL) was added to the reaction mixture. After sealing the vial with parafilm, the reaction mixture was stirred and irradiated with a 34W blue LED with a cooling fan to keep the temperature around 40 $^\circ\text{C}$ (Figure S4-4). After 16 h, water was added and extracted three times with AcOEt. After volatiles were removed under reduced pressure, purification by flash column chromatography on silica gel to give the P–C bond formation product **7c**.

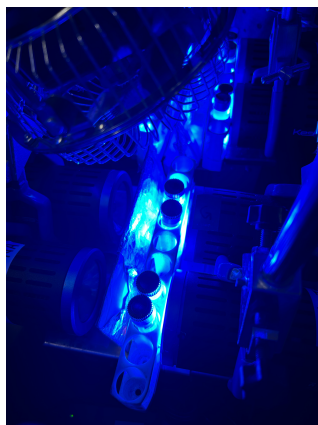
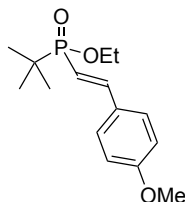


Figure S4-4. Light set-up

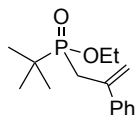
11. Characterization Data for P–C Bond Formation Products

Ethyl *tert*-Butyl(4-methoxystyryl)phosphinate (**7a**)



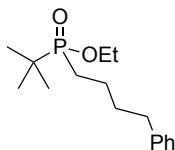
The reaction was carried out according to **procedure H**. The product **7a** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–40:60, hexane/AcOEt) (Figure 4-6; 22.6 mg, 0.080 mmol, 80% isolated yield). Pale yellow oil. **IR** (neat) 651, 767, 830, 941, 1036, 1173, 1257, 1307, 1511, 1604 cm^{-1} . The ratio of E/Z (2.1:1) was determined by ^1H NMR analysis. **^1H NMR** (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.8$ Hz, $0.32 \times 2\text{H}$), 7.52–7.43 (m, $0.68 \times 3\text{H}$), 7.25 (dd, $J = 41.2, 15.2$ Hz, $0.32 \times 1\text{H}$), 6.93–6.87 (m, 2H), 6.17 (dd, $J = 20.8, 17.6$ Hz, $0.68 \times 1\text{H}$), 5.57 (t, $J = 15.2$ Hz, $0.32 \times 1\text{H}$), 4.11 (m, 1H), 3.95 (m, 1H), 3.84 (s, $0.68 \times 3\text{H}$), 3.82 (s, $0.32 \times 3\text{H}$), 1.33–1.24 (m, 3H), 1.20–1.15 (m, 9H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 161.1, 160.5, 149.5, 149.5, 132.5, 129.2, 128.2 (d, $J_{\text{C-P}} = 7.0$ Hz), 128.0 (d, $J_{\text{C-P}} = 18.0$ Hz), 114.2, 114.1 (d, $J_{\text{C-P}} = 111.6$ Hz), 113.5, 111.4 (d, $J_{\text{C-P}} = 117.6$ Hz), 60.6 (d, $J_{\text{C-P}} = 7.0$ Hz), 60.3 (d, $J_{\text{C-P}} = 7.2$ Hz), 55.4, 55.2, 33.3 (d, $J_{\text{C-P}} = 102.6$ Hz), 32.1 (d, $J_{\text{C-P}} = 103.6$ Hz), 24.2, 24.2, 16.6 (d, $J_{\text{C-P}} = 6.0$ Hz), 16.5 (d, $J_{\text{C-P}} = 6.8$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 50.7, 48.7. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{O}_3\text{P}$; 283.1458, found 283.1459.

Ethyl *tert*-Butyl(2-phenylallyl)phosphinate (**7b**)



The reaction was carried out according to **procedure H**. The product **7b** was purified by flash column chromatography on silica gel (Biotage Selekt, 95:5–40:60, hexane/AcOEt) (Figure 4-6; 17.3 mg, 0.065 mmol, 65% isolated yield). Pale yellow oil. **IR** (neat) 701, 776, 823, 941, 1037, 1201, 1235, 1366, 1478, 2975 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.51 (d, $J = 7.2$ Hz, 2H), 7.36–7.32 (m, 2H), 7.28 (m, 1H), 5.55 (d, $J = 4.4$ Hz, 1H), 5.39 (d, $J = 4.4$ Hz, 1H), 4.00 (m, 1H), 3.77 (m, 1H), 3.10–2.96 (m, 2H), 1.19 (d, $J = 15.2$ Hz, 9H), 1.08 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 141.2, 138.8 (d, $J_{\text{C-P}} = 10.8$ Hz), 128.3, 127.6, 126.3, 117.3 (d, $J_{\text{C-P}} = 8.0$ Hz), 61.4 (d, $J_{\text{C-P}} = 7.0$ Hz), 33.5 (d, $J_{\text{C-P}} = 92.6$ Hz), 31.1 (d, $J_{\text{C-P}} = 78.4$ Hz), 24.5, 16.6 (d, $J_{\text{C-P}} = 5.0$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 57.7. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{P}$; 267.1508, found 267.1506.

Ethyl *tert*-Butyl(4-phenylbutyl)phosphinate (7c)



The reaction was carried out according to **procedures I**. The product **7c** was purified by flash column chromatography on silica gel (Biotage Selekt, 90:10–20:80, hexane/AcOEt) (Figure 4-6; 20.3 mg, 0.072 mmol, 72% isolated yield). Pale yellow oil. **IR** (neat) 698, 745, 826, 941, 1040, 1195, 1232, 1363, 1478, 2949 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 7.30–7.26 (m, 2H), 7.20–7.16 (m, 3H), 4.07 (quint, $J = 7.2$ Hz, 2H), 2.64 (t, $J = 7.2$ Hz, 2H), 1.77–1.61 (m, 6H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.14 (d, $J = 14.8$ Hz, 9H). **^{13}C NMR** (100.6 MHz, CDCl_3) δ 142.0, 128.3, 128.3, 125.8, 60.8 (d, $J_{\text{C-P}} = 6.0$ Hz), 35.6, 33.0 (d, $J_{\text{C-P}} = 91.6$ Hz), 33.0 (d, $J_{\text{C-P}} = 14.0$ Hz), 24.5, 24.0 (d, $J_{\text{C-P}} = 84.4$ Hz), 21.4 (d, $J_{\text{C-P}} = 5.0$ Hz), 16.8 (d, $J_{\text{C-P}} = 5.0$ Hz). **^{31}P NMR** (162 MHz, CDCl_3) δ 62.7. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{28}\text{O}_2\text{P}$; 283.1821, found 283.1820.

12. Cyclic Voltammetry (CV) Measurements

CV measurements were carried out under nitrogen atmosphere in acetonitrile solutions with 0.1 M of tetrabutylammonium hexafluorophosphate (Bu_4NPF_6) as a supporting electrolyte. Measurements were made with a glassy carbon electrode (area = 0.07 cm^2), an Ag/AgNO_3 reference electrode, and a Pt wire counter electrode. The concentration of the sample solution was fixed at 10 mM and the sweep rates were set to 100 mV/s.

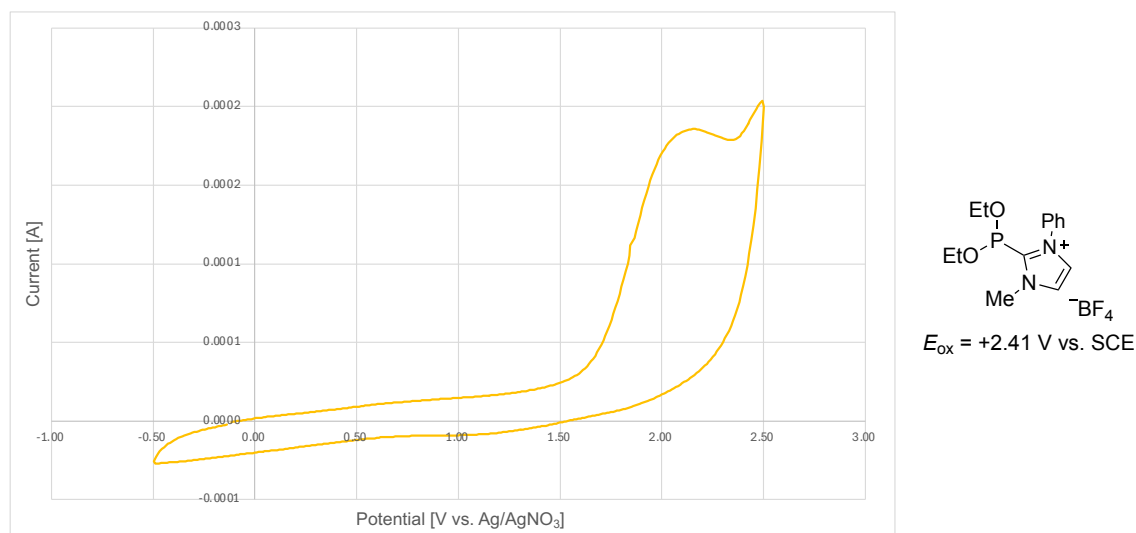


Figure S4-5. Cyclic voltammogram of **2a** (oxidation wave)

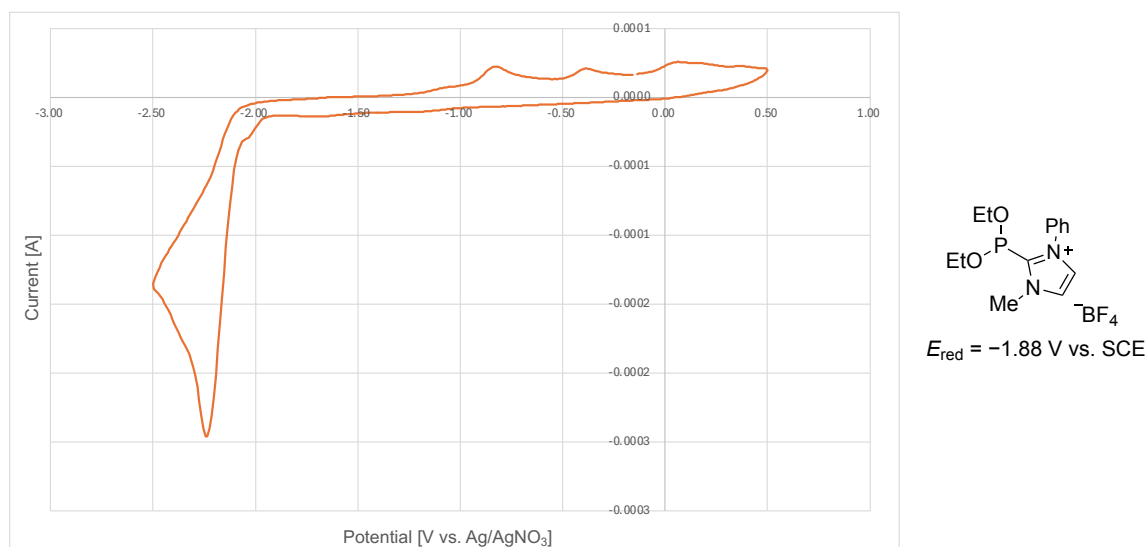


Figure S4-6. Cyclic voltammogram of **2a** (reduction wave)

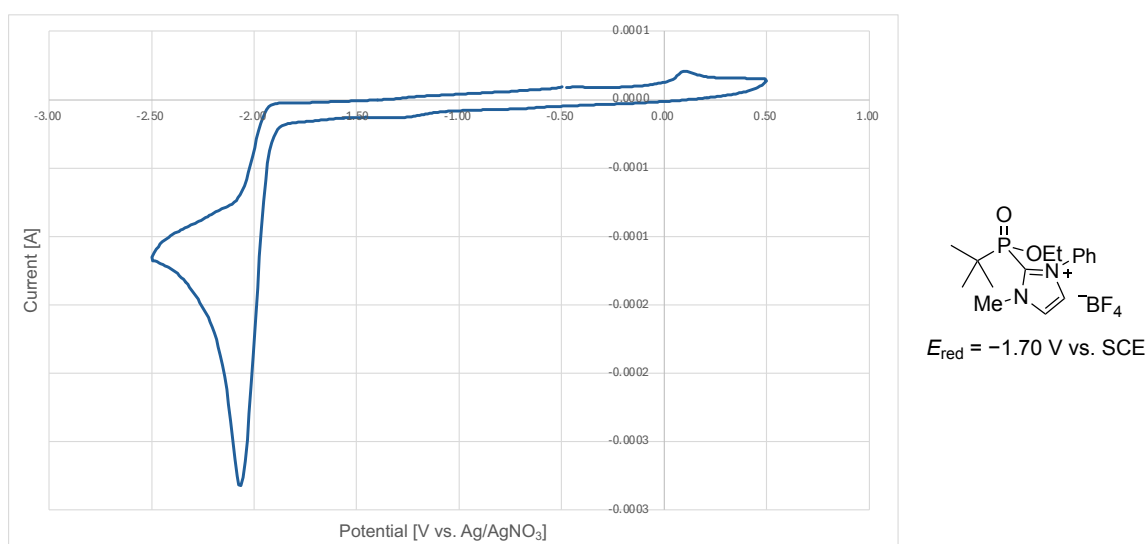


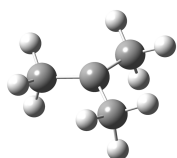
Figure S4-7. Cyclic voltammogram of **3aa**

13. DFT Calculation

All the restricted and unrestricted density functional theory (DFT) calculations were performed with the Gaussian 16 package.¹⁹ The method (U)wB97XD functional with the 6-31+G(d) basis set with SMD model (acetone) was used for the geometry optimization and normal vibrational mode analysis. The IRC calculations were performed for each transition state to confirm the transition state connecting the reaction pathway between the starting materials and the products.

(U)wB97XD/6-31+G(d)(SMD)					
	E (hartree)	G _{corr} (hartree)	Gibbs (hartree)	Gibbs (kcal/mol)	ΔG (kcal/mol)
<i>tert</i> -Butyl radical	-157.748690814	0.088370	-157.660321	-98616.56232	
P-1	-954.783497037	0.238852	-954.544645	-597067.8664	
P-1 + <i>tert</i> -Butyl radical				-695684.4287	0
TS-1	-1112.53776579	0.349918	-1112.187848	-695673.7214	10.70731242
Int-1	-1112.55566300	0.349634	-1112.206029	-695685.0936	0.664906713
P-2	-1299.81607856	0.250487	-1299.565591	-812878.5371	
P-2 + <i>tert</i> -Butyl radical				-911495.0994	0
TS-2	-1457.57268634	0.362999	-1457.209688	-911484.9513	10.14811524
Int-2	-1457.57580712	0.365406	-1457.210401	-911485.3973	9.702133602

tert-Butyl radical



Minimum frequencies (cm⁻¹) = 127.5694

133.0187

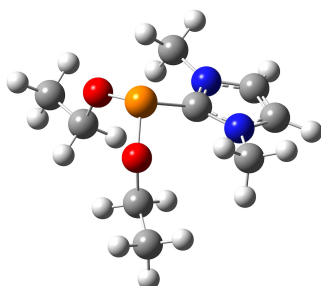
136.7448

Charge = 0 Multiplicity = 2

C	0.00015100	0.00008400	-0.17027500
C	-0.95056600	1.13906600	0.01714600
H	-1.12913400	1.34694800	1.08824900
H	-0.56491500	2.06760200	-0.42213900
H	-1.93087800	0.92841300	-0.42849900
C	1.46197900	0.25348800	0.01715800
H	2.07315000	-0.54230700	-0.42682300
H	1.76902400	1.21014000	-0.42379700
H	1.73225900	0.29849200	1.08828200
C	-0.51142200	-1.39257500	0.01711900
H	0.16384000	-2.13695200	-0.42312300
H	-0.60823600	-1.64867800	1.08830000

H	-1.50596700	-1.52404400	-0.42733500
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P-1



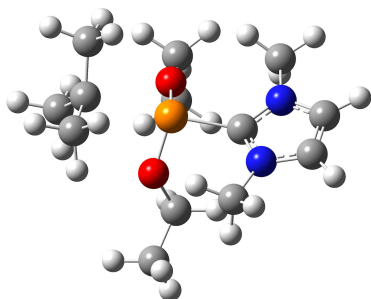
Minimum frequencies (cm ⁻¹) = -23.7499	79.9873	98.2695
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Charge = 1 Multiplicity = 1

P	0.21227100	0.60068600	1.28229600
O	-0.70624300	1.77106600	0.63748600
O	1.73632100	0.79053100	0.76283000
C	-0.35245400	-0.89599700	0.26126600
C	-0.44584100	-2.94467200	-0.60308600
C	-1.71396800	-2.47515400	-0.52039700
C	-0.92530900	2.10136300	-0.75407300
H	-0.04985200	2.63723900	-1.12654200
H	-1.04321100	1.18033900	-1.33574900
C	-2.15208400	2.98091500	-0.84128800
H	-2.33221400	3.24402700	-1.88880700
H	-3.03902500	2.47168100	-0.45350300
H	-2.00233000	3.90494600	-0.27441300
C	2.18820900	1.06043300	-0.58457000
H	1.94923100	2.09955000	-0.82272000
H	1.65707500	0.40803300	-1.28738300
C	3.68414900	0.84731200	-0.63635800
H	4.04324300	1.07007000	-1.64646500
H	4.18958800	1.51840500	0.06490000
H	3.95461800	-0.18377100	-0.39172400
H	-0.05546900	-3.88468400	-0.96030200
H	-2.65865000	-2.92078400	-0.79024100
N	0.38021100	-1.96752200	-0.10300100
N	-1.64138100	-1.21900900	0.02922800

C	-2.83407900	-0.41986300	0.30780500
H	-2.64487400	0.26869300	1.12834400
H	-3.12163900	0.13395100	-0.58753100
H	-3.63463800	-1.10349300	0.58912100
C	1.82707300	-2.15482900	0.00112700
H	2.30558500	-1.85029000	-0.93125900
H	2.21915700	-1.57428400	0.83261900
H	2.01272500	-3.21402600	0.17854300

TS-1



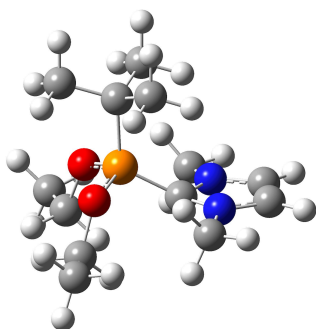
Minimum frequencies (cm^{-1}) = -163.6002 40.8612 50.6574

Charge = 1 Multiplicity = 2

P	0.38303400	-0.04058000	-0.43153700
O	0.65145300	-1.08631200	0.78388000
O	0.66843600	1.47776300	0.07859800
C	2.66971200	-0.32712200	-1.08004200
C	2.71635300	-1.78620400	-1.44954700
H	3.72382300	-2.04766800	-1.81031900
H	2.49539100	-2.42802900	-0.59044500
H	2.01046900	-2.02175100	-2.25476500
C	3.45857500	0.05173800	0.14572400
H	3.30034700	1.09924200	0.42324900
H	3.21132500	-0.58386000	1.00193000
H	4.53498700	-0.07294300	-0.05848500
C	2.78696500	0.63115000	-2.23571300
H	2.59331600	1.66363500	-1.92510200
H	3.80763200	0.59553400	-2.64813500
H	2.09581500	0.37416400	-3.04663900

C	-1.54366400	-0.02172500	-0.33651700
C	-3.66740000	0.52615300	-0.75289600
C	-3.58192300	-0.82498800	-0.78057700
C	0.00411800	-1.21817200	2.06235800
H	0.37589800	-0.43758800	2.73064800
H	-1.07746100	-1.08633200	1.94980400
C	0.34099100	-2.58681100	2.61144500
H	-0.13648800	-2.71484500	3.58845800
H	-0.01254400	-3.37880900	1.94416600
H	1.42292500	-2.69380000	2.73860600
C	0.58720400	1.93113800	1.44194200
H	1.35025800	1.40874200	2.02711000
H	-0.39962500	1.68668600	1.85348400
C	0.83990900	3.42142500	1.46063100
H	0.81387600	3.78071900	2.49451900
H	1.82475200	3.64830600	1.04016600
H	0.08078200	3.96122000	0.88663200
H	-4.50592000	1.18931300	-0.89735900
H	-4.32854200	-1.58395000	-0.95411800
N	-2.40384700	1.00754300	-0.49189800
N	-2.26726700	-1.14546600	-0.53779100
C	-1.77063800	-2.51782700	-0.51743300
H	-0.75938100	-2.55870800	-0.92287400
H	-1.77736900	-2.90425800	0.50305200
H	-2.42895500	-3.12316000	-1.14019300
C	-2.11564900	2.43732100	-0.40225100
H	-2.05498800	2.74247800	0.64373500
H	-1.18124700	2.66135500	-0.91218000
H	-2.93322200	2.97039900	-0.88664500

Int-1



Minimum frequencies (cm^{-1}) = 24.1792

51.1539

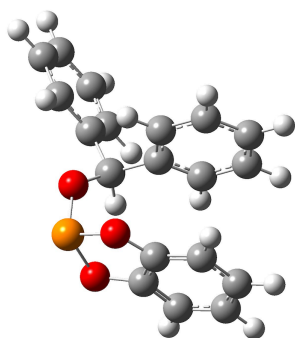
53.9791

Charge = 1 Multiplicity = 2

P	0.49872800	-0.01814500	-0.20068400
O	1.18979700	-1.36362600	0.28097000
O	1.28369200	1.27897300	0.27020300
C	0.78307600	-0.03318400	-2.01382600
C	0.07538700	-1.27423000	-2.58081200
H	0.18834300	-1.27190600	-3.67067400
H	0.51248700	-2.20162100	-2.19771600
H	-0.99735400	-1.27055800	-2.35615900
C	2.28606800	-0.07693600	-2.31998500
H	2.80478000	0.79994400	-1.92079700
H	2.75435700	-0.97801100	-1.91238500
H	2.42114200	-0.08600700	-3.40791900
C	0.14648700	1.24319000	-2.58694400
H	0.63599000	2.14636800	-2.20937400
H	0.25759900	1.22888800	-3.67687900
H	-0.92435600	1.30180700	-2.36058900
C	-1.13006200	0.04275400	0.47012100
C	-3.25418400	0.79773400	0.19092800
C	-3.30459100	-0.55266600	0.19056500
C	1.41738200	-1.75260200	1.66594300
H	2.30198100	-1.21534900	2.01550500
H	0.55520000	-1.45454800	2.26834300
C	1.64619600	-3.24428200	1.69755200
H	1.85899300	-3.54735900	2.72774800
H	0.76610800	-3.79185700	1.34903200

H	2.50312100	-3.51609300	1.07375800
C	1.56335900	1.64413000	1.65194100
H	2.42189400	1.05237800	1.97764900
H	0.69731700	1.39382000	2.27060900
C	1.88324400	3.11886300	1.68851700
H	2.14156800	3.39869300	2.71486300
H	2.73832800	3.34372500	1.04384100
H	1.02941400	3.72240500	1.36883700
H	-4.04756800	1.52504500	0.10821000
H	-4.15021300	-1.21843600	0.10817500
N	-1.94098500	1.18975500	0.33947700
N	-2.02393400	-1.04113500	0.33889500
C	-1.71166200	-2.43871600	0.54891700
H	-0.94953700	-2.78242300	-0.15533200
H	-1.36417100	-2.61152500	1.57280100
H	-2.62089200	-3.01800000	0.38283300
C	-1.52608600	2.55987900	0.55148000
H	-1.15323800	2.70075400	1.57144600
H	-0.74983900	2.85129600	-0.16094900
H	-2.39354200	3.20403400	0.40101100

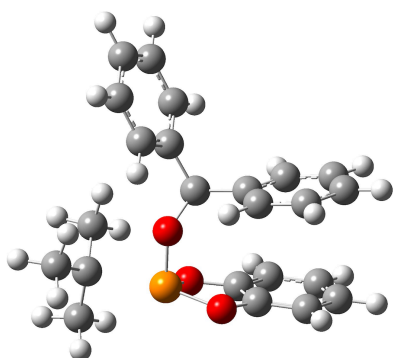
P-2



Minimum frequencies (cm^{-1}) = 23.1089		33.1471	52.2733
Charge = 0 Multiplicity = 1			
P	-0.64154800	-2.37617600	-0.87966600
O	-1.33244800	-2.30477700	0.65371200
O	0.72188500	-1.51374000	-0.68590200
C	0.98787400	-0.44572200	0.24540100

H	0.61218300	-0.74823000	1.22778600
O	-1.76281000	-1.29409900	-1.51279900
C	-2.22384200	-1.25888700	0.73274200
C	-2.82962900	-0.79172100	1.88237100
C	-2.46745700	-0.67935600	-0.50834200
C	-3.70493500	0.29246200	1.74804500
H	-2.62669000	-1.24805100	2.84543200
C	-3.33144200	0.38752200	-0.65411500
C	-3.95162100	0.87021500	0.50368600
H	-4.19612000	0.68758900	2.63178000
H	-3.50378300	0.83545300	-1.62667800
H	-4.63252600	1.71217500	0.42713500
C	2.49326700	-0.27584900	0.33020200
C	3.32219400	-0.54422400	-0.75960800
C	3.05207500	0.21710000	1.51064000
C	4.69437500	-0.32253700	-0.66689900
H	2.89663100	-0.93573300	-1.67812200
C	4.42283600	0.44250100	1.60132300
H	2.41034300	0.42630700	2.36322900
C	5.24844300	0.17283100	0.51151200
H	5.33182700	-0.53890900	-1.51956900
H	4.84631900	0.82388300	2.52608800
H	6.31865000	0.34493100	0.58162200
C	0.31237700	0.85261800	-0.15644100
C	-0.27409800	1.64872600	0.82674400
C	0.29817400	1.27883900	-1.48529700
C	-0.87648600	2.85779200	0.48735100
H	-0.27525600	1.31348400	1.86080300
C	-0.31454600	2.48015000	-1.82682400
H	0.75064200	0.66104200	-2.25570000
C	-0.90232100	3.27327700	-0.84131300
H	-1.33897000	3.46554900	1.25966700
H	-0.33261500	2.79971700	-2.86488700
H	-1.38187000	4.20995500	-1.11073600

TS-2



Minimum frequencies (cm^{-1}) = -183.2829

13.0211

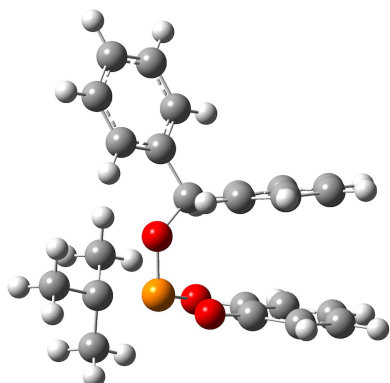
30.5931

Charge = 0 Multiplicity = 2

P	-0.06619600	-1.82999000	-0.91066400
O	-0.76969900	-1.98404400	0.61536500
O	0.79307400	-0.44199700	-0.80647300
C	1.78252300	-3.08224400	-0.01836500
C	1.16707300	-4.44744800	0.13538400
H	1.93357900	-5.16094300	0.47710400
H	0.36145000	-4.44991700	0.87693300
H	0.77116700	-4.82313600	-0.81507100
C	2.17541100	-2.40082800	1.26533700
H	2.51591700	-1.37412200	1.09526000
H	1.35869500	-2.39055700	1.99307800
H	3.01688000	-2.94911600	1.72024900
C	2.77662300	-2.94335900	-1.14002700
H	3.06734000	-1.89833600	-1.29174200
H	3.68929900	-3.50963700	-0.89653900
H	2.38465400	-3.34032000	-2.08322700
C	0.66506500	0.59020800	0.17947500
H	0.43316100	0.12969300	1.14525500
O	-1.56437000	-1.21974000	-1.54818800
C	-1.98223600	-1.34582700	0.69481400
C	-2.70573300	-1.13246800	1.85106300
C	-2.42942600	-0.90608300	-0.54922000
C	-3.92105900	-0.44727700	1.73040500
H	-2.33687900	-1.47925400	2.81081700
C	-3.63016200	-0.23030700	-0.67567300

C	-4.37290400	-0.00409600	0.48870600
H	-4.51398600	-0.25826700	2.61999500
H	-3.96815200	0.12042500	-1.64501800
H	-5.31579600	0.52986600	0.41906300
C	2.00772800	1.28878000	0.29253700
C	2.87167200	1.38698600	-0.79918400
C	2.36816200	1.87842600	1.50546500
C	4.08068000	2.06793400	-0.67674100
H	2.60214900	0.92236100	-1.74230400
C	3.57470100	2.56264500	1.62625700
H	1.70036900	1.79998300	2.36019600
C	4.43511800	2.65889400	0.53430600
H	4.74816100	2.13524100	-1.53127200
H	3.84538000	3.01458200	2.57629400
H	5.37890300	3.18831500	0.62810700
C	-0.44121300	1.57077300	-0.16930000
C	-1.25205900	2.08057200	0.84387900
C	-0.64525800	1.98541600	-1.48594300
C	-2.26389300	2.99038000	0.54653100
H	-1.10481600	1.74901900	1.86868600
C	-1.66085600	2.88803200	-1.78531200
H	-0.02216800	1.58372500	-2.27949000
C	-2.47292100	3.39313000	-0.76998600
H	-2.89749300	3.37151700	1.34226000
H	-1.82075800	3.19747300	-2.81437600
H	-3.26838300	4.09408100	-1.00636500

Int-2



Minimum frequencies (cm^{-1}) = 14.0270

26.8070

41.4252

Charge = 0 Multiplicity = 2

P	0.25589500	1.81546700	-0.70833700
O	1.08838200	1.73535500	0.73828700
O	-0.80904700	0.58420800	-0.72261100
C	-0.94758800	3.22596700	-0.05066400
C	-0.09325700	4.47747500	0.13836500
H	-0.73823600	5.32007300	0.41909200
H	0.65123800	4.34584500	0.93008400
H	0.42929300	4.75258000	-0.78589900
C	-1.61641300	2.79449200	1.25407200
H	-2.22306000	1.89275800	1.11825000
H	-0.88754000	2.61438000	2.04927700
H	-2.28887900	3.59681600	1.58872100
C	-1.98549300	3.43118500	-1.15260700
H	-2.58501600	2.52867700	-1.31320100
H	-2.66752300	4.24107800	-0.86370800
H	-1.51732300	3.71086000	-2.10373900
C	-0.86462900	-0.48285700	0.23582500
H	-0.58398100	-0.09333200	1.21995100
O	1.63219100	0.94753300	-1.51384100
C	2.21357000	0.95110100	0.69899200
C	2.98074800	0.61222600	1.79440500
C	2.51194900	0.51279400	-0.59100600
C	4.08950600	-0.21310100	1.57187000
H	2.72081900	0.96714500	2.78646400

C	3.61148400	-0.30277400	-0.81318800
C	4.39546400	-0.66230500	0.28832600
H	4.71288100	-0.50494000	2.41138000
H	3.83884400	-0.65788900	-1.81298600
H	5.25627900	-1.30676500	0.13600400
C	-2.30173600	-0.96738300	0.30345000
C	-3.20372800	-0.74154500	-0.73602700
C	-2.71704800	-1.68737900	1.42611200
C	-4.50603100	-1.23188000	-0.65255200
H	-2.89026000	-0.17607900	-1.60726900
C	-4.01642000	-2.17780300	1.50792100
H	-2.01791500	-1.86443900	2.24013300
C	-4.91597600	-1.95116800	0.46687300
H	-5.20151700	-1.04810900	-1.46666300
H	-4.32840500	-2.73312700	2.38787500
H	-5.93172000	-2.33063900	0.53093000
C	0.08947400	-1.60580500	-0.13142000
C	0.88196400	-2.19300100	0.85341700
C	0.17448800	-2.06617000	-1.44628000
C	1.75965200	-3.22601300	0.52976100
H	0.82787100	-1.82772100	1.87580100
C	1.05602300	-3.09109500	-1.77264200
H	-0.43683000	-1.60663000	-2.21762100
C	1.85120100	-3.67368500	-0.78511500
H	2.38082300	-3.66840400	1.30320600
H	1.12455600	-3.43693100	-2.80020000
H	2.54174400	-4.47163000	-1.04283100

第四章 实验项 参考文献

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総括

第一章 *N*-ヘテロ環カルベン (NHC) によるアルデヒド、アルケン、 α -ブロモカルボニルを用いた δ -ケトカルボニル合成法の開発に成功した。本反応では、NHCとアルデヒドから形成するエノラート型Breslow中間体から α -ブロモカルボニルへの一電子移動が起点となり、エノラート型Breslow中間体由来のケチルラジカルの高寿命性にに基づきアルケンのラジカルリレー型アルキルアシル化が進行する。本手法では、アルキル求電子剤として第三級 α -ブロモエステルや α -ブロモアミドを適用でき、有機分子触媒のみで第四級炭素を有する複雑な δ -ケトカルボニルを一挙に構築することが可能である。

第二章 有機光酸化還元触媒による脂肪族カルボン酸を用いた α -ケトカルボニルの脱炭酸型アルキル化反応の開発に成功した。 α -ケトカルボニルの一電子還元によって生じるケチルラジカルは、高いラジカル安定化エネルギーを有し、長寿命ラジカルとして機能する。そのため、本有機光酸化還元触媒系において長寿命ラジカル効果(PRE: persistent radical effect)が作動し、脂肪族カルボン酸由来の短寿命なアルキルラジカルと α -ケトカルボニル由来の長寿命なケチルラジカルの選択的なクロスカップリングが進行する。本手法では、第一級から第三級脂肪族カルボン酸や α -アミノ酸が許容され、多様なアルキル置換基を有する複雑な α -ヒドロキシカルボニルの合成が可能であった。

第三章 光駆動型ラジカル-極性交差機構 (RPC: radical-polar crossover) により発生したカルボカチオン等価体を活用することで、核酸リン原子の第三級アルキル化反応の開発に成功した。本RPC機構では、*N*-メチルベンゾ[*b*]フェノチアジン (PTH) 由来のPTHラジカルカチオンの長寿命性が鍵となる。すなわち、可視光照射下、PTHから第三級脂肪族カルボン酸誘導体への一電子移動により、脱炭酸を経て短寿命なアルキルラジカルと長寿命なPTHラジカルカチオンが発生する。これら二種のラジカルがPREに基づき選択的にクロスカップリングすることで、カルボカチオン等価体であるアルキルスルホニウムを形成する。発生したカルボカチオン等価体と二つのデオキシヌクレオシド構造および脱離基の置換した亜リン酸エステルの反応により、Michaelis-Arbuzov型アルキル化反応が進行し、第三級アルキルホスホン酸ジエステル体が生成する。また、自動固相合成法を用いることで、本化学構造を導入したオリゴヌクレオチドの合成にも成功した。この堅牢な第三級アルキルホスホン酸ジエステル修飾核酸が生物学的利用能の向上に寄与し、新たな核酸医薬品の創出に繋がることが期待される。

第四章 二官能性リン(III)試薬であるイミダゾリウムホスホナイトを活用することで、多様な置換様式を有するアルキルリン(V)化合物の合成法の開発に成功した。本手法では、1) 有機光酸化還元触媒と脂肪族カルボン酸誘導体を用いたイミダゾリウムホスホナイトの脱炭酸型アルキル化反応によるC(sp³)-P結合形成、2) S_NP(V)反応によるリン(V)-ヘテロ原子結合形成、という二段階の過程を経る。C(sp³)-P結合形

成段階において、ホスホナイト試薬へのアルキルラジカルが付加によって生じるホスホラニルラジカル中間体がイミダゾリウム置換基による安定化を受ける。この安定化効果により、効率的なアルキルラジカルの捕捉が可能となる。本手法により、リン中心に第一級から第三級のアルキル基と様々なヘテロ原子置換基を一挙に導入でき、従来法では達成困難な非対称アルキルリン(V)化合物の構築が可能となった。

以上、著者は有機分子触媒や有機光酸化還元触媒によるラジカルの安定化効果を活用した四つの新規分子変換反応の開発に成功した。これらの手法により、遷移金属を用いずにラジカル反応を精密に制御し、従来の極性反応では達成困難な複雑かつ嵩高い分子骨格を構築できる。本論文によって開拓された Fsp^3 の高い新たなケミカルスペースが、革新的な新薬の創出に繋がることを期待する。

論文目録

第一章

“N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Synthesis of δ -Ketocarboxyls”

Kenji Ota, Kazunori Nagao, Hirohisa Ohmiya

Org. Lett. **2020**, *22*, 3922–3925.

第二章

“Synthesis of Sterically Hindered α -Hydroxycarbonyls through Radical–Radical Coupling”

Kenji Ota, Kazunori Nagao, Hirohisa Ohmiya

Org. Lett. **2021**, *23*, 4420–4425.

第三章

“Synthesis of tertiary alkylphosphonate oligonucleotides through light-driven radical-polar crossover reactions”

Kenji Ota, Kazunori Nagao, Dai Hata, Haruki Sugiyama, Yasutomo Segawa, Ryosuke Tokunoh, Tomohiro Seki, Naoya Miyamoto, Yusuke Sasaki, Hirohisa Ohmiya

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第四章

“Synthesis of alkylphosphor(V) compounds using imidazolium phosphonites”

Kenji Ota, Kazunori Nagao, Hirohisa Ohmiya

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