

博士論文

化学選択性の発現を目指した脱炭酸型縮合反応の開発  
及び基質認識型有機光触媒の創製

2022 年度

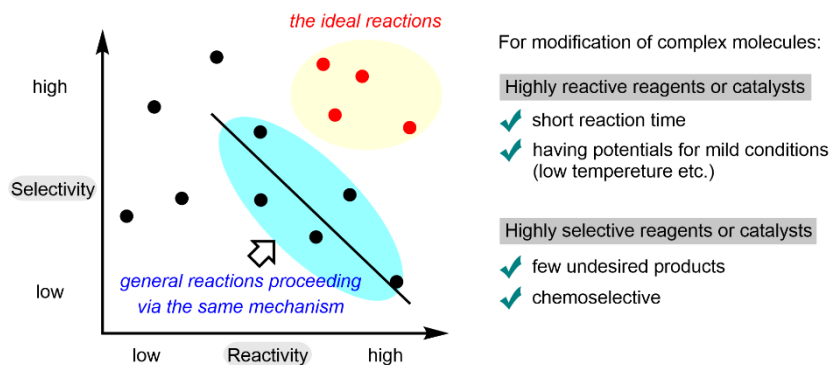
加藤 夏己

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




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## 第一章 総論

医薬品や機能性材料など我々の生活を支える有用物質の多くは有機化合物であり、その供給法を実現しものづくりの根幹を支える有機合成化学は重要な学問領域である。その発展に伴いこれまでに多様な分子変換反応や試薬、触媒が開発され、現在小さく単純な分子の変換反応は低反応性の官能基を含め容易に実現可能となりつつある。一方で、医薬品や生物活性物質のような複数の官能基を有している複雑で高付加価値な分子の精密な化学変換は、現代有機化学の技術を持ってしても未だ容易ではない。特に構造活性相関研究に向けた多様な誘導体の供給には類似する反応性を示す官能基を含む複数の反応点の中でも所望の部位を選択的に変換することが求められる。そのような方法論の実現には高い反応性と選択性を両立した反応剤や触媒の開発が必要であるが、一般に同一反応機構で進行する場合においては、反応性・選択性の原理の観点から反応性を向上させると選択性が低下するためにその実現は困難である (Figure 1)。そのような具体例の一つとして、例えばヒドリド還元剤を用いたカルボニル基の還元反応が挙げられる。低反応性試薬である  $\text{NaBH}_4$  を用いた場合にはカルボニル基の求電子性が低いアミドは還元されず、高反応性試薬である  $\text{LiAlH}_4$  を用いた際にはアミドは還元可能である反面、カルボン酸誘導体を非選択的に還元する。そのため、求電子性の高いカルボニル基を持つケトンやアルデヒド存在下においては保護基を必要とするが、環境調和の観点から廃棄物が少なく効率的な手法の開発が望まれる。加えて、選択性の向上のために反応性を低下させることは、その実現には反応性と選択性を兼ね備えることが必要であり、いかにして所望の反応を短時間かつ温和な条件下において選択的に促進可能な優れた試薬や触媒を開発するかが鍵となる。



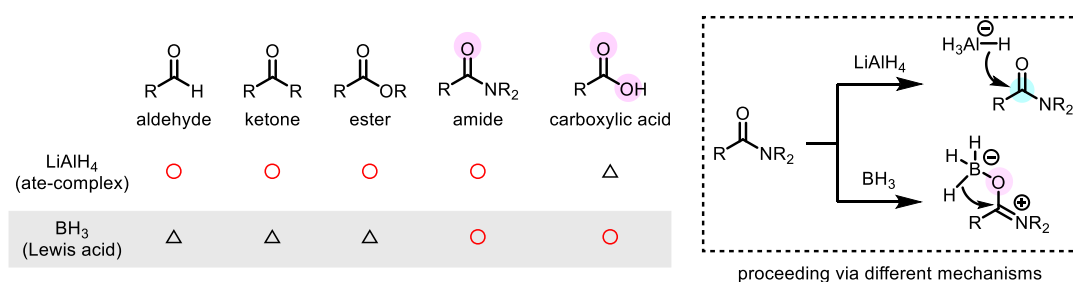
#### Reduction of Carbonyl Group by Hydridic Reductant

					
	aldehyde	ketone	ester	amide	carboxylic acid
NaBH <sub>4</sub>	○	○	△	×	×
LiBH <sub>4</sub>	○	○	○	×	×
LiAlH <sub>4</sub>	○	○	○	○	△

High ————— Electrophilicity ————— Low

**Figure 1. Relationship of Reactivity and Selectivity**

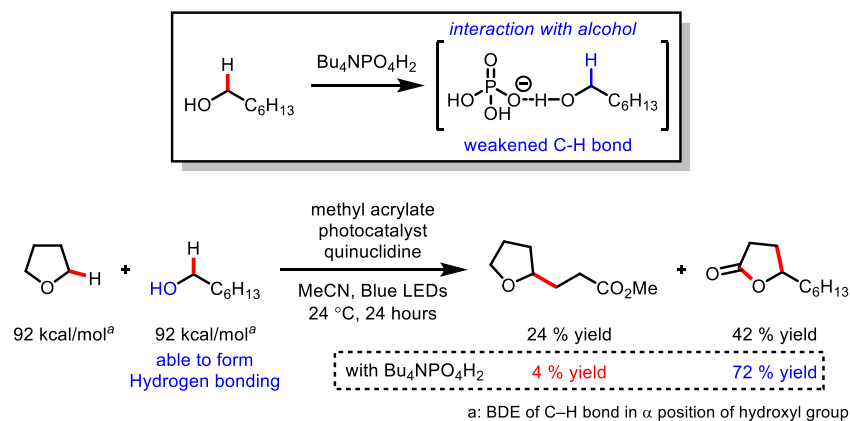
その実現方法の一つとして、反応性を決定づけている要因を従来反応から変更することが挙げられる (Figure 2)。上述のカルボニル還元の場合では、アト錯体型還元剤の代わりにルイス酸部位を有する還元剤であるボランを用いた場合には、アミドを選択的に還元することが可能である。この選択性の違いは、カルボニル基の求電子性の高さではなく、ルイス塩基性の高さで反応性が決定することで発現しており、反応進行を支配する要因が異なる試薬を用いれば、既存の選択性とは違ったユニークな選択性が見られる可能性があることを示している。



**Figure 2. Reduction of Carbonyl Group via Different Mechanisms**

また異なるアプローチとして、分子認識による反応性や選択性を制御することも可能である (Scheme 1)。例えば、水素原子移動型反応 (Hydrogen-Atom-Transfer reaction: HAT) に対し低反応性を示すアルコール  $\alpha$  位の C-H 結合は、アルコールが水素結合することで HAT 反応への反応性が向上することが知られている<sup>1</sup>。本相互作用を利用し、MacMillan らはアルコール  $\alpha$  位の

C-H 結合と同等の反応性の C-H 結合を有する基質との競合実験において、リン酸塩を添加することにより選択性を向上させることに成功している<sup>2</sup>。このように、相互作用による分子認識を利用することで、特定の低反応基質に対してのみ高い反応性を発現させる反応剤の設計が可能である。



**Scheme 1. Control of Reactivity and Selectivity by Substrate Recognition**

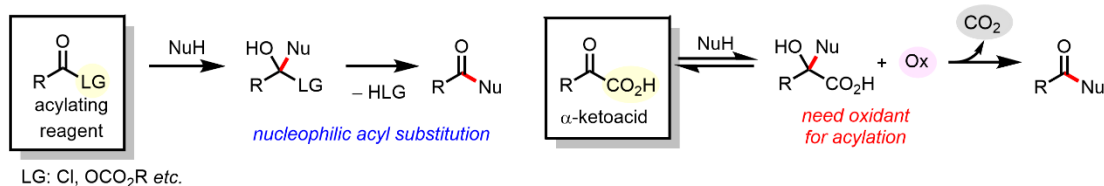
以上を踏まえ、筆者は高い反応性と選択性を兼ね備えた方法論の開発を目指し、アシル化反応と可視光レドックス触媒反応を題材とした研究に取り組むこととした (Figure 3)。

カルボン酸誘導体合成に用いられるアシル化剤は、脱離基を有しており求核アシル置換反応によって目的物を与える。一方で脱離基の代わりにカルボン酸がアシル基に隣接している  $\alpha$ -ケト酸は、求核付加段階に加え二酸化炭素の放出を伴う酸化過程を経ることで縮合反応が進行する<sup>3</sup>。筆者は、従来の試薬と異なる機構でのアシル化反応では既存の手法とは異なる反応性・選択性を発現できるのではないかと期待し、 $\alpha$ -ケト酸を用いた新規縮合反応の開発を目指すこととした。

また、可視光レドックス触媒を用いた反応は酸化還元電位によって反応性が議論されるため、その絶対値が大きい値を示す触媒は高い反応性を有する<sup>4</sup>。しかし、酸化還元電位の絶対値が大きい触媒の開発は、選択性の低下が予想されるだけでなく、低エネルギーである可視光を用いる故にその実現はそもそも困難だと考えられる。筆者は、光触媒に対して相互作用部位を導入することで一電子移動を高効率的に促進する触媒開発が可能と考えた。

上記の着想に基づき検討を重ねた結果 以下に示す反応の開発に成功した。その内容について次章以降でその詳細を述べる。

### ① Development of a New Acylating Reagent



### ② Introduction of Substrate Recognition Site to Photoredox Catalyst

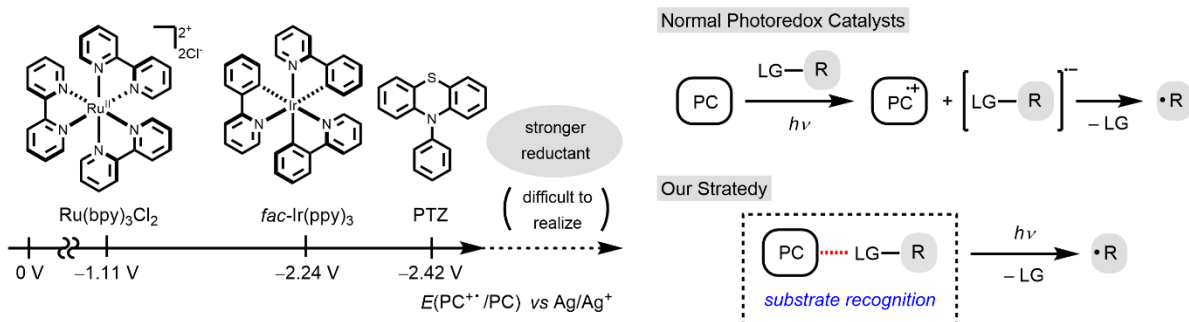
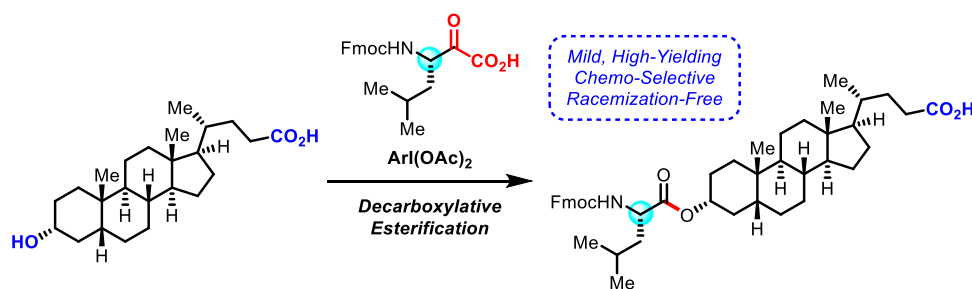


Figure 3. Our Strategy

## (1) 超原子価ヨウ素による脱炭酸型エステル化反応の開発 (第二章 第二節)

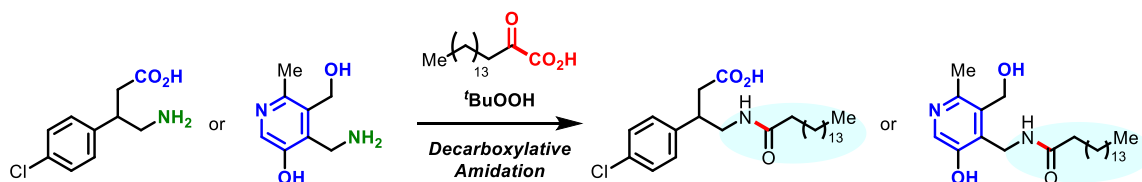
アルコールを求核剤として用い、酸化剤として超原子価ヨウ素を  $\alpha$ -ケト酸に作用させることで対応するエステルを高収率で得ることに成功した (Scheme 2)。本合成法は、無保護のカルボン酸を有する基質に対して  $\alpha$ -ケト酸選択的にアシル化が可能であり、アミノ酸由来のケト酸を用いた際には光学純度を損なわないといった特徴を有する。



Scheme 2. Decarboxylative Esterification Mediated by Hypervalent Iodine

## (2) ヒドロペルオキシドによるアミンの化学選択的アシル化法の開発 (第二章 第三節)

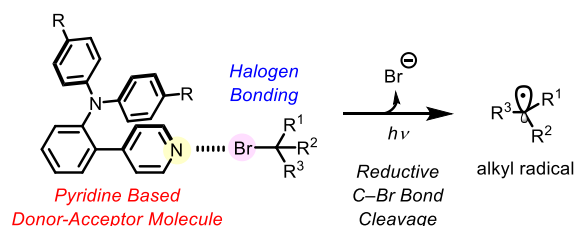
$\alpha$ -ケト酸とアミン存在下、外部酸化剤としてヒドロペルオキシドを用いることで官能基共存性の高い脱炭酸型アミド化法を開発した (Scheme 3)。本反応は幅広いアミンとの縮合が可能であり、無保護カルボン酸や求核部位を有する種々の医薬品の選択的アシル化が可能であった他、種々のペプチド合成にも応用可能であった。



Scheme 3. Chemoselective Acylation of Amines Mediated by Hydroperoxide

(3) 新規ピリジン含有 D-A 型分子の開発とハロゲン結合を介した還元的 C–Br 結合切断によるアルキルラジカル発生への応用 (第三章 第二節)

筆者は、基質認識と電子の授受を同時に行えるピリジンを触媒構造に組み込んだドナー・アクセプター型分子が、不活性臭化アルキルも含めた幅広い臭化アルキルから円滑にアルキルラジカルを発生可能であることを見出した (Scheme 4)。また、不活性臭化アルキルと活性塩化アルキルとの競合実験では、基質の基底状態での酸化還元電位に依らず臭化アルキルと選択的に反応しており、他の光触媒とは異なる化学選択性が見られた。本結果は、基質認識部位を導入することで既存の光触媒には見られない高い反応性と選択性を付与できることを示す重要な知見である。



Scheme 4. Reductive C–Br Bond Cleavage by Pyridine-based Donor-Acceptor Molecules

## 第二章 $\alpha$ -ケト酸を用いた脱炭酸型縮合反応の開発

### 第一節 序論

エステルやアミドといったカルボン酸誘導体は有機合成化学において最も基本的な化合物群であり、農薬や食品、医薬品、有機材料など幅広い分野において重要なためその効率的な合成法の開発は古くから活発に研究されてきた。これまでに酸ハロゲン化物や酸無水物といった古典的なアシル化剤以外にもアルデヒドや、チオエステル等様々なアシル等価体を利用する方法<sup>5</sup>、HATU や COMU など縮合剤を用いる方法<sup>6</sup>などが開発されている (Figure 5)。また、環境調和の観点から最近では触媒的アミド化反応の開発も精力的に行われており、本研究領域は益々の発展を見せている<sup>7-9</sup>。一方、構造活性相関研究を加速しうることから、近年では医薬品など多数の求核部位を有する分子のアシル化が可能な分子変換技術の開発が期待されており、その観点から高い反応性と選択性を兼ね備えた新たな縮合反応の開発は依然として重要な研究課題である。そのような背景のもと、筆者は高反応性と選択性を発現し得る新規アシル化剤の探索を目指し研究に着手したが、その過程で興味深い反応性を示す  $\alpha$ -ケト酸という部分構造に着目した。

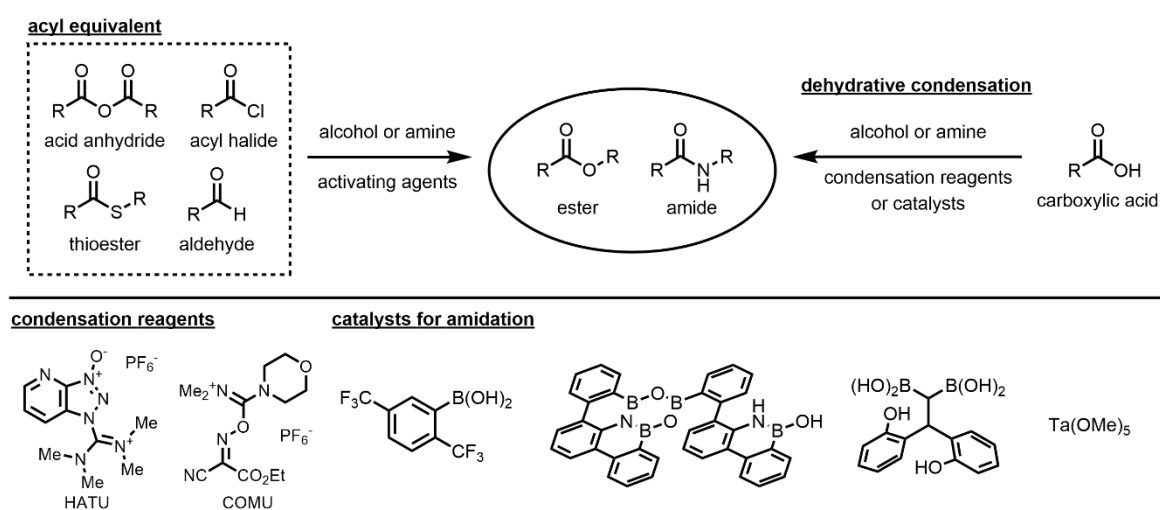
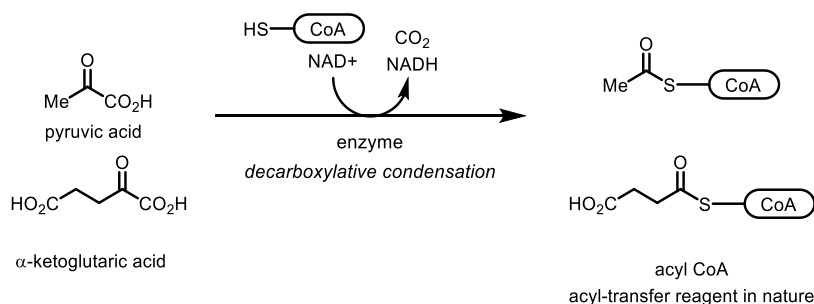


Figure 4. Condensation Reaction

### $\alpha$ -ケト酸

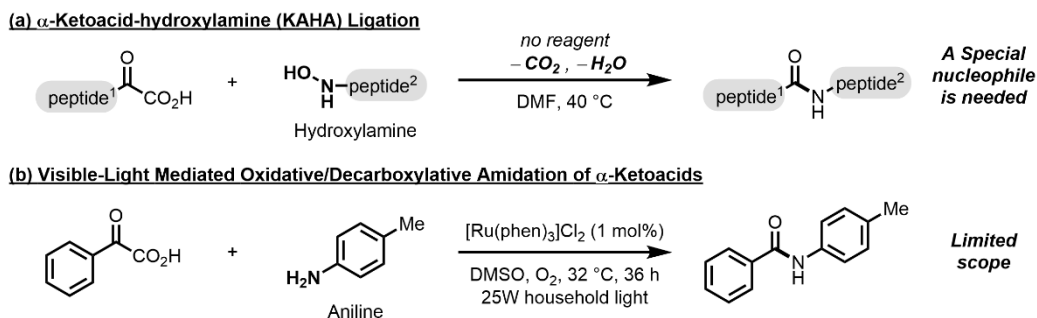
$\alpha$ -ケト酸は、ピルビン酸や  $\alpha$ -ケトグルタル酸などの生合成中間体に見られる重要な部分構造であり、アルデヒドと同じ酸化度を有する有機合成化学上興味深い出発原料である (Figure 6)<sup>10</sup>。実際、生体反応としては酵素反応による  $\text{NAD}^+$  の還元反応を伴った  $\alpha$ -ケト酸の酸化的脱炭酸反応によるアシル CoA の合成が知られており、生体内の活性なアシル化剤として重要な役割を果たしている。





**Figure 5. Biochemical Reaction of  $\alpha$ -Ketoacid in Nature**

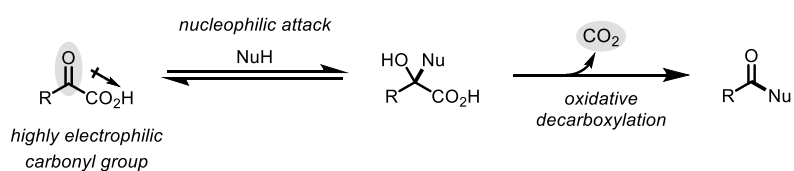
上記のような生体反応だけでなく、近年  $\alpha$ -ケト酸の脱炭酸型縮合反応がいくつか報告されており<sup>11, 12</sup>、代表的なものとして Bode らによって報告された KAHA ligation が挙げられる (Scheme 5a)<sup>11</sup>。本法は基質を加温攪拌するのみで高化学選択的にアミドを与え、廃棄物が二酸化炭素と水のみでの画期的な手法であり、近年ではペプチドの化学ライゲーシオンにも応用されている。また、光照射下で酸素を酸化剤として用いた縮合剤を必要としないアミド化法も報告されており (Scheme 5b)<sup>12</sup>、 $\alpha$ -ケト酸が合成化学上有用なアシル化剤として機能し得ることを示している。一方で、KAHA ligation は生体直交型反応への応用が可能な特異性を持つ優れた方法論である反面、使用できる求核剤が特定のものに限定されるという課題を有している。実際、KAHA ligation の求核剤としてヒドロキシルアミンの調製が必要であり、 $\alpha$ -ケト酸を複雑分子のアシル化等にも利用できる一般性の高いアシル化剤として展開する際には、脂肪族アミンやアルコールといったより単純な求核剤を使用可能な手法の開発が望まれる。なお、Lei らによって報告された酸素存在下での脱炭酸型アミド化反応ではより単純な求核剤としてアニリン誘導体を用いていたが、脂肪族アミンへ適用する際には大過剰量のアミンが必要であるといった制限があった。また、その実用的な応用例は現状アミド化に留まっており、エステルやチオエステルといったその他のカルボン酸誘導体合成へと展開している例は報告されていなかった。このように、 $\alpha$ -ケト酸は魅力的なアシル化剤としての可能性を秘めているのにも関わらず、その特徴は最大限活かされていないと考えられる。



**Scheme 5. Oxidative Amidation of  $\alpha$ -Ketoacids**

筆者は、以下に示す  $\alpha$ -ケト酸の反応性に関する考察に基づき、より単純な求核剤を用いた際にも高い反応性と化学選択性を併せ持つ新規アシル化法の実現が可能であると考えた。 $\alpha$ -ケト酸を用いた脱炭酸型縮合反応は、① カルボン酸  $\alpha$  位に位置するカルボニル基への求核剤の付加、② 脱炭酸を伴った酸化、の二つの過程によって構成されている (Scheme 6)。ピルビン酸は室温条件下においても容易にアセタールを形成することから<sup>13</sup>、隣接するカルボキシ基によりケトン基は高い求電子性を有すると予想され、幅広い求核剤に適用可能な高活性アシル化剤として働き得る。更に、脱炭酸を駆動力として利用すれば、 $\alpha$ -ケト酸は高反応性と選択性を兼ね備えた魅力的なアシル化剤としての利用が期待できる。

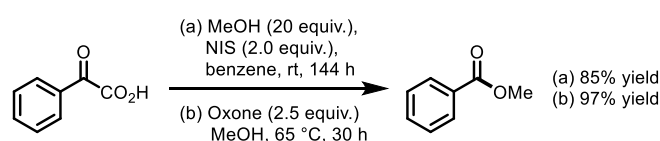
以上を踏まえ後述の戦略のもと、 $\alpha$ -ケト酸の酸化的脱炭酸過程を効果的に促進し得る種々の酸化剤を検討し単純な求核剤のアシル化反応を開発することを目指し研究に取り組んだ。



**Scheme 6. Overview of Decarboxylative Condensation of  $\alpha$ -Ketoacids with Nucleophiles**

## 第二節 $\alpha$ -ケト酸を用いた脱炭酸型エステル化反応の開発

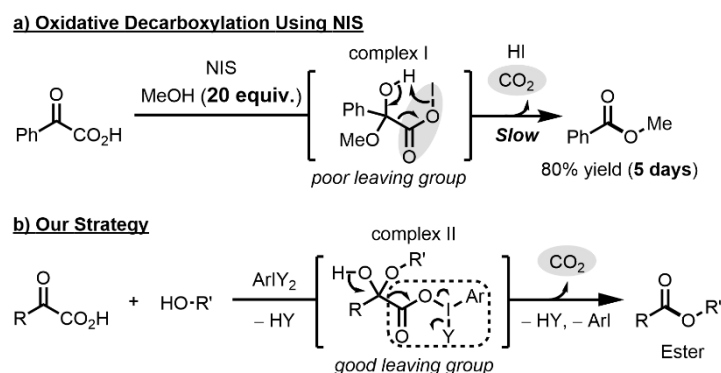
まず始めに  $\alpha$ -ケト酸を用いた新規エステル化法の開発を目指し研究を開始した。前節で述べたように  $\alpha$ -ケト酸とアルコールは速やかに反応しアセタールを形成し得るにも関わらず、筆者が研究を開始した時点では脱炭酸型エステル化反応は既に 2 例報告されていたものの種々のアルコールにも適用可能なアシル化剤としての応用可能性が十分に検討されているとは言い難かった<sup>14</sup>。Beeb らや Ahmed らはそれぞれ *N*-iodosuccinimide (NIS) や Oxone<sup>®</sup> を酸化剤として用いたエステル化反応を報告していたが、これらの反応は基質適用範囲が狭いばかりでなく、溶媒量あるいは大過剰量のアルコールや長い反応時間を必要としていた (Scheme 7)。



Scheme 7. Previous Reports on Decarboxylative Esterification

### 戦略

筆者は上述の NIS を用いた既知例では活性な中間体 I の生成が遅いこと、または NIS によりヨウ素化されたカルボキシ基は脱離能が低く酸化的脱炭酸過程の効率が低い可能性があることが低反応性の原因と予想した (Scheme 8a)<sup>14a</sup>。筆者はより円滑に脱炭酸過程が進行する酸化剤を探索することとし、カルボキシ基に配位可能な三価の超原子価ヨウ素化合物に着目した<sup>15</sup>。すなわち、超原子価ヨウ素試薬を  $\alpha$ -ケト酸に作用させることで、リガンド交換により活性な複合体 II を速やかに形成することを期待した。また、中間体 I に比べ中間体 II ではヨウ素がより電子不足であるためカルボキシル基がより効果的な脱離基として振る舞うことでアルコールとの酸化的脱炭酸が円滑に進行すると考えた (Scheme 8b)。本戦略に基づき種々検討した結果、超原子価ヨウ素を用いたエステル化反応を新たに開発したので以下その詳細について報告する。



Scheme 8. Our Strategy for Decarboxylative Esterification

## 条件検討

フェネチルアルコール (**1**)と  $\alpha$ -ケト酸 **2** をヨードソベンゼン (**4**)存在下、ジクロロメタン中室温、遮光条件下にて攪拌したところ対応するエステル **3** を 28%と低収率ながらも得ることに成功した (Table 1, entry 1)。そこで、収率の改善を目指し、種々の超原子価ヨウ素試薬 **5–8** を試した。Koser 試薬 (**5**)や PIFA (**6**)でも反応は進行したが、反応の進行に伴って生じる酸のためか、副生成物が見られ収率の大幅な改善には至らなかった (entries 2, 3)。そこでより酸性度の低い酸を配位子に持つジアセトキシヨードベンゼン(**7**)を用いることで 61%まで目的物の収率が向上した (entry 4)。環状の超原子価ヨウ素試薬である ABBX (**8**)は目的物を全く与えなかった (entry 5)。なお、Beebsらによって報告されている NIS (**9**)を酸化剤として検討したが、低収率に留まった (entry 6)。一方で、いずれの超原子価ヨウ素を使用しても、依然として原料のアルコールが回収されたため、より高い酸化力を有することが期待できる超原子価ヨウ素試薬 **10** に変更したところ目的物の収率が 70%まで向上した。また、超原子価ヨウ素試薬と  $\alpha$ -ケト酸を 1.5 等量に増やすことで 97%の収率と高収率でエステルを得ることに成功した。なお、本反応はグラムスケールでの合成にも容易に適用可能であり、市販のジアセトキシヨードベンゼンを用いても反応時間を延長することで 95%の収率で対応するエステル化体 **3** を与えた。

Table 1. Optimization of Hypervalent-Iodine

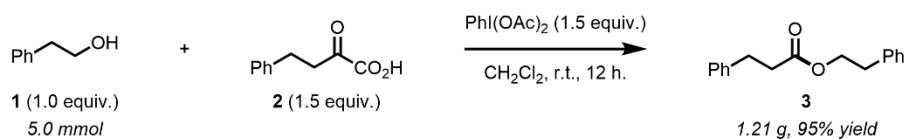
entry	hypervalent iodine (III)	yield (%) <sup>a</sup>	
		<b>3</b>	<b>1</b>
1	PhIO ( <b>4</b> )	26	73
2	PhI(OH)OTs ( <b>5</b> )	47	34
3	PhI(OCOCF <sub>3</sub> ) <sub>2</sub> ( <b>6</b> )	30	44
4	PhI(OAc) <sub>2</sub> ( <b>7</b> )	61	35
5	ABBX ( <b>8</b> )	0	100
6	NIS ( <b>9</b> )	12	56
7	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> I(OAc) <sub>2</sub> ( <b>10</b> )	70	30
8 <sup>b</sup>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> I(OAc) <sub>2</sub>	92 (97)	6 (-)

ABBX (**8**)

3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I(OAc)<sub>2</sub> (**10**)

a: Determined by <sup>1</sup>H NMR spectra using dimethylterephthalate as an internal standard. Isolated yield in parentheses. b: 1.5 equiv. of **2** and 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I(OAc)<sub>2</sub> were used.

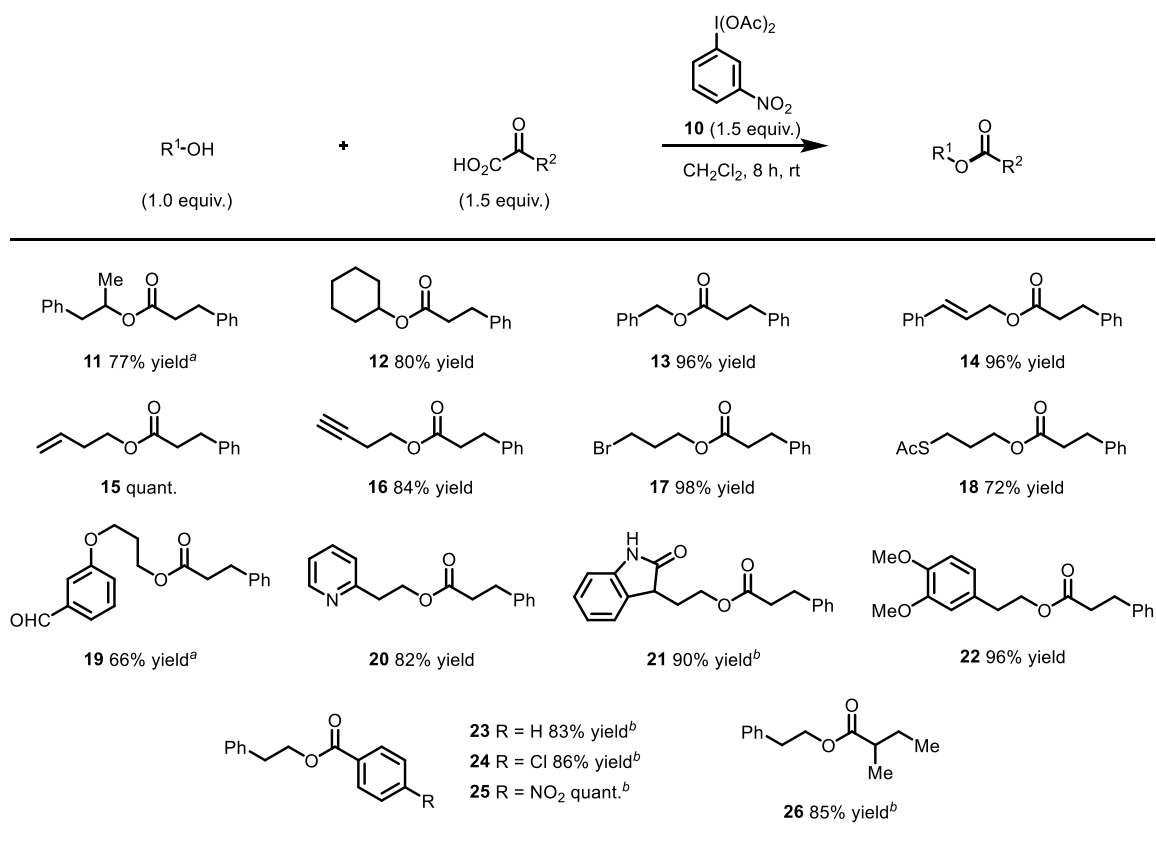
### Gram Scale Synthesis



## 基質適用範囲の検討

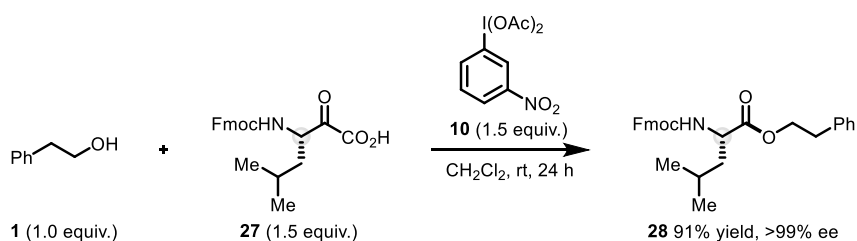
見出した最適条件を用いて、様々な基質に対し本エステル化反応を検討した (Table 2)。始めに、アルコールの基質適用範囲を検討したところ、第二級アルコールにおいても、反応時間の延長は見られるが鎖状・環状を問わずいずれも良好な収率で目的物を与えた (11, 12)。また、ベンジル位やアリル位に水酸基を有するアルコールのエステル化においても、対応するアルデヒドを与えることなく高収率でエステル化反応が進行した (13, 14)。さらに末端アルケンや末端アルキンといった官能基も共存可能であった (15, 16)。臭化アルキルやチオエステル、アルデヒドなどといった求電子部位を分子内に有する基質でも求核剤が  $\alpha$ -カルボニル基以外に反応することなく目的物を与えた (17–19)。超原子価ヨウ素は種々の電子豊富な芳香環を酸化することが知られているが<sup>15</sup>、ピリジンエタノールやオキシインドール、3,5-ジメチルカテコール部位を有するいずれの基質に対しても、本反応はそれぞれ対応するエステル化体を高収率で与えた (20–22)。次に、 $\alpha$ -ケト酸の基質適用範囲について検討した。芳香族ケト酸を用いることで、対応する安息香酸エステルを良好な収率で得ることに成功した (23–25)。また、カルボニル  $\alpha$  位で分岐した基質に関しても、反応時間に延長は見られるものの高収率で目的物 26 を与えた。

Table 2. Substrate Scope of Decarboxylative Esterification



Isolated yields. a: The reaction was performed for 24 hours. b: The reaction was performed for 48 hours.

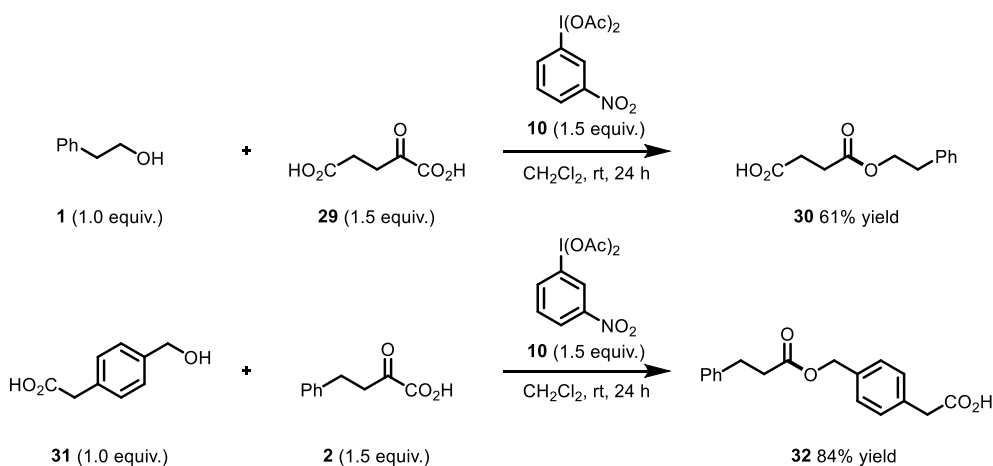
次に、本脱炭酸型エステル化をアミノ酸エステルの合成に適用した (Scheme 9)。アミノ酸を用いた縮合反応においては  $\alpha$  位のエピメリ化が常に懸念されるが、Bode らの報告例に従って Fmoc アミノ酸から 2 工程で合成した光学純品のアミノケト酸 **27** を用いることで光学純度を損なうことなく対応するエステル化体 **28** を 91% と高収率で得ることに成功した<sup>12c, 16</sup>。



Scheme 9. Esterification of Chiral  $\beta$ -Amino- $\alpha$ -ketoacid

### 化学選択的なアシル化反応の検討

本エステル化反応では従来の脱水縮合とは異なる機構で目的物を与えるため、カルボン酸の脱水縮合は競合しないと予想した。そこで、無保護のカルボキシ基存在下での検討を行ったところ、 $\alpha$ -ケトグルタル酸 **29** やヒドロキシ酸 **31** を用いても  $\alpha$ -ケト酸特異的に反応が進行し目的のエステル化体のみを良好な収率で与えた (**30, 32**) (Scheme 10)。

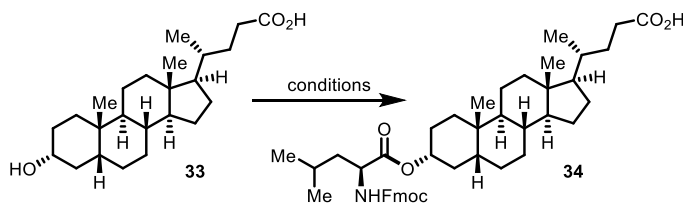


Scheme 10. Chemoselective Esterification of  $\alpha$ -Ketoacids

上記の知見を活かし、本反応の応用例としてステロールの選択的エステル化を検討した (Table 3)。すなわちステロイド D 環側鎖にカルボキシ基を有するリトコール酸 (**33**) に対して、先ほどのアミノケト酸 **27** を作用させたところ対応するアミノ酸エステルを 78% の収率で光学純度を損なうことなく得ることに成功した (entry 1)。このような分子変換は通常縮合剤と Fmoc-Leu-OH (**35**) を用いた脱水縮合条件下では困難であり、今回見出した脱炭酸型縮合の優位点であると考え

ている (entries 2–4)。

**Table 3.  $\alpha$ -Ketoacid-Specific Esterification and Comparison with Dehydrative Condensations**



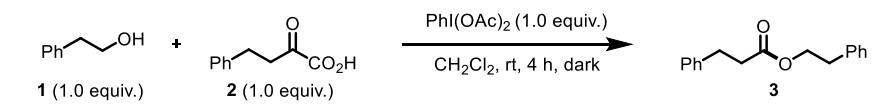
entry	conditions <sup>a</sup>	yield (%)
1	Fmoc-Leu-CO <sub>2</sub> H (27), 10	78
2	Fmoc-Leu-OH (35), HATU, DIPEA	<5
3	Fmoc-Leu-OH (35), COMU, DIPEA	<5
4	Fmoc-Leu-OH (35), PyBOP, DIPEA	<5

a: The reactions proceeded in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 12 h.

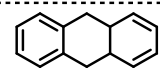
### 推定反応機構

最後に、見出した脱炭酸型エステル化の反応機構に関していくつかの対照実験を行った (Table 4)。超原子価ヨウ素化合物は光照射下ラジカル種を生成することが報告されているため、本反応においてもラジカル機構が関与していることが考えられたが、これまでの検討は全て遮光条件下行っていること、及び室内光の照射のみでは収率が変化しなかったことからその可能性は低い (entries 1, 2)<sup>17</sup>。更に、キセノンランプを用いた光照射下での反応では収率が大きく低下し、ラジカルスカベンジャーであるジヒドロアントラセン **36** を添加しても収率の低下は 10%程度に留まったことから、本エステル化はラジカル経由の反応では無いと考えられる (entries 3, 4)。

**Table 4. Mechanistic Studies**



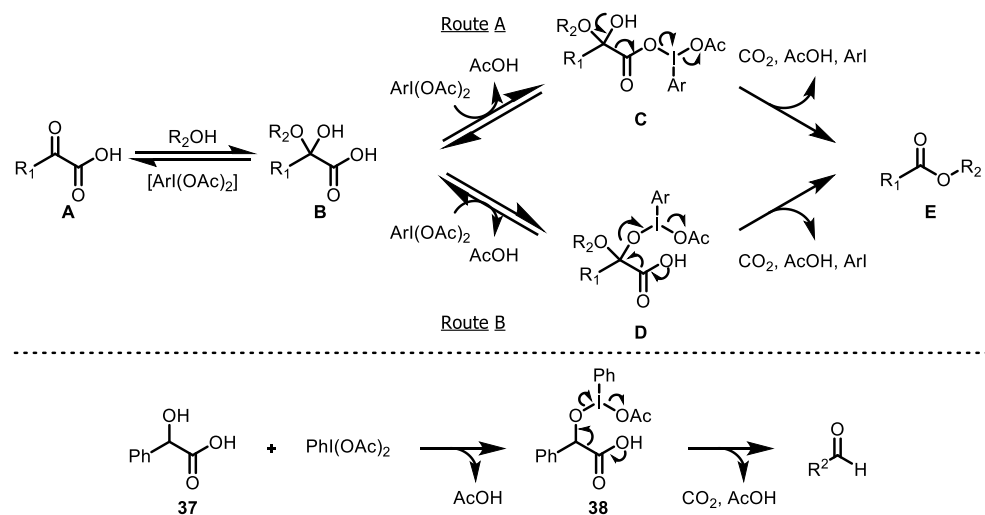
entry	deviation from standard conditions	yield (%) <sup>a</sup>
1	none	65
2	no shield from room light	65
3	light irradiation with xenon light	28
4	addition of 9,10-dihydroanthracene	54



9,10-dihydroanthracene (**36**)

a: Determined by <sup>1</sup>H NMR spectra using dimethylterephthalate as an internal standard.

本反応の推定される反応機構を以下に示す (Scheme 11)。 $\alpha$ -ケト酸 **A** のカルボニル基がアルコールの求核攻撃を受け、四面体中間体 **B** を形成し酸化的脱炭酸を経てエステル化体 **E** を得る。その際に、カルボン酸が超原子価ヨウ素と結合した遷移状態 **C** を経て進行する Route A と、ヘミアセタールの酸素原子に結合する遷移状態 **D** を経て進行する Route B の二つの経路が考えられる。なお、以前に超原子価ヨウ素によるマンデル酸(**37**)の脱炭酸反応が一例のみ報告されており<sup>18</sup>、Route B に近い中間体 **38** を経由する反応機構が提唱されていた。しかし、その根拠は示されておらず、我々の検討においても反応機構がどちらか断定するに至る決定的な結果は得られていない。



**Scheme 11. Plausible Mechanism**

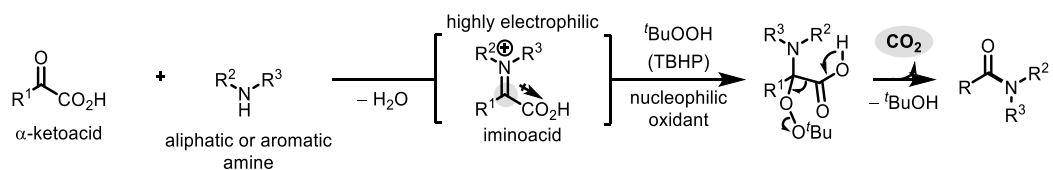


### 第三節 ヒドロペルオキシドによるアミンの化学選択的アシル化法の開発

アミノ基は、有機合成化学において最も基本的な官能基の一つであり、そのアシル化反応は天然物をはじめ医薬品や有機材料において重要な役割を果たしているアミド含有化合物を与えるため、古くから研究対象とされてきた。また、アミドはペプチドを構成する重要な官能基でもあり、近年の創薬科学におけるペプチド化合物のニーズの高まりからより一層その合成法の開発は興味を持たれるところである。中でも従来の活性型エステルを用いたアミド化では達成困難なアミンの化学選択的なアシル化反応の開発は、多数の官能基を有する複雑化合物を取り扱うことの多い医薬化学において極めて重要な課題である。そこで、 $\alpha$ -ケト酸を用いれば高い反応性と選択性を兼ね備えたアミンのアシル化反応の開発に繋がると考えたが、前節のエステル化反応で見出した超原子価ヨウ素試薬は求電子的な酸化剤であるため、アミド化反応へ適用する際にはアミンの酸化などの副反応が問題であった。また、Leiらによって報告された光照射下でのアミド化反応においても、求電子的な酸化剤である酸素を用いているためか大過剰量の脂肪族アミンが必要である<sup>12a</sup>。これらのことから筆者は、酸化的脱炭酸に利用する酸化剤がアミンと共存可能であることが新規脱炭酸型アミド化反応を開発する鍵であると考え、後述の戦略を考案した。

#### 戦略

筆者は、 $\alpha$ -ケト酸を用いた化学選択的なアシル化反応の開発を目指し研究を開始した。その際 $\alpha$ -ケト酸に対してアミンを作用させることで形成されるイミノ酸も $\alpha$ -ケト酸と同様に隣接するカルボキシ基によって高い求電子性を有することに着目した。この形成されたイミノ酸に対して、ヒドロペルオキシドのような求核性を持つ適切な酸化剤を作用させることで、望まない酸化反応を起こさずに脱炭酸型アシル化が円滑に進行するのではないかと期待した (Scheme 12)。



Scheme 12. Our Strategy for Decarboxylative Condensation Reaction

## 条件検討

まず  $\alpha$ -ケト酸を用いたアミンのアシル化反応を検討した (Table 5)。アミン **39** と  $\alpha$ -ケト酸 **2** に対して安価な過酸化物である TBHP の 70%水溶液を CH<sub>3</sub>CN 中室温で作用させることで、92%と高い収率で目的とするアミド **40** を得ることに成功した (entry 1)。同じく安価な CHP (**41**)を用いても良好な収率でアミド **40** が得られたが、*m*CPBA (**42**)を用いた際には求核性の低下のためか低収率であった (entries 2, 3)。続いて、ペプチドや複数の官能基を有する医薬品といった高極性化合物への適用を視野に入れ種々の極性溶媒が使用可能かを検討した。その結果、DMF や DMSO、エタノールのような極性溶媒を用いても総じて良好な結果を与え、基質の溶解性に応じて溶媒の使い分けが可能であることが示された (entries 4–6)。また炭酸カリウムを添加すれば、アミン求核剤は塩酸塩として使用できることが分かった (entry 7)。最後に、見出した反応条件と既知の2つの光反応条件を比較した。それぞれ報告されている反応条件に従い同じ基質を用いて反応を行ったが、目的とするアミドは低収率に留まった (entries 8, 9)<sup>12a,b</sup>。これらの結果から、今回見出した反応条件の優位性が示されたと同時に、反応機構もラジカル中間体を想定している既存法とは異なることが示唆された。また、今回見出した方法は大スケール合成にも適用可能で、アミドを良好な収率 89%で合成することができた。本法の特徴は、遮光やアルゴン置換等の特殊な操作を一切必要とせず、試薬と基質を室温で混合するだけの極めて簡便な実験操作で所望のアミド体 **40** へ変換できることである。

Table 5. Optimization for Acylation of Amine

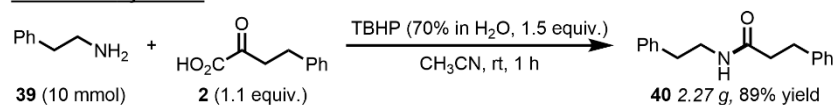
entry	deviation from entry 1	yield (%)
1	none	92
2	CHP ( <b>41</b> ) instead of TBHP	79
3	<i>m</i> CPBA ( <b>42</b> ) instead of TBHP	8 <sup>a</sup>
4	DMF instead of MeCN	88
5	DMSO instead of MeCN	83
6	EtOH instead of MeCN	88
7	amine·HCl + K <sub>2</sub> CO <sub>3</sub> instead of amine	96
8	[Ru(phen) <sub>3</sub> ]Cl <sub>2</sub> ( <b>43</b> ), O <sub>2</sub> , DMSO, light, 48 h	32 <sup>a</sup>
9	O <sub>2</sub> , 1,4-dioxane, H <sub>2</sub> O, light, 48 h	0 <sup>a</sup>

CHP (**41**)

[Ru(phen)<sub>3</sub>]<sup>2+</sup> (**43**)

Isolated yield. a: Determined by <sup>1</sup>H NMR spectra using dimethylterephthalate as an internal standard.

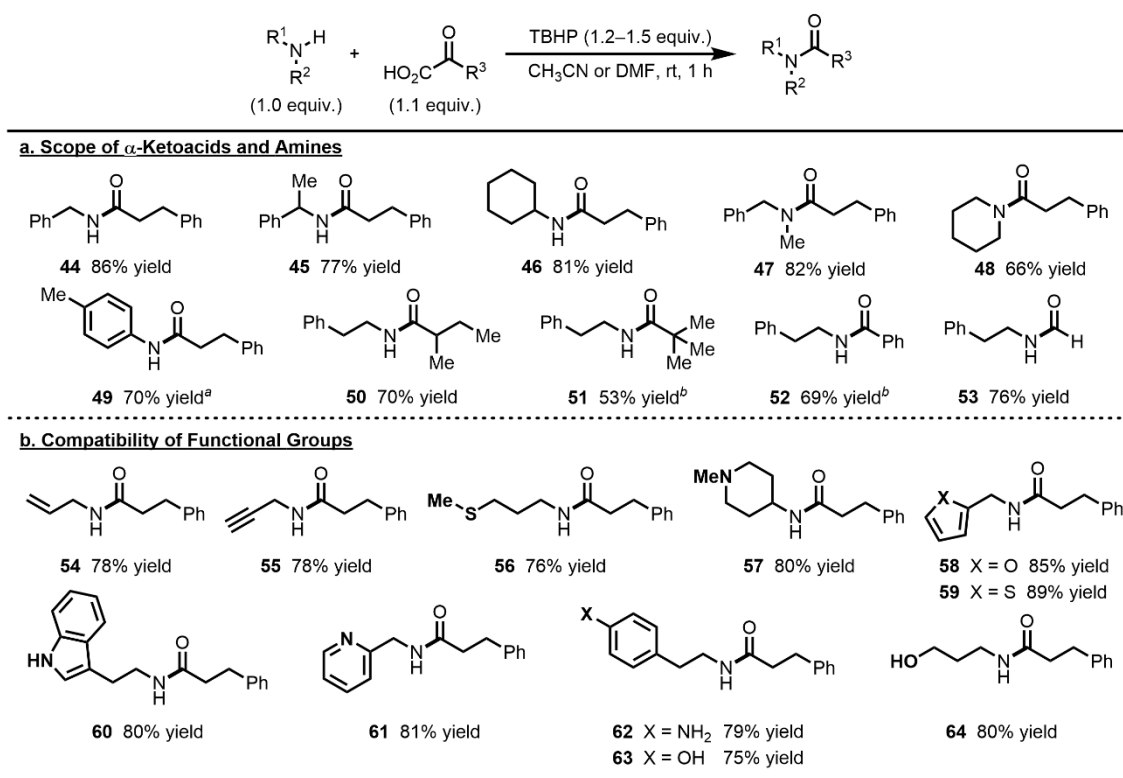
### Gram-scale Synthesis



## 基質適用範囲の検討

次に見出した最適条件を用いて本反応の基質適用範囲を検討した (Table 6a)。まず、ベンジルアミンや1-フェネチルアミン、シクロヘキシルアミンを用いた場合でも81%の収率で目的物を与えた (44-46)。また、KAHA ligation では反応機構上進行しないと考えられる *N*-メチルベンジルアミンやピペリジンをを用いた第三級アミド合成を検討したところ、それぞれ良好な収率で目的物を得ることに成功した (47, 48)<sup>11d</sup>。さらに、求核剤としてアニリンを用いた場合も反応時間の延長は見られるものの対応するアニリドを与え、脂肪族や芳香族を問わず様々なアミンを利用できる一般性の高い反応であることがわかった (49)。続いて、 $\alpha$ -ケト酸の適用範囲についても検討した。カルボニル  $\alpha$  位で分岐した基質を用いても反応は進行し (50)、ピバロイル基やベンゾイル基、ホルミル基を有する  $\alpha$ -ケト酸を用いることでそれぞれ対応するアシル基をアミンに導入することにも成功している (51-53)。続いて、本反応の官能基共存性を明らかにするために、分子内に様々な官能基を有する基質を検討した (Table 6b)。末端アルケンやアルキンといった不飽和結合を有する基質を用いても本反応に全く影響を与えることなく目的物を与えた (54, 55)。また、本反応は酸化条件であるため、スルフィドや第三級アミノ基といった官能基を有する基質を用いる際には競合する酸化反応が懸念されたが、実際には問題なくそれぞれアミド化が進行した (56, 57)。加えて、フランやチオフェン、インドール、ピリジンなどの複素芳香環を有する基質を用いた際にも良好な収率で目的物を与えた (58-61)。更に、無保護のフェノールやアニリン、アルコールといった求核部位が分子内に存在する場合においても脂肪族アミン選択的に反応は進行した (62-64)。

Table 6. Substrate Scope for Simple Amines and  $\alpha$ -Ketoacids

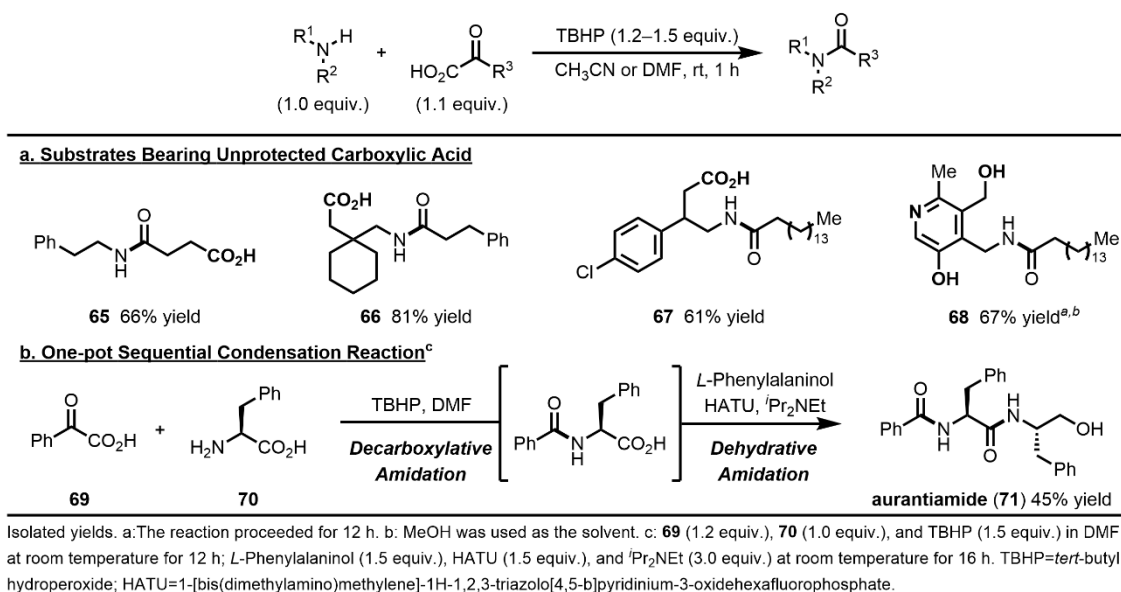


Isolated yields. a: The reaction proceeded for 12 h. b:  $\alpha$ -Ketoacid (1.5 equiv.) and TBHP (2.0 equiv.) were used. TBHP=*tert*-butyl hydroperoxide

### $\alpha$ -ケト酸選択的なアミド化反応の検討

超原子価ヨウ素を用いたエステル化反応と同様、無保護のカルボキシ基が分子内に存在しても  $\alpha$ -ケト酸特異的に縮合するといった特徴が本アミド化反応でも見られた (Table 7a)。すなわち  $\alpha$ -ケトグルタル酸やギャバペンチンといった基質に適用した場合には、脱水縮合は競合せずに脱炭酸型縮合のみが選択的に進行した (**65**, **66**)。以上に述べた本反応の化学選択性を利用して、バクロフェンやピリドキサミンといった多数の官能基を有する医薬品分子の化学選択的なアミド化も良好な収率で実現した (**67**, **68**)。本結果は、本アミド化法が複数の反応点を有する複雑分子の Late-stage でのアシル化法へと展開し得ること示す重要な知見である。更に、既存の脱水縮合反応と組み合わせることで無保護のアミノ酸の両末端をワンポットで修飾することが可能と考えた。実際に無保護のフェニルアラニン (**70**) に対し両末端のアミド結合を連続的に形成することで生物活性物質オウランチアミド (**61**) をワンポットで合成することにも成功した (Table 7b)<sup>19</sup>。

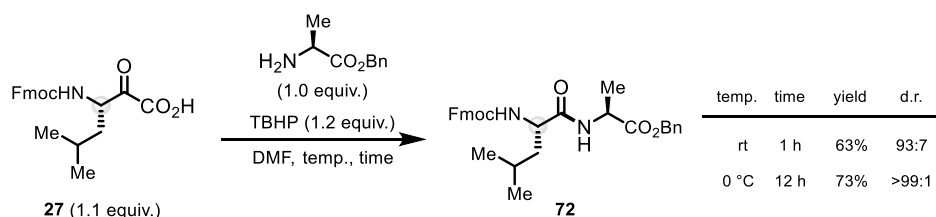
**Table 7. Substrate Scope for Compounds Bearing Unprotected Carboxylic Acids and Nucleophiles**



## ペプチド合成への応用

近年中・高分子のペプチドは、創薬モダリティとして注目が集まっている魅力的な化合物群である。最近では薬理活性、代謝安定性、細胞膜透過性に優れたペプチド医薬品の探索を志向して *N*-メチルアミノ酸や  $\alpha,\alpha$ -二置換アミノ酸といった非天然型アミノ酸含有ペプチドが注目を集めており、その効率的な合成法の開発が活発に行われている。筆者は今回見出した脱炭酸型アミド化反応において幅広い官能基共存性が見られたため、種々のアミノ酸を用いたペプチド合成にも適用可能かを検証することとした。

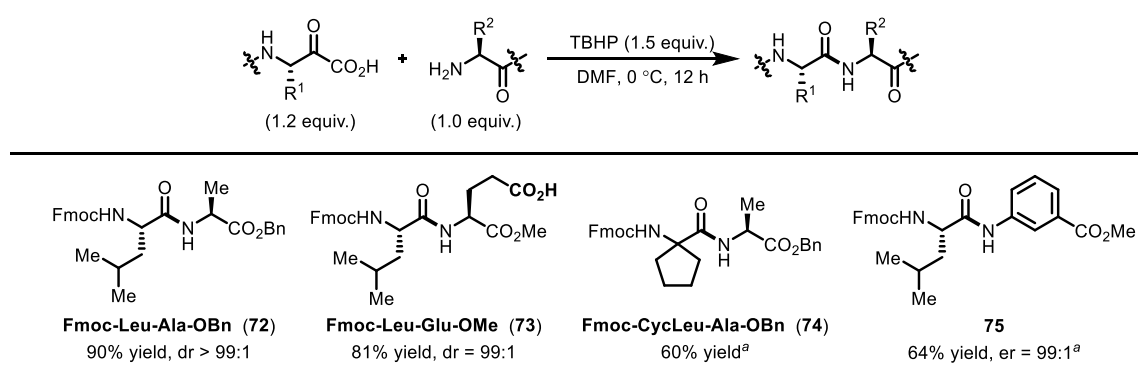
まず、合成した  $\alpha$ -ケト酸 **27** を用いて種々のジペプチド合成の検討を行った<sup>11c, 16</sup>。合成したロイシン由来の  $\alpha$ -ケト酸をアラニンベンジルエステルと TBHP 存在下混合し、室温で一時間攪拌したところ目的のジペプチド **72** を 52% の収率で得ることに成功した (Scheme 13)。この際カルボニル  $\alpha$  位の若干のエピメリ化が観測されたが、反応温度を 0 °C へと低下させることで反応時間の延長は見られたもののエピメリ化の抑制に成功し、目的のジペプチドを良好な収率及びジアステレオ比で得ることに成功した。



**Scheme 13. Dipeptide Synthesis and Evaluation of Epimerization**

上記の条件に加え、試薬の当量を 1.5 当量に増やすことでジペプチド Fmoc-Leu-Ala-OBn (**72**)を 90%収率、単一のジアステレオマーとして得ることに成功した (Table 8)。また、単純な基質を用いた際に見られた化学選択性はペプチド合成においても例外ではなく、側鎖が無保護のグルタミン酸を基質として用いても 81%の収率で目的とするジペプチド Fmoc-Leu-Glu-OMe (**73**)を与えた。加えて、 $\alpha,\alpha$ -二置換アミノ酸や芳香族アミノ酸といった特殊な基質を用いた際も良好に反応は進行した (**74, 75**)。

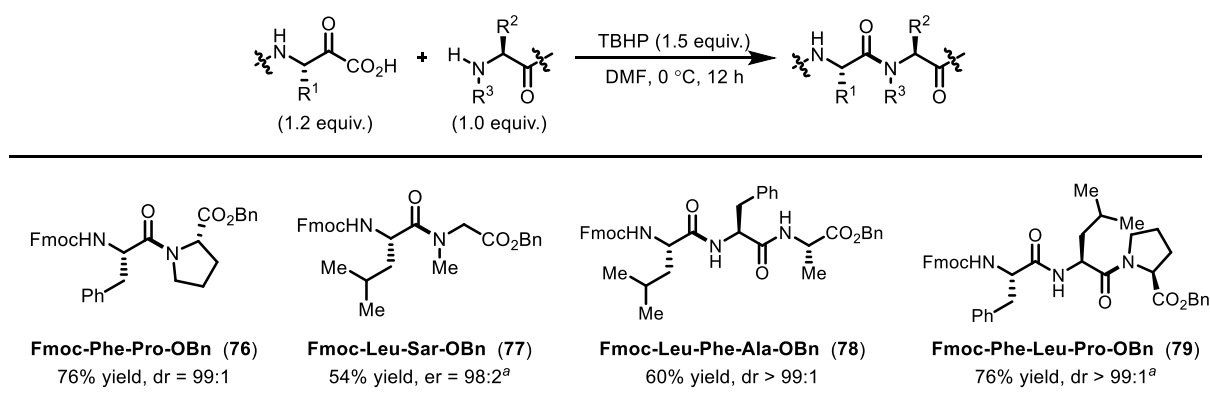
**Table 8. Substrate Scope for Dipeptide Synthesis**



Isolated yields. Er and dr values were estimated by chiral SFC analysis. a: The reaction was carried out at room temperature.

次に、プロリンや *N*-メチルアミノ酸といった第二級アミンを用いた検討を行ったところ、対応する第三級アミドが良好な収率で得られた (**76, 77**) (Table 9)。また、ジペプチドとのカップリングもそれぞれ良好な収率及び高いジアステレオ比で目的物を与えた (**78**)。脱水縮合においてオリゴペプチド C 末端での縮合は、N 末端アミドのカルボニル基が活性エステルと反応する分子内環化を経てアズラクトンが形成するため、エピメリ化が懸念される。本反応においてロイシンを C 末端に有するジペプチドケト酸とプロリンとの縮合を検討したところ、室温条件下で単一ジアステレオマーとして目的物を得ることに成功した (**79**)。今後アミノ酸残基の一般性を検討する必要があるものの、本結果は本反応がポリペプチド鎖同士の連結を志向したフラグメント縮合法への展開が期待できると考えられる<sup>16, 20</sup>。

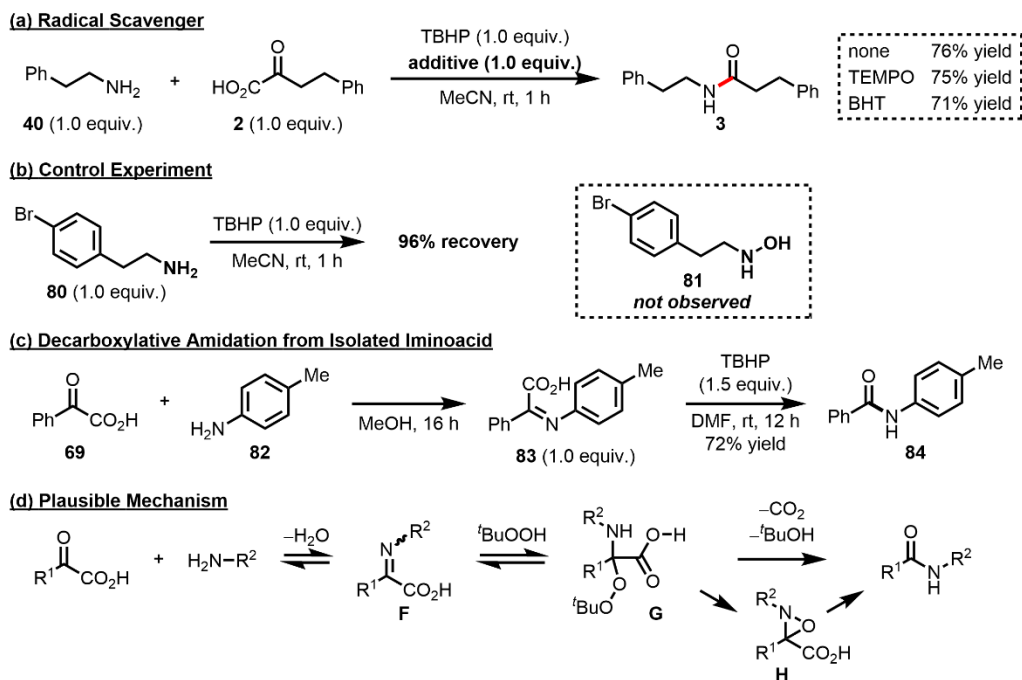
**Table 9. Substrate Scope for 3°Amide and Tripeptides Synthesis**



Isolated yields. Er and dr values were estimated by chiral SFC analysis. a: The reaction proceeded for 24 h at room temperature.

## 反応機構解析

最後に今回見出した脱炭酸型アシル化反応の機構解析を行った (Scheme 14)。TBHP は一般にラジカル開始剤としても知られているが、本反応では TEMPO や BHT といったラジカル捕捉剤を添加しても反応に影響を与えないことから、非ラジカル経路で進行していることが示唆された (Scheme 14a)。続いて、TBHP をアミン **80** のみに作用させる対照実験を行ったところ、<sup>1</sup>H NMR においてアミン **80** の酸化は確認されず原料を定量的に回収する結果となった (Scheme 14b)。すなわち、アミンが TBHP によって系内でヒドロキシルアミン **81** に酸化され、KAHA ligation が進行するという可能性が本結果から否定される。さらに、単離可能な  $\alpha$ -イミノ酸を用いた反応についても検討した (Scheme 14c)。p-トルイジン (**82**) と芳香族  $\alpha$ -ケト酸を混合することで  $\alpha$ -イミノ酸 **83** が安定に単離できることが報告されており<sup>13b</sup>、その報告例を参考に合成・単離した  $\alpha$ -イミノ酸に対して TBHP を作用させたところ良好な収率で対応するアミド **84** を与えた。このことから、 $\alpha$ -イミノ酸は本脱炭酸型アミド化の反応中間体であることが強く示唆された。以上の結果から、今回見出したアミド化反応は当初の想定通り、 $\alpha$ -ケト酸とアミンから生成した  $\alpha$ -イミノ酸に TBHP が付加し中間体 **G** を与え、続く脱炭酸と *t*-ブチルアルコールの脱離によって目的とするアミドを与えていると筆者は想定している (Scheme 14d)。中間体 **G** から目的物を与える機構としては中間体 **G** から直接脱炭酸と *t*-ブチルアルコールの脱離が起こるものを想定しているが、Bode らによって報告されているオキサジリジン中間体 **H** を経由するものも可能性として考えられる<sup>12d</sup>。なお、後任者によって詳細な機構解析が行われており、重酸素標識実験から目的物のアミドカルボニル酸素は TBHP 由来であること、また DFT 計算により当初の想定通り中間体 **G** からの直接的な脱炭酸機構で進行していることが示唆されている<sup>19</sup>。



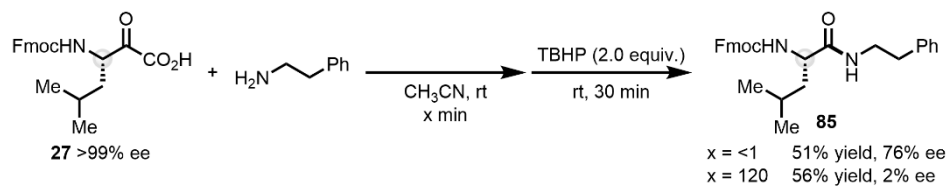
Scheme 14. Mechanistic Studies

### エピメリ化機構の考察

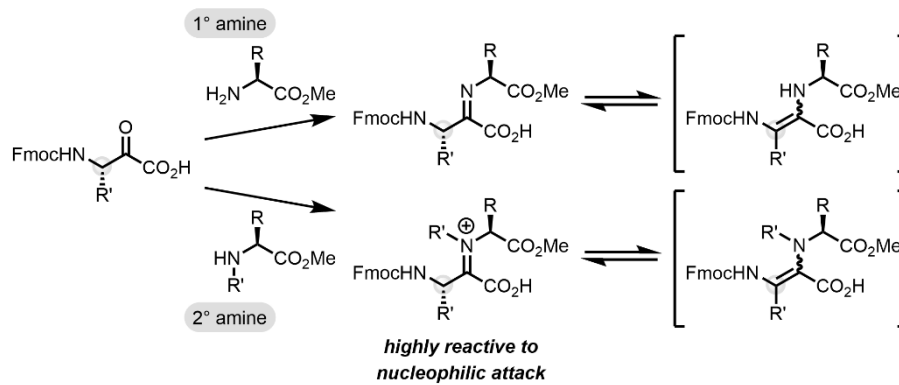
また、更なる機構解析として発生したエピメリ化の原因を考察するために次のような混合実験を行った (Scheme 15a)。すなわち、 $\alpha$ -ケト酸 **27** とフェネチルアミン **39** を一定時間混合し TBHP を加えたところ、ジペプチド合成では良好な結果を与えていたにも関わらず **27** と **39** の混合時間が長くなるにつれて、生成物 **85** の ee が低下していた。従って本脱炭酸型アミド化反応においては、脱水縮合で見られるようなアズラクトンを経由したエピメリ化ではなく、イミノ酸からエナミンへと互変異性が起こることで光学活性が失われていると考えられる (Scheme 15b)。本結果は、本反応におけるエピメリ化の過程には N 末端アミドが関与しないことを示しており、エピメリ化の抑制が達成されればフラグメントカップリングへの展開が期待される。また、第三級アミド合成において室温条件下でエピメリ化が見られなかった理由としては、 $\alpha$ -ケト酸と第二級アミンから生成するイミニウム中間体の求電子性が高いことが考えられる。なお、本脱炭酸型縮合におけるアミノ酸置換基のエピメリ化への影響に関して DFT 計算や実験化学的な考察、及び添加剤によるエピメリ化抑制の検討が後任者によって詳細に行われている<sup>19</sup>。すなわち、本反応においては  $\beta$ -アミノ- $\alpha$ -ケト酸の側鎖が嵩高いほど、あるいは求核剤の側鎖の嵩が小さいほどエピメリ化が見られない傾向があり、エピメリ化が観測される基質においてもハロゲン化物イオン源を添加することでエピメリ化が抑制されることが明らかにされている。



**(a) Experiment on Epimerization**



**(b) Plausible Mechanism of Epimerization**



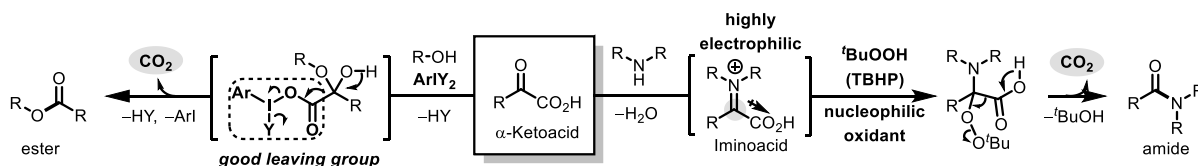
**Scheme 15. Evaluation of Epimerization**

#### 第四節 結論

筆者は、 $\alpha$ -ケト酸と種々の求核剤との縮合反応を適切な酸化剤を作用させることで達成した。それぞれの反応は高い収率で種々の目的物を与えただけでなく、ユニークな化学選択性の発現も見られており、 $\alpha$ -ケト酸のより一般性の高いアシル化剤としての利用に成功したと考えられる (Scheme 16)。

まず始めに、外部酸化剤として超原子価ヨウ素を作用させることで、様々なアルコールと円滑に反応し高い収率でエステル化体を与えることを見出した。本エステル化反応は光学活性なアミノ酸由来の  $\alpha$ -ケト酸を用いた際に、光学純度を損なうことなく目的物を得ることが可能であった。また、無保護のカルボン酸存在下  $\alpha$ -ケト酸選択的な縮合が可能であり、脱水縮合では困難であったリトコール酸の選択的なアシル化においても問題なく目的物を与えた。

次に、TBHP を用いた  $\alpha$ -ケト酸の新規脱炭酸型アミド化反応を見出した。本反応は温和な条件下で進行し、様々な官能基存在下高い収率でアミド化体を与えた。本反応において、多数の官能基を有する医薬品分子や無保護のカルボン酸存在下での選択的なアシル化が進行し、縮合剤と組み合わせることで生理活性物質の連続縮合をワンポットで行うことに成功した。また、ペプチド合成への応用も可能であり、KAHA Ligation では達成困難であった第三級アミド合成にも適用可能であった他、ペプチド C 末端からの縮合反応も円滑に進行した。今後は多数の官能基を有する複雑分子への更なる適用の拡大や、ペプチドフラグメントカップリング反応への応用が期待される<sup>16,19</sup>。



Scheme 16. Summary of Decarboxylative Condensation

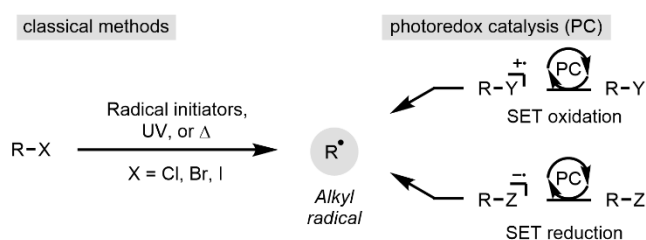
### 第三章 ピリジンによる基質認識を志向した新規有機触媒の開発

#### 第一節 序論

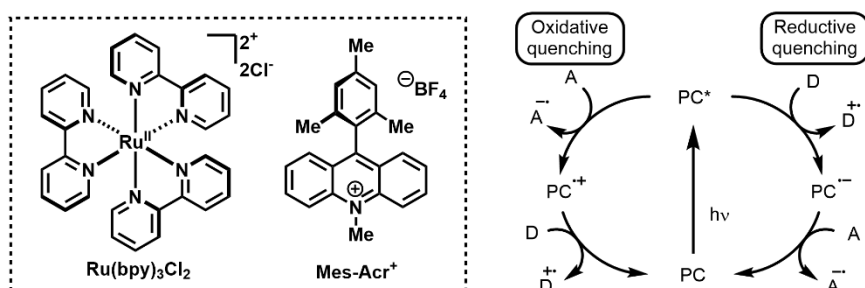
#### 可視光レドックス触媒のアルキルラジカル発生への利用

アルキルラジカルは二電子機構では達成困難な炭素-炭素結合形成を容易に実現可能という利点から天然物や高分子の合成において幅広く利用されている<sup>21</sup>。従来、その発生にはUV照射やラジカル開始剤が用いられていたが<sup>22</sup>、近年それらを代替できる可視光レドックス触媒の利用が精力的に研究されている (Scheme 17)<sup>3</sup>。可視光レドックス触媒は、比較的小さな光エネルギーを有する可視光を用いて簡便にラジカルを発生させられるため環境調和の観点から大きな注目を集めている。また、触媒分子が酸化剤・還元剤の役割を両立できることから、古典的なラジカル条件では達成困難な反応設計を可能にする魅力的な化合物群である。それに加え、基質と触媒の酸化還元電位の大小関係によって反応進行の可否が予測可能であることから、合理的な反応設計が容易という特徴がある。これらの利点から、イリジウム錯体などの金属錯体だけでなく、合成が容易で高価な遷移金属元素を含まない有機光触媒に至るまで、異なる酸化還元電位を持つ様々な光触媒が合成されてきた<sup>23</sup>。一方で、可視光から得られるエネルギーには上限があることから絶対値が大きい酸化還元電位を示す触媒の開発は容易ではなく、酸化還元電位の絶対値が既存触媒を上回る値を示す基質の酸化及び還元反応は依然として困難であった。

#### a) Methods for Alkyl Radical Generation



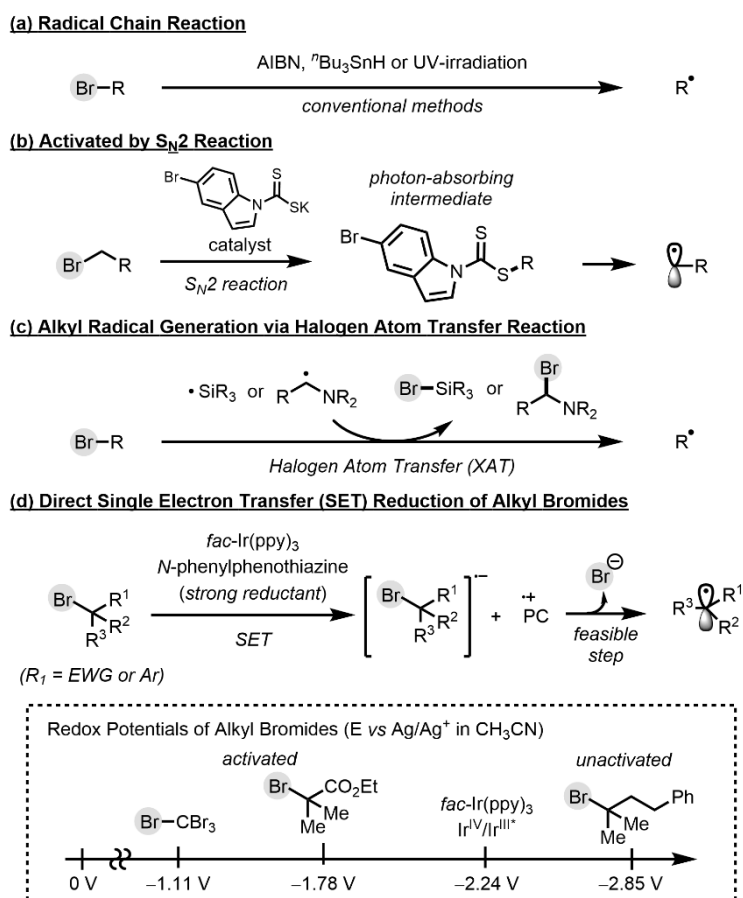
#### b) Photoredox Catalysis and its Characteristics



Scheme 17. Alkyl Radical Generation by Photoredox Catalysts

## 臭化アルキルのラジカル前駆体としての利用

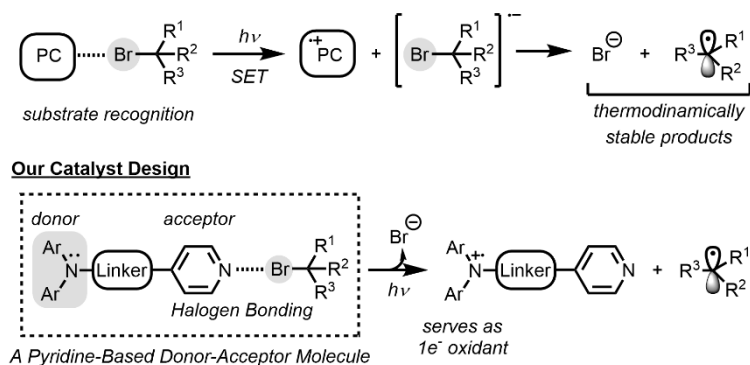
臭化アルキルはラジカル開始剤を用いる古典的な手法において汎用されるラジカル前駆体であり、取扱い容易で様々な化合物が安価に市販されている魅力的な化合物群である (Scheme 18a)<sup>22</sup>。しかし本化合物を光触媒反応系へと利用する際には、不活性臭化アルキルと呼ばれる酸化還元電位が大きな負の値を示す基質が存在するために工夫が必要であった。例えば、Melchiorre らによって報告されたチオカルバマート触媒による S<sub>N</sub>2 反応を経た活性化法や<sup>25</sup>、MacMillan や Leonori らによるハロゲン原子移動 (Halogen Atom Transfer: XAT)を利用する手法などが最近報告されている (Scheme 18b, c)<sup>26</sup>。これらの報告は臭化アルキルのラジカル発生における有用性を示す手法である一方で、適用範囲が良好に S<sub>N</sub>2 反応を起こせる基質に限られることや、多くの場合化学量論量の試薬が追加で必要になる等、依然として改善の余地が大きいと考えられる。そのような観点では、光触媒による直接的な一電子還元は添加剤を必要としない理想的な方法論であるが、上述の通り不活性臭化アルキルを含めた様々な臭化アルキルへの適用は難しくその報告例は遷移金属触媒を用いた数例に限られていた<sup>27</sup>。また、電子求引基が隣接している活性臭化アルキルにおいてもこれまで既存の光触媒による直接的なアルキルラジカルの発生には、*fac*-Ir(ppy)<sub>3</sub><sup>28</sup> やフェノチアジン (PTZ)<sup>29</sup> などの還元力の高い触媒が必要であった (Scheme 18d)<sup>30</sup>。



Scheme 18. Alkyl Radical Generation from Alkyl Bromides

## 戦略

以上の背景を踏まえ、筆者は不活性基質を含む臭化アルキルから容易にアルキルラジカルを発生可能な新規光触媒の開発を目指し研究に着手した。筆者は、一電子移動 (Single Electron Transfer: SET)後に発生する臭化アルキルのラジカルアニオン種からのアルキルラジカル発生は速やかに進行しうることから、SET 段階の効率を上げることが本課題の解決の鍵だと考えた (Scheme 19)。すなわち、臭化アルキルとの相互作用部位を光触媒に導入することで必ずしも絶対値の大きい酸化還元電位を示さなくとも高反応性を発現する触媒が開発可能と考え、ピリジン含有ドナー・アクセプター (D-A)型分子を新たに設計した。ピリジン部位は電子受容性アクセプター (A)部位としてだけでなくルイス塩基部位として臭化アルキルと相互作用をすることで、続く光励起によって電子供与性ドナー (D)部位から一電子を基質へと受け渡す役割を期待した。また、D 部位としてはルイス塩基性が低く、対応するカチオンラジカルが **persistent** ラジカルとして後続反応における一電子酸化反応の促進が可能なジアーリアルミンを導入することで、設計した分子が光レドックス触媒として機能すると予想した<sup>31</sup>。

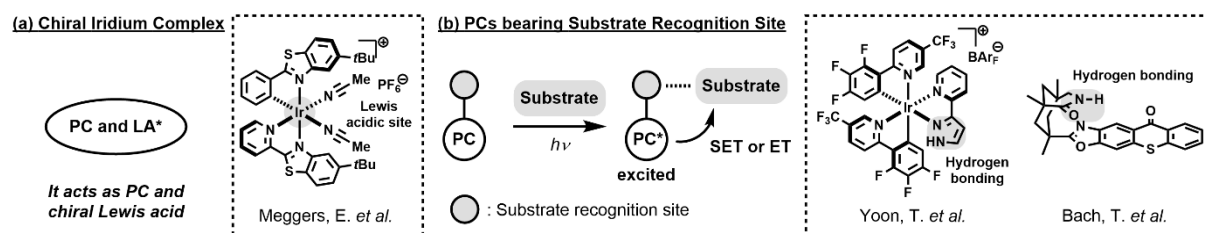


Scheme 19. Our Catalyst Design

## 基質認識型光触媒

上述のように可視光レドックス触媒はその有用性の高さから、これまで様々な酸化還元電位を有するものが開発されてきたが、それらのほとんどは基質との明確な相互作用部位を持たず、一電子移動反応やエネルギー移動反応 (Electron Transfer: ET)といった素反応を促進するのみであった。最近になり、物理化学的性質の調整だけでなく、光触媒に基質との相互作用部位を組み込むことでより精密な反応制御を目指す試みが報告され始めている<sup>32, 33</sup>。例えば、中心金属がキラルルイス酸としての役割を同時に持つことで SET 後に発生したラジカル種の付加反応を立体的に制御する光触媒が Meggers らによって報告されている (Figure 7a)<sup>32</sup>。また、水素結合ドナー部位を導入されたイリジウム錯体や有機触媒による不斉[2+2]環化反応がそれぞれ Yoon や Bach らによって報告されている<sup>33</sup>。一方で、いずれの例においても立体選択性の制御を目指した検討であるため、反応性制御の可否については検討されていない (Figure 7b)。そのため、基質認識部位の導

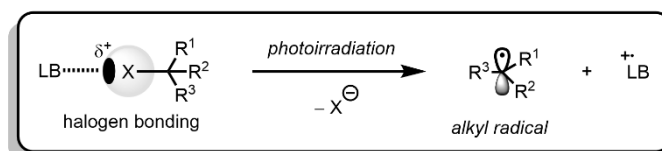
入により高い反応性の発現が実現可能なことを示すことで、本戦略が今後の光触媒設計における重要な指針のひとつとなり得る。



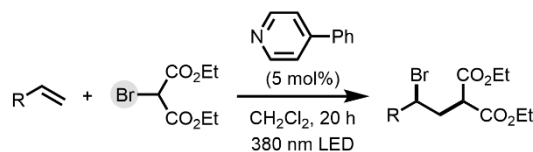
**Figure 7. Photocatalysts bearing Substrate Recognition Site**

### ハロゲン結合を用いた光照射下でのアルキルラジカル発生反応

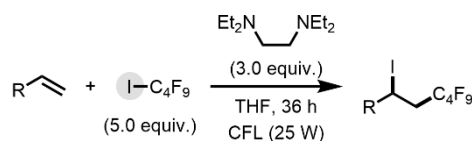
一般に、高周期ハロゲン含有分子はルイス塩基とハロゲン結合 (XB) と呼ばれる非結合性相互作用を形成することが知られている (Scheme 20)。XB 結合を形成している分子のうちルイス酸性部位を有する電子不足なハロゲン原子は XB ドナーと呼ばれ、これまでに様々な XB ドナー型有機触媒が開発されてきた<sup>34</sup>。最近では、本相互作用を利用した光照射下でのアルキルラジカル発生法として、Itoh らによるピリジンを用いた触媒的手法や、Chen らによる第三級アミンを用いる手法が幾つか報告されており、本報告は触媒設計におけるハロゲン結合の有用性を示している<sup>35,36</sup>。一方で、その適用は活性臭化アルキルに留まり、多くの例において対応するラジカルカチオンが不安定なために化学量論以上の第三級アミンを必要としており、本相互作用の応用可能性が十分に活かされているとは言い難い。



**(a) Catalytic Atom-Transfer-Radical-Addition Reaction**



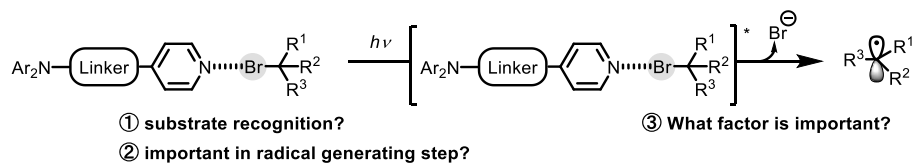
**(b) Single Electron Reduction Using Aliphatic Amines**



**Scheme 20. Alkyl Radical Generation through Halogen Bonding**

以上の着想のもと、種々のピリジン含有 D-A 型分子を合成し、その触媒活性を検討することと

した。その際、本戦略において①触媒-基質間における相互作用の有無、②触媒と基質の相互作用がアルキルラジカル発生に重要か、③アルキルラジカル発生段階に重要な因子は何か、の三点が鍵となると考え、反応検討と併せて機構解析にも重点を置いて研究に取り組んだ (Scheme 21)。



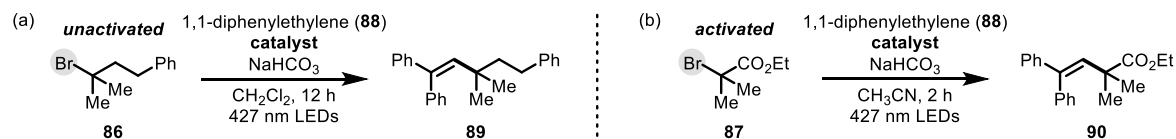
**Scheme 21. Overview of the Key Points for a Pyridine-based Molecule in Alkyl Radical Generation**

## 第二節 新規ピリジン含有 D-A 型分子の開発とハロゲン結合を介した還元的 C-Br 結合切断によるアルキルラジカル発生への応用

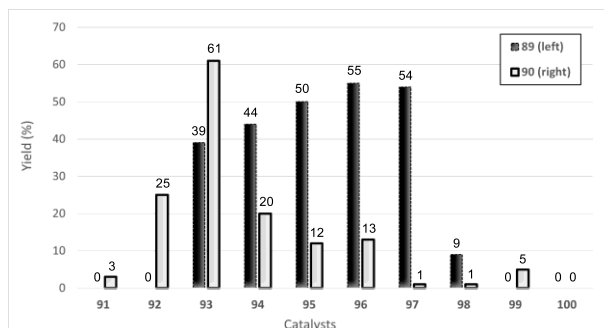
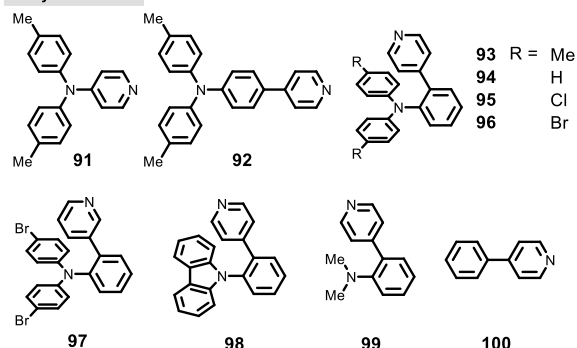
### 触媒構造最適化の検討

はじめに、前述の設計に基づきジアリールアミンとピリジン部位からなるいくつかの D-A 分子を合成し、臭化アルキル **86** および **87** のアルケニル化における活性を評価した (Scheme 22)。まず、Kessil® LED ( $\lambda_{em} = 427 \text{ nm}$ )を用いて、不活性臭化アルキル **86** と 1,1-diphenylethylene **88** に対して光照射下 10 mol% の 4-アミノピリジン **91** を作用させたところ、目的物は全く得られなかった。著者は **91** の光吸収効率が低いことが低収率の原因と考え、より長波長の光を吸収し得る分子としてベンゼン環を導入し共役系を拡張させた誘導体 **92** の検討を行った。その結果、不活性臭化アルキル **86** に対しては活性を示さなかったものの、活性臭化アルキル **87** のアルケニル化は低収率ながらも進行した。更に触媒 **92** のいくつかの類縁体を検討したところ、ピリジンおよびジアリールアミノ基がオルト位に導入された触媒 **93-96** は顕著に高い触媒活性を示し、その中でも触媒 **96** は目的物 **89** を最も高い収率で与えた。また、これらの新規オルト置換触媒は、活性臭化アルキル **87** の反応においても効率よく目的物を与えた。興味深いことに、活性臭化アルキル **87** を用いたアルケニル化反応に対する触媒スクリーニングでは、電子豊富なジアリールアミノ基を有する触媒が、**86** の反応とは対照的に高い触媒活性を示すことが示された。本結果は、活性臭化アルキルを用いた際にはピリジン部位のルイス塩基性の向上によりハロゲン結合を強くすることが重要である可能性を示唆している。一方で、不活性臭化アルキル **86** からのアルキルラジカル生成には、電子求引性基がジアリールアミン部位に導入された触媒が高い活性を示していた。触媒 **96** の蛍光波長は触媒 **93-95** に比べ短くなっていることから、HOMO-LUMO 間のエネルギー差が不活性臭化アルキルを用いた際の触媒活性に影響している可能性が考えられる。更なる知見を得るため、4-ピリジル基の代わりに 3-ピリジル基を導入した触媒 **97** を用いてオルト型触媒においてアミノフェニル基とピリジン環が分子内で空間的に相互作用をしている可能性を検証した。その結果、活性臭化アルキル **87** に対する触媒活性が低かった一方で、不活性臭化アルキル **86** を用いた際には目的物 **89** を 54%収率で与えており、アミノフェニル基とピリジン環の分子内における空間的な相互作用が高い反応性に重要である可能性が示唆された。また、カルバゾイル基やジメチルアミノ基が触媒のドナー部位として適切でないこと、ブロモマロン酸エステルといった非常に活性された基質を用いた反応で用いられていた 4-フェニルピリジン (**100**)は目的物を与えなかったことから<sup>35b</sup>、触媒活性にはピリジンに適切なドナー部位を導入することが重要であることが示されている。最後に、本反応は光触媒及び光照射が必須であることを対照実験で確認している。





#### Catalyst Structures



Scheme 22. Catalyst Screening

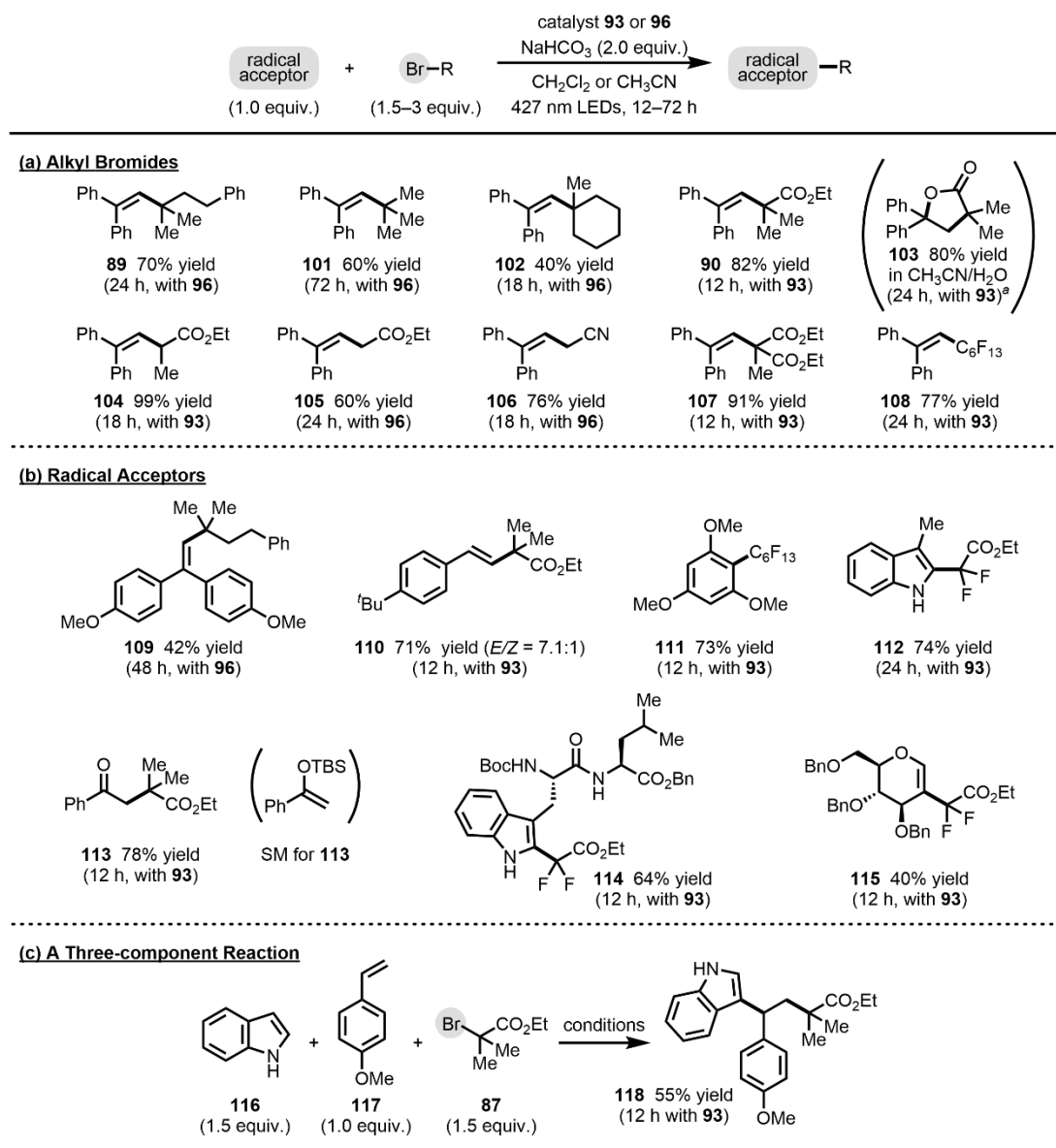
### 基質適用範囲の検討

次に、種々の臭化アルキルの基質適用範囲を調べることにした (Table 10)。まず始めに、触媒構造最適化で用いていた臭化アルキル **86** に対し反応時間を 24 時間へと延長することで 70% の収率で目的物を得ることに成功した (Table 10a)。また、更なる時間の延長により 1 mmol へとスケールを上げて同等の収率で目的物を与えた。続いて、第三級臭化アルキルとして臭化 *tert*-ブチルや、1-臭化-1-メチルシクロヘキシルを用いてもそれぞれ中程度の収率で反応が進行した (**101**, **102**)。第三級臭化アルキルにおいては良好に反応が進行している一方で、第二級及び第一級臭化アルキルを用いた際には目的物は低収率に留まった。

続いて活性臭化アルキルの検討を行ったところ、第三級、第二級、第一級いずれの基質を用いてもそれぞれ反応は円滑に進行した (**90**, **104**, **105**) (Table 10b)。アセトニトリルと水との混合溶媒を用いた際にはラクトン **103** が収率よく得られた。エステル以外の電子求引基を有する基質として、ブromoアセトニトリルやマロン酸エステルを検討したところ、問題なく反応は進行した (**106**, **107**)。また、化合物の物性や代謝安定性の向上が期待できるパーフルオロアルキル基の導入にも適用可能であった (**108**)。

続いてラジカル受容体の一般性についても検討を行った (Table 10c)。ジフェニルエチレン誘導体や、スチレンとの反応も良好に進行している他 (**109**, **110**)、電子豊富な芳香環であるフルオログリシノールやインドール、シリルエノールエーテルも良好に目的物を与えた (**111–113**)。グルカールやトリプトファン含有ペプチドなどをラジカル受容体として用いてもアルキル基の導入が問題なく進行している (**114**, **115**)。また、ブromoイソ酪酸 **87** とスチレン存在下インドール **116** を添加することでスチレン **117** の二官能基化が進行することを見出し、三成分連結体 **118** を得ることに成功している。

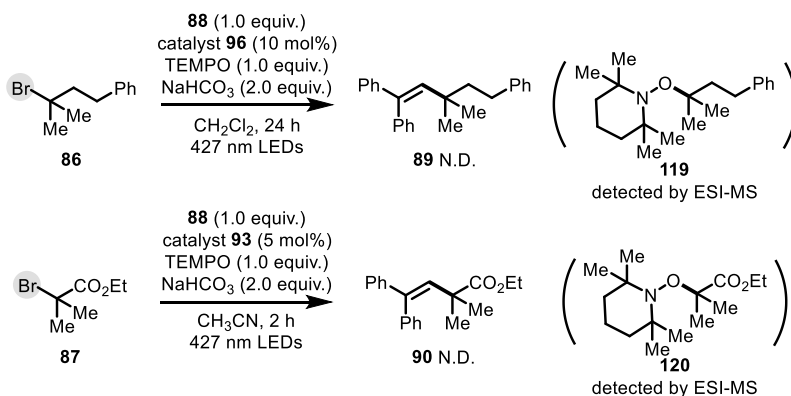
**Table 10. Substrate Scope**



Isolated yields. Catalyst **93** was used in CH<sub>3</sub>CN, while catalyst **96** was used in CH<sub>2</sub>Cl<sub>2</sub>. a: The reaction was performed in CH<sub>3</sub>CN/H<sub>2</sub>O = 4:1 (v/v).

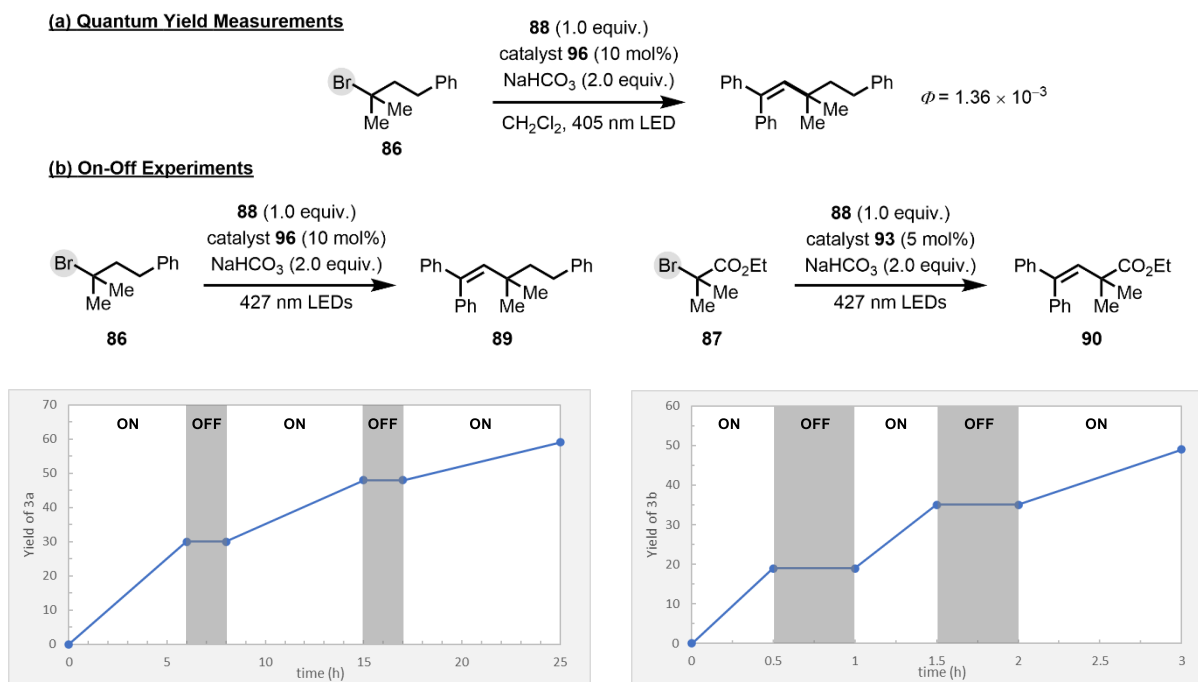
## 反応機構解析

最後に今回見出したピリジン含有 D-A 型分子の働きについて考察すべく、種々の反応機構解析を行った。まず始めに、本反応におけるラジカル中間体の関与を検証するために、ラジカル捕捉実験を行った (Scheme 23)。臭化アルキル **86**, **87** を用いたアルケニル化反応において、ラジカル捕捉剤として TEMPO を加えたところ、目的物は得られず対応する TEMPO 付加体 **119**, **120** の生成が微量ながらも観測された。本結果から、本反応はラジカル機構で進行していると考えられる。



### Scheme 23. Radical Trapping Experiment

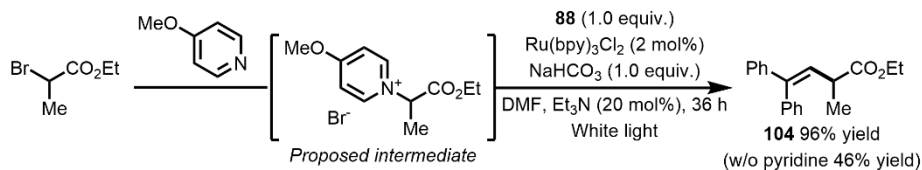
次に、本反応がラジカル連鎖機構で進行している可能性を検証した (Scheme 24)。伊藤らの報告を含め、光照射下ハロゲン結合を利用してアルキルラジカルを発生させている場合にはラジカル連鎖機構で進行している可能性が考えられる<sup>35, 36</sup>。一般に連鎖機構で進行する反応の量子収率は1以上を示すことが知られているが、不活性臭化アルキル **86** を用いたアルケニル化反応の量子収率を算出したところ、 $\Phi = 1.36 \times 10^{-3}$  という非常に低い値が得られた (Scheme 24a)。更に、臭化アルキル **86** 及び **87** を用いた実験で光照射の On-Off 実験を行ったところ光非照射時において収率の向上が見られなかった (Scheme 24b)。以上の結果から、連鎖機構で進行しているわけではなく、本反応は当初の想定通り可視光レドックスとして働いていることが考えられる。



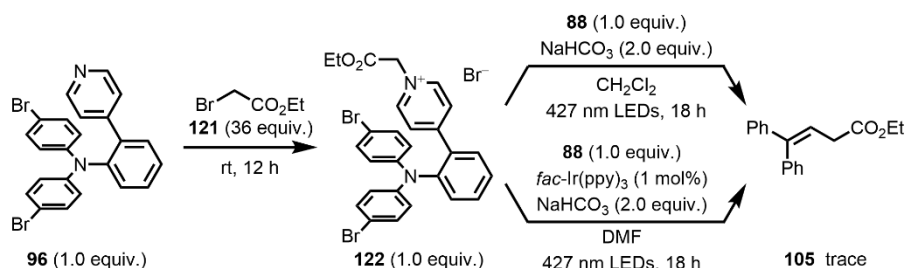
Scheme 24. Investigations on Radical Chain Reaction

次に、本反応でのピリジニウム塩の関与を検証した。Lei らは過去にハロゲン化アルキルを用いた同様の報告例において、ピリジン添加により生成するピリジニウム中間体が光触媒による一電子還元を受け反応が促進される機構を提唱していた (Scheme 25a)<sup>30d</sup>。今回見出した触媒が、対応する触媒ピリジニウム塩を経由してアルキルラジカルを発生させる可能性を検証した。触媒 **96** と臭化アルキル **121** を混合したが、ピリジニウム塩 **122** の生成速度は非常に遅いものであった。別途調製したピリジニウム塩 **122** を光照射下ジフェニルエチレンと混合したところ、アルケニル化体 **105** はほとんど得られず、光触媒を更に添加した場合にも反応は進行しなかったことから本反応においてピリジニウム塩 **122** はアルキルラジカル発生の中間体ではないと考えられる (Scheme 25b)。更に、比較実験として Lei らの提唱中間体であるピリジニウム塩 **123** を合成し Lei らの反応条件に付したところ、同じく全く目的物は得られなかった (Scheme 25c)。加えて、アルキルピリジニウムの一電子還元により生じるピリジンラジカルがアルキルラジカルを放出するには、ピリジン 2,6 位の置換基による立体効果が必須であるという DFT 計算結果が Kozlowski らにより報告されている (Scheme 25d)<sup>37</sup>。これらの結果を総合すると、Lei らが報告しているピリジンの加速効果は、今回筆者が提案した戦略と同様にピリジン-臭素原子間の非共有結合性相互作用によるものである可能性が高い<sup>30d</sup>。

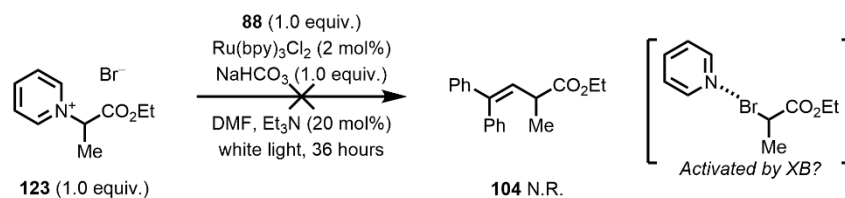
**(a) Previous Reports on Activation of Alkyl Bromides via Pyridinium Generation**



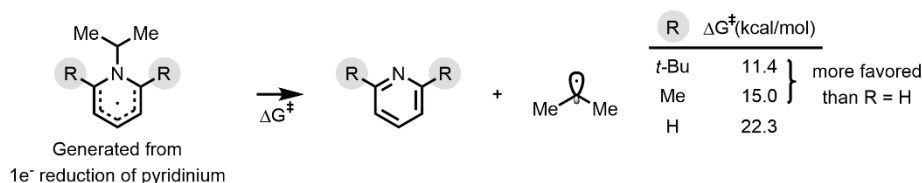
**(b) Investigation of Alkyl Radical Generation from Pyridinium Salts**



**(c) Test Experiments of Pyridine-Mediated C-Br Bond Cleavage in Precedent Reports**

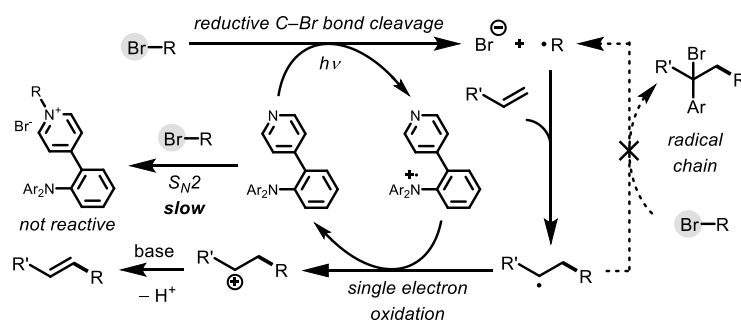


**(d) DFT Calculations on Importance of 2, 6-Substituents at Pyridinium Ring**



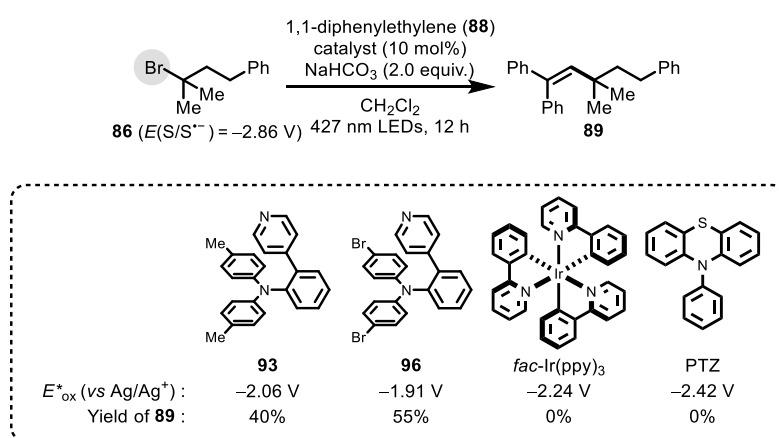
**Scheme 25. Investigations on Alkyl Radical Generation from Pyridinium Salts**

以上の実験結果に基づき、想定触媒サイクルを以下に示す (Scheme 26)。今回見出した触媒は臭化アルキルから直接アルキルラジカルの生成を促進し、ラジカルアクセプターと反応した後、触媒の対応するラジカルカチオンによってアルキルラジカルがカチオンに酸化されて目的生成物が得られると考えられる。



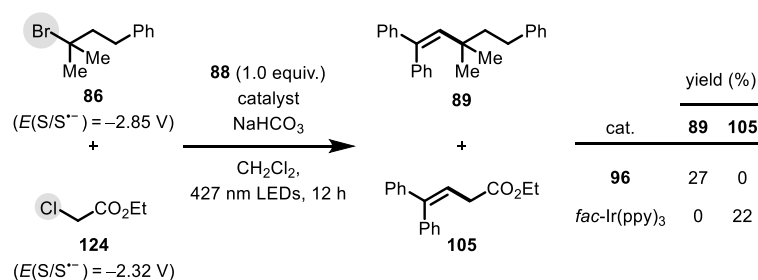
**Scheme 26. Proposed Catalytic Cycle**

最後に、アルキルラジカル生成段階をより詳細に調べるために、いくつかの機構解析実験を更に行った (Scheme 27)。まず始めに、合成した触媒の励起状態における酸化還元電位を測定したところ、**93** と **96** の酸化還元電位は  $-2.1\text{ V vs Ag/Ag}^+$  よりも大きい値を示し、*fac*-Ir(ppy)<sub>3</sub> ( $E(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}*}) = -2.24\text{ V vs Ag/Ag}^+$ ) や PTZ ( $E(\text{PC}^+/\text{PC}^*) = -2.42\text{ V vs Ag/Ag}^+$ ) に比べ還元力が低い触媒であることが分かった。しかし、**93** と **96** のみが不活性臭化アルキル **86** ( $E(\text{S}/\text{S}^{\cdot-}) = -2.85\text{ V}$ ) に対して高い触媒活性を示した一方で、*fac*-Ir(ppy)<sub>3</sub> と PTZ は全く活性が見られなかった。これらの結果は、典型的な可視光レドックス反応とは異なり、本触媒は基底状態での酸化還元電位のみならずも依存しない電子移動反応が可能であることを示唆している。



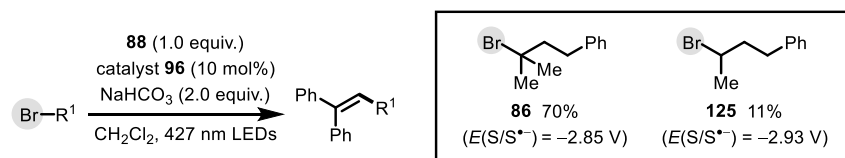
**Scheme 27. Redox Potentials of Catalysts in Excited States**

このような本触媒の特徴は、異なるハロゲン化アルキルを用いた競合実験によっても示唆されている (Scheme 28)。すなわち、不活性臭化アルキル **86** と活性塩化アルキル **124** を用いて **96** 存在下反応させると、**86** の酸化還元電位が大きく負の値を示すのにも関わらず、**89** を選択的に与えた。また、*fac*-Ir(ppy)<sub>3</sub> を用いた場合には、活性塩化アルキル **124** のみが目的物を与えた。これらの実験も、基質の基底状態での酸化還元電位に依存しない反応性を示す本触媒のユニークな特徴を示している。



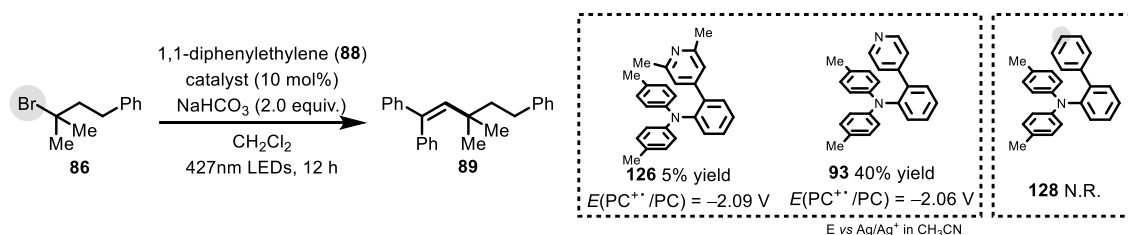
**Scheme 28. Competitive Experiments with Alkyl Halides**

また、本触媒系において第二級臭化アルキル **125** は、酸化還元電位が同等であるにも関わらず 3 級臭化アルキル **86** よりもはるかに反応性が低い (Scheme 31a)。このことは、生成するアルキルラジカルの安定性がアルキルラジカル発生段階に重要であることを示している。



Scheme 29. Comparison of Alkyl Bromides

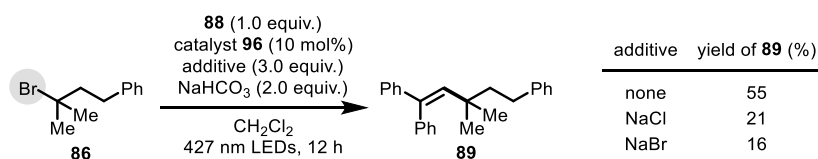
続いて、相互作用部位として働き得るピリジン環窒素のアルケニル化反応における重要性を評価することとした。ピリジン部位の 2,6 位にメチル基を有し、ピリジンのルイス塩基性部位周辺がより立体的に嵩高い触媒 **126** を検討したところ、**93** と比較して励起状態の還元力がほぼ同じ ( $E(\text{PC}^{+\bullet}/\text{PC}^*) = -2.09 \text{ V vs Ag/Ag}^+$ ) にもかかわらず、反応性の大幅な低下が観測された (Scheme 29)。本結果に加え、ピリジル基をフェニル基に置換した触媒 **128** では反応が全く進行しなかったことから、ピリジンのルイス塩基性窒素原子が本触媒の高い反応性に重要な可能性が示された。



Scheme 29. The Importance of the Lewis-Basic Site

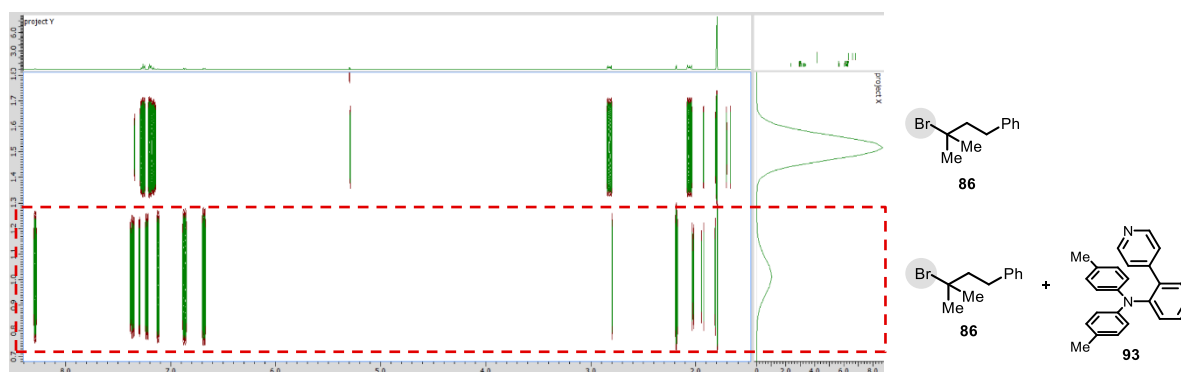
更に、ハロゲン結合アクセプターとして競合的に作用する Cl や Br などのハロゲン化物アニオンを過剰量添加による反応の抑制が見られた (Table 11)。これらの結果は、本触媒と臭化アルキルの間のハロゲン結合の存在は本触媒の反応性に重要であることを示している。

Table 11. Inhibition Effect of Halide Anion



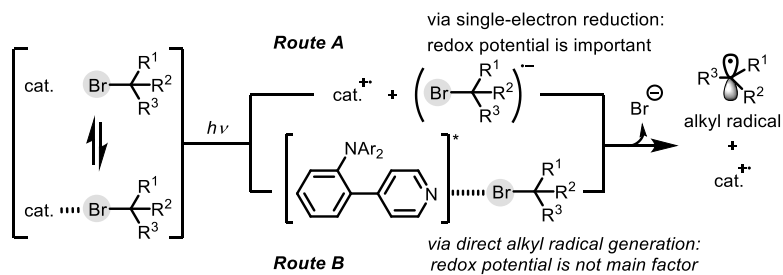
また、臭化アルキル **86** と触媒 **93** の混合溶媒を  $^1\text{H DOSY NMR}$  で測定したところ、基質-触媒複

合体の形成が示唆されている (Scheme 30)。しかし、反応が進行しない基質や触媒においても複合体の形成が見られていることから、基底状態における触媒-基質複合体形成及び光励起に対するハロゲン結合の重要性は現時点では未だ不明である。



**Scheme 30. Mechanistic Studies on Interaction between Substrate and Catalyst**

以上の観測結果から、今回見出した触媒は、従来の一電子還元 (Route A) ではなく、臭化アルキルから直接アルキルラジカルが直接生成する機構 (Route B) を介して、アルキルラジカルの生成を促進すると現在予想している (Scheme 31)。今後、更なる検討により詳細な機構について明らかにすることが望まれる。

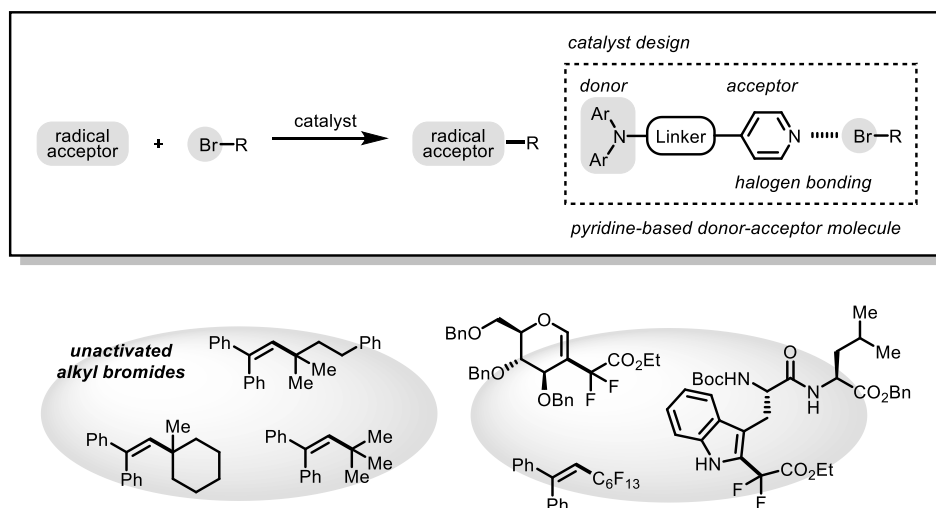


**Scheme 31. Mechanistic Insights on Alkyl Radical Generating Step**



### 第三節 結論

今回筆者はハロゲン結合を介した臭化アルキルとの複合体形成を想定した新規有機光触媒の開発を行い、光レドックス触媒として高活性な複合型ピリジン分子を見出すことに成功した (Scheme 32)。本触媒系は基質の基底状態での酸化還元電位に依らず、不活性基質を含む種々の臭化アルキルからのラジカル付加反応を促進でき、良好な収率でアルケニル化体を与えた。また、不活性臭化アルキルと活性塩化アルキルとの競合実験では、酸化還元電位に依らず臭化アルキルと選択的に反応しており、他の光触媒とは異なる化学選択性が見られた。種々の機構解析の結果、触媒-基質間の相互作用の存在が示唆された他、相互作用部位である可能性が高いピリジンのルイス塩基部位が反応の進行に重要であることが示された。また、従来の光触媒とは異なり、発生するアルキルラジカルの安定性がアルキルラジカル発生段階に重要である可能性が示唆されている。今後より詳細な機構解析により本触媒の活性向上に重要な因子を明らかにすることが期待される。



Scheme 32. Summary of the Reductive Cleavage of C-Br Bonds by Pyridine-based D-A Catalysis

## 第四章 総括

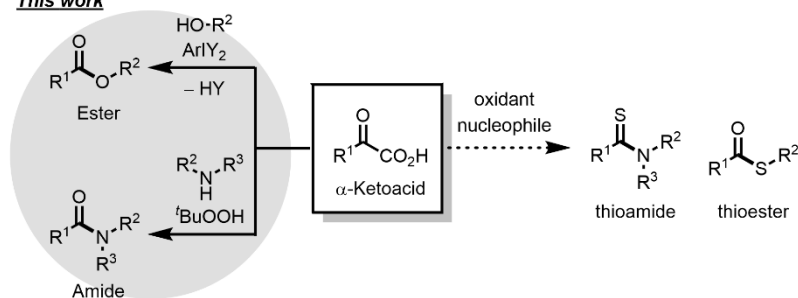
以上述べたように筆者は、 $\alpha$ -ケト酸と単純な求核剤を適切な酸化剤と共存させることで化学選択的な脱炭酸型縮合反応を達成し、ピリジンを基質認識部位として導入したドナー・アクセプター型分子を設計することで新規有機光触媒の開発にも成功した (Scheme 33)。

筆者は、 $\alpha$ -ケト酸が従来の脱水縮合とは異なる機構でカルボン酸誘導体を与えることに着目し、本化学種が高反応性と化学選択性を両立し得る新たなアシル化剤としての利用が可能と考えた。本戦略のもと、種々の単純な求核剤との新規脱炭酸型縮合の開発に取り組み、それぞれ超原子価ヨウ素を用いたエステル化反応と官能基共存性が高い化学選択的なアミド化反応の開発に成功した。これらの研究は、 $\alpha$ -ケト酸の一般的なアシル化剤としての有用性を支持する重要な知見である。更に、酸化剤と求核剤の組み合わせを工夫することでその他のカルボン酸誘導体合成への応用可能性を示す基礎的な検討でもあり、今後の展開が期待される (Scheme 33a)<sup>38, 39</sup>。

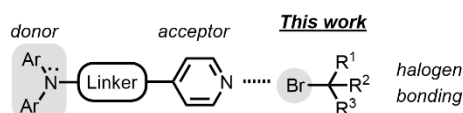
最後に、筆者は基質認識による効率的な一電子移動反応が可能な新規有機光触媒の開発を目指し、ピリジン含有ドナー・アクセプター型分子を設計した。本分子は基質の基底状態での酸化還元電位に依らず不活性基質を含めた種々の臭化アルキルから触媒的にアルキルラジカルを発生させることが可能であり、種々のラジカル受容体を用いたアルケニル化反応も良好に進行した。本研究は酸化還元電位によって支配されていた反応性を相互作用の利用により制御した例であり、本戦略が光触媒設計の新たな指針となり得ることを示すものだと考えられる。また、今後はハロゲン結合に留まらずルイス酸性を有する還元電位の高い低活性基質への更なる適用が期待される (Scheme 33b)。

### (a) Decarboxylative Condensation Reactions Using $\alpha$ -Ketoacid with Normal Nucleophiles

#### *This work*



### (b) A Pyridine-Based Donor-Acceptor Molecule



Scheme 33. Summary

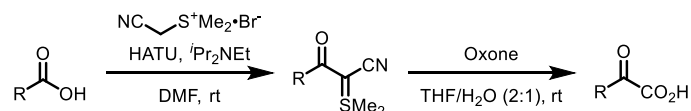
## 実験項

### General Information

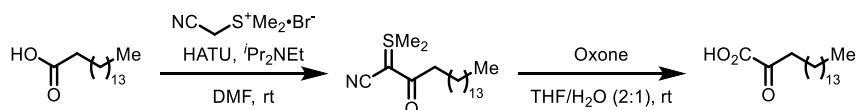
All reactions were carried out under air with no precautions taken to exclude moisture unless otherwise noted. All materials and solvents were purchased from Tokyo Chemical Industry Co., Ltd., FUJIFILM Wako Pure Chemical Corporation, Merck KGaA, and other commercial suppliers and were used without purification. The Kessil® PR160L-390nm, PR160L-427nm, and PR160L-456nm were used as the blue LED light source for the reactions (<https://kessil.com/science/PR160L.php>). Analytical thin-layer chromatography was performed with Merck Silica gel 60. Column chromatography was performed on Fuji Silysia silica gel (BW-300, COOH, DIOL, NH). Preparative medium pressure liquid chromatography was performed with Büchi Pure Chromatography Instrument C-815 using Fuji Silysia Chromatorex Q-Pack (SI50). <sup>1</sup>H NMR spectra were recorded on JEOL JNM-ECA 500 (500 MHz) and JNM-ECZ 600 (600 MHz) and are reported in ppm relative to Me<sub>4</sub>Si ( $\delta$  0.00) in CDCl<sub>3</sub> and internal residual solvents (acetone-*d*<sub>6</sub>  $\delta$  2.04 and dimethylsulfoxide-*d*<sub>6</sub>  $\delta$  2.49). Data reported as: integration; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz. Protondecoupled <sup>13</sup>C NMR spectra were recorded on JEOL JNM-ECA 500 (126 MHz) and JNM-ECZ 600 (151 MHz) and are reported in ppm relative to CDCl<sub>3</sub> ( $\delta$  77.0 and acetone-*d*<sub>6</sub>  $\delta$  29.8 and dimethylsulfoxide-*d*<sub>6</sub>  $\delta$  39.7). <sup>19</sup>F NMR were recorded on JEOL JNM-ECA 500 (471 MHz) and JNM-ECZ 600 (565 MHz) and are reported in ppm. High-resolution mass spectra were obtained on a SHIMADZU LCMS-IT-TOF fitted with an ESI-MS and JEOL JMS-700 double-focusing mass spectrometer, Thermo Scientific Exactive Plus. Infrared spectra were recorded on JASCO FT/IR-4100 Fourier-transform infrared spectrometer ATR (attenuated total reflectance). Supercritical Fluid Chromatography (SFC) analysis was performed on Waters ACQUITY UPC2 equipped with a UV detector. Optical rotations were determined with JASCO P-2200KDT polarimeter and are the average of five measurements and reported as follows:  $[\alpha]_D^{25}$  °C<sub>λ</sub> concentration (c = g / 100 mL, solvent). All melting points were measured on BÜCHI M-565 melting point apparatus and are uncorrected. Reactions under microwave irradiation were performed with Biotage Initiator+.

## Experiments in chapter 2

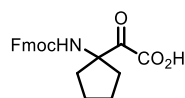
### General Procedure for Preparation of $\alpha$ -Ketoacids (GP1)<sup>11c</sup>



A 200 mL round bottom flask was charged with a stir bar, carboxylic acid (1.0 equiv.), sulfonium bromide (1.25 equiv.) and DMF (0.5 M) under Ar atmosphere. To the mixture were added DIPEA (3.0 equiv.) and HATU (1.25 equiv.). After stirring for 75 min, the reaction was quenched by water, concentrated under reduced pressure to remove DMF and extracted with MTBE. The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford sulfonium ylide as a white solid. A 200 mL round bottom flask was charged with a stir bar, sulfonium ylide and THF/H<sub>2</sub>O (2:1, 0.5 M). To the solution was added Oxone (4.0 equiv.) in one portion. After stirring for 90 min, the reaction was quenched by dimethylsulfide (4.0 equiv.), concentrated under reduced pressure to remove THF and extracted with MTBE. The combined organic layers were then washed with 10% aqueous citric acid and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford corresponding  $\alpha$ -ketoacids.

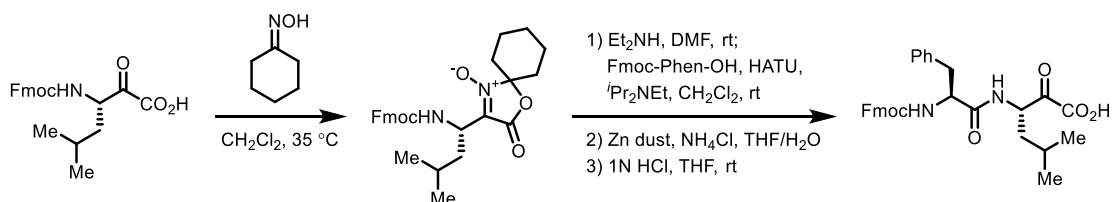


**2-Oxoheptadecanoic acid:** The reaction was performed according to **GP1** to afford  $\alpha$ -ketoacid in 80% yield over 2 steps as a white solid. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  2.96 (2H, t,  $J$  = 7.4 Hz), 1.69-1.63 (2H, m), 1.37-1.23 (24H, m), 0.88 (3H, t,  $J$  = 6.9 Hz). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  196.1, 159.3, 37.2, 31.9, 29.64, 29.60, 29.5, 29.4, 29.2, 28.9, 23.1, 22.7, 14.1. HRMS (ESI)  $m/z$ : [M-H]<sup>-</sup> Calcd for C<sub>17</sub>H<sub>32</sub>O<sub>3</sub> 283.2279; Found: 283.2280. IR (ATR): 3079, 2917, 2849, 1712 cm<sup>-1</sup>. Melting Point: 71.7-72.4 °C



**Fmoc-CycLeu-CO<sub>2</sub>H:** The reaction was performed according to **GP1** to afford Fmoc-CycLeu-CO<sub>2</sub>H in 42% yield over 2 steps as an amorphous solid. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.76 (2H, d,  $J$  = 7.4 Hz), 7.55 (2H, d,  $J$  = 7.4 Hz), 7.41 (2H, t,  $J$  = 7.4 Hz), 7.32 (2H, t,  $J$  = 7.4 Hz), 5.45 (1H, brs), 4.50-4.38 (2H, br), 4.18 (1H, t,  $J$  = 6.3 Hz), 2.34 (2H, brs), 1.95-1.65 (6H, br). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  195.4, 194.6, 161.4, 156.6,

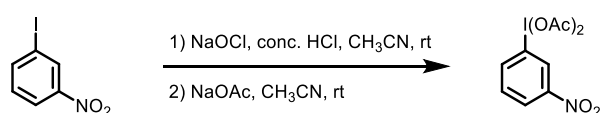
143.5, 141.2, 127.83, 127.78, 127.1, 124.9, 124.8, 120.1, 120.0, 69.1, 68.4, 67.5, 66.5, 47.1, 47.0, 36.8, 36.3, 24.4, 24.3. **HRMS (ESI) *m/z***:  $[M-H]^-$  C<sub>22</sub>H<sub>21</sub>NO<sub>5</sub> 378.1347; Found: 378.1347. **IR (ATR)**: 3324, 1706, 1519 cm<sup>-1</sup>. **Melting Point**: 139.8-140.0 °C.



**Fmoc-Phe-Leu-CO<sub>2</sub>H**<sup>40</sup>: A 200 mL round bottom flask was charged with a stir bar, crude Fmoc-Leu-OH (10 mmol, 1.5 equiv.), cyclohexanone oxime (755 mg, 6.67 mmol, 1.00 equiv.) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) under Ar atmosphere and the mixture was stirred at 35 °C. After stirring for 14 hours, the mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (BW-300 SiO<sub>2</sub>, 80 mL, 0% → 10% → 15% EtOAc/hexane) to afford nitron (1.25 mg, 2.62 mmol, 26% yield) as a white solid. A 50 mL round bottom flask was charged with a stir bar, nitron (904 mg, 1.85 mmol, 1.0 equiv.) and DMF (25 mL) and to the stirring mixture was added Et<sub>2</sub>NH (957 μL, 9.25 mmol, 5.0 equiv.). After stirring for 4 hours at room temperature, the mixture was diluted with <sup>i</sup>PrOH and filtered through a cotton plug and the filtrate was concentrated under reduced pressure to give a crude amine. A 50 mL round bottom flask was charged with a stir bar, the crude amine (1.85 mmol, 1.05 equiv.), Fmoc-Phe-OH (678 mg, 1.75 mmol, 1.0 equiv.) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL). To the stirring mixture was added <sup>i</sup>Pr<sub>2</sub>NEt (914 μL, 5.4 mmol, 3.0 equiv.) and HBTU (997 mg, 2.63 mmol, 1.5 equiv.). After stirring for 17 hours at room temperature, the mixture was washed with saturated aqueous NH<sub>4</sub>Cl (3 x 25 mL) and brine (1 x 25 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 70 mL, 10% → 20% → 25% → 30% EtOAc/hexane) to afford a dipeptide nitron (300 mg, 1.43 mmol, 82% yield) as a white solid. A 50 mL round bottom flask was charged with a stir bar, the dipeptide nitron (717 mg, 1.08 mmol, 1.0 equiv.) and zinc dust (353 mg, 5.40 mmol, 5.0 equiv.). To the mixture were added THF (10 mL) and saturated aqueous NH<sub>4</sub>Cl (10 mL). After stirring for 23 hours at room temperature, the mixture was filtered through a short Celite pad and the filtrate was extracted with Et<sub>2</sub>O (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (BW-300 SiO<sub>2</sub>, 70 mL, 10% → 20% → 25% EtOAc/hexane) to afford a cyclic imine as a white solid. A 50 mL round bottom flask was charged with a stir bar and the cyclic imine and THF (5 mL) and aqueous 1N HCl (5 mL) were added. After stirring for 24 hours at 40 °C, the mixture was diluted with additional aqueous 1N HCl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL),

dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting white solid was triturated with Et<sub>2</sub>O, collected and dried under reduced pressure to afford Fmoc-Phe-Leu-OH in 29% yield over 2 steps as a white solid. **<sup>1</sup>H-NMR (500 MHz, DMSO-*d*<sub>6</sub>)**: δ 8.53 (1H, d, *J* = 6.9 Hz), 7.86 (2H, d, *J* = 7.8 Hz), 7.68-7.59 (3H, m), 7.41-7.37 (2H, m), 7.33-7.23 (6H, m), 7.20-7.16 (1H, m), 4.82-4.77 (1H, m), 4.33-4.27 (1H, m), 4.14-4.08 (3H, m), 2.97 (1H, d, *J* = 13.3 Hz), 2.79-2.72 (1H, m), 1.70-1.62 (1H, m), 1.57-1.48 (2H, m), 0.90-0.80 (6H, m). **<sup>13</sup>C-NMR (126 MHz, DMSO-*d*<sub>6</sub>)**: δ 195.6, 172.1, 163.2, 155.8, 143.8, 143.7, 140.6, 138.1, 129.2, 128.1, 127.6, 127.0, 126.3, 125.4, 125.3, 120.1, 65.6, 55.7, 53.6, 46.5, 37.9, 37.4, 24.4, 23.0, 21.2. **HRMS (ESI) *m/z***: [M+H]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub> 529.2333; found: 529.2335. **IR (ATR)**: 3300, 1741, 1690, 1628, 1536 cm<sup>-1</sup>. **Melting Point**: 158.3-159.4 °C. **Optical Rotation**: [α]<sup>26</sup><sub>D</sub> -10.6 (c 0.10, MeOH).

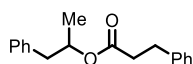
### Preparation of 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I(OAc)<sub>2</sub> (**10**)



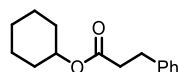
A 100 mL round bottom flask was charged with a stir bar, 3-iodonitrobenzene (4.98 g, 20.0 mmol, 1.0 equiv.), and CH<sub>3</sub>CN (40 mL). To the stirred mixture was added sodium hypochlorite solution (8.5–13.5% in H<sub>2</sub>O, 60 mL) and then conc. HCl (40 mL) dropwise. After stirring for 90 mins at room temperature, a yellow precipitate was collected by the filtration. The solid was washed with water (10 mL x 3) and hexane (15 mL x 3), and dried under reduced pressure to afford 3-nitro(dichloro)iodobenzene (5.44 g, 17.0 mmol, 85% yield) as yellow solid. A 200 mL round bottom flask was charged with a stir bar, 3-nitro(dichloro)iodobenzene (5.44 g, 17.0 mmol, 1.0 equiv.), and CH<sub>3</sub>CN (34 mL) under Ar atmosphere. To the mixture was added NaOAc (2.79 g, 34.0 mmol, 2.0 equiv.) and covered with aluminum foil. After stirring for 16 hours at room temperature, inorganic salts were removed by Celite filtration and the filtrate was concentrated under reduced pressure. The resulting solid was recrystallized from AcOH/Hexane to afford 3-nitro(diacetoxy)iodobenzene **10** (2.90 g, 7.91 mmol, 47%) as a white solid. **<sup>1</sup>H-NMR (500 MHz, acetone-*d*<sub>6</sub>)**: δ 9.11 (1H, t, *J* = 1.9 Hz), 8.68 (1H, ddd, *J* = 8.0, 1.8, 1.1 Hz), 8.53 (1H, ddd, *J* = 8.3, 2.3, 0.9 Hz), 7.93 (1H, t, *J* = 8.0 Hz), 1.93 (6H, s). **<sup>13</sup>C-NMR (126 MHz, acetone-*d*<sub>6</sub>)**: δ 177.0, 149.5, 141.9, 132.8, 130.8, 127.3, 121.5, 20.1. **Anal. Calcd for C<sub>10</sub>H<sub>10</sub>INO<sub>6</sub>**: C, 32.72; H, 2.75; N, 3.82. Found: C, 32.60; H, 2.64; N, 3.77. **IR (ATR)**: 1643, 1527, 1343, 815, 714 cm<sup>-1</sup>. **Melting Point**: 150.3-150.6 °C.

**General Procedure for Decarboxylative Esterification (GP2)**: A sealed tube was charged with a stir bar, alcohol (0.200 mmol, 1.0 equiv.), α-ketoacid (0.300 mmol, 1.5 equiv.) and CH<sub>2</sub>Cl<sub>2</sub> (1 mL). To the mixture was added 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I(OAc)<sub>2</sub> **10** (110 mg, 0.300 mmol, 1.5 equiv.) in one portion then the tube was capped and covered with aluminum foil. After stirring for indicated time at room temperature, the mixture was

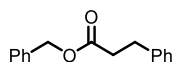
concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO<sub>2</sub>, EtOAc/hexane) to provide the desired ester.



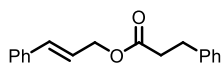
**1-Phenylpropan-2-yl 3-phenylpropanoate (11):** The reaction was performed according to **GP2** for an hour and gave product **11** in 77% yield as a colorless oil. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.27-7.26 (4H, m), 7.22-7.16 (6H, m), 5.12 (1H, td, *J* = 6.4, 6.4 Hz), 2.90-2.87 (3H, m), 2.73 (1H, dd, *J* = 13.6, 6.4 Hz), 2.56 (2H, t, *J* = 6.4 Hz), 1.19 (3H, d, *J* = 6.3 Hz). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>): δ 172.3, 140.5, 137.5, 129.4, 128.4, 128.3, 128.2, 126.4, 126.2, 71.5, 42.2, 36.1, 30.9, 19.4. HRMS (ESI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>21</sub>O<sub>2</sub> 269.1530; Found: 269.1536. IR (ATR): 1730 cm<sup>-1</sup>.



**Cyclohexyl 3-phenylpropanoate (12):** The reaction was performed according to **GP2** for an hour and gave product **12** in 90% yield as a colorless oil. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.28-7.27 (2H, m), 7.20-7.19 (3H, m), 4.76-4.74 (1H, m), 2.94 (2H, t, *J* = 7.7 Hz), 2.61 (2H, t, *J* = 7.7 Hz), 1.80-1.78 (2H, m), 1.69-1.68 (2H, m), 1.53-1.52 (1H, m), 1.39-1.32 (4H, m), 1.26-1.22 (1H, m). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>): δ 172.4, 140.6, 128.4, 128.3, 126.1, 72.6, 36.2, 31.6, 31.0, 25.3, 23.7. HRMS (ESI) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>20</sub>O<sub>2</sub>Na: 255.1356; Found: 255.1368. IR (ATR): 1729 cm<sup>-1</sup>.

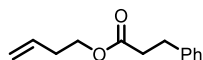


**Benzyl 3-phenylpropanoate (13):** The reaction was performed according to **GP2** for an hour and gave product **13** in 96% yield as a colorless oil. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.37-7.25 (7H, m), 7.21-7.18 (3H, m), 5.11 (2H, s), 2.97 (2H, t, *J* = 7.9 Hz), 2.69 (2H, t, *J* = 7.7 Hz). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>): δ 172.7, 140.4, 135.9, 128.52, 128.48, 128.3, 128.2, 126.2, 66.3, 35.9, 30.9. (One peak is missing due to overlapping.) HRMS (ESI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>17</sub>O<sub>2</sub> 241.1223; Found: 241.1218. IR (ATR): 1734 cm<sup>-1</sup>.

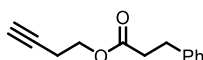


**Cinnamyl 3-phenylpropanoate (14):** The reaction was performed according to **GP2** for an hour and gave product **14** in 96% yield as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.38 (2H, d, *J* = 7.4 Hz), 7.31-7.28 (5H, m), 7.21-7.19 (3H, m), 6.62 (1H, d, *J* = 15.8 Hz), 6.25 (1H, dt, *J* = 15.8, 6.5 Hz), 4.73 (2H, d, *J* = 6.3 Hz), 2.98 (2H, t, *J* = 7.7 Hz), 2.68 (2H, t, *J* = 7.9 Hz). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 172.7, 140.4,

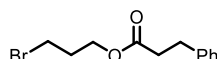
136.2, 134.2, 128.6, 128.5, 128.3, 128.0, 126.6, 126.3, 123.1, 65.1, 35.9, 30.9. **HRMS (ESI)  $m/z$ :**  $[M+Na]^+$  Calcd for  $C_{18}H_{18}O_2Na$  289.1199; Found: 289.1196. **IR (ATR):** 1734  $cm^{-1}$ .



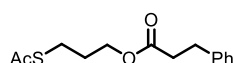
**But-3-en-1-yl 3-phenylpropanoate (15):** The reaction was performed according to **GP2** for an hour and gave product **15** in quantitative yield as a colorless oil.  **$^1H$ -NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  7.28 (2H, t,  $J = 7.4$  Hz), 7.21-7.20 (3H, m), 5.75 (1H, ddt,  $J = 17.2, 10.3, 6.9$  Hz), 5.10-5.06 (2H, m), 4.13 (2H, t,  $J = 6.7$  Hz), 2.95 (2H, t,  $J = 7.9$  Hz), 2.63 (2H, t,  $J = 7.9$  Hz), 2.36 (2H, td,  $J = 6.8, 6.8$  Hz).  **$^{13}C$ -NMR (126 MHz,  $CDCl_3$ ):**  $\delta$  172.9, 140.5, 133.9, 128.4, 128.3, 126.2, 117.2, 63.5, 35.8, 33.0, 30.9. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for  $C_{13}H_{17}O_2$  205.1223; Found: 205.1229. **IR (ATR):** 1736  $cm^{-1}$ .



**But-3-yn-1-yl 3-phenylpropanoate (16):** The reaction was performed according to **GP2** for an hour and gave product **16** in 84% yield as a colorless oil.  **$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  7.29-7.27 (2H, m), 7.21-7.20 (3H, m), 4.18 (2H, t,  $J = 6.7$  Hz), 2.96 (2H, t,  $J = 7.9$  Hz), 2.66 (2H, t,  $J = 7.7$  Hz), 2.50 (2H, td,  $J = 6.7, 2.6$  Hz), 1.99 (1H, t,  $J = 2.6$  Hz).  **$^{13}C$  NMR (126 MHz,  $CDCl_3$ ):**  $\delta$  172.6, 140.3, 128.5, 128.3, 126.3, 80.0, 69.9, 62.1, 35.7, 30.9, 18.9. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for  $C_{13}H_{15}O_2$  203.1067; Found: 203.1069. **IR (ATR):** 1738  $cm^{-1}$ .



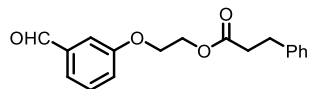
**3-Bromopropyl 3-phenylpropanoate (17):** The reaction was performed according to **GP2** for an hour and gave product **17** in 98% yield as a colorless oil.  **$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  7.29 (2H, t,  $J = 7.4$  Hz), 7.22-7.20 (3H, m), 4.20 (2H, t,  $J = 6.0$  Hz), 3.36 (2H, t,  $J = 6.4$  Hz), 2.96 (2H, t,  $J = 7.7$  Hz), 2.65 (2H, t,  $J = 7.7$  Hz), 2.15-2.10 (2H, m).  **$^{13}C$  NMR (126 MHz,  $CDCl_3$ ):**  $\delta$  172.7, 140.3, 128.5, 128.2, 126.3, 62.1, 35.8, 31.6, 30.9, 29.4. **HRMS (ESI)  $m/z$ :**  $[M+Na]^+$  Calcd for  $C_{19}H_{22}O_4Na$  293.0148; Found: 293.0151. **IR (ATR):** 1736  $cm^{-1}$ .



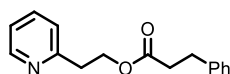
**3-(Acetylthio)propyl 3-phenylpropanoate (18):** The reaction was performed according to **GP2** for an hour and gave product **18** in 75% yield as a pale yellow oil.  **$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  7.29-7.28 (2H, m), 7.21-7.19 (3H, m), 4.11 (2H, t,  $J = 6.2$  Hz), 2.96 (2H, t,  $J = 7.7$  Hz), 2.86 (2H, t,  $J = 7.2$  Hz), 2.65 (2H, t,  $J =$



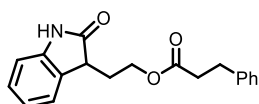
7.7 Hz), 2.33 (3H, s), 1.88 (2H, tt,  $J = 6.6, 6.6$  Hz).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.6, 172.8, 140.4, 128.5, 128.3, 126.3, 62.8, 35.8, 30.9, 30.6, 28.6, 25.6. HRMS (ESI)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_3\text{SNa}$  267.1055; Found: 267.1050. IR (ATR): 1736, 1692  $\text{cm}^{-1}$ .



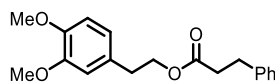
**2-(3-Formylphenoxy)ethyl 3-phenylpropanoate (19):** The reaction was performed according to GP2 for an hour and gave product **19** in 72% yield as a colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.98 (1H, s), 7.50-7.44 (2H, m), 7.39 (1H, s), 7.28-7.17 (6H, m), 4.45 (2H, t,  $J = 4.6$  Hz), 4.20 (2H, t,  $J = 4.9$  Hz), 2.97 (2H, t,  $J = 7.7$  Hz), 2.69 (2H, t,  $J = 7.7$  Hz).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  192.0, 172.7, 159.0, 140.2, 137.8, 130.1, 128.5, 128.3, 126.3, 124.0, 122.0, 112.7, 66.1, 62.5, 35.7, 30.8. HRMS (ESI)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{18}\text{H}_{19}\text{O}_4$  299.1278; Found: 299.1274. IR (ATR): 1737, 1698  $\text{cm}^{-1}$ .



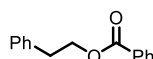
**2-(pyridin-2-yl)ethyl 3-phenylpropanoate (20):** The reaction was performed according to GP2 for an hour and gave product **20** in 82% yield as a pale yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (1H, d,  $J = 4.0$  Hz), 7.59 (1H, td,  $J = 7.7, 1.8$  Hz), 7.28-7.26 (2H, m), 7.19-7.13 (5H, m), 4.47 (2H, t,  $J = 6.7$  Hz), 3.09 (2H, t,  $J = 6.7$  Hz), 2.91 (2H, t,  $J = 7.9$  Hz), 2.60 (2H, t,  $J = 7.7$  Hz).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.8, 158.0, 149.4, 140.4, 136.4, 128.4, 128.2, 126.2, 123.4, 121.6, 163.6, 37.3, 35.8, 30.8. HRMS (ESI)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_2$  256.1332; Found: 256.1337. IR (ATR): 1733  $\text{cm}^{-1}$ .



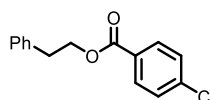
**2-(2-Oxindolin-3-yl)ethyl 3-phenylpropanoate (21):** The reaction was performed according to GP2 for an hour and gave product **21** in 90% yield as a pale yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (1H, br s), 7.28-7.16 (7H, m), 7.03 (1H, t,  $J = 7.4$  Hz), 6.87 (1H, d,  $J = 7.7$  Hz), 4.29 (1H, dt,  $J = 12.6, 6.3$  Hz), 4.17 (1H, dt,  $J = 12.6, 6.3$  Hz), 3.49 (1H, t,  $J = 6.2$  Hz), 2.89 (2H, t,  $J = 7.7$  Hz), 2.54 (2H, t,  $J = 7.6$  Hz), 2.35-2.21 (2H, m).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  179.4, 172.7, 140.4, 128.54, 128.47, 128.3, 128.1, 126.2, 124.3, 122.4, 109.7, 61.1, 42.9, 35.6, 30.7, 29.1. HRMS (ESI)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{19}\text{H}_{20}\text{NO}_3$  310.1438, Found: 310.1436. IR (ATR): 3208, 1706  $\text{cm}^{-1}$ .



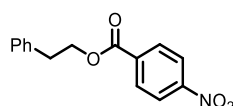
**But-3-en-1-yl 3-phenylpropanoate (22):** The reaction was performed according to **GP2** for an hour and gave product **22** in 95% yield as a pale yellow oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.28 (2H, t,  $J$  = 7.4 Hz), 7.22-7.17 (3H, m), 6.80 (1H, d,  $J$  = 7.7 Hz), 6.74-6.72 (2H, m), 4.26 (2H, t,  $J$  = 7.0 Hz), 3.86 (6H, s), 2.93 (2H, t,  $J$  = 7.9 Hz), 2.86 (2H, t,  $J$  = 7.2 Hz), 2.62 (2H, t,  $J$  = 7.9 Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  172.8, 148.8, 147.7, 140.4, 130.2, 128.5, 128.2, 126.2, 120.8, 112.0, 111.1, 65.1, 55.9, 55.8, 35.9, 34.6, 30.9. **HRMS (ESI)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>22</sub>O<sub>4</sub>Na: 337.1410; Found: 337.1420. **IR (ATR):** 1732 cm<sup>-1</sup>.



**But-3-en-1-yl 3-phenylpropanoate (23):** The reaction was performed according to **GP2** for an hour and gave product **23** in 83% yield as a colorless oil. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  8.02 (2H, t,  $J$  = 4.2 Hz), 7.55 (1H, t,  $J$  = 7.4 Hz), 7.43 (2H, t,  $J$  = 7.7 Hz), 7.31-7.26 (5H, m), 4.53 (2H, t,  $J$  = 7.0 Hz), 3.08 (2H, t,  $J$  = 7.0 Hz). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  166.5, 137.9, 132.9, 130.2, 129.5, 128.9, 128.5, 128.3, 126.6, 65.5, 35.2. **HRMS (ESI)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>14</sub>O<sub>2</sub>Na 249.0886; Found: 249.0888. **IR (ATR):** 1716 cm<sup>-1</sup>.

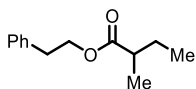


**Phenethyl 4-chlorobenzoate (24):** The reaction was performed according to **GP2** for an hour and gave product **24** in 86% yield as a colorless oil. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.94 (2H, d,  $J$  = 8.3 Hz), 7.40 (2H, d,  $J$  = 8.3 Hz), 7.33 (2H, t,  $J$  = 7.6 Hz), 7.28-7.23 (3H, m), 4.53 (2H, t,  $J$  = 6.9 Hz), 3.08 (2H, t,  $J$  = 6.9 Hz). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  165.6, 139.3, 137.7, 130.9, 128.9, 128.69, 128.67, 128.6, 126.6, 65.7, 35.2. **HRMS (ESI)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>13</sub>O<sub>2</sub>ClNa 283.0496; Found: 283.0503. **IR (ATR):** 1718 cm<sup>-1</sup>.

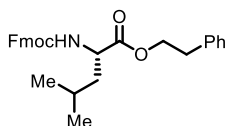


**Phenethyl 4-nitrobenzoate (25):** The reaction was performed according to **GP2** for an hour and gave product **25** in quantitative yield as a white solid. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  8.28 (2H, d,  $J$  = 7.2 Hz), 8.16 (2H, d,  $J$  = 6.9 Hz), 7.34 (2H, t,  $J$  = 6.9 Hz), 7.28-7.27 (3H, m), 4.59 (2H, t,  $J$  = 6.9 Hz), 3.11 (2H, t,  $J$  = 6.7 Hz). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  164.6, 150.5, 137.4, 135.6, 130.6, 128.9, 128.6, 126.8, 123.5, 66.3, 35.1. **HRMS (FAB)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>13</sub>NO<sub>4</sub>Na 294.0742; Found: 294.0740. **IR (ATR):**

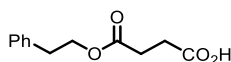
1724, 1526  $\text{cm}^{-1}$ . **Melting Point:** 56.9-59.1  $^{\circ}\text{C}$ .



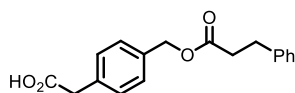
**Phenethyl 2-methylbutanoate (26):** The reaction was performed according to **GP2** for an hour and gave product **26** in 85% yield as a colorless oil.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.31-7.29 (2H, m), 7.26-7.22 (3H, m), 4.33-4.26 (2H, m), 2.94 (2H, t,  $J = 7.0$  Hz), 2.34 (1H, qt,  $J = 7.0, 7.0$  Hz), 1.64 (1H, ddq,  $J = 14.0, 7.0, 7.0$  Hz), 1.44 (1H, ddq,  $J = 14.0, 7.0, 7.0$  Hz), 1.11 (3H, d,  $J = 6.9$  Hz), 0.85 (3H, t,  $J = 7.4$  Hz).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  176.7, 137.9, 128.9, 128.4, 126.5, 64.6, 41.0, 35.2, 26.7, 16.6, 11.6. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{13}\text{H}_{18}\text{O}_2\text{Na}$  229.1199; Found: 229.1203. **IR (ATR):** 1732  $\text{cm}^{-1}$ .



**Phenethyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-leucinate (28):** The reaction was performed according to **GP2** for an hour and gave product **28** in 91% yield as a white solid.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.76 (2H, d,  $J = 7.7$  Hz), 7.59 (2H, t,  $J = 6.2$  Hz), 7.39 (2H, t,  $J = 7.4$  Hz), 7.31-7.28 (4H, m), 7.23-7.20 (3H, m), 5.16 (1H, d,  $J = 8.9$  Hz), 4.40-4.30 (5H, m), 4.22 (1H, t,  $J = 7.0$  Hz), 2.95 (2H, t,  $J = 7.0$  Hz), 1.68-1.43 (3H, m), 0.91-0.89 (6H, m).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.1, 155.9, 143.9, 143.7, 141.3, 137.3, 128.9, 128.5, 127.7, 127.0, 126.6, 125.1, 120.0, 119.9, 66.9, 65.7, 52.4, 47.1, 34.9, 24.6, 22.7, 21.8. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{29}\text{H}_{32}\text{NO}_4$  458.2326; Found: 458.2316. **IR (ATR):** 3338, 1721  $\text{cm}^{-1}$ . **Melting Point:** 77.1-79.1  $^{\circ}\text{C}$ . **Optical rotation:**  $[\alpha]^{25}_{\text{D}} -10.888$  (c 1.05,  $\text{CHCl}_3$ ).

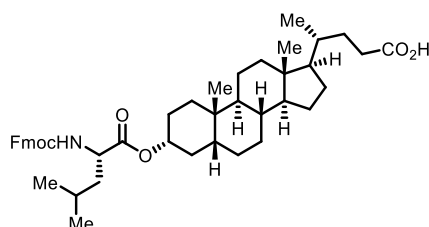


**4-Oxo-4-phenethoxybutanoic acid (30):** The reaction was performed according to **GP2** for an hour and gave product **30** in 61% yield as a colorless oil.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.32-7.30 (2H, m), 7.25-7.22 (3H, m), 4.32 (2H, t,  $J = 7.0$  Hz), 2.94 (2H, t,  $J = 7.0$  Hz), 2.68-2.60 (4H, m).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  177.9, 172.0, 137.6, 128.9, 128.5, 126.6, 65.3, 35.0, 28.8. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{12}\text{H}_{15}\text{O}_4$  223.0965; Found: 223.0959. **IR (ATR):** 1733, 1712  $\text{cm}^{-1}$ .



**2-(4-(((3-Phenylpropanoyl)oxy)methyl)phenyl)acetic acid (32):** The reaction was performed according to

GP2 for an hour and gave product **32** in 84% yield as a white solid. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.28-7.26 (6H, m), 7.21-7.18 (3H, m), 5.09 (2H, s), 3.65 (2H, s), 2.96 (2H, t,  $J = 7.9$  Hz), 2.68 (2H, t,  $J = 7.7$  Hz). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  177.1, 172.7, 140.3, 135.0, 133.2, 129.6, 128.55, 128.49, 128.3, 126.3, 65.9, 40.6, 35.9, 30.9. **HRMS (ESI)  $m/z$ :**  $[M-H]^-$  Calcd for C<sub>18</sub>H<sub>17</sub>O<sub>4</sub> : 297.1132, Found: 297.1132. **IR (ATR):** 1733, 1699 cm<sup>-1</sup>. **Melting Point:** 60.4-62.6 °C.



**(R)-4-((3R,5R,8R,9S,10S,13R,14S,17R)-3-((((9H-Fluoren-9-yl)methoxy)carbonyl)-L-leucyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoic acid (**34**):** The reaction was performed according to GP2 for an hour and gave product **34** in 60% yield as a colorless oil. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.76 (2H, d,  $J = 7.4$  Hz), 7.61-7.59 (2H, m), 7.39 (2H, t,  $J = 7.3$  Hz), 7.31 (2H, t,  $J = 7.4$  Hz), 5.32 (1H, d,  $J = 8.6$  Hz), 4.79-4.76 (1H, m), 4.53-4.45 (1H, m), 4.40-4.33 (1H, m), 4.30-4.18 (2H, m), 2.42-2.38 (1H, m), 2.29-2.22 (1H, m), 1.91-1.18 (23H, m), 1.07-0.88 (18H, m), 0.61 (3H, s). **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  180.0, 172.8, 156.0, 144.0, 143.6, 141.2, 127.7, 127.6, 127.01, 126.97, 125.2, 125.1, 119.9, 75.6, 66.9, 56.2, 55.8, 52.7, 47.1, 42.6, 41.9, 41.6, 40.3, 39.9, 35.7, 35.3, 34.9, 34.5, 32.1, 31.1, 30.7, 28.1, 26.9, 26.5, 26.1, 24.7, 24.1, 23.2, 22.9, 21.8, 20.7, 18.2, 11.9. **HRMS (ESI)  $m/z$ :**  $[M+Na]^+$  Calcd for C<sub>45</sub>H<sub>61</sub>NO<sub>6</sub>Na 734.4397; Found: 734.4391. **IR (ATR):** 1706 cm<sup>-1</sup>. **Optical rotation:**  $[\alpha]^{25}_D + 17.12$  (c 0.51, CHCl<sub>3</sub>).

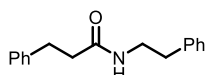
## Experiments in chapter 2

### General Procedure for Decarboxylative Amidation (GP3):

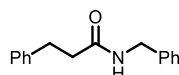
A sealed tube was charged with a stir bar, amine (1.0 equiv.), and TBHP (1.2-1.5 equiv.), and a solvent. To the stirring mixture was added the solution of  $\alpha$ -ketoacid (1.1 equiv.) in the solvent in one portion by a pipette and the tube was capped and covered with aluminum foil. After stirring for 1 h at room temperature, the mixture was concentrated under reduce pressure. The crude residue was purified by flash column chromatography to afford a corresponding amide.

### General Procedure for Peptide Synthesis (GP4):

A sealed tube was charged with a stir bar, amine (1.0 equiv.), and DMF and cooled to 0 °C. To the stirring mixture were added TBHP (70% in H<sub>2</sub>O, 1.5 equiv.) and the solution of  $\alpha$ -ketoacid (1.2 equiv.) in DMF by a pipette and the tube was capped and covered with aluminum foil. After stirring for 12 h at 0 °C, the reaction was quenched by saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> then extracted with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford a corresponding peptide. The ee or dr of the product was estimated by chiral SFC analysis.

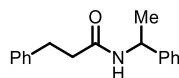


**N-Phenethyl-3-phenylpropanamide (40):** The reaction was performed according to **GP3** for an hour and gave product **40** in 92% yield as a white crystalline solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.31-7.24 (4H, m), 7.23-7.17 (4H, m), 7.08 (2H, d,  $J$  = 7.4 Hz), 5.36 (1H, brs), 3.48 (2H, q,  $J$  = 6.5 Hz), 2.94 (2H, t,  $J$  = 7.6 Hz), 2.73 (2H, t,  $J$  = 6.9 Hz), 2.42 (2H, t,  $J$  = 7.6 Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  172.0, 140.8, 138.8, 128.7, 128.6, 128.5, 128.4, 126.4, 126.2, 40.5, 38.5, 35.6, 31.7. **HRMS (ESI)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>19</sub>NONa 276.1359; Found: 276.1359. **IR (ATR):** 3299, 1636, 1548 cm<sup>-1</sup>. **Melting Point:** 96.4-96.6 °C.

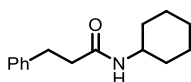


**N-Benzyl-3-phenylpropanamide (44):** The reaction was performed according to **GP3** for an hour and gave product **44** in 86% yield as a white crystalline solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.31-7.26 (5H, m), 7.22-7.20 (5H, m), 7.14 (2H, d,  $J$  = 6.9 Hz), 5.60 (1H, brs), 4.40 (2H, d,  $J$  = 5.7 Hz), 3.00 (2H, t,  $J$  = 7.7 Hz), 2.52 (2H, t,  $J$  = 7.7 Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  171.8, 140.7, 138.1, 128.7, 128.6, 128.4, 127.7, 127.5, 126.3, 43.6, 38.5, 31.7. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>18</sub>NO 240.1383; Found: 240.1383.

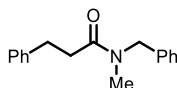
**IR (ATR):** 3284, 1636, 1539  $\text{cm}^{-1}$ . **Melting Point:** 82.9-83.5  $^{\circ}\text{C}$ .



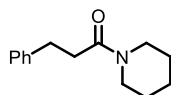
***N*-(1-Phenylethyl)-3-phenylpropanamide (45):** The reaction was performed according to **GP3** for an hour and gave product **45** in 77% yield as a white solid.  **$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.32-7.18 (10H, m), 5.48 (1H, brs), 5.10 (1H, dq,  $J = 7.5, 7.0$  Hz), 2.97 (2H, t,  $J = 7.7$  Hz), 2.48 (2H, t,  $J = 7.7$  Hz), 1.41 (3H, d,  $J = 6.9$  Hz).  **$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.0, 143.0, 140.7, 128.6, 128.5, 128.4, 127.2, 126.2, 126.1, 48.6, 38.6, 31.7, 21.5. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}$  254.1539; Found: 254.1538. **IR (ATR):** 3304, 1636, 1536  $\text{cm}^{-1}$ . **Melting Point:** 54.5-55.0  $^{\circ}\text{C}$ .



***N*-Cyclohexyl-3-phenylpropanamide (46):** The reaction was performed according to **GP3** for an hour and gave product **46** in 81% yield as a white solid.  **$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.30-7.27 (2H, m), 7.21-7.20 (3H, m), 5.11 (1H, brs), 3.77-3.71 (1H, m), 2.96 (2H, t,  $J = 7.6$  Hz), 2.43 (2H, t,  $J = 7.7$  Hz), 1.84-1.82 (2H, m), 1.66-1.56 (3H, m), 1.35-1.32 (2H, m), 1.12-1.10 (1H, m), 1.04-0.97 (2H, m).  **$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.0, 140.9, 128.44, 128.37, 126.2, 48.0, 38.8, 33.1, 31.8, 25.4, 24.8. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{15}\text{H}_{22}\text{NO}$  232.1696; Found: 232.1698. **IR (ATR):** 3303, 1633, 1538  $\text{cm}^{-1}$ . **Melting Point:** 109.7-110.0  $^{\circ}\text{C}$ .

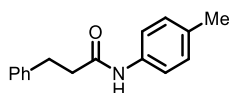


***N*-Benzyl-*N*-methyl-3-phenylpropanamide (47):** The reaction was performed according to **GP3** for an hour and gave product **47** in 82% yield as a colorless oil.  **$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.35-7.08 (10H, m), 4.60 (1.2H, s), 4.47 (0.8H, s), 3.06-2.98 (2H, m), 2.95 (1.2H, s), 2.84 (1.8H, s), 2.72-2.64 (2H, m). (The peaks were observed as a mixture of amide rotamers.)  **$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  172.5, 172.2, 141.3, 141.2, 137.3, 136.5, 128.9, 128.5, 128.4, 128.0, 127.5, 127.3, 126.2, 126.1, 53.2, 50.8, 35.4, 34.9, 34.7, 33.9, 31.5, 31.3. (The peaks were observed as a mixture of amide rotamers.) **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}$  254.1539; Found: 254.1538. **IR (ATR):** 1645  $\text{cm}^{-1}$ .

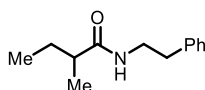


**1-(1-Piperidinyl)-3-phenylpropanamide (48):** The reaction was performed according to **GP3** for an hour

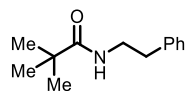
and gave product **48** in 66% yield as a colorless oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.31-7.25 (2H, m), 7.25-7.17 (3H, m), 3.56 (2H, t,  $J = 5.4$  Hz), 3.33 (2H, t,  $J = 5.6$  Hz), 2.96 (2H, t,  $J = 8.0$  Hz), 2.62 (2H, t,  $J = 9.0$  Hz), 1.65-1.57 (2H, m), 1.56-1.49 (2H, m), 1.49-1.41 (2H, m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  170.4, 141.4, 128.43, 128.40, 126.0, 46.6, 42.7, 35.2, 31.6, 26.3, 25.5, 24.5. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for C<sub>14</sub>H<sub>20</sub>NO 218.1539; Found: 218.1537. **IR (ATR):** 2932, 2854, 1635, 1455 cm<sup>-1</sup>.



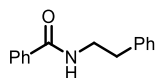
***N*-(*p*-Tolyl)-3-phenylpropanamide (49):** The reaction was performed according to **GP3** for an hour and gave product **49** in 70% yield as a white crystalline solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.36-7.27 (4H, m), 7.27-7.18 (3H, m), 7.10 (2H, d,  $J = 8.0$  Hz), 6.94 (1H, brs), 3.05 (2H, t,  $J = 7.6$  Hz), 2.64 (2H, t,  $J = 7.7$  Hz), 2.30 (3H, s). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  170.2, 140.7, 135.1, 133.9, 129.4, 128.6, 128.4, 126.3, 120.0, 39.4, 31.6, 20.8. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for C<sub>16</sub>H<sub>18</sub>NO 240.1388; Found: 240.1386. **IR (ATR):** 3298, 1654, 1524 cm<sup>-1</sup>. **Melting Point:** 129.2-129.5 °C.



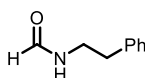
***N*-Phenethyl-2-methylbutanamide (50):** The reaction was performed according to **GP3** for an hour and gave product **50** in 70% yield as a white crystalline solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.31 (2H, t,  $J = 7.4$  Hz), 7.25-7.19 (3H, m), 5.39 (1H, brs), 3.58-3.50 (2H, m), 2.84-2.81 (2H, m), 2.03-2.00 (1H, m), 1.67-1.58 (1H, m), 1.43-1.35 (1H, m), 1.09 (3H, d,  $J = 6.9$  Hz), 0.86 (3H, t,  $J = 7.4$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  176.4, 138.9, 128.8, 128.6, 126.4, 43.2, 40.3, 35.8, 27.2, 17.5, 11.9. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for C<sub>13</sub>H<sub>20</sub>NO 205.1539; Found: 205.1538. **IR (ATR):** 3291, 1643, 1548 cm<sup>-1</sup>. **Melting Point:** 54.9-55.3 °C.



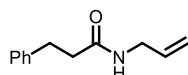
***N*-Phenethylpivalamide (51):** The reaction was performed according to **GP3** for an hour and gave product **51** in 53% yield as a white crystalline solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.32 (2H, t,  $J = 7.7$  Hz), 7.26-7.20 (3H, m), 5.61 (1H, brs), 3.50 (2H, q,  $J = 6.6$  Hz), 2.82 (2H, t,  $J = 6.6$  Hz), 1.14 (9H, s). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  178.3, 139.0, 128.8, 128.6, 126.5, 40.6, 38.6, 35.6, 27.5. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for C<sub>13</sub>H<sub>20</sub>NO 206.1539; Found: 206.1533. **IR (ATR):** 3342, 1634, 1532 cm<sup>-1</sup>. **Melting Point:** 87.5-88.5 °C



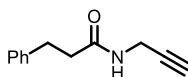
**N-Phenethylbenzamide (52):** The reaction was performed according to **GP3** for an hour and gave product **52** in 69% yield as a white crystalline solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.70-7.68 (2H, m), 7.49 (1H, tt,  $J = 7.4, 1.5$  Hz), 7.41 (2H, t,  $J = 7.4$  Hz), 7.35-7.32 (2H, m), 7.27-7.23 (3H, m), 6.11 (1H, brs), 3.73 (2H, q,  $J = 6.5$  Hz), 2.95 (2H, t,  $J = 6.9$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  167.4, 138.9, 134.6, 131.4, 128.8, 128.7, 128.5, 126.8, 126.6, 41.1, 35.6. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>16</sub>NO 226.1226; Found: 226.1217. **IR (ATR):** 3344, 1638, 1543 cm<sup>-1</sup>. **Melting Point:** 114.3-114.7 °C.



**N-Phenethylformamide (53):** The reaction was performed according to **GP3** for an hour and gave product **53** in 76% yield as a colorless oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  8.13 (0.83H, s), 7.93 (0.17H, d,  $J = 12.0$  Hz), 7.32 (2H, t,  $J = 7.4$  Hz), 7.24-7.18 (3H, m), 5.57 (1H, brs), 3.58 (1.66H, d,  $J = 6.6$  Hz), 3.48 (0.34H, d,  $J = 6.8$  Hz), 2.87-2.80 (2H, m). (The peaks were observed as a mixture of amide rotamers.) **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  164.4, 161.2, 138.4, 137.5, 128.8, 128.7, 128.6, 126.8, 126.6, 43.1, 39.1, 37.7, 35.4. (The peaks were observed as a mixture of amide rotamers.) **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>9</sub>H<sub>12</sub>NO 150.0913; Found: 150.0906. **IR (ATR):** 3283, 1660, 1537 cm<sup>-1</sup>.



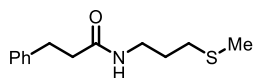
**N-Allyl-3-phenylpropanamide (54):** The reaction was performed according to **GP3** for an hour and gave product **54** in 78% yield as a colorless oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.28 (2H, t,  $J = 7.3$  Hz), 7.23-7.19 (3H, m), 5.81-5.73 (1H, m), 5.37 (1H, brs), 5.10-5.05 (2H, m), 3.87-3.83 (2H, m), 2.98 (2H, t,  $J = 7.7$  Hz), 2.50 (2H, t,  $J = 7.7$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  171.8, 140.8, 134.1, 128.5, 128.3, 126.2, 116.3, 41.8, 38.5, 31.7. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>16</sub>NO 190.1226; Found: 190.1226. **IR (ATR):** 3285, 1640, 1548 cm<sup>-1</sup>.



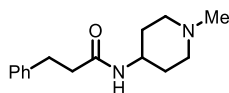
**N-Propynyl-3-phenylpropanamide (55):** The reaction was performed according to **GP3** for an hour and gave product **55** in 78% yield as a colorless oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.29 (2H, t,  $J = 7.4$  Hz), 7.22-7.18 (3H, m), 5.56 (1H, brs), 4.03 (2H, dd,  $J = 5.2, 2.3$  Hz), 2.97 (2H, t,  $J = 7.7$  Hz), 2.50 (2H, t,  $J = 7.7$  Hz), 2.21 (1H, t,  $J = 2.6$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  171.7, 140.6, 128.6, 128.3, 126.3, 79.4, 71.6, 38.2, 31.5, 29.2. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>14</sub>NO 188.1070; Found: 188.1070. **IR (ATR):**



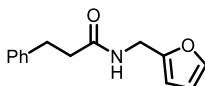
3276, 3258, 1635, 1543  $\text{cm}^{-1}$ . **Melting Point:** 66.0-66.3  $^{\circ}\text{C}$ .



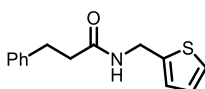
**N-Methylthiopropyl-3-phenylpropanamide (56):** The reaction was performed according to **GP3** for an hour and gave product **56** in 76% yield as a colorless oil.  **$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.29 (2H, t,  $J = 7.7$  Hz), 7.22-7.18 (3H, m), 5.50 (1H, brs), 3.32 (2H, q,  $J = 6.5$  Hz), 2.97 (2H, t,  $J = 7.7$  Hz), 2.47 (2H, t,  $J = 7.7$  Hz), 2.41 (2H, t,  $J = 7.2$  Hz), 2.06 (3H, s), 1.76-1.70 (2H, m).  **$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  172.1, 140.8, 128.5, 128.3, 126.2, 38.50, 38.47, 31.7, 31.5, 28.4, 15.4. **HRMS (FAB)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{13}\text{H}_{20}\text{NOS}$  238.1266; Found: 238.1258. **IR (ATR):** 3289, 1644, 1550  $\text{cm}^{-1}$ .



**N-(4-methylpiperidinyl)-3-phenylpropanamide (57):** The reaction was performed according to **GP3** for an hour and gave product **57** in 80% yield as a yellow solid.  **$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.29-7.26 (2H, m), 7.21-7.18 (3H, m), 5.28 (1H, brd,  $J = 7.2$  Hz), 3.77-3.70 (1H, m), 2.95 (2H, t,  $J = 7.6$  Hz), 2.70 (2H, brd,  $J = 8.3$  Hz), 2.45 (2H, t,  $J = 7.6$  Hz), 2.24 (3H, s), 2.04 (2H, t,  $J = 10.9$  Hz), 1.84-1.81 (2H, m), 1.33 (2H, qd,  $J = 11.5, 4.0$  Hz).  **$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.4, 140.8, 128.5, 128.4, 126.3, 54.4, 46.2, 45.9, 38.7, 32.2, 31.8. **HRMS (FAB)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}$  247.1810; Found 247.1814. **IR (ATR):** 3293, 1640, 1557  $\text{cm}^{-1}$ . **Melting Point:** 73.9-76.8  $^{\circ}\text{C}$ .

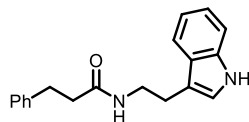


**N-(2-Furanylmethyl)-3-phenylpropanamide (58):** The reaction was performed according to **GP3** for an hour and gave product **58** in 85% yield as a white solid.  **$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.34-7.33 (1H, m), 7.29-7.26 (2H, m), 7.21-7.18 (3H, m), 6.31-6.30 (1H, m), 6.16 (1H, d,  $J = 2.9$  Hz), 5.61 (1H, brs), 4.41 (2H, d,  $J = 5.7$  Hz), 2.98 (2H, t,  $J = 7.7$  Hz), 2.50 (2H, t,  $J = 7.7$  Hz).  **$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.8, 151.2, 142.1, 140.7, 128.5, 128.3, 126.2, 110.4, 107.4, 38.3, 36.4, 31.6. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{14}\text{H}_{16}\text{NO}_2$  230.1176; Found: 230.1169. **IR (ATR):** 3287, 1646, 1548  $\text{cm}^{-1}$ . **Melting Point:** 57.5-58.5  $^{\circ}\text{C}$ .

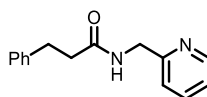


**N-(2-Thiophenylmethyl)-3-phenylpropanamide (59):** The reaction was performed according to **GP3** for an hour and gave product **59** in 89% yield as a white solid.  **$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.29-7.26 (2H, m), 7.22-7.18 (4H, m), 6.93 (1H, dd,  $J = 5.2, 3.4$  Hz), 6.90-6.89 (1H, m), 5.63 (1H, brs), 4.58 (2H, d,  $J = 5.7$

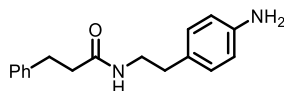
Hz), 2.99 (2H, t,  $J = 7.7$  Hz), 2.50 (2H, t,  $J = 7.7$  Hz).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.7, 140.73, 140.68, 128.5, 128.3, 126.8, 126.2, 126.0, 125.2, 38.3, 38.2, 31.6. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{14}\text{H}_{16}\text{NOS}$  246.0953; Found: 246.0960. **IR (ATR):** 3289, 1631, 1538  $\text{cm}^{-1}$ . **Melting Point:** 89.5-90.3  $^\circ\text{C}$ .



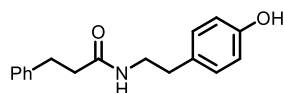
***N*-(2-(1*H*-Indol-3-yl)ethyl)-3-phenylpropanamide (60):** The reaction was performed according to **GP3** for an hour and gave product **60** in 80% yield as a white solid.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 (1H, brs), 7.56 (1H, d,  $J = 7.7$  Hz), 7.37 (1H, d,  $J = 8.3$  Hz), 7.29-7.26 (2H, m), 7.22-7.17 (4H, m), 7.12 (1H, t,  $J = 7.4$  Hz), 6.87 (1H, s), 5.38 (1H, brs), 3.57 (2H, q,  $J = 6.4$  Hz), 2.96-2.89 (4H, m), 2.40 (2H, t,  $J = 7.6$  Hz).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.0, 140.9, 136.3, 128.5, 128.4, 127.2, 126.2, 122.1, 122.0, 119.4, 118.6, 112.8, 111.2, 39.6, 38.5, 31.7, 25.2. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}$  293.1648; Found: 293.1639. **IR (ATR):** 3406, 3277, 1635, 1525  $\text{cm}^{-1}$ . **Melting Point:** 71.7-72.3  $^\circ\text{C}$ .



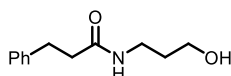
***N*-(2-Pyridinylmethyl)-3-phenylpropanamide (61):** The reaction was performed according to **GP3** for an hour and gave product **61** in 81% yield as a white solid.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.51 (1H, d,  $J = 4.0$  Hz), 7.64 (1H, t,  $J = 7.4$  Hz), 7.29-7.26 (2H, m), 7.22-7.17 (5H, m), 6.63 (1H, brs), 4.55 (2H, d,  $J = 5.2$  Hz), 3.01 (2H, t,  $J = 7.7$  Hz), 2.59 (2H, t,  $J = 7.7$  Hz).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.1, 156.3, 148.9, 140.8, 136.7, 128.4, 128.3, 126.1, 122.3, 122.0, 44.4, 38.3, 31.6. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}$  241.1341; Found: 241.1349. **IR (ATR):** 3286, 1651, 1549  $\text{cm}^{-1}$ . **Melting Point:** 54.3-55.3  $^\circ\text{C}$ .



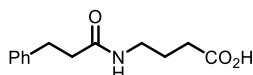
***N*-(4-Aminophenethyl)-3-phenylpropanamide (62):** The reaction was performed according to **GP3** for an hour and gave product **62** in 79% yield as a white solid.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33-7.24 (3H, m), 7.22-7.19 (3H, m), 6.87 (2H, d,  $J = 8.0$  Hz), 6.61 (2H, d,  $J = 8.0$  Hz), 5.29 (1H, brs), 3.60 (2H, brs), 3.42 (2H, q,  $J = 6.5$  Hz), 2.94 (2H, t,  $J = 7.7$  Hz), 2.62 (2H, t,  $J = 6.6$  Hz), 2.41 (2H, t,  $J = 7.7$  Hz).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.9, 144.8, 140.9, 129.5, 128.6, 128.5, 128.4, 126.2, 115.4, 40.7, 38.6, 34.7, 31.7. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}$  269.1648; Found: 269.1646. **IR (ATR):** 3385, 3304, 1636, 1544  $\text{cm}^{-1}$ . **Melting Point:** 104.4-105.2  $^\circ\text{C}$ .



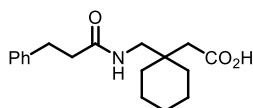
**N-(4-Hydroxyphenethyl)-3-phenylpropanamide (63):** The reaction was performed according to **GP3** for an hour and gave product **63** in 75% yield as a white solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.30-7.26 (2H, m), 7.23-7.16 (3H, m), 6.94 (2H, d,  $J$  = 8.0 Hz), 6.75 (2H, d,  $J$  = 8.6 Hz), 5.30 (1H, brs), 4.95 (1H, brs), 3.44 (2H, q,  $J$  = 6.5 Hz), 2.94 (2H, t,  $J$  = 7.4 Hz), 2.66 (2H, t,  $J$  = 6.9 Hz), 2.42 (2H, t,  $J$  = 7.7 Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  172.1, 154.3, 140.8, 130.7, 129.8, 128.5, 128.4, 126.3, 115.4, 40.7, 38.6, 34.7, 31.7. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>20</sub>NO<sub>2</sub> 270.1489; Found: 270.1488. **IR (ATR):** 3251, 1614, 1540 cm<sup>-1</sup>. **Melting Point:** 117.1-117.7 °C.



**N-(3-Hydroxypropyl)-3-phenylpropanamide (64):** The reaction was performed according to **GP3** for an hour and gave product **64** in 80% yield as a white solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.31-7.26 (2H, m), 7.22-7.20 (3H, m), 5.66 (1H, brs), 3.51 (2H, q,  $J$  = 5.7 Hz), 3.38 (2H, q,  $J$  = 6.1 Hz), 2.99-2.95 (3H, m), 2.51 (2H, t,  $J$  = 7.4 Hz), 1.62-1.57 (2H, m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  173.3, 140.6, 128.5, 128.3, 126.3, 59.1, 38.4, 36.2, 32.1, 31.7. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>18</sub>NO<sub>2</sub> 208.1332; Found: 208.1328. **IR (ATR):** 3292, 3087, 1645, 1558 cm<sup>-1</sup>. **Melting Point:** 57.1-57.6 °C.

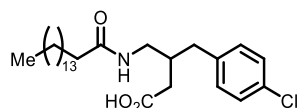


**N-2-Phenylethylsuccinamic acid (65):** The reaction was performed according to **GP3** for an hour and gave product **65** in 80% yield as a white crystalline solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.34-7.31 (2H, m), 7.26-7.23 (1H, m), 7.20-7.18 (2H, m), 5.68 (1H, brs), 3.56 (2H, q,  $J$  = 6.6 Hz), 2.83 (2H, t,  $J$  = 6.7 Hz), 2.69 (2H, t,  $J$  = 6.3 Hz), 2.47 (2H, t,  $J$  = 6.2 Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  176.3, 172.2, 138.5, 128.73, 128.68, 126.6, 40.8, 35.4, 30.7, 29.7. **HRMS (ESI)  $m/z$ :** [M-H]<sup>-</sup> Calcd for C<sub>12</sub>H<sub>14</sub>NO<sub>3</sub> 220.0979; Found: 220.0976. **IR (ATR):** 3305, 1689, 1639, 1544 cm<sup>-1</sup>. **Melting Point:** 106.8-108.0 °C.

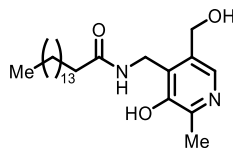


**N-(3-Phenylpropanoyl)gabapentin (66):** The reaction was performed according to **GP3** for an hour and gave product **66** in 81% yield as a white solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.29-7.26 (2H, m), 7.22-7.18 (3H, m), 6.30 (1H, brs), 3.19 (2H, d,  $J$  = 6.9 Hz), 2.99 (2H, t,  $J$  = 7.3 Hz), 2.60 (2H, t,  $J$  = 7.4 Hz), 2.05 (2H, s), 1.48-1.42 (5H, m), 1.32-1.24 (3H, m), 1.18-1.12 (2H, m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  174.6, 173.9,

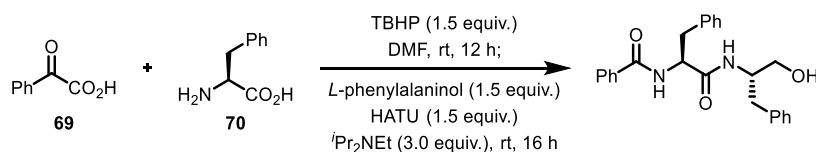
140.1, 128.6, 128.4, 126.5, 47.1, 40.9, 38.1, 37.1, 33.9, 31.6, 25.7, 21.2. **HRMS (FAB)  $m/z$ :**  $[M-H]^-$  Calcd for  $C_{18}H_{26}NO_3$   $[M+H]^+$ : 304.1913; Found: 304.1906. **IR (ATR):** 3295, 3028, 1713, 1615, 1558  $cm^{-1}$ . **Melting Point:** 128.5-129.5  $^{\circ}C$ .



**3-(4-Chlorophenyl)-4-palmitamidobutanoic acid (67):** The reaction was performed according to **GP3** for an hour and gave product **67** in 61% yield as a white solid.  **$^1H$ -NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  7.30 (2H, d,  $J = 8.6$  Hz), 7.14 (2H, d,  $J = 8.0$  Hz), 5.52 (1H, dd,  $J = 10.9, 5.7$  Hz), 3.66-3.60 (1H, m), 3.38-3.34 (2H, m), 2.71 (1H, dd,  $J = 15.8, 7.2$  Hz), 2.71 (1H, dd,  $J = 15.8, 7.2$  Hz), 2.09 (2H, t,  $J = 7.4$  Hz), 1.55-1.47 (2H, br), 1.31-1.23 (24H, m), 0.88 (3H, t,  $J = 6.9$  Hz).  **$^{13}C$ -NMR (126 MHz,  $CDCl_3$ ):**  $\delta$  175.2, 174.1, 139.6, 133.0, 129.0, 128.9, 44.1, 41.2, 38.2, 36.6, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.6, 22.7, 14.1. **HRMS (FAB)  $m/z$ :**  $[M+H]^+$  Calcd for  $C_{26}H_{43}ClNO_3$  452.2931; Found: 452.2935. **IR (ATR):** 3292, 2923, 2853, 1717, 1645, 1551  $cm^{-1}$ . **Melting Point:** 90.8-91.1  $^{\circ}C$ .

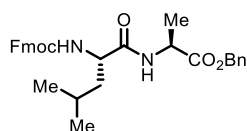


**N-((3-Hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methyl)palmitamide (68):** The reaction was performed according to **GP3** for an hour and gave product **68** in 67% yield as a white solid.  **$^1H$ -NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  7.64 (1H, s), 6.81 (1H, s), 4.67 (2H, s), 4.41 (2H, d,  $J = 6.3$  Hz), 2.48 (3H, s), 2.17 (2H, t,  $J = 7.7$  Hz), 1.95 (2H, brs), 1.57 (2H, t,  $J = 6.9$  Hz), 1.31-1.23 (24H, m), 0.92-0.82 (3H, t,  $J = 7.2$  Hz).  **$^{13}C$ -NMR (126 MHz,  $CDCl_3$ ):**  $\delta$  176.2, 150.8, 149.7, 138.3, 133.4, 131.4, 61.4, 35.9, 35.7, 31.9, 29.7, 29.63, 29.61, 29.59, 29.5, 29.4, 29.3, 29.2, 29.1, 25.3, 22.6, 19.1, 14.1. **HRMS (FAB)  $m/z$ :**  $[M+H]^+$  Calcd for  $C_{24}H_{43}N_2O_3$  407.3274; Found: 407.3278. **IR (ATR):** 3298, 3077, 2921, 2852, 1636, 1549  $cm^{-1}$ . **Melting Point:** 49.6-53.0  $^{\circ}C$ .

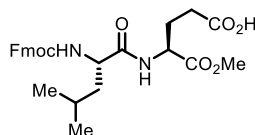


**Aurantiamide<sup>18</sup> (71):** The reaction was performed according to **GP3** for 12 hours and *L*-Phenylalaninol (22.7 mg, 0.150 mmol, 1.5 equiv.), HATU (57.0 mg, 0.150 mmol, 1.5 equiv.) and *i*Pr<sub>2</sub>NEt (52.4  $\mu$ L, 0.300

mmol, 3.0 equiv.) were added to the reaction mixture. After stirring for 16 h at room temperature, the mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography gave product **71** in 45% yield as a white solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.72 (2H, d,  $J = 7.2$  Hz), 7.53 (1H, t,  $J = 7.4$  Hz), 7.44 (2H, t,  $J = 7.6$  Hz), 7.34-7.26 (5H, m), 7.21-7.06 (5H, m), 6.83 (1H, d,  $J = 7.7$  Hz), 6.02 (1H, d,  $J = 8.0$  Hz), 4.78 (1H, td,  $J = 8.6, 6.0$  Hz), 4.13-4.08 (1H, m), 3.47-3.39 (2H, m), 3.25 (1H, dd,  $J = 13.7, 6.0$  Hz), 3.05 (1H, dd,  $J = 13.6, 8.7$  Hz), 2.78 (1H, dd,  $J = 13.7, 7.4$  Hz), 2.69 (1H, dd,  $J = 13.7, 7.4$  Hz), 2.03 (1H, t,  $J = 5.8$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  170.8, 167.2, 137.3, 136.7, 133.5, 132.0, 129.4, 129.1, 128.8, 128.6, 128.5, 127.2, 127.1, 126.6, 63.4, 55.2, 52.9, 38.6, 36.8. **HRMS (FAB)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>Na 425.1841; Found: 425.1840. **IR (ATR):** 3286, 1711, 1633, 1531 cm<sup>-1</sup>. **Melting Point:** 181.5-183.4 °C **Optical Rotation:** [ $\alpha$ ]<sub>D</sub><sup>25</sup> -17.9 (c 0.12, CHCl<sub>3</sub>).

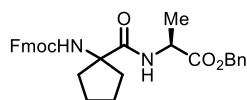


**Fmoc-Leu-Ala-OBn (72):** The reaction was performed according to **GP4** for an hour and gave product **72** in 90% yield, dr > 99:1 as a white solid. The dr of the product was estimated by chiral SFC analysis: Trefoil CEL1, 1.0 mL/min, 10% MeOH/CO<sub>2</sub>,  $\lambda = 210$ -400 nm,  $t_{R(72)} = 11.7$  min,  $t_{R(eps-72)} = 12.6$  min. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.75 (2H, d,  $J = 7.2$  Hz), 7.57 (2H, d,  $J = 6.9$  Hz), 7.40-7.26 (9H, m), 6.55 (1H, d,  $J = 7.2$  Hz), 5.30 (1H, d,  $J = 8.3$  Hz), 5.19 (1H, d,  $J = 12.2$  Hz), 5.13 (1H, d,  $J = 12.2$  Hz), 4.61 (1H, t,  $J = 7.0$  Hz), 4.43-4.34 (2H, m), 4.20 (2H, t,  $J = 6.7$  Hz), 1.72-1.57 (2H, m), 1.54-1.50 (1H, m), 1.40 (3H, d,  $J = 6.9$  Hz), 0.93-0.88 (6H, m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  172.4, 171.8, 156.2, 143.8, 143.7, 141.3, 135.2, 128.6, 128.5, 128.2, 127.7, 127.0, 125.0, 120.0, 119.9, 67.2, 67.0, 53.3, 48.2, 47.1, 41.6, 24.6, 22.9, 21.9, 18.2. **HRMS (FAB)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>35</sub>N<sub>2</sub>O<sub>5</sub> 515.2546; Found: 515.2540. **IR (ATR):** 3287, 1703, 1658, 1537 cm<sup>-1</sup>. **Melting Point:** 102.6-103.0 °C **Optical Rotation:** [ $\alpha$ ]<sub>D</sub><sup>21</sup> -21.4 (c 0.62, CHCl<sub>3</sub>).

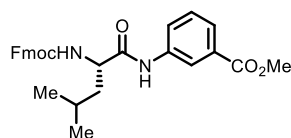


**Fmoc-Leu-Glu-OMe (73):** The reaction was performed according to **GP4** for an hour and gave product **74** in 81% yield, dr = 99:1 as a white solid. The dr of the product was estimated by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 15% MeOH/CO<sub>2</sub>,  $\lambda = 210$ -400 nm,  $t_{R(73)} = 5.0$  min,  $t_{R(eps-73)} = 6.8$  min. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.75 (2H, d,  $J = 7.4$  Hz), 7.58 (2H, t,  $J = 8.6$  Hz), 7.39 (2H, t,  $J = 7.4$  Hz), 7.34-7.24 (2H, m), 6.95 (1H, s), 5.55 (1H, s), 4.64-4.59 (1H, m), 4.51-4.26 (3H, m), 4.23-4.19 (1H, m), 3.71 (3H, s), 2.47-2.34 (2H, m), 2.26-2.19 (1H, m), 2.02-1.94 (1H, m), 1.72-1.59 (2H, m), 1.59-1.48 (1H, m), 0.94-0.89 (6H, m).

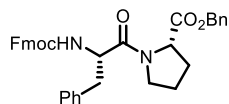
m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  176.3, 172.9, 171.8, 156.4, 143.8, 143.6, 141.25, 141.23, 127.7, 127.1, 125.1, 120.0, 67.3, 53.3, 52.5, 51.6, 47.0, 41.4, 30.0, 26.8, 24.6, 22.8, 22.1. **HRMS (FAB) *m/z*:** [M+Na]<sup>+</sup> Calcd for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>7</sub>Na 519.2107; Found: 519.2103. **IR (ATR):** 3304, 1706, 1663, 1535 cm<sup>-1</sup>. **Melting Point:** 108.6-112.8 °C **Optical Rotation:** [ $\alpha$ ]<sub>D</sub><sup>25</sup> 45.5 (c 2.25, CHCl<sub>3</sub>).



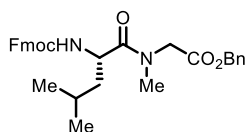
**Fmoc-CycLeu-Ala-OBn (74):** The reaction was performed according to **GP4** for an hour and gave product **74** in 60% yield as a white solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.77 (2H, d, *J* = 7.4 Hz), 7.59-7.56 (2H, m), 7.41-7.38 (2H, m), 7.33-7.30 (7H, m), 7.05 (1H, brs), 5.17 (1H, d, *J* = 12.0 Hz), 5.10 (1H, d, *J* = 11.5 Hz), 5.04 (1H, brs), 4.58 (1H, brs), 4.44 (2H, d, *J* = 6.6 Hz), 4.20 (1H, s), 2.28 (1H, brs), 2.19 (1H, brs), 1.90 (2H, brs), 1.72-1.65 (4H, m), 1.38 (3H, brs). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  173.4, 172.8, 155.5, 143.7, 141.3, 135.4, 128.5, 128.3, 128.1, 127.7, 127.0, 124.92, 124.89, 120.0, 67.1, 67.0, 66.6, 48.4, 47.2, 37.2, 36.5, 24.0, 18.2. **HRMS (FAB) *m/z*:** [M+H]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub> 513.2389; Found: 513.2387. **IR (ATR):** 3322, 1705, 1658, 1521 cm<sup>-1</sup>. **Melting Point:** 108.5-109.1 °C **Optical Rotation:** [ $\alpha$ ]<sub>D</sub><sup>26</sup> -6.7 (c 0.78, CHCl<sub>3</sub>).



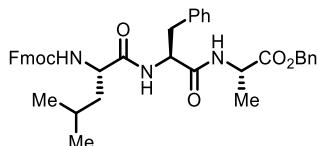
**Methyl (S)-3-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-methylpentanamido)benzoate (75):** The reaction was performed according to **GP4** for an hour and gave product **75** in 63% yield, er = 99:1 as a white solid. The er of the product was estimated by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 15% MeOH/CO<sub>2</sub>,  $\lambda$  = 210-400 nm,  $t_{R(75)}$  = 6.5 min,  $t_{R(ent-75)}$  = 9.5 min. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  8.19 (1H, brs), 8.06 (1H, s), 7.83 (1H, d, *J* = 8.3 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.76 (2H, d, *J* = 7.4 Hz), 7.57 (2H, d, *J* = 7.4 Hz), 7.43-7.35 (3H, m), 7.33-7.24 (2H, m), 5.15 (1H, brs), 4.50 (2H, d, *J* = 5.7 Hz), 4.29 (1H, brs), 4.22 (1H, t, *J* = 6.5 Hz), 3.91 (3H, s), 1.80 (1H, s), 1.69 (2H, s), 1.03-0.90 (6H, m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  170.5, 166.6, 156.7, 143.5, 141.3, 137.8, 130.8, 129.1, 127.79, 127.77, 127.1, 125.5, 124.9, 124.4, 120.8, 120.0, 67.2, 54.2, 52.2, 47.1, 40.6, 24.7, 22.9, 22.0. **HRMS (FAB) *m/z*:** [M+H]<sup>+</sup> Calcd for C<sub>29</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub> 487.2233; Found: 487.2239. **IR (ATR):** 3297, 1723, 1672, 1543 cm<sup>-1</sup>. **Melting Point:** 157.5-158.2 °C **Optical Rotation:** [ $\alpha$ ]<sub>D</sub><sup>26</sup> -38.5 (c 0.85, CHCl<sub>3</sub>).



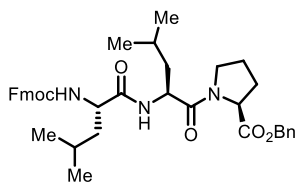
**Fmoc-Phe-Pro-OBn (76):** The reaction was performed according to **GP4** for an hour and gave product **76** in 77% yield, er = 99:1 as a white solid. The dr of the product was estimated by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 30% MeOH/CO<sub>2</sub>,  $\lambda$  = 210-400 nm,  $t_{R(eps-76)}$  = 6.6 min,  $t_{R(76)}$  = 8.2 min. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.78-7.71 (2H, m), 7.60-7.50 (2H, m), 7.46-7.20 (13.8H, m), 6.93 (0.2H, brs), 5.74 (0.2H, d,  $J$  = 8.0 Hz), 5.67 (0.8H, d,  $J$  = 8.6 Hz), 5.22 (0.8H, d,  $J$  = 12.6 Hz), 5.19 (0.8H, d,  $J$  = 13.7 Hz), 5.11 (0.2H, d,  $J$  = 12.6 Hz), 5.08 (0.2H, d,  $J$  = 12.6 Hz), 4.73 (0.8H, q,  $J$  = 7.4 Hz), 4.60-4.45 (1.2H, m), 4.38-4.30 (1H, dd,  $J$  = 10.3, 7.5 Hz), 4.28-4.20 (1H, dd,  $J$  = 10.3, 7.5 Hz), 4.20-4.11 (1H, m), 3.65-3.58 (1H, m), 3.40-3.32 (0.2H, m), 3.25-3.20 (0.8H, m), 3.10 (1H, dd,  $J$  = 13.7, 6.9 Hz), 2.94 (1H, dd,  $J$  = 13.7, 6.9 Hz), 2.19-2.16 (1H, m), 2.00-1.84 (3H, m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  171.6, 170.4, 155.7, 143.8, 141.2, 136.2, 136.0, 135.6, 135.2, 129.7, 129.4, 128.58, 128.55, 128.4, 128.3, 128.1, 128.0, 127.6, 127.05, 127.01, 126.9, 125.2, 125.1, 119.9, 67.0, 66.9, 59.1, 53.7, 47.0, 46.9, 38.9, 29.0, 24.8. **HRMS (FAB)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>36</sub>H<sub>35</sub>N<sub>2</sub>O<sub>5</sub> 575.2546; Found: 575.2549. **IR (ATR):** 3280, 1718, 1641, 1534 cm<sup>-1</sup>. **Melting Point:** 97.1-98.5 °C **Optical Rotation:**  $[\alpha]^{25}_D$  -44.8 (c 1.30, CHCl<sub>3</sub>).



**Fmoc-Leu-Sar-OBn (77):** The reaction was performed according to **GP4** for an hour and gave product **77** in 54% yield, er = 98:2 as an amorphous solid. The er of the product was estimated by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 20% MeOH/CO<sub>2</sub>,  $\lambda$  = 210-400 nm,  $t_{R(77)}$  = 5.4 min,  $t_{R(ent-77)}$  = 11.3 min. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.76 (2H, d,  $J$  = 7.4 Hz), 7.63-7.54 (2H, m), 7.41-7.26 (9H, m), 5.51 (0.85H, d,  $J$  = 8.9 Hz), 5.42 (0.15H, d,  $J$  = 8.3 Hz), 5.18 (1H, d,  $J$  = 12.0 Hz), 5.15 (1H, d,  $J$  = 12.3 Hz), 4.79 (0.85H, td,  $J$  = 9.2, 4.2 Hz), 4.58-4.46 (1.15H, m), 4.39-4.28 (2H, m), 4.22 (1H, t,  $J$  = 7.0 Hz), 4.03 (0.15H, d,  $J$  = 18.1 Hz), 3.85 (0.85H, d,  $J$  = 17.2 Hz), 3.15 (2.55H, s), 3.00 (0.45H, s), 1.78-1.71 (1H, m), 1.58-1.47 (2H, m), 1.09 (2.45H, d,  $J$  = 6.6 Hz), 1.09 (2.55H, d,  $J$  = 6.9 Hz), 1.09 (0.9H, d,  $J$  = 6.6 Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  173.4, 168.7, 156.2, 143.9, 143.7, 141.2, 135.2, 128.7, 128.6, 128.5, 128.3, 127.6, 127.04, 127.02, 125.2, 119.9, 67.4, 67.1, 67.0, 51.3, 49.7, 49.2, 48.8, 47.2, 47.1, 42.3, 42.2, 36.4, 35.3, 24.5, 24.4, 23.4, 23.3, 21.64, 21.58. **HRMS (FAB)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>35</sub>N<sub>2</sub>O<sub>5</sub> 515.2546; Found: 515.2548. **IR (ATR):** 3295, 1746, 1717, 1646, 1533 cm<sup>-1</sup>. **Optical Rotation:**  $[\alpha]^{25}_D$  -17.4 (c 0.11, CHCl<sub>3</sub>).



**Fmoc-Leu-Phe-Ala-OBn (78):** The reaction was performed according to **GP4** for an hour and gave product **78** in 60% yield, dr > 99:1 as a white solid. The dr of the product was estimated by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 15% MeOH/CO<sub>2</sub>,  $\lambda = 210\text{-}400$  nm,  $t_{R(78)} = 9.5$  min,  $t_{R(epi-78)} = 13.9$  min. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.77 (2H, d,  $J = 7.4$  Hz), 7.57 (2H, d,  $J = 7.2$  Hz), 7.42-7.31 (10H, m), 7.22-7.15 (4H, m), 6.53 (1H, d,  $J = 7.2$  Hz), 6.40 (1H, d,  $J = 6.0$  Hz), 5.14 (2H, s), 5.02 (1H, d,  $J = 6.9$  Hz), 4.67-4.60 (1H, m), 4.55-4.48 (1H, m), 4.48-4.40 (1H, m), 4.34 (1H, t,  $J = 8.0$  Hz), 4.19 (1H, t,  $J = 7.0$  Hz), 4.12 (1H, brs), 3.07 (2H, d,  $J = 6.3$  Hz), 1.46-1.35 (6H, m), 0.90 (6H, s). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  172.12, 172.08, 170.2, 156.2, 143.70, 143.67, 141.3, 136.3, 135.27, 135.25, 129.2, 128.6, 128.5, 128.4, 128.1, 127.7, 127.0, 126.9, 125.02, 124.97, 119.99, 119.96, 67.05, 66.99, 54.1, 53.6, 48.2, 47.1, 41.2, 38.0, 34.5, 24.6, 22.8, 21.8, 18.0. **HRMS (FAB)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>40</sub>H<sub>44</sub>N<sub>3</sub>O<sub>6</sub> 662.3230; Found: 662.3237. **IR (ATR):** 3284, 1741, 1705, 1646, 1535 cm<sup>-1</sup>. **Melting Point:** 170.6-171.3 °C **Optical Rotation:**  $[\alpha]^{24}_D -31.5$  (c 0.28, CHCl<sub>3</sub>).



**Fmoc-Phe-Leu-Ala-OBn (79):** The reaction was performed according to **GP4** for an hour and gave product **79** in 76% yield, dr > 99:1 as a white solid. The dr of the product was estimated by chiral SFC analysis: Trefoil CEL2, 1.0 mL/min, 5% MeOH/CO<sub>2</sub>,  $\lambda = 210\text{-}400$  nm,  $t_{R(79)} = 180$  min,  $t_{R(epi-79)} = 195$  min. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.76 (2H, d,  $J = 7.4$  Hz), 7.57-7.50 (2H, m), 7.41-7.20 (12H, m), 7.14 (2H, d,  $J = 6.3$  Hz), 6.55 (1H, d,  $J = 8.6$  Hz), 5.26 (1H, d,  $J = 8.0$  Hz), 5.19 (1H, d,  $J = 12.0$  Hz), 5.08 (1H, d,  $J = 12.3$  Hz), 4.73 (1H, q,  $J = 7.5$  Hz), 4.57-4.54 (1H, m), 4.48-4.43 (2H, m), 4.32-4.27 (1H, m), 4.18 (1H, t,  $J = 6.7$  Hz), 3.73-3.71 (1H, m), 3.59-3.57 (1H, m), 3.08-2.90 (2H, m), 2.23-2.21 (1H, m), 2.08-1.90 (3H, m), 1.60-1.49 (1H, m), 1.43 (2H, t,  $J = 6.6$  Hz), 0.93 (3H, d,  $J = 6.3$  Hz), 0.84 (3H, d,  $J = 6.6$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  171.6, 170.7, 170.5, 155.8, 143.8, 143.7, 141.3, 136.2, 135.5, 129.4, 128.7, 128.6, 128.3, 128.2, 127.7, 127.1, 127.0, 125.1, 125.0, 120.0, 67.01, 66.98, 58.8, 55.8, 49.0, 47.1, 46.8, 41.7, 38.3, 29.0, 24.8, 24.5, 23.3, 21.8. **HRMS (FAB)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>42</sub>H<sub>46</sub>N<sub>3</sub>O<sub>6</sub> 688.3387; Found: 688.3381. **IR (ATR):** 3289, 1726, 1637, 1539 cm<sup>-1</sup>. **Melting Point:** 125.2-126.8 °C **Optical Rotation:**  $[\alpha]^{26}_D -51.6$  (c 0.38, CHCl<sub>3</sub>).



## Experiments in chapter 3

### Preparation Procedure for catalysts:

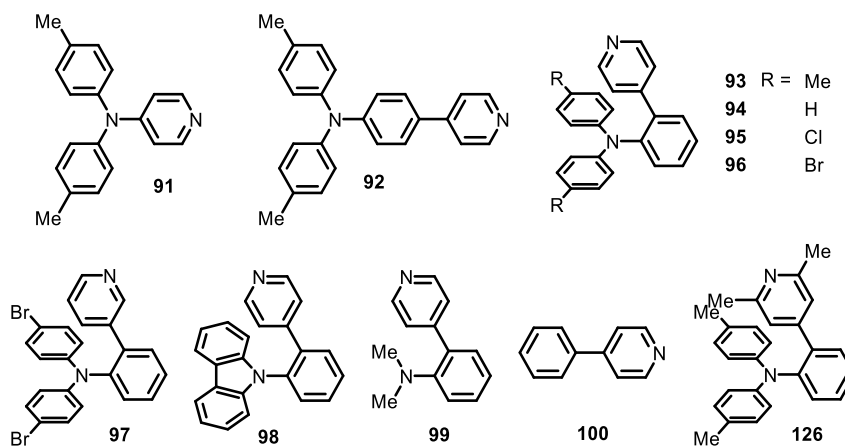
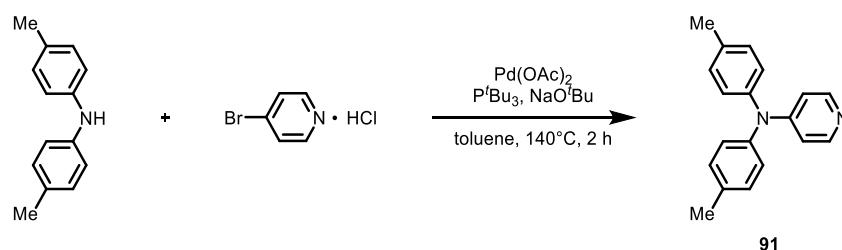


Figure 8. Structure of Pyridine-Based Photocatalysts

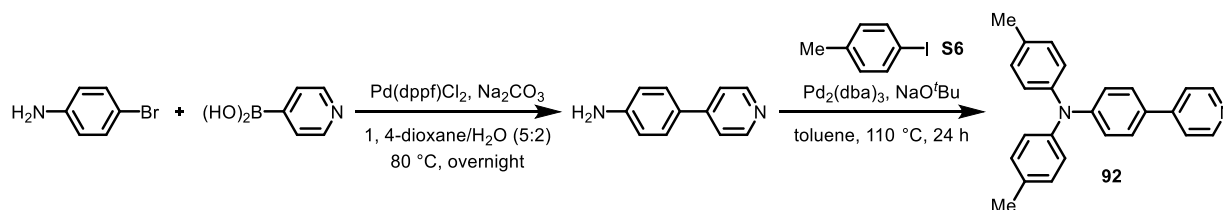
### Preparation Procedure for 91:



A microwave vial was charged with a stir bar, *p,p'*-ditolylamine (986.4 mg, 5.00 mmol, 1.0 equiv.), 4-bromopyridine hydrochloride (1.17 g, 6.02 mmol, 1.20 equiv.), and Pd(OAc)<sub>2</sub> (44.8 mg, 0.200 mmol, 4 mol%) and carried into a glove box. The mixture was dissolved in toluene (10 mL) and to the mixture were added NaO<sup>t</sup>Bu (1.44 g, 15.0 mmol, 3.0 equiv.) and P<sup>t</sup>Bu<sub>3</sub> (40.5 mg, 0.200 mmol, 4 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at 140 °C, the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 0% → 30% EtOAc/hexane) to afford **91** (465.0 mg, 1.69 mmol, 38% yield) as a pale brown oil. Compound **91** is air sensitive and gradually getting brown along with the production of 8-methyl-5-(*p*-tolyl)-5*H*-pyrido[4,3-*b*]indole under atmospheric condition.

***N,N*-Di-*p*-tolylpyridin-4-amine (89):** <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 8.18 (2H, d, *J* = 4.8 Hz), 7.16 (4H, d, *J* = 8.3 Hz), 7.08 (4H, d, *J* = 9.0 Hz), 6.67 (2H, d, *J* = 4.8 Hz), 2.34 (6H, s). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>): δ 153.8, 150.0, 142.5, 135.4, 130.4, 126.6, 111.9, 21.0. HRMS (ESI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub> 275.1543; Found: 275.1545. IR (ATR): 3028, 2923, 2863, 1587, 1552, 810, 750 cm<sup>-1</sup>.

### Preparation Procedure for 92:

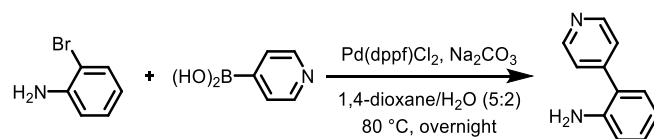


A 200 mL round bottom flask was charged with a stir bar, 4-bromoaniline (344.1 mg, 2.00 mmol, 1.0 equiv.), 4-pyridylboronic acid (245.8 mg, 2.00 mmol, 1.0 equiv.), Na<sub>2</sub>CO<sub>3</sub> (847.9 mg, 8.00 mmol, 4.0 equiv.), and Pd(dppf)Cl<sub>2</sub> (73.2 mg, 0.100 mmol, 5 mol%) under Ar atmosphere. To the stirring mixture were added 1,4-dioxane/H<sub>2</sub>O (5:2, 20 mL). After stirring overnight at 80 °C, the mixture was cooled down to room temperature, concentrated under reduced pressure to remove 1,4-dioxane. The resulting aqueous solution was acidified with 1N aqueous HCl and washed with EtOAc (3 x 25 mL). The aqueous layer was basified with 4M aqueous NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (2 x 25 mL), water (3 x 25 mL), and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 30% → 80% EtOAc/hexane) to afford aniline (146.2 mg, 0.859 mmol, 43% yield) as a yellow solid.

A microwave vial was charged with a stir bar, aniline (105.0 mg, 0.617 mmol, 1.0 equiv.), 4-iodotoluene (268.2 mg, 1.23 mmol, 2.0 equiv.), and Pd<sub>2</sub>(dba)<sub>3</sub> (27.5 mg, 0.0300 mmol, 5 mol%) and carried into a glove box. The mixture was dissolved in toluene (5 mL) and to the mixture were added NaO<sup>t</sup>Bu (118.2 mg, 1.23 mmol, 2.0 equiv.), and P<sup>t</sup>Bu<sub>3</sub> (12.5 mg, 0.0618 mmol, 10 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at 140 °C, the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 0% → 30% EtOAc/hexane) to afford **92** (130.1 mg, 0.371 mmol, 60% yield) as a white solid.

**4-Methyl-N-(4-(pyridin-4-yl)phenyl)-N-(p-tolyl)aniline (92):** <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 8.60 (2H, d, *J* = 6.2 Hz), 7.49 (2H, d, *J* = 9.0 Hz), 7.47 (2H, d, *J* = 6.2 Hz), 7.11 (4H, d, *J* = 7.6 Hz), 7.07 (2H, d, *J* = 9.0 Hz), 7.04 (4H, d, *J* = 8.3 Hz), 2.34 (6H, s). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>): δ 149.9, 149.4, 144.6, 133.4, 130.1, 129.7, 127.5, 125.2, 121.5, 120.8, 20.9. (one aromatic peak was missing due to overlapping) **HRMS (ESI) *m/z***: [M+H]<sup>+</sup> Calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub> 351.1856; Found: 351.1859. **IR (ATR)**: 3031, 2921, 1597, 1510, 946, 816 cm<sup>-1</sup>. **Melting Point**: 137.4-138.0 °C.

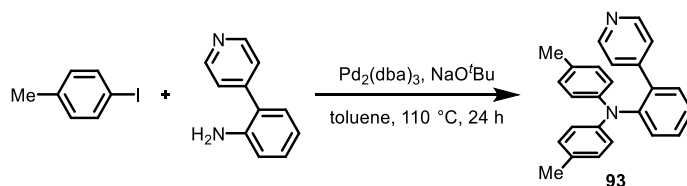
### Preparation Procedure for 2-(Pyridin-4-yl)aniline (**129**):



A 200 mL round bottom flask was charged with a stir bar, 2-bromoaniline (339.2  $\mu$ L, 3.00 mmol, 1.0 equiv.), 4-pyridylboronic acid (479.4 mg, 3.90 mmol, 1.30 equiv.), Na<sub>2</sub>CO<sub>3</sub> (1.27 g, 12.0 mmol, 4.0 equiv.), and Pd(dppf)Cl<sub>2</sub> (109.8 mg, 0.150 mmol, 5 mol%) under Ar atmosphere. To the stirring mixture were added 1,4-dioxane/H<sub>2</sub>O (5:2, 30 mL). After stirring overnight at 80 °C, the mixture was cooled down to room temperature and concentrated under reduced pressure to remove 1,4-dioxane. The aqueous solution was acidified with 1N aqueous HCl and washed with EtOAc (3 x 25 mL). The aqueous layer was basified with 4M aqueous NaOH and extracted by CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (2 x 25 mL), water (3 x 25 mL), and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 30%  $\rightarrow$  80% EtOAc/hexane) to afford 2-(Pyridin-4-yl)aniline **129** (428.7 mg, 2.52 mmol, 84% yield) as a brown solid.

**2-(Pyridin-4-yl)aniline:** <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  8.67 (2H, d,  $J$  = 5.5 Hz), 7.42 (2H, d,  $J$  = 6.2 Hz), 7.21 (1H, t,  $J$  = 7.6 Hz), 7.13 (1H, d,  $J$  = 7.6 Hz), 6.85 (1H, t,  $J$  = 7.9 Hz), 6.78 (1H, d,  $J$  = 6.9 Hz), 3.80 (2H, br s). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  150.3, 147.6, 143.3, 130.1, 129.7, 124.4, 123.9, 118.9, 116.0. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>11</sub>H<sub>11</sub>N<sub>2</sub> 171.0917; Found: 171.0914. **IR (ATR):** 3330, 3205, 3061, 3029, 1600, 822, 750 cm<sup>-1</sup>. **Melting Point:** 84.8-85.0 °C.

### Preparation Procedure for **93**:

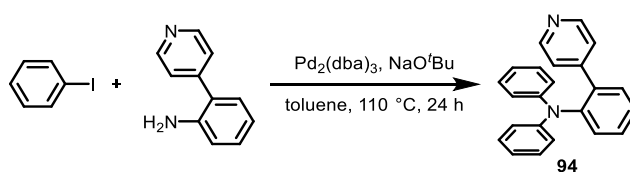


A microwave vial was charged with a stir bar, aniline **129** (340.4 mg, 2.00 mmol, 1.0 equiv.), 4-iodotoluene **S6** (872.2 mg, 4.00 mmol, 2.0 equiv.), and Pd<sub>2</sub>(dba)<sub>3</sub> (91.6 mg, 0.100 mmol, 5 mol%) and carried into a glove box. The mixture was dissolved in toluene (10 mL) and to the mixture were added NaO<sup>t</sup>Bu (384.4 mg, 4.00 mmol, 2.0 equiv.) and P<sup>t</sup>Bu<sub>3</sub> (40.5 mg, 0.200 mmol, 10 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at 140 °C, the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 0%  $\rightarrow$  30% EtOAc/hexane) to afford **93** (283.9 mg,

0.810 mmol, 41% yield) as a white solid.

**2-(Pyridin-4-yl)-*N,N*-di-*p*-tolylaniline (93):** <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.34 (2H, d, *J* = 7.8 Hz), 7.38 (1H, td, *J* = 7.4, 1.7 Hz), 7.28-7.26 (3H, m), 7.12 (2H, d, *J* = 7.8 Hz), 6.88 (4H, d, *J* = 8.6 Hz), 6.72 (4H, d, *J* = 8.6 Hz), 2.21 (6H, s). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ 149.2, 147.8, 145.4, 145.1, 137.0, 131.2, 131.1, 129.9, 129.4, 129.1, 125.4, 123.4, 122.2, 20.6. **HRMS (FAB) *m/z*:** [M+H]<sup>+</sup> Calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub> 351.1861; Found: 351.1860. **Anal. Calcd for C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>:** C, 85.68; H, 6.33; N, 7.99. Found: C, 85.86; H, 6.34; N, 8.00. **IR (ATR):** 3027, 2979, 2915, 2861, 1603, 1501, 811, 755 cm<sup>-1</sup> **Melting Point:** 142.5-144.0 °C.

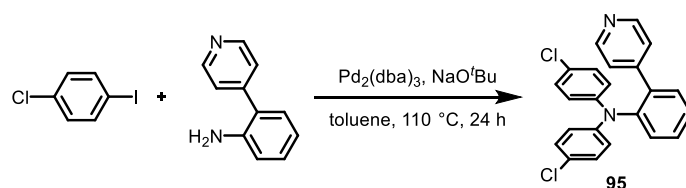
#### Preparation Procedure for 94:



A microwave vial was charged with a stir bar, aniline (524.0 mg, 3.08 mmol, 1.0 equiv.), iodobenzene (1.26 g, 6.18 mmol, 2.0 equiv.), and Pd<sub>2</sub>(dba)<sub>3</sub> (91.6 mg, 0.10 mmol, 10 mol%) and carried into a glove box. The mixture was dissolved in toluene (10 mL) and to the mixture were added NaO<sup>t</sup>Bu (592.0 mg, 6.16 mmol, 2.0 equiv.) and P<sup>t</sup>Bu<sub>3</sub> (40.5 mg, 0.200 mmol, 20 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at 140 °C, the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 0% → 30% EtOAc/hexane) to afford **94** (524.0 mg, 1.63 mmol, 53 % yield) as a white solid.

***N,N*-Diphenyl-2-(pyridin-4-yl)aniline (94):** <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.34 (2H, d, *J* = 6.8 Hz), 7.44-7.39 (1H, m), 7.33-7.31 (3H, m), 7.11-7.06 (6H, m), 6.85-6.82 (6H, m). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ 149.2, 147.7, 147.2, 145.0, 137.2, 131.3, 130.0, 129.4, 128.9, 125.9, 123.4, 122.2, 121.8. **HRMS (ESI) *m/z*:** [M+H]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>19</sub>N<sub>2</sub> 323.1548; Found: 323.1551. **IR (ATR):** 3030, 1579, 1483, 821, 751 cm<sup>-1</sup>. **Melting Point:** 166.1-167.5 °C.

#### Preparation Procedure for 95:

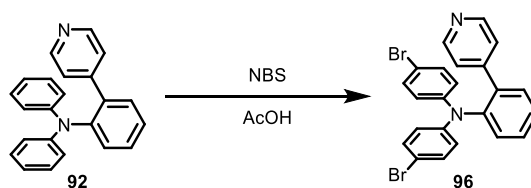


A microwave vial was charged with a stir bar, aniline (170.2 mg, 1.00 mmol, 1.0 equiv.), 1-chloro-4-

iodobenzene (476.9 mg, 2.00 mmol, 2.0 equiv.), and Pd<sub>2</sub>(dba)<sub>3</sub> (45.8 mg, 0.0500 mmol, 5 mol%) and carried into a glove box. The mixture was dissolved in toluene (10 mL) and to the mixture were added NaO<sup>t</sup>Bu (192.2 mg, 2.00 mmol, 2.0 equiv.) and P<sup>t</sup>Bu<sub>3</sub> (20.2 mg, 0.0998 mmol, 10 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at 140 °C, the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 0% → 30% EtOAc/hexane) to afford **95** (130.0 mg, 0.332 mmol, 33 % yield) as a white solid.

***N,N*-Bis(4-chlorophenyl)-2-(pyridin-4-yl)aniline (95):** <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 8.38 (2H, d, *J* = 7.2 Hz), 7.43 (1H, td, *J* = 7.5, 3.0 Hz), 7.35-7.26 (3H, m), 7.05 (4H, d, *J* = 9.0 Hz), 6.75 (4H, d, *J* = 9.0 Hz). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>): δ 149.5, 147.3, 145.5, 144.1, 137.3, 131.4, 130.3, 129.13, 129.06, 127.1, 126.5, 123.21, 123.15. HRMS (ESI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>2</sub> 391.0763; Found: 391.0768. IR (ATR): 3062, 3033, 1590, 1483, 822, 763, 733 cm<sup>-1</sup>. Melting Point: 145.7-146.2 °C.

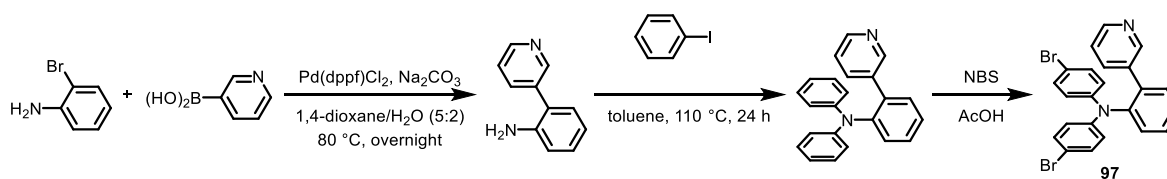
#### Preparation Procedure for 96:



A 200 mL round bottom flask was charged with a stir bar, compound **92** (1.18 g, 3.66 mmol, 1.0 equiv.), *N*-bromosuccinimide (NBS, 1.26 g, 7.08 mmol, 1.9 equiv.) and to the mixture was added CHCl<sub>3</sub> (32 mL) and AcOH (0.2 mL) under Ar atmosphere. The mixture was stirred for 30 min at room temperature then warmed up to 50 °C. After stirring overnight, the mixture was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 0% → 20% EtOAc/hexane) to afford **96** (1.59 g, 3.31 mmol, 90% yield) as a white solid.

***N,N*-Bis(4-bromophenyl)-2-(pyridin-4-yl)aniline (96):** <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.40 (2H, d, *J* = 6.3 Hz), 7.45-7.42 (1H, m), 7.34-7.31 (3H, m), 7.19 (4H, d, *J* = 8.5 Hz), 7.06 (2H, d, *J* = 6.3 Hz), 6.70 (4H, d, *J* = 8.5 Hz). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>): δ 149.5, 147.2, 145.9, 143.9, 137.3, 132.0, 131.5, 130.3, 129.2, 126.6, 123.5, 123.2, 114.6. HRMS (FAB) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>17</sub>Br<sub>2</sub>N<sub>2</sub> 478.9758; Found: 478.9760. Anal. Calcd for C<sub>23</sub>H<sub>16</sub>Br<sub>2</sub>N<sub>2</sub>: C, 57.53; H, 3.36; N, 5.83. Found: C, 57.29; H, 3.54; N, 5.71. IR (ATR): 3061, 1707, 1578, 1477, 814, 760 cm<sup>-1</sup>. Melting Point: 174.2-174.4 °C.

### Preparation Procedure for 97:



A 200 mL round bottom flask was charged with a stir bar, 2-bromoaniline (746.9  $\mu\text{L}$ , 6.60 mmol, 1.0 equiv.), 3-pyridylboronic acid (814.1 mg, 6.62 mmol, 1.0 equiv.),  $\text{Na}_2\text{CO}_3$  (2.80 g, 26.4 mmol, 4.0 equiv.), and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (242.3 mg, 0.331 mmol, 5 mol%) under Ar atmosphere. To the stirring mixture were added 1,4-dioxane/ $\text{H}_2\text{O}$  (5:2, 66 mL). After stirring overnight at 80  $^\circ\text{C}$ , the mixture was cooled down to room temperature and concentrated under reduced pressure to remove 1,4-dioxane. The aqueous solution was acidified with 1N aqueous HCl and washed with EtOAc (3 x 25 mL). The aqueous layer was basified with 4M aqueous NaOH and extracted by  $\text{CH}_2\text{Cl}_2$  (3 x 25 mL). The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  (2 x 25 mL), water (3 x 25 mL), and brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography ( $\text{SiO}_2$ , 10%  $\rightarrow$  80% EtOAc/hexane) to afford aniline (1.01 g, 5.93 mmol, 90% yield) as a white solid.

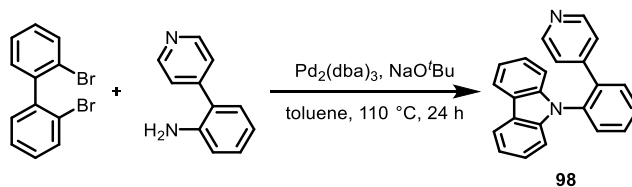
A microwave tube was charged with a stir bar, aniline (1.0 g, 5.87 mmol, 1.0 equiv.), and  $\text{Pd}_2(\text{dba})_3$  (100.0 mg, 0.109 mmol, 1.8 mol%) and carried into a glove box. The mixture was dissolved in toluene (12 mL) and to the mixture were added iodotoluene (1.32 mL, 11.8 mmol, 2.0 equiv.),  $\text{NaO}^t\text{Bu}$  (1.13 g, 11.8 mmol, 2.0 equiv.), and  $\text{P}^t\text{Bu}_3$  (119.4 mg, 0.590 mmol, 10 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at 150  $^\circ\text{C}$ , the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography ( $\text{SiO}_2$ , 0%  $\rightarrow$  35% EtOAc/hexane) to afford (536.6 mg, 1.66 mmol, 28% yield) as a white solid.

A 200 mL round bottom flask was charged with a stir bar, compound (536.6 mg, 1.66 mmol, 1.0 equiv.), and NBS (573.1 mg, 3.22 mmol, 1.9 equiv.) and to the mixture were added  $\text{CHCl}_3$  (15 mL) and AcOH (0.10 mL) under Ar atmosphere. The mixture was stirred for 30 min at room temperature then warmed up to 50  $^\circ\text{C}$ . After stirring overnight, the mixture was concentrated under reduced pressure and the crude residue was purified by flash column chromatography ( $\text{SiO}_2$ , 0%  $\rightarrow$  10% hexane/ $\text{CH}_2\text{Cl}_2$ , 5%  $\rightarrow$  10%  $\text{CH}_2\text{Cl}_2$ /EtOAc) to afford **97** (595.9 mg, 1.24 mmol, 75% yield) as a white solid.

***N,N*-Bis(4-bromophenyl)-2-(pyridin-3-yl)aniline (97):**  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.45 (1H, d,  $J$  = 2.1 Hz), 8.38 (1H, dd,  $J$  = 4.8, 1.4 Hz), 7.42-7.41 (2H, m), 7.36-7.31 (2H, m), 7.29 (1H, d,  $J$  = 7.6 Hz), 7.18 (4H, d,  $J$  = 9.0 Hz), 7.08 (1H, dd,  $J$  = 7.6, 4.8 Hz), 6.70 (4H, d,  $J$  = 9.0 Hz).  $^{13}\text{C-NMR}$  (151 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.1, 148.2, 146.0, 144.2, 136.5, 135.6, 135.1, 132.0, 130.0, 129.1, 126.6, 123.5, 122.9, 114.5. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{23}\text{H}_{17}\text{N}_3\text{Br}_2$  478.9753; Found: 478.9745. **IR (ATR):** 3033, 2924, 1579, 1485,

818, 724  $\text{cm}^{-1}$ . **Melting Point:** 140.4-141.5  $^{\circ}\text{C}$ .

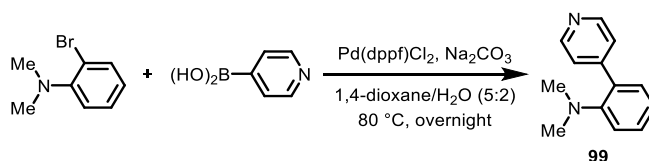
#### Preparation Procedure for 98:



A Microwave vial was charged with a stir bar, aniline (170.2 mg, 1.00 mmol, 1.0 equiv.), 2,2'-dibromobiphenyl (312.0 mg, 1.00 mmol, 1.0 equiv.), and  $\text{Pd}_2(\text{dba})_3$  (45.8 mg, 0.0500 mmol, 5 mol%) and carried into a glove box. The mixture was dissolved in toluene (10 mL) and to the mixture were added  $\text{NaO}'\text{Bu}$  (192.2 mg, 2.00 mmol, 2.0 equiv.) and  $\text{P}'\text{Bu}_3$  (20.2 mg, 0.0998 mmol, 10 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at  $140\text{ }^{\circ}\text{C}$ , the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography ( $\text{SiO}_2$ , 0%  $\rightarrow$  30% EtOAc/hexane) to afford 98 (110.0 mg, 0.343 mmol, 34% yield) as a white solid.

**9-(2-(Pyridin-4-yl)phenyl)-9H-carbazole (98):**  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.21 (2H, d,  $J = 6.2$  Hz), 8.06 (2H, d,  $J = 7.6$  Hz), 7.68-7.63 (3H, m), 7.56-7.55 (1H, m), 7.30-7.24 (2H, m), 7.22 (2H, t,  $J = 7.8$  Hz), 7.04 (2H, d,  $J = 8.3$  Hz), 6.92 (2H, d,  $J = 3.1$  Hz).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.6, 146.4, 141.9, 138.3, 134.9, 131.1, 130.3, 130.1, 129.2, 125.9, 123.1, 122.4, 120.3, 119.9, 109.6. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{23}\text{H}_{17}\text{N}_2$  321.1386; Found: 321.1389. **IR (ATR):** 3055, 1598, 827, 746  $\text{cm}^{-1}$ . **Melting Point:** 173.3-173.6  $^{\circ}\text{C}$ .

#### Preparation Procedure for 99:

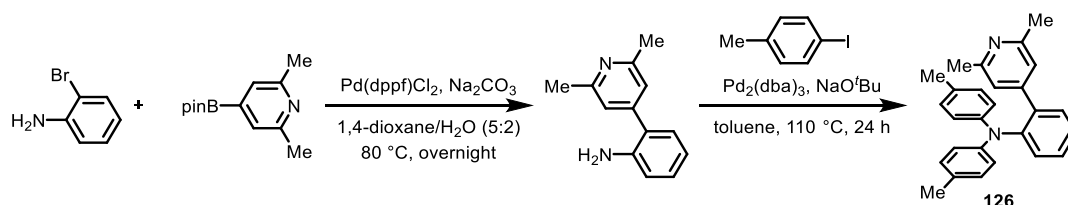


A 200 mL round bottom flask was charged with a stir bar, 2-bromo-*N,N*-dimethylaniline (719.7  $\mu\text{L}$ , 5.00 mmol, 1.0 equiv.), 4-pyridylboronic acid (614.6 mg, 5.00 mmol, 1.00 equiv.),  $\text{Na}_2\text{CO}_3$  (2.12 g, 20.0 mmol, 4.0 equiv.), and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (182.9 mg, 0.250 mmol, 5 mol%) under Ar atmosphere. To the stirring mixture were added 1,4-dioxane/ $\text{H}_2\text{O}$  (5:2, 50 mL). After stirring overnight at  $80\text{ }^{\circ}\text{C}$ , the mixture was cooled down to room temperature and the mixture was concentrated under reduced pressure to remove 1,4-dioxane. The aqueous solution was acidified with 1N aqueous HCl and washed with EtOAc (3 x 25 mL). The aqueous layer was basified with 4M aqueous NaOH and extracted by  $\text{CH}_2\text{Cl}_2$  (3 x 25 mL). The combined organic

layers were washed with saturated aqueous NaHCO<sub>3</sub> (2 x 25 mL), water (3 x 25 mL), and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 30% → 80% EtOAc/hexane) to afford aniline **99** (497.6 mg, 2.51 mmol, 50% yield) as a colorless oil.

***N,N*-Dimethyl-2-(pyridin-4-yl)aniline (99):** <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 8.61 (2H, d, *J* = 5.5 Hz), 7.54 (2H, d, *J* = 5.5 Hz), 7.33 (1H, t, *J* = 7.6 Hz), 7.22 (1H, d, *J* = 7.6 Hz), 7.07 (1H, d, *J* = 7.6 Hz), 7.04 (1H, t, *J* = 7.6 Hz), 2.56 (6H, s). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>): δ 151.3, 149.9, 131.3, 131.0, 129.4, 123.4, 121.7, 117.9, 43.6. (One aromatic peak was missing due to overlapping) **HRMS (ESI) *m/z*:** [M+H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>15</sub>N<sub>2</sub> 199.1230; Found: 199.1225. **IR (ATR):** 3061, 3025, 2979, 2940, 2867, 2835, 2785, 1596, 827, 760 cm<sup>-1</sup>.

#### Preparation Procedure for **126**:



A 200 mL round bottom flask was charged with a stir bar, 2-bromoaniline (298.8 μL, 2.62 mmol, 1.2 equiv.), 2,6-dimethyl-4-pyridylboronic acid<sup>40</sup> (529.9 mg, 2.27 mmol, 1.00 equiv.), Na<sub>2</sub>CO<sub>3</sub> (962.3 mg, 9.08 mmol, 4.0 equiv.), and Pd(dppf)Cl<sub>2</sub> (93.1 mg, 0.127 mmol, 6 mol%) under Ar atmosphere. To the stirring mixture were added 1,4-dioxane/H<sub>2</sub>O (5:2, 23 mL). After stirring overnight at 80 °C, the mixture was cooled down to room temperature and concentrated under reduced pressure to remove 1,4-dioxane. The aqueous solution was acidified with 1N aqueous HCl and washed with EtOAc (3 x 25 mL). The aqueous layer was basified with 4M aqueous NaOH and extracted by CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (2 x 25 mL), water (3 x 25 mL), and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 30% → 80% EtOAc/hexane) to afford aniline (115.0 mg, 0.580 mmol, 26% yield) as a brown solid.

A microwave vial was charged with a stir bar, aniline (115.0 mg, 0.58 mmol, 1.0 equiv.), 4-iodotoluene (252.9 mg, 1.16 mmol, 2.0 equiv.), and Pd<sub>2</sub>(dba)<sub>3</sub> (26.5 mg, 0.0289 mmol, 5 mol%) and carried into a glove box. The mixture was dissolved in toluene (6 mL) and to the mixture were added NaO<sup>t</sup>Bu (111.5 mg, 1.16 mmol, 2.0 equiv.) and P<sup>t</sup>Bu<sub>3</sub> (11.7 mg, 0.578 mmol, 10 mol%). The vial was capped, carried out of the glove box, and placed on a microwave reactor. After stirring 2 hours at 140 °C, the mixture was cooled down to room temperature, filtered through a Celite pad, and concentrated under reduced pressure. The crude residue was



purified by flash column chromatography (SiO<sub>2</sub>, 0% → 20% EtOAc/hexane) to afford **126** (65.9 mg, 0.174 mmol, 30% yield) as a white solid.

**2-(2,6-Dimethylpyridin-4-yl)-N,N-di-*p*-tolylaniline (126):** <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.35-7.32 (1H, m), 7.25-7.21 (3H, m), 6.88 (4H, d, *J* = 8.0 Hz), 6.71-6.70 (6H, m), 2.34 (6H, s), 2.22 (6H, s). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>): δ 156.8, 148.4, 145.5, 145.3, 137.3, 131.0, 130.9, 129.4, 129.3, 128.8, 125.0, 122.4, 120.1, 24.3, 20.6. HRMS (ESI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>27</sub>H<sub>27</sub>N<sub>2</sub> 379.2169; Found: 379.2179. IR (ATR): 3026, 2923, 2860, 1604, 1503, 950, 818 cm<sup>-1</sup>. Melting Point: 129.4-129.9 °C.

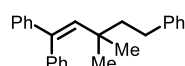
### Procedure for the alkenylation

#### General Procedure for Reaction of Unactivated Alkyl Bromides (GP5):

A borosilicate glass tube was charged with a stir bar, catalyst **96** (2.40 mg, 0.0100 mmol, 10 mol%), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.) and carried into a glove box. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture were added radical acceptor (0.100 mmol, 1.0 equiv.) and alkyl bromide (0.300 mmol, 3.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor equipped with two LED lamps (at 4 cm from tube) and a fan (Yamazen YCS-C188). After stirring for 12–72 hours under 427 nm LEDs irradiation (the temperature of the reaction mixture is usually 35–40 °C), the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography to afford desired product.

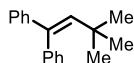
#### General Procedure for Reaction of Activated Alkyl Bromides (GP6):

A borosilicate glass tube was charged with a stir bar, catalyst **93** (0.00500 mmol, 5 mol%), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.) and carried into a glove box. The mixture was dissolved in solvent and to the mixture were added radical acceptor (0.100 mmol, 1.0 equiv.) and alkyl bromide. The tube was capped, carried out of the glove box, and placed on a photoreactor equipped with two LED lamps (at 4 cm from tube) and a fan (Yamazen YCS-C188). After stirring for 12–72 hours under 427 nm LEDs irradiation (the temperature of the reaction mixture is usually 35–40 °C), the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography to afford desired product.

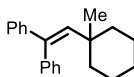


**(3,3-Dimethylpent-1-ene-1,1,5-triyl)tribenzene (89):** The reaction was performed according to **GP5** for 24 hours and gave product **89** in 70% yield as a colorless oil. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 7.35-7.14 (15H, m), 6.07 (1H, s), 2.64-2.63 (2H, m), 1.63-1.62 (2H, m), 0.96 (6H, s). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>): δ 144.1,

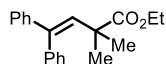
143.1, 140.6, 140.1, 138.6, 130.2, 128.3, 128.0, 127.8, 126.9, 126.8, 126.7, 125.6, 47.0, 37.2, 31.7, 29.0. (One aromatic peak was missing due to overlapping) **HRMS (ESI)  $m/z$** :  $[M+Na]^+$  Calcd for  $C_{25}H_{26}Na$  349.1927; Found: 349.1927. **IR (ATR)**: 3057, 3026, 2952, 2863, 1597, 1492, 1451  $cm^{-1}$ .



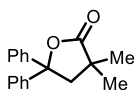
**(3,3-Dimethylbut-1-ene-1,1-diyl)dibenzene (101)**: The reaction was performed according to **GP5** for 72 hours and gave product **101** in 60% yield as a colorless oil.  **$^1H$ -NMR (500 MHz,  $CDCl_3$ )**:  $\delta$  7.29-7.20 (4H, m), 7.17-7.08 (7H, m), 6.01 (1H, s), 0.89 (9H, s).  **$^{13}C$ -NMR (126 MHz,  $CDCl_3$ )**:  $\delta$  144.0, 140.7, 140.1, 139.0, 130.3, 128.0, 127.7, 126.8, 126.7, 126.5, 33.9, 18.4. **HRMS (ESI)  $m/z$** :  $[M+H]^+$  Calcd for  $C_{18}H_{21}$  237.1638; Found: 237.1631. **IR (ATR)**: 2954, 1718, 1452, 1365  $cm^{-1}$ .



**(2-(1-Methylcyclohexyl)ethene-1,1-diyl)dibenzene (102)**: The reaction was performed according to **GP5** for 18 hours and gave product **102** in 40% yield as a colorless oil.  **$^1H$ -NMR (500 MHz,  $CDCl_3$ )**:  $\delta$  7.34-7.16 (10H, m), 6.02 (1H, s), 1.47-1.37 (7H, m), 1.22-1.20 (1H, m), 1.06-1.04 (2H, m), 0.99 (3H, s).  **$^{13}C$ -NMR (126 MHz,  $CDCl_3$ )**:  $\delta$  144.4, 140.9, 140.3, 139.1, 129.9, 128.0, 127.8, 126.83, 126.75, 126.7, 39.4, 37.1, 29.5, 26.1, 23.0. **HRMS (ESI)  $m/z$** :  $[M+H]^+$  Calcd for  $C_{21}H_{25}$  277.1951; Found: 277.1941. **IR (ATR)**: 3057, 3025, 2924, 2853, 1491, 1450, 942  $cm^{-1}$ .

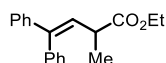


**Ethyl 2,2-dimethyl-4,4-diphenylbut-3-enoate (90)**: The reaction was performed according to **GP6** for 24 hours and gave product **90** in 82% yield as a colorless oil.  **$^1H$ -NMR (500 MHz,  $CDCl_3$ )**:  $\delta$  7.33-7.30 (3H, m), 7.25-7.20 (5H, m), 7.14-7.12 (2H, m), 6.09 (1H, s), 3.72 (2H, q,  $J = 7.2$  Hz), 1.30 (6H, s), 1.13 (3H, t,  $J = 7.2$  Hz).  **$^{13}C$ -NMR (126 MHz,  $CDCl_3$ )**:  $\delta$  176.3, 143.3, 141.4, 139.3, 134.2, 130.1, 128.0, 127.8, 127.22, 127.20, 127.1, 60.4, 44.0, 27.8, 13.9. **HRMS (ESI)  $m/z$** :  $[M+H]^+$  Calcd for  $C_{20}H_{23}O_2$  295.1693; Found: 295.1691. **IR (ATR)**: 2977, 2931, 2873, 1726, 1450, 1386, 1028  $cm^{-1}$ .

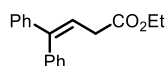


**4,4-Diphenylbut-3-enitrile (103)**: A borosilicate glass tube was charged with a stir bar, catalyst **93** (1.75 mg, 0.005 mmol, 5 mol%),  $NaHCO_3$  (16.8 mg, 0.200 mmol, 2.0 equiv.) and carried into a glove box. The mixture was dissolved in  $CH_3CN$  (2.0 mL) and to the mixture were added 1,1-diphenylethylene **86** (17.7  $\mu L$ ,

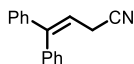
0.100 mmol, 1.0 equiv.) and alkyl bromide **87** (22.4  $\mu$ L, 0.150 mmol, 1.5 equiv.). The tube was capped with septum and carried out of the glove box, and to the mixture was added distilled water (0.5 mL) by a syringe. The mixture was deoxygenated by the bubbling of Ar gas and the tube was placed on a photoreactor equipped with two LED lamps (at 4 cm from tube) and a fan (Yamazen YCS-C188). After stirring for 24 hours under 427nm LEDs irradiation (The temperature of the reaction mixture is usually 40-50  $^{\circ}$ C), the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 15 mL, 0% $\rightarrow$ 5% EtOAc/hexane) to afford product **103** in 80% yield as a white solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.46 (4H, d,  $J$  = 7.2 Hz), 7.33 (4H, t,  $J$  = 7.2 Hz), 7.24 (2H, t,  $J$  = 7.2 Hz), 2.93 (2H, s), 1.15 (6H, s). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  181.2, 144.7, 128.6, 127.5, 125.0, 86.1, 49.9, 40.6, 25.8. **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>19</sub>O<sub>2</sub> 267.1380; Found: 267.1374. **IR (ATR):** 2974, 2936, 2876, 1772, 1234, 1157 cm<sup>-1</sup>. **Melting Point:** 116.6-116.8 $^{\circ}$ C.



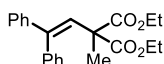
**Ethyl 2-methyl-4,4-diphenylbut-3-enoate (104):** The reaction was performed according to **GP6** for 18 hours and gave product **104** in 99% yield as a colorless oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.38 (2H, t,  $J$  = 7.6 Hz), 7.32 (1H, t,  $J$  = 7.2 Hz), 7.27-7.19 (7H, m), 6.11 (1H, d,  $J$  = 9.6 Hz), 4.12 (2H, q,  $J$  = 7.1 Hz), 3.25 (1H, dq,  $J$  = 9.6, 7.1 Hz), 1.26-1.23 (6H, m). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  174.9, 142.9, 141.9, 139.4, 129.7, 128.3, 128.1, 127.9, 127.34, 127.29, 60.6, 40.4, 18.5, 14.2. (One aromatic peak is missing due to overlapping) **HRMS (ESI)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>20</sub>O<sub>2</sub>Na 303.1356; Found: 303.1350. **IR (ATR):** 2979, 2933, 2879, 1730, 1488, 1450, 1242, 1177 cm<sup>-1</sup>.



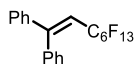
**4,4-Diphenylbut-3-enitrile (105):** The reaction was performed according to **GP6** for 24 hours and gave product **105** in 64% yield as a colorless oil. **<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  7.31 (2H, t,  $J$  = 7.6 Hz), 7.27-7.25 (1H, m), 7.20-7.18 (5H, m), 7.12 (2H, d,  $J$  = 7.6 Hz), 6.19 (1H, t,  $J$  = 7.2 Hz), 4.08 (2H, q,  $J$  = 7.3 Hz), 3.08 (2H, d,  $J$  = 7.6 Hz), 1.19 (4H, t,  $J$  = 7.2 Hz). **<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):**  $\delta$  171.9, 144.6, 142.0, 139.2, 129.8, 128.3, 128.1, 127.41, 127.35, 120.5, 60.7, 35.5, 14.2. (One aromatic carbon peak is missing due to overlapping) **HRMS (ESI)  $m/z$ :** [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>14</sub>N 267.1380; Found: 267.1374. **IR (ATR):** 3029, 2976, 2927, 1735, 1170 cm<sup>-1</sup>.



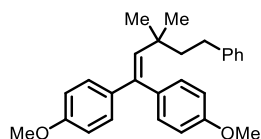
**4,4-Diphenylbut-3-enitrile (106):** The reaction was performed according to **GP6** for 18 hours and gave product **106** in 76% yield as a white solid. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.43 (2H, t,  $J = 7.2$  Hz), 7.39-7.38 (1H, m), 7.32-7.30 (3H, m), 7.24-7.22 (2H, m), 7.18 (2H, d,  $J = 7.2$  Hz), 6.04 (1H, t,  $J = 7.6$  Hz), 3.15 (2H, d,  $J = 7.6$  Hz). **<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):**  $\delta$  147.5, 140.7, 138.0, 129.4, 128.8, 128.4, 128.2, 128.1, 127.4, 118.2, 115.4, 18.4. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for C<sub>16</sub>H<sub>14</sub>N 220.1121; Found: 220.1115. **IR (ATR):** 3038, 2917, 2245, 1488, 1442, 1405, 1305, 1254, 1175 cm<sup>-1</sup>. **Melting Point:** 97.1-97.6°C.



**Diethyl 2-(2,2-diphenylvinyl)-2-methylmalonate (107):** The reaction was performed according to **GP6** for 12 hours and gave product **107** in 91% yield as a colorless oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.34-7.30 (3H, m), 7.29-7.21 (5H, m), 7.13 (2H, d,  $J = 6.9$  Hz), 6.66 (1H, s), 4.03-3.97 (2H, m), 3.95-3.88 (2H, m), 1.50 (3H, s), 1.18 (6H, t,  $J = 7.2$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  171.1, 142.9, 138.4, 132.1, 130.0, 128.1, 127.8, 127.5, 127.4, 127.32, 127.29, 61.4, 55.4, 23.3, 13.8. **HRMS (ESI)  $m/z$ :**  $[M+H]^+$  Calcd for C<sub>22</sub>H<sub>25</sub>O<sub>4</sub> 353.1747; Found: 353.1737. **IR (ATR):** 3055, 2984, 2934, 1735, 1451, 1377, 1254, 1201, 1108 cm<sup>-1</sup>.

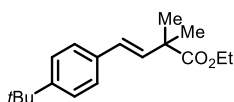


**1-(Perfluorohexyl)-4,4-diphenylprop-3-ene (108):** The reaction was performed according to **GP6** for 18 hours and gave product **108** in 77% yield as a white solid. **<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  7.39-7.32 (6H, m), 7.25-7.23 (4H, m), 6.09 (1H, t,  $J = 14.8$  Hz). **<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):** 154.3, 140.6, 137.4, 129.5, 129.0, 128.5, 128.3, 128.0, 127.8, 118.22-108.31 (m), 112.7 (t,  $J = 20.2$  Hz). **<sup>19</sup>F-NMR (471 MHz, CDCl<sub>3</sub>):**  $\delta$  -80.6 (3F, t,  $J = 9.9$  Hz), -103.4 (2F, q,  $J = 13.2$  Hz), -121.4 (2F, s), -122.7 (2F, s), -122.8 (2F, d,  $J = 8.9$  Hz), -126.0 (2F, td,  $J = 14.4, 7.2$  Hz). **HRMS (ESI)  $m/z$ :**  $[M+Na]^+$  Calcd for C<sub>20</sub>H<sub>11</sub>F<sub>13</sub>Na 521.0545; Found: 521.0542. **IR (ATR):** 3032, 2926, 2858, 1490, 1446, 1362, 1237, 1189, 1141, 1108 cm<sup>-1</sup>. **Melting Point:** 54.6-55.2°C.

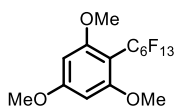


**4,4'-(3,3-Dimethyl-4-phenylbut-1-ene-1,1-diyl)bis(methoxybenzene) (109):** The reaction was performed according to **GP6** for 48 hours and gave product **109** in 42% yield as a white solid. **<sup>1</sup>H-NMR (600 MHz,**

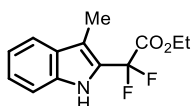
**CDCl<sub>3</sub>**):  $\delta$  7.27-7.26 (2H, m), 7.18-7.10 (7H, m), 6.87 (2H, d,  $J = 7.2$  Hz), 6.78 (2H, d,  $J = 7.2$  Hz), 5.96 (1H, s), 3.83 (3H, s), 3.78 (3H, s), 2.64-2.61 (2H, m), 1.63-1.60 (2H, m), 0.96 (6H, s). **<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>)**:  $\delta$  158.5, 158.4, 143.3, 139.2, 137.2, 137.1, 133.1, 131.2, 128.28, 128.26, 127.9, 125.5, 113.3, 113.1, 55.3, 55.2, 47.0, 37.1, 31.6, 29.2. **HRMS (ESI)  $m/z$** :  $[M+H]^+$  Calcd for C<sub>27</sub>H<sub>31</sub>O<sub>2</sub> 387.2319; Found: 387.2304. **IR (ATR)**: 2952, 2843, 1606, 1509, 1461, 1248, 953 cm<sup>-1</sup>.



**Ethyl 4-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-enoate (110)**: The reaction was performed according to **GP6** for 18 hours and gave product **110** in 71% yield ( $E:Z = 7.1:1$ ) as a colorless oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  7.32 (3.72H, m), 7.08 (0.28H, d,  $J = 8.6$  Hz), 6.45 (0.14H, d,  $J = 12.0$  Hz), 6.41 (0.86H, d,  $J = 16.6$  Hz), 6.35 (0.86H, d,  $J = 16.0$  Hz), 5.59 (0.14H, d,  $J = 12.6$  Hz), 4.14 (1.72H, q,  $J = 7.1$  Hz), 3.61 (0.28H, q,  $J = 7.1$  Hz), 1.39 (6H, s), 1.30 (9H, s), 1.25 (3H, t,  $J = 7.2$  Hz). **<sup>13</sup>C-NMR (151MHz, CDCl<sub>3</sub>)**:  $\delta$  176.5, 176.4, 150.5, 149.7, 136.1, 134.3, 133.7, 129.0, 128.2, 127.6, 126.0, 125.4, 124.7, 60.7, 60.4, 44.3, 43.6, 34.5, 31.3, 27.8, 25.0, 14.2, 13.7. **HRMS (ESI)  $m/z$** :  $[M+H]^+$  Calcd for C<sub>18</sub>H<sub>27</sub>O<sub>2</sub> 275.2006; Found: 275.2002. **IR (ATR)**: 2964, 1729, 1467, 1373, 1245, 1142 cm<sup>-1</sup>.

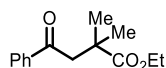


**1,3,5-Trimethoxy-2-(perfluorohexyl)benzene (111)**: The reaction was performed according to **GP6** for 18 hours and gave product **111** in 73% yield as a colorless oil. **<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)**:  $\delta$  6.14 (2H, s), 3.84 (3H, s), 3.80 (6H, s). **<sup>13</sup>C-NMR (151MHz, CDCl<sub>3</sub>)**:  $\delta$  163.8, 161.7, 120.7-115.1 (m), 114.7-106.3 (m), 98.6 (t,  $J = 18.0$  Hz), 91.6, 56.3, 55.3. **<sup>19</sup>F-NMR (565 MHz, CDCl<sub>3</sub>)**:  $\delta$  -80.69 (3F, t,  $J = 10.3$  Hz), -102.55 (2F, s), -121.79-122.31 (4F, m), -122.51 (2F, s), -126.01 (2F, s). **HRMS (ESI)  $m/z$** :  $[M+H]^+$  Calcd for C<sub>15</sub>H<sub>12</sub>O<sub>3</sub>F<sub>13</sub> 487.0573; Found: 487.0568. **IR (ATR)**: 2943, 2850, 1600, 1466, 1419, 1239, 1202, 1151, 1107 cm<sup>-1</sup>.

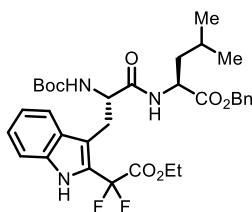


**Ethyl 2,2-difluoro-2-(3-methyl-1*H*-indol-2-yl)acetate (112)**: The reaction was performed according to **GP6** for 18 hours and gave product **112** in 74% yield as a pale yellowish oil. **<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)**:  $\delta$  8.35 (1H, brs), 7.62 (1H, d,  $J = 8.0$  Hz), 7.38 (1H, d,  $J = 7.6$  Hz), 7.29 (1H, t,  $J = 7.6$  Hz), 7.17 (1H, t,  $J =$

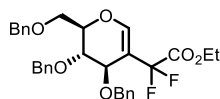
8.2 Hz), 4.34 (2H, q,  $J = 7.1$  Hz), 2.42 (3H, s), 1.34 (3H, t,  $J = 7.2$  Hz).  $^{13}\text{C-NMR}$  (151MHz,  $\text{CDCl}_3$ ):  $\delta$  163.4 (t,  $J = 36.2$  Hz), 135.5, 128.5, 124.3, 123.3 (t,  $J = 29.0$  Hz), 120.1, 119.8, 113.9, 111.5, 111.4 (t,  $J = 251.6$  Hz), 63.5, 13.9, 8.5.  $^{19}\text{F-NMR}$  (565 MHz,  $\text{CDCl}_3$ ):  $\delta$  -101.48 (d,  $J = 1.8$  Hz). **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{13}\text{H}_{14}\text{NO}_2\text{F}_2$  254.0987; Found: 254.0983. **IR (ATR):** 3403, 2982, 2931, 1760, 1300, 1239, 1095  $\text{cm}^{-1}$ .



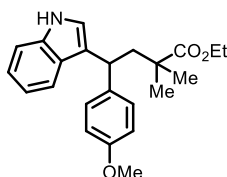
**Ethyl 2,2-dimethyl-4-oxo-4-phenylbutanoate (113):** The reaction was performed according to **GP6** for 18 hours and gave product **113** in 78% yield as a pale yellowish oil.  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ): 7.94 (2H, d,  $J = 7.2$  Hz), 7.56 (1H, t,  $J = 7.2$  Hz), 7.46 (2H, t,  $J = 7.2$  Hz), 4.14 (3H, q,  $J = 7.0$  Hz), 3.29 (2H, s), 1.32 (6H, s), 1.21 (3H, t,  $J = 7.0$  Hz).  $^{13}\text{C-NMR}$  (151 MHz,  $\text{CDCl}_3$ ):  $\delta$  197.6, 177.3, 137.0, 133.1, 128.5, 127.9, 60.5, 48.5, 40.0, 25.8, 14.1. **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_3$  235.1329; Found: 235.1324. **IR (ATR):** 2975, 2931, 1730, 1688, 1454, 1192, 1137  $\text{cm}^{-1}$ .



**tert-Butyl ((S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1H-indol-3-yl)propanoyl)-L-leucinate (114):** The reaction was performed according to **GP6** for 12 hours and gave product **114** in 64% yield as a white solid.  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.42 (1H, s), 7.71 (1H, d,  $J = 8.0$  Hz), 7.39-7.26 (7H, m), 7.16 (1H, t,  $J = 7.6$  Hz), 6.31 (1H, d,  $J = 8.0$  Hz), 5.25 (1H, d,  $J = 7.7$  Hz), 5.05 (1H, d,  $J = 12.3$  Hz), 5.02 (1H, d,  $J = 12.3$  Hz), 4.59-4.51 (1H, m), 4.50-4.40 (1H, m), 4.35 (2H, q,  $J = 7.1$  Hz), 3.41-3.15 (2H, m), 1.59-1.55 (2H, m), 1.49-1.46 (1H, m), 1.34-1.28 (12H, m), 0.90-0.85 (6H, m).  $^{13}\text{C-NMR}$  (151MHz,  $\text{CDCl}_3$ ):  $\delta$  172.2, 171.1, 163.5 (t,  $J = 36.2$  Hz), 155.3, 135.6, 135.3, 128.6, 128.4, 128.2, 127.8, 124.53, 124.46 (t,  $J = 30.0$  Hz), 120.7, 120.2, 112.9, 111.5, 111.3 (t,  $J = 251.6$  Hz), 79.8, 66.9, 64.0, 55.1, 50.7, 41.8, 28.1, 27.4, 24.6, 22.8, 22.0, 13.9.  $^{19}\text{F-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  -100.44 (1F, d,  $J = 268.8$  Hz), -101.17 (1F, d,  $J = 266.6$  Hz). **HRMS (ESI)  $m/z$ :**  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{33}\text{H}_{41}\text{N}_3\text{O}_7\text{F}_2\text{Na}$  652.2805; Found: 652.2812. **IR (ATR):** 3290, 2965, 1743, 1672, 1504, 1161, 1092  $\text{cm}^{-1}$ . **Optical Rotation:**  $[\alpha]^{26}_{\text{D}}$  -23.9 (c 0.038,  $\text{CHCl}_3$ ).

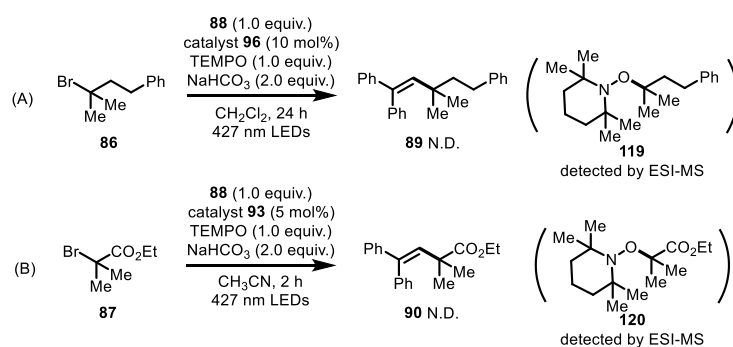


**Ethyl 2-((2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-yl)-2,2-difluoroacetate (115):** The reaction was performed according to **GP6** for 12 hours and gave product **115** in 40% yield as a pale yellowish oil. **<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  7.34-7.20 (15H, m), 6.97 (1H, s), 4.61-4.54 (2H, m), 4.51-4.47 (4H, m), 4.42 (1H, s), 4.12-4.02 (3H, m), 3.86 (1H, d,  $J = 3.4$  Hz), 3.77 (1H, dd,  $J = 10.7, 6.5$  Hz), 3.64 (1H, dd,  $J = 10.3, 3.4$  Hz), 1.12 (3H, dt,  $J = 20.4, 8.1$  Hz). **<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):**  $\delta$  164.0 (dd,  $J = 37.6, 33.2$  Hz), 146.7 (dd,  $J = 12.3, 9.4$  Hz), 137.7, 137.6, 137.4, 128.5, 128.4, 128.3, 128.0, 127.9, 127.81, 127.77, 127.7, 113.4 (t,  $J = 250.0$  Hz), 105.7 (dd,  $J = 26.0, 21.7$  Hz), 76.37, 73.39, 72.6, 72.3, 72.0, 70.1 (d,  $J = 2.9$  Hz), 67.7, 62.7, 13.8. **<sup>19</sup>F-NMR (565 MHz, CDCl<sub>3</sub>):**  $\delta$ : -102.60 (d,  $J = 255.5$  Hz), -108.68 (d,  $J = 255.5$  Hz). **HRMS (ESI)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>31</sub>H<sub>32</sub>O<sub>6</sub>F<sub>2</sub>Na 561.2059; Found: 561.2042. **IR (ATR):** 3031, 2924, 2865, 1764, 1659, 1457, 1366, 1101 cm<sup>-1</sup>. **Optical Rotation:** [ $\alpha$ ]<sub>D</sub><sup>25</sup> +41.6 (c 0.19, CHCl<sub>3</sub>).



**Ethyl 4-(1H-indol-3-yl)-4-(4-methoxyphenyl)-2,2-dimethylbutanoate (118):** The reaction was performed according to **GP6** for 12 hours and gave product **118** in 55% yield as a pale yellowish oil. **<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  7.87 (1H, s), 7.46 (1H, d,  $J = 7.6$  Hz), 7.23 (1H, d,  $J = 8.3$  Hz), 7.17 (2H, d,  $J = 7.6$  Hz), 7.06 (1H, t,  $J = 7.6$  Hz), 6.97 (1H, t,  $J = 7.6$  Hz), 6.87 (1H, s), 6.71 (2H, d,  $J = 9.0$  Hz), 4.20 (1H, t,  $J = 6.9$  Hz), 3.68 (3H, s), 3.49-3.48 (2H, m), 2.41 (1H, dd,  $J = 13.8, 4.8$  Hz), 2.32 (1H, dd,  $J = 14.5, 7.6$  Hz), 1.16 (3H, s), 1.10 (3H, s), 0.94 (3H, t,  $J = 7.2$  Hz). **<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):**  $\delta$  177.5, 157.7, 136.8, 136.5, 129.1, 126.5, 121.9, 121.3, 120.8, 119.4, 119.2, 113.4, 111.0, 60.0, 55.2, 46.3, 41.9, 38.6, 26.4, 25.8, 13.8. **HRMS (ESI)  $m/z$ :** [M+Na]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>27</sub>NO<sub>3</sub>Na 388.1883; Found: 388.1880. **IR (ATR):** 3377, 2968, 2928, 1719, 1509, 1464, 1251, 1187, 950 cm<sup>-1</sup>.

## Radical Trapping Experiments:



### Experiment Using Unactivated Alkyl Bromide **86** (Equation A):

A borosilicate glass tube was charged with a stir bar, catalyst **96** (4.80 mg, 0.0100 mmol, 10 mol%), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.), and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 15.6 mg, 0.100 mmol, 1.0 equiv.) and carried into a glove box. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (17.7  $\mu$ L, 0.100 mmol, 1.0 equiv.) and alkyl bromide **86** (68.0 mg, 0.300 mmol, 3.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor. After stirring for 24 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. A traceable amount of **119** was not observed on TLC and <sup>1</sup>H NMR spectra of the crude mixture and TEMPO-adduct was detected by ESI-MS spectroscopy.

**TEMPO adduct 119: HRMS (ESI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>34</sub>NO 304.2635; Found: 304.2625.**

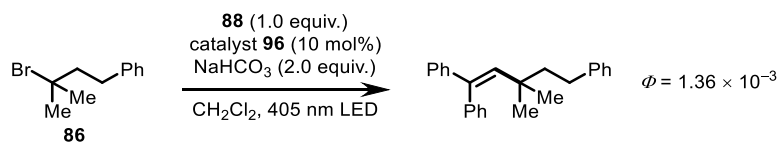
### Experiment Using Activated Alkyl Bromide **87** (Equation B):

A borosilicate glass tube was charged with a stir bar, catalyst **93** (1.75 mg, 0.00499 mmol, 5 mol%), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.), and TEMPO (15.6 mg, 0.100 mmol, 1.0 equiv.) and carried into a glove box. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (17.7  $\mu$ L, 0.100 mmol, 1.0 equiv.) and alkyl bromide **87** (14.9  $\mu$ L, 0.100 mmol, 1.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor. After stirring for 24 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. A traceable amount of **120** was not observed on TLC and <sup>1</sup>H NMR spectra of the crude mixture and TEMPO-adduct was detected by ESI-MS spectroscopy.

**TEMPO adduct 120: HRMS (ESI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>30</sub>NO<sub>3</sub> 272.2220; Found: 272.2222.**



### Quantum Yield Measurements:



A quantum yield ( $\Phi$ ) of the alkenylation using alkyl bromide **84** was determined under irradiation of 405 nm LED light (ASAHI SPECTRA CL-H1-405-9-1, full width at half maximum = 15 nm) on an ASAHI SPECTRA CL-1503 at 298 K. The quantum yield is calculated using the following equation:

$$\Phi = (1 \times R/I)$$

where  $R$  ( $\text{mol} \cdot \text{s}^{-1}$ ) is the rate of formation of **89**,

and  $I$  ( $\text{einstein} \cdot \text{s}^{-1}$ ) is the rate of photon flux of the incident light.

The total number of incident photons was determined using a standard actinometer as follows. A test tubes containing an aqueous solution of potassium ferrioxalate ( $\text{K}_3[\text{Fe}^{\text{III}}(\text{C}_2\text{O}_4)_3]$ , 6.00 mM, 2.00 mL) was placed on a photoreactor equipped with the 405 nm LED lamp (at 0.5 cm from tube) and a fan (Yamazen YCS-C188) and irradiated using the 405 nm LED light for 4, 8 or 12 seconds at 298 K, respectively. At the end of the irradiation, 100  $\mu\text{L}$  of each the actinometer solution were diluted by a sodium acetate buffer solution (1.0 mol/L, 150  $\mu\text{L}$ ), 0.100% phenanthroline aqueous solution (0.500 mL), and distilled water (4.25 mL), and the solution was kept under dark for 10 min. UV-Vis spectra were recorded on JASCO V-660 and the absorbance at 510 nm due to  $[\text{Fe}(\text{phen})_3]^{2+}$  ( $\epsilon = 11050 \text{ M}^{-1} \cdot \text{cm}^{-1}$  at  $\lambda_{\text{max}} = 510 \text{ nm}$ )<sup>42</sup> was measured. The same experiments were repeated three times. The total number of incident photons was determined using the quantum yield for the photodecomposition of ferrioxalate ( $\Phi = 1.14$  at 405–407 nm)<sup>42</sup> to be  $7.17 \times 10^{-7} \text{ einstein} \cdot \text{s}^{-1}$  [rate of formation of  $[\text{Fe}(\text{phen})_3]^{2+}$  ( $\text{mol} \cdot \text{s}^{-1}$ ) =  $(2.0 \times 10^{-3} \text{ L}) \times 9.03 \times 10^{-2}$  (slope of a inset)  $\times 50$  (rate of dilution) / 11050 ( $\epsilon$ ) =  $8.17 \times 10^{-7} \text{ mol} \cdot \text{s}^{-1}$ ,  $I = 8.17 \times 10^{-7} / 1.14 = 7.17 \times 10^{-7} \text{ einstein} \cdot \text{s}^{-1}$ ].

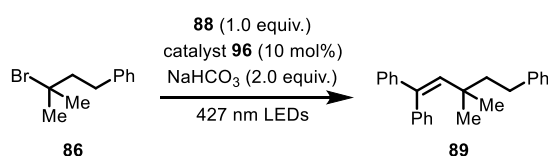
A borosilicate glass tube was charged with a stir bar, catalyst **96** (9.60 mg, 0.0200 mmol, 10 mol%),  $\text{NaHCO}_3$  (33.6 mg, 0.400 mmol, 2.0 equiv.), and dimethyl terephthalate (19.4 mg, 0.0999 mmol) and carried into a glove box. The mixture was dissolved in  $\text{CD}_2\text{Cl}_2$  (2.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (35.3  $\mu\text{L}$ , 0.200 mmol, 1.0 equiv.) and alkyl bromide **86** (136.3 mg, 0.600 mmol, 3.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor using 405 nm LED light. After stirring for 2 hours under 405 nm LED irradiation, the tube was removed from photoreactor, and carried into glove box. 250  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 2 hours then was carried out of the glove box and placed on a photoreactor. After stirring for 4 hours under 405 nm LED irradiation, the tube was removed from photoreactor, and carried into glove box. 250  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 4 hours then the tube was carried out of the glove box

and placed on a photoreactor. After stirring for 6 hours under 405 nm LED irradiation, the tube was removed from photoreactor and carried into glove box. 250  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 6 hours, then the tube was carried out of the glove box and placed on a photoreactor. After stirring for 8 hours under 405 nm LED irradiation, the tube was removed from photoreactor, and carried into glove box. 250  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 8 hours. Yields of **89** at 2, 4, 6, and 8 hours were determined by NMR analysis of the above-mentioned samples containing dimethyl terephthalate as an internal standard. The same measurements were repeated twice more (the results are shown in Figure 6d and 6f), and the average value of reaction rate was  $9.72 \times 10^{-10} \text{ mol}\cdot\text{s}^{-1}$ .

Finally, the quantum yield of the production of **89** was calculated by following equation:

$$\Phi = (9.72 \times 10^{-10} \text{ mol}\cdot\text{s}^{-1} / 7.17 \times 10^{-7} \text{ einstein}\cdot\text{s}^{-1}) = 1.36 \times 10^{-3}$$

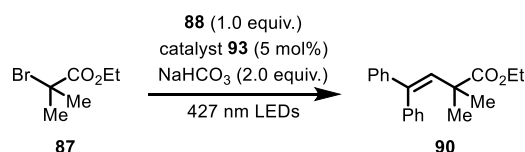
### Light On-Off Experiments:



### Experiment Using Unactivated Alkyl Bromide **86** (a):

A borosilicate glass tube was charged with a stir bar, catalyst **96** (14.4 mg, 0.0300 mmol, 10 mol%),  $\text{NaHCO}_3$  (50.4 mg, 0.600 mmol, 2.0 equiv.), and dimethyl terephthalate (19.4 mg, 0.100 mmol) and carried into a glove box. The mixture was dissolved in  $\text{CD}_2\text{Cl}_2$  (3.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (52.9  $\mu\text{L}$ , 0.300 mmol, 1.0 equiv.) and alkyl bromide **86** (204.4 mg, 0.900 mmol, 3.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor. After stirring for 6 hours under 427 nm LEDs irradiation, the tube was removed from photoreactor, and carried into glove box. 500  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 6 hours then the tube was capped and covered with aluminum foil. After stirring for 2 hours in the dark, 500  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 8 hours then the tube was carried out of the glove box and placed on a photoreactor. After stirring for 7 hours under 427 nm LEDs irradiation, the tube was removed from photoreactor, and carried into glove box. 500  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 15 hours then the tube was capped and covered with aluminum foil. After stirring for 2 hours in the dark, 500  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 17 hours then the tube was carried out of the glove box and placed on a photoreactor. After stirring for 8 hours under 427 nm LEDs irradiation, the tube was removed from photoreactor, and carried into glove box. 500  $\mu\text{L}$  of the reaction mixture was taken as a sample for NMR analysis at 25 hours. Yields of **89** at 6, 8, 15, 17, and 25 hours were determined by NMR analysis of the above-mentioned samples containing dimethyl terephthalate as an internal standard.

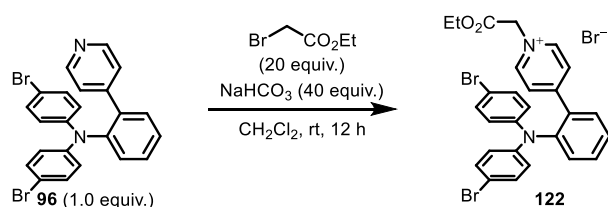
**NMR Yield of 89:** 30% yield (6 hours) → 30% yield (8 hours) → 48% yield (15 hours) → 48% yield (17 hours) → 59% yield (25 hours).



**Experiment Using Unactivated Alkyl Bromide 87 (a):** The reaction was performed according to the procedure above.

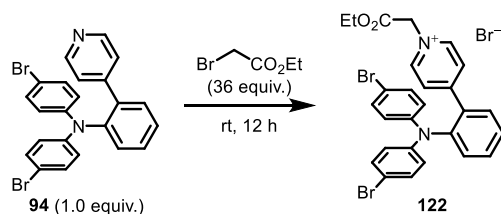
**NMR Yield of 90:** 19% yield (0.5 hour) → 19% yield (1 hour) → 35% yield (1.5 hours) → 35% yield (2 hours) → 49% yield (3 hours).

#### Investigation on Rate of Pyridinium Salt 122 Formation in Solution:



A borosilicate glass tube was charged with a stir bar, catalyst **96** (2.40 mg, 0.00500 mmol, 1.0 equiv.), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 40.0 equiv.), and carried into a glove box. The mixture was dissolved in CD<sub>2</sub>Cl<sub>2</sub> (1.0 mL), added alkyl bromide (11.0 μL, 0.100 mmol, 20.0 equiv.) and the tube was capped and carried out of the glove box. After stirring for 2 hours, the volatiles were removed under reduced pressure. The conversion of catalyst **96** was determined by <sup>1</sup>H NMR spectra of the crude mixture (<5 % conversion).

#### Preparation of Pyridinium Salt 122 in Neat Conditions:

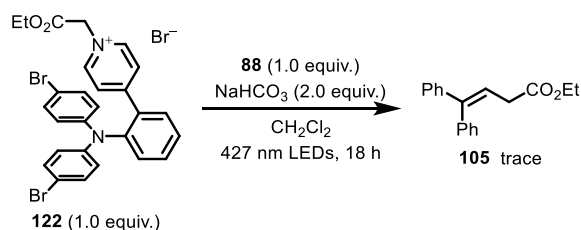


A 10 mL borosilicate glass tube was charged with a stir bar, catalyst **96** (120.1 mg, 0.250 mmol, 1.0 equiv.), and ethyl bromoacetate (1.0 mL, 9.04 mmol, 36.2 equiv.) and stirred for 12 hours at room temperature. The ethyl bromoacetate was removed under reduced pressure, washed by hexane (3 x 3 mL), dried under reduced pressure to afford pyridinium salt **122** as an orange solid (140 mg, 0.216 mmol, 87% yield).

**4-(2-(Bis(4-bromophenyl)amino)phenyl)-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (122):** <sup>1</sup>H-

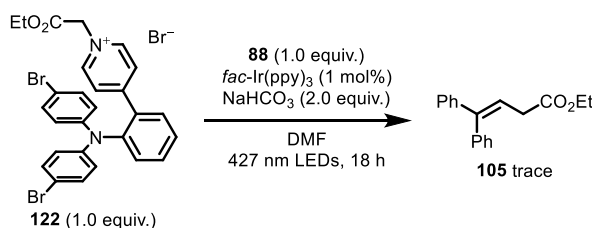
**NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  9.10 (2H, d,  $J = 5.7$  Hz), 7.80 (2H, d,  $J = 6.3$  Hz), 7.57 (1H, t,  $J = 7.4$  Hz), 7.46 (1H, d,  $J = 6.9$  Hz), 7.41 (1H, t,  $J = 7.4$  Hz), 7.33 (1H, d,  $J = 8.0$  Hz), 7.27 (4H, d,  $J = 8.6$  Hz), 6.72 (4H, d,  $J = 8.6$  Hz), 6.11 (2H, s), 4.29 (2H, q,  $J = 7.1$  Hz), 1.32 (3H, t,  $J = 7.2$  Hz). **<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  165.5, 157.2, 145.9, 145.3, 144.8, 133.1, 132.7, 132.1, 131.5, 128.9, 127.0, 126.4, 124.1, 116.0, 63.3, 60.4, 14.1. **HRMS (ESI)  $m/z$ :** [M]<sup>+</sup> Calcd for C<sub>27</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>Br<sub>2</sub> 565.0121; Found: 565.0116. **IR (ATR):** 2926, 1759, 1708, 1644, 1516, 1306, 921 cm<sup>-1</sup> **Melting Point:** 135.5-136.5°C

#### Attempt to Use Pyridinium Salt **122** in Optimal Conditions:



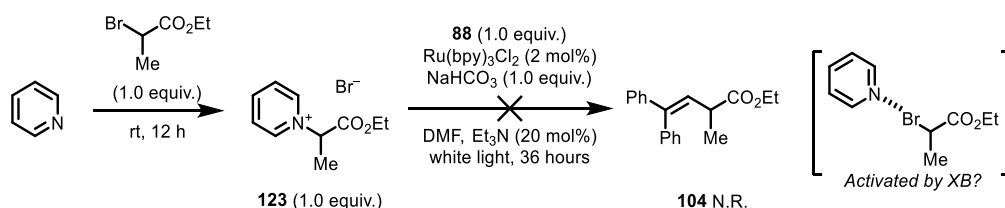
A borosilicate glass tube was charged with a stir bar, pyridinium salt **122** (64.7 mg, 0.100 mmol, 1.0 equiv.), and NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.), and carried into a glove box. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture was added 1,1-diphenylethylene **88** (17.7  $\mu$ L, 0.100 mmol, 1.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor. After stirring for 18 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. A traceable amount of **105** was not observed on TLC and <sup>1</sup>H NMR spectra of the crude mixture.

#### Attempt to Use Pyridinium Salt **120** in *fac*-Ir(ppy)<sub>3</sub>-Catalyzed Conditions:



A borosilicate glass tube was charged with a stir bar, *fac*-Ir(ppy)<sub>3</sub> (0.15 mg, 0.000229 mmol, 1 mol%), pyridinium salt **122** (12.7 mg, 0.0196 mmol, 1.0 equiv.), and NaHCO<sub>3</sub> (3.40 mg, 0.0405 mmol, 2.1 equiv.), and carried into a glove box. The mixture was dissolved in DMF (200  $\mu$ L) and to the mixture were added 1,1-diphenylethylene **88** (3.50  $\mu$ L, 0.0198 mmol, 1.0 equiv.), the tube was capped and carried out of the glove box and placed on a photoreactor. After stirring for 18 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. A traceable amount of **105** was not observed on TLC and <sup>1</sup>H NMR spectra of the crude mixture.

### Test Experiments of Pyridine-Mediated C–Br Bond Cleavage in Precedent Reports:

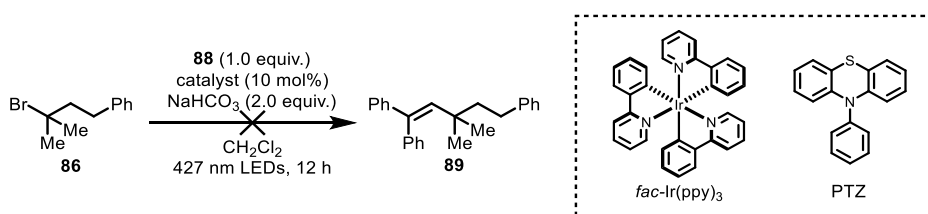


A 10 mL borosilicate glass tube was charged with a stir bar, pyridine (500  $\mu$ L, 6.21 mmol, 1.61 equiv.), and ethyl bromoacetate (500  $\mu$ L, 3.86 mmol, 1.0 equiv.) and stirred at rt for 2 hours. The volatiles were removed under reduced pressure, washed by hexane (3 x 3 mL), dried under reduced pressure to afford pyridinium salt **123** (962 mg, 0.216 mmol, 96% yield) as a colorless oil.

**1-(1-Ethoxycarbonyl-ethyl)-pyridinium bromide (123):** <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.63 (2H, d,  $J$  = 5.7 Hz), 8.65 (1H, t,  $J$  = 7.7 Hz), 8.22 (2H, t,  $J$  = 7.2 Hz), 6.76 (1H, q,  $J$  = 7.3 Hz), 4.34-4.24 (2H, m), 2.10 (3H, d,  $J$  = 7.4 Hz), 1.32 (3H, t,  $J$  = 7.2 Hz). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  168.0, 146.4, 145.2, 128.2, 67.7, 63.6, 18.7, 13.9. HRMS (ESI)  $m/z$ : [M]<sup>+</sup> Calcd for C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub>:180.1019; found: 180.1014. IR (ATR): 3410, 3052, 2982, 1739, 1631 cm<sup>-1</sup>

A borosilicate glass tube was charged with a stir bar, Ru(bpy)<sub>3</sub>Cl<sub>2</sub> (3.7 mg, 0.00494 mmol, 2 mol%), **123** (130.1 mg, 0.500 mmol, 1.0 equiv.), NaHCO<sub>3</sub> (21.0 mg, 0.250 mmol, 1.0 equiv.), and carried into a glove box. The mixture was dissolved in DMF (1.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (44.2  $\mu$ L, 0.250 mmol, 1.0 equiv.), Et<sub>3</sub>N (13.9  $\mu$ L, 0.100 mmol, 0.20 equiv.), the tube was capped and carried out of the glove box. After stirring for 36 hours under white light irradiation, the volatiles were removed under reduced pressure. A traceable amount of **104** was not observed on TLC and <sup>1</sup>H NMR spectra of the crude mixture.

### Attempt to Use Conventional Photocatalysts:



### The Use of *fac*-Ir(ppy)<sub>3</sub>:

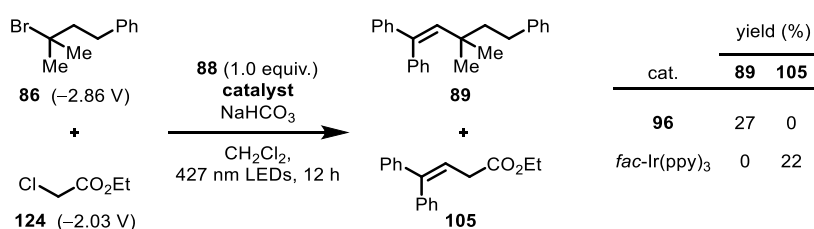
According to GP5, 1,1-diphenylethylene **88** (17.7  $\mu$ L, 0.100 mmol, 1.0 equiv.) reacted with alkyl bromide **86** (68.0 mg, 0.300 mmol, 3.0 equiv.) and *fac*-Ir(ppy)<sub>3</sub> (6.50 mg, 0.0993 mmol, 10 mol%) and NaHCO<sub>3</sub> (16.8

mg, 0.200 mmol, 2.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) for 12 hours. A traceable amount of **89** was not observed on TLC and <sup>1</sup>H NMR spectra of the crude mixture.

### The Use of *N*-phenylphenothiazine (PTZ):

According to **GP5**, 1,1-diphenylethylene **88** (17.7 μL, 0.100 mmol, 1.0 equiv.) reacted with alkyl bromide **86** (68.0 mg, 0.300 mmol, 3.0 equiv.) and PTZ (2.75 mg, 0.00999 mmol, 10 mol%) and NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) for 12 hours. A traceable amount of **89** was not observed on TLC and <sup>1</sup>H NMR spectra of the crude mixture.

### Competitive Experiments with Alkyl Halides:



### With Catalyst **96**:

A borosilicate glass tube was charged with a stir bar, **96** (4.80 mg, 0.0100 mmol, 10 mol%), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.) and carried into a glove box. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (17.7 μL, 0.100 mmol, 1.0 equiv.) and alkyl bromide **86** (22.7 mg, 0.0999 mmol, 1.0 equiv.), and Ethyl chloroacetate **123** (10.7 μL, 0.100 mmol, 1.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor. After stirring for 12 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. The yields of products **89** and **105** were determined by <sup>1</sup>H NMR spectra of the crude mixture using dimethyl terephthalate as an internal standard.

**NMR Yield: 89:** 27% yield; **105:** 0% yield.

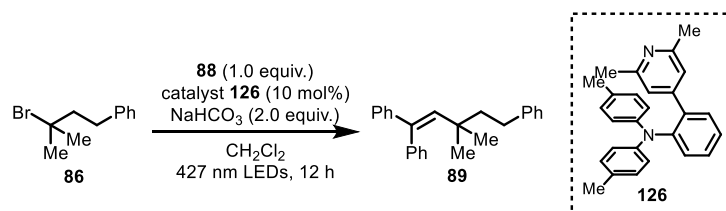
### With *fac*-Ir(ppy)<sub>3</sub>:

A borosilicate glass tube was charged with a stir bar, *fac*-Ir(ppy)<sub>3</sub> (6.55mg, 0.0100 mmol, 10 mol%), and NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.) and carried into a glove box. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (17.7 μL, 0.100 mmol, 1.0 equiv.) and alkyl bromide **86** (22.7 mg, 0.0999 mmol, 1.0 equiv.), and Ethyl chloroacetate **123** (10.7 μL, 0.100 mmol, 1.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor. After stirring for 12 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. The yields of products **89** and **105** were determined by <sup>1</sup>H NMR spectra of the crude mixture using dimethyl

terephthalate as an internal standard.

**NMR Yield of 89:** 0% yield; **105:** 22% yield.

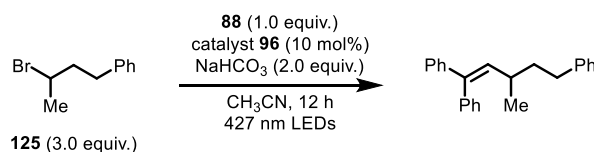
### The Reaction Using Catalyst 126:



According to **GP5**, 1,1-diphenylethylene **88** (17.7  $\mu$ L, 0.100 mmol, 1.0 equiv.) reacted with alkyl bromide **86** (68.0 mg, 0.300 mmol, 3.0 equiv.) and catalyst **126** (3.78 mg, 0.00999 mmol, 10 mol%) and NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL).

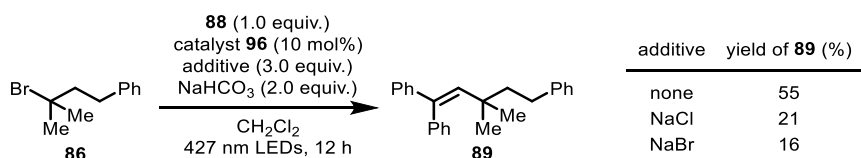
**NMR Yield:** 5% yield

### Reaction of Secondary Alkyl Bromide 125:



**(3-Methylpent-1-ene-1,1,5-triyl)tribenzene:** The reaction was performed according to **GP5** for 72 hours and gave product **125** in 11% yield as a colorless oil. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  7.39-7.08 (15H, m), 5.91 (1H, d,  $J$  = 10.3 Hz), 2.65-2.59 (1H, m), 2.50-2.44 (1H, m), 2.42-2.34 (1H, m), 1.65 (2H, q,  $J$  = 7.7 Hz), 1.06 (3H, d,  $J$  = 6.9 Hz). <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  142.7, 142.6, 140.7, 140.4, 135.8, 129.8, 128.3, 128.21, 128.16, 128.1, 127.1, 126.85, 126.79, 125.5, 39.6, 34.0, 33.7, 21.4. HRMS (ESI)  $m/z$ : [M+H]<sup>+</sup> Calcd for C<sub>24</sub>H<sub>25</sub>: 313.1951; found: 313.1940. IR (ATR): 3057, 3026, 2956, 2925, 2857, 1494, 1449 cm<sup>-1</sup>

### Inhibition Effect of Halide Anions:



### Addition of NaCl:

A borosilicate glass tube was charged with a stir bar, **96** (4.80 mg, 0.0100 mmol, 10 mol%), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.), NaCl (17.5 mg, 0.299 mmol, 3.0 equiv.) and carried into a glove box. The

mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (17.7 μL, 0.100 mmol, 1.0 equiv.), alkyl bromide **86** (68.0 mg, 0.100 mmol, 1.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor<sup>1</sup>. After stirring for 2 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. The yield of product **86** was determined by <sup>1</sup>H NMR spectra of the crude mixture using dimethyl terephthalate as an internal standard.

**NMR Yield of 89:** 21% yield

#### **Addition of NaBr:**

A borosilicate glass tube was charged with a stir bar, **96** (4.80 mg, 0.0100 mmol, 10 mol%), NaHCO<sub>3</sub> (16.8 mg, 0.200 mmol, 2.0 equiv.), NaBr (30.9 mg, 0.300 mmol, 3.0 equiv.) and carried into a glove box. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to the mixture were added 1,1-diphenylethylene **88** (17.7 μL, 0.100 mmol, 1.0 equiv.), alkyl bromide **86** (68.0 mg, 0.100 mmol, 1.0 equiv.). The tube was capped, carried out of the glove box, and placed on a photoreactor. After stirring for 2 hours under 427 nm LEDs irradiation, the volatiles were removed under reduced pressure. The yield of product **89** was determined by <sup>1</sup>H NMR spectra of the crude mixture using dimethyl terephthalate as an internal standard.

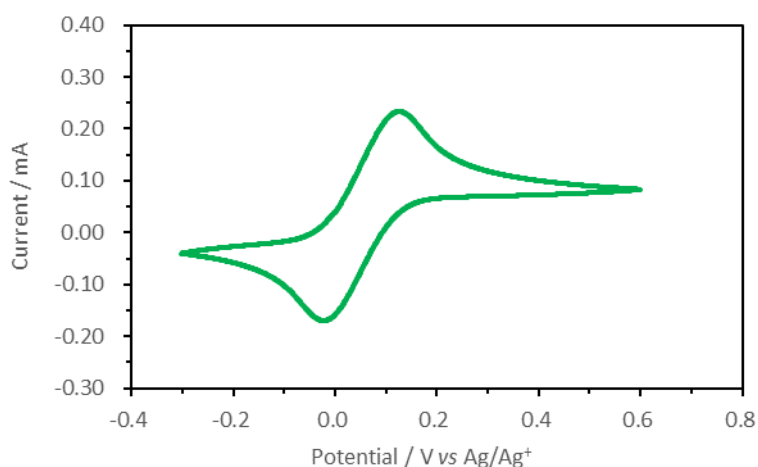
**NMR Yield of 89:** 16% yield.



### Experimental Detail of Electrochemical Analysis

The redox potentials of compounds in ground state were determined by either or both of differential pulse voltammetry (DPV) and cyclic voltammetry (CV) depending on their stability in the analyses. Both DPV and CV analyses were performed using a ECstat-302 with a glassy carbon working electrode, a Ag/Ag<sup>+</sup> reference electrode (0.1 M AgNO<sub>3</sub> + 0.1 M TBAP in CH<sub>3</sub>CN), and a Pt wire counter electrode (EC Frontier CO., Ltd.). All measurements were taken at room temperature in a 10 mM CH<sub>3</sub>CN solution of the substrate containing 100 mM of tetrabutylammonium hexfluorophosphate as supporting electrolyte. The scan rate was 80 mV/s for CV and 100 mV/s for DPV. For conversion to the SCE couple, it is known that Fc/Fc<sup>+</sup> is 380 mV more positive than SCE in CH<sub>3</sub>CN<sup>43</sup> and we found that the Fc/Fc<sup>+</sup> is 53 mV more positive than Ag/Ag<sup>+</sup> in CH<sub>3</sub>CN shown as below; 327 mV may be added to obtained potentials in Ag/Ag<sup>+</sup> in order to determine potentials against SCE.

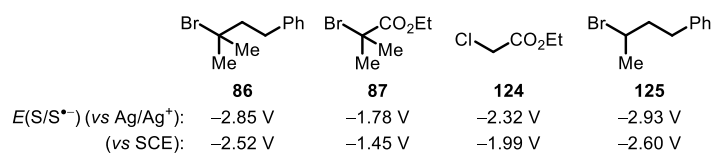
### Ferrocene:



$$E_{pc} = -0.0208 \text{ V vs Ag/Ag}^+$$

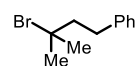
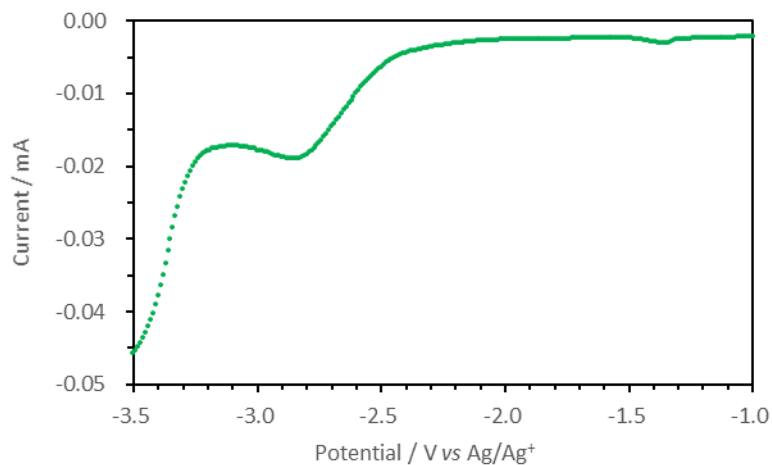
$$E_{pa} = +0.127 \text{ V vs Ag/Ag}^+$$

$$E_{1/2}(\text{Fe}^{3+}/\text{Fe}^{2+}) = +0.053 \text{ V vs Ag/Ag}^+$$



**Figure 8.** Summary of Redox Potentials of Substrates

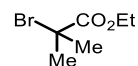
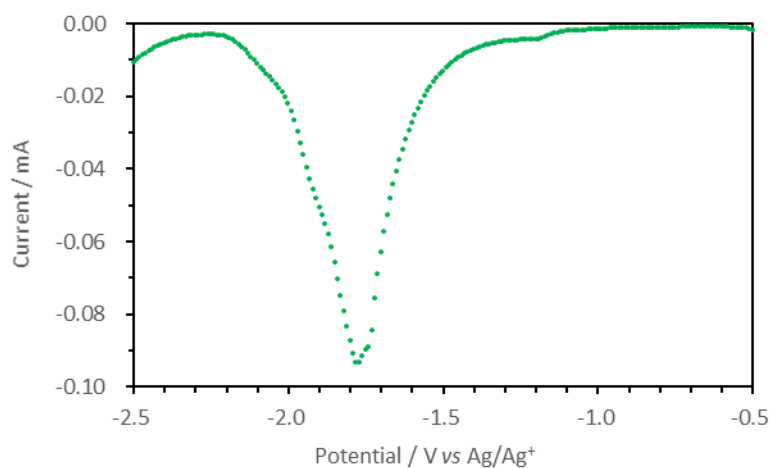
### DPV Analysis of Alkyl Bromide 86:



$$E(S/S^{\cdot-}) = -2.85 \text{ V vs Ag/Ag}^+$$

$$E(S/S^{\cdot-}) = -2.52 \text{ V vs SCE}$$

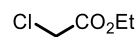
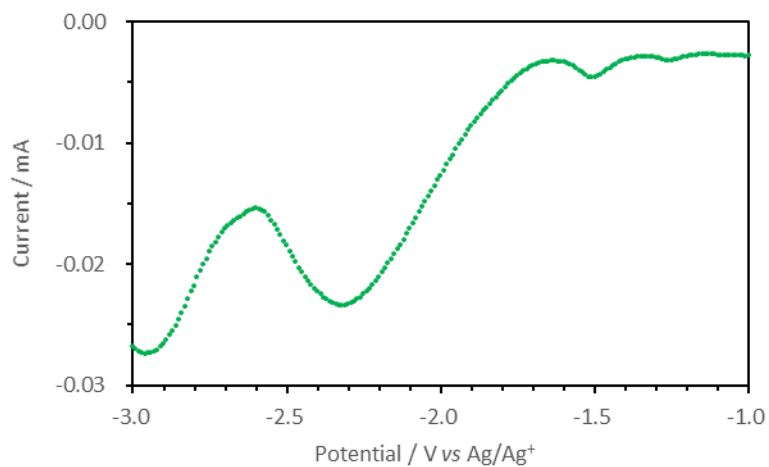
### DPV Analysis of Alkyl Bromide 87:



$$E(S/S^{\cdot-}) = -1.78 \text{ V vs Ag/Ag}^+$$

$$E(S/S^{\cdot-}) = -1.45 \text{ V vs SCE}$$

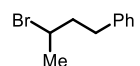
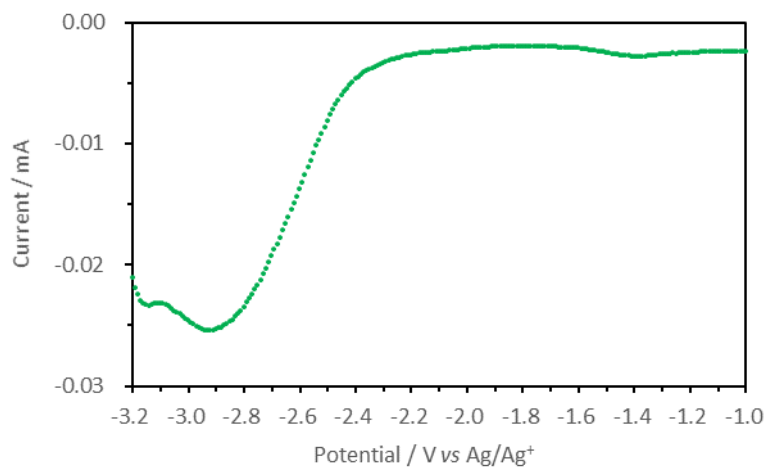
### DPV Analysis of Alkyl Chloride 124:



$$E(S/S^*) = -2.32 \text{ V vs Ag/Ag}^+$$

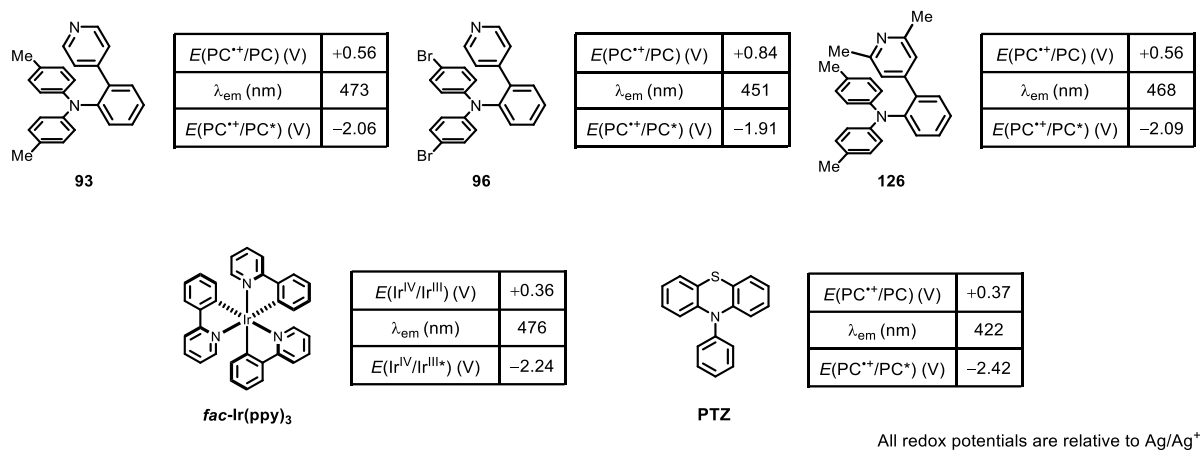
$$E(S/S^*) = -1.99 \text{ V vs SCE}$$

### DPV Analysis of Secondary Alkyl Bromide 125:



$$E(S/S^*) = -2.93 \text{ V vs Ag/Ag}^+$$

$$E(S/S^*) = -2.60 \text{ V vs SCE}$$



**Figure 9.** Summary of Redox Potentials of Catalysts

### Determination of Redox Potentials of Photocatalysts

The Excited state potentials are estimated using the Rehm-Weller equations as given<sup>44</sup>:

$$E(\text{cat}^+/\text{cat}^*) = E(\text{cat}^+/\text{cat}) - E_{0,0}$$

$$\text{where } E_{0,0} = hc / \lambda_{\text{max}} = 1238.9 \text{ nm} / \lambda_{\text{max}}$$

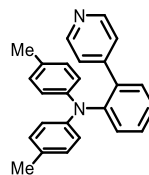
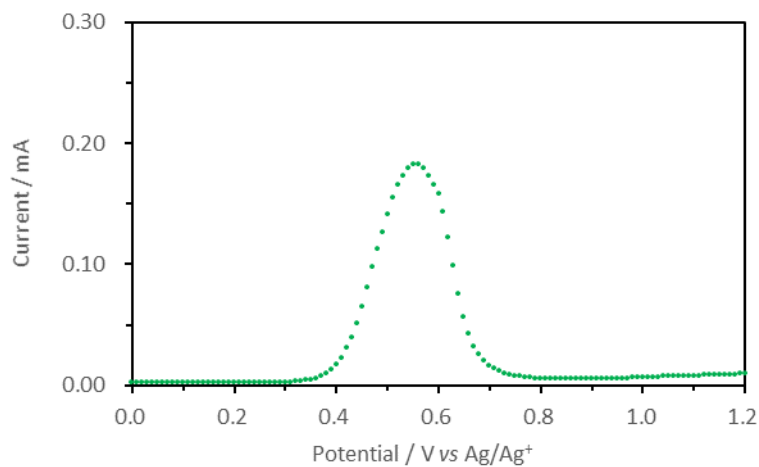
( $\lambda_{\text{max}}$  is the maximum emission wavelength)

As for the *fac*-Ir(ppy)<sub>3</sub>,  $E_{0,0}$  is approximated as the high-energy onset of phosphorescence where the emission intensity is 10% of that obtained at the maximum emission wavelength (10%  $\lambda_{\text{max}}$ ), using the “10% rule”<sup>45-48</sup> because of poor overlap between the absorption and emission spectra. These estimates were corroborated by approximating the HOMO-LUMO gap as the difference between the onset of oxidation and the onset of reduction.<sup>49,50</sup>

In the cases with *fac*-Ir(ppy)<sub>3</sub> and *N*-phenylphenothiazine, the spectra data and calculated values of redox potentials are consistent with data of reported literatures.<sup>29, 51</sup>

Luminescence intensities were recorded using Horiba FluoroMax for all experiments. The solutions of photocatalyst in CH<sub>3</sub>CN (330  $\mu\text{M}$ ) in a quartz cuvette were excited at 390 nm and the luminescence intensity was collected between 300 to 800 nm.

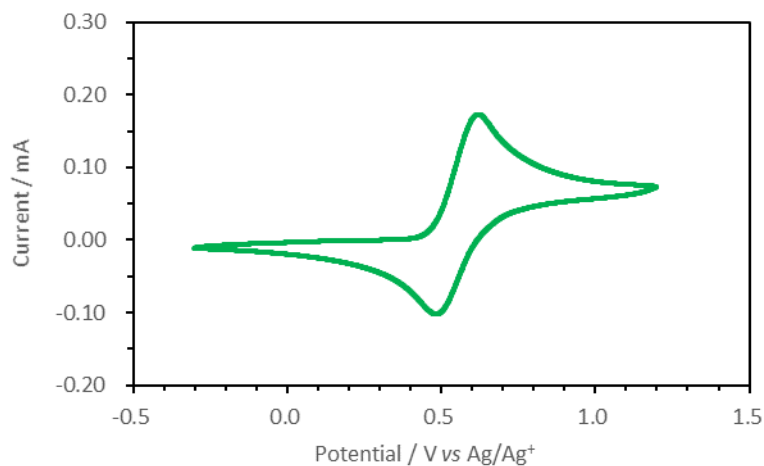
### DPV Analysis of Photocatalyst 93:



$$E(\text{PC}^{+}/\text{PC}) = +0.56 \text{ V vs Ag/Ag}^{+}$$

$$E(\text{PC}^{+}/\text{PC}) = +0.89 \text{ V vs SCE}$$

### CV Analysis of Photocatalyst 93:



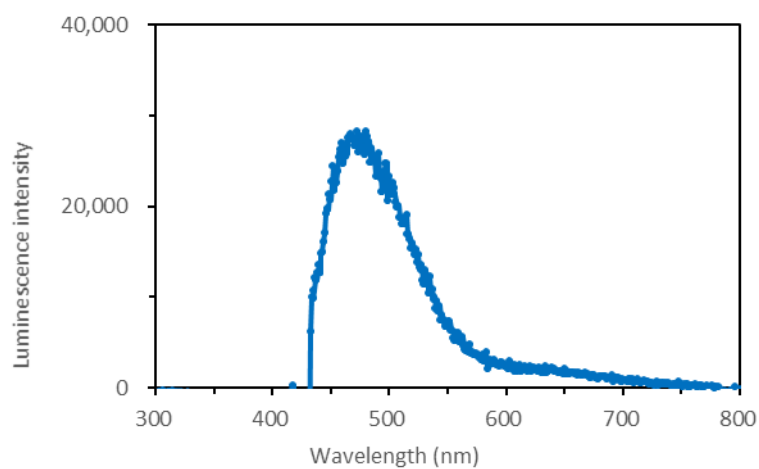
$$E_{pc} = +0.622 \text{ V vs Ag/Ag}^{+}$$

$$E_{pa} = +0.485 \text{ V vs Ag/Ag}^{+}$$

$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.554 \text{ V vs Ag/Ag}^{+}$$

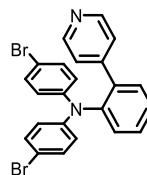
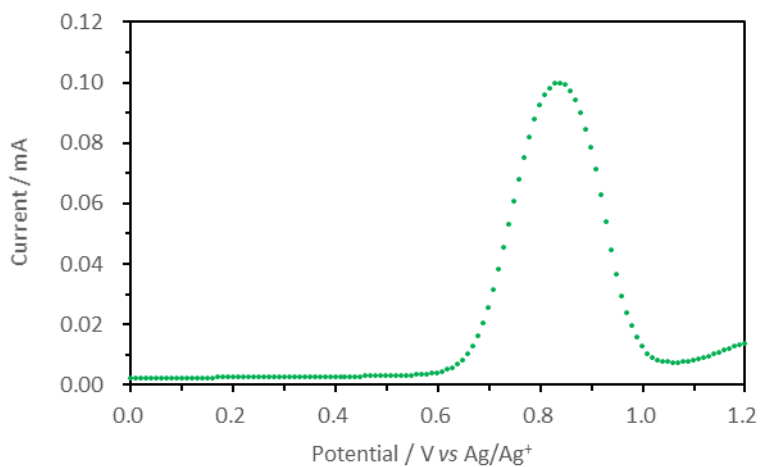
$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.881 \text{ V vs SCE}$$

### Luminescence Intensity of Photocatalyst 93:



$$\lambda_{\text{max}} = 473 \text{ nm}$$

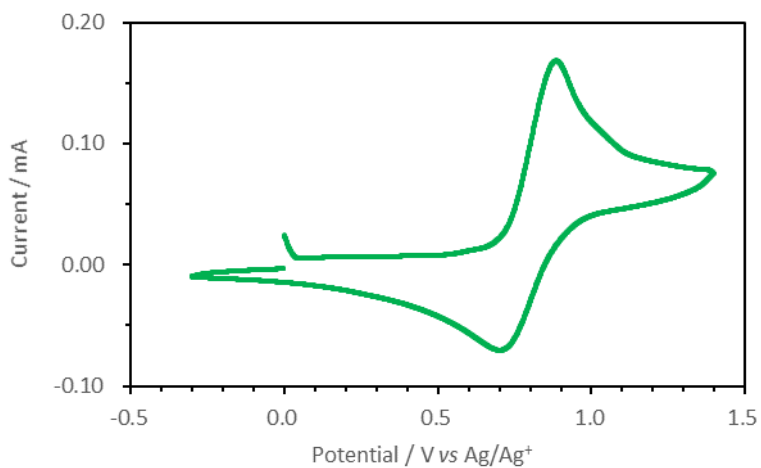
### DPV Analysis of Photocatalyst 96:



$$E(\text{PC}^{+}/\text{PC}) = +0.84 \text{ V vs Ag/Ag}^{+}$$

$$E(\text{PC}^{+}/\text{PC}) = +1.17 \text{ V vs SCE}$$

### CV Analysis of Photocatalyst 96:



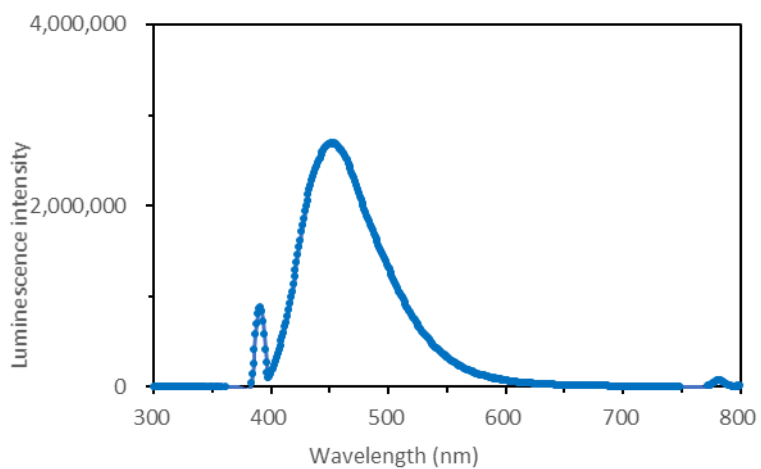
$$E_{pc} = +0.887 \text{ V vs Ag/Ag}^{+}$$

$$E_{pa} = +0.703 \text{ V vs Ag/Ag}^{+}$$

$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.795 \text{ V vs Ag/Ag}^{+}$$

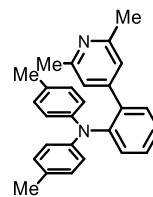
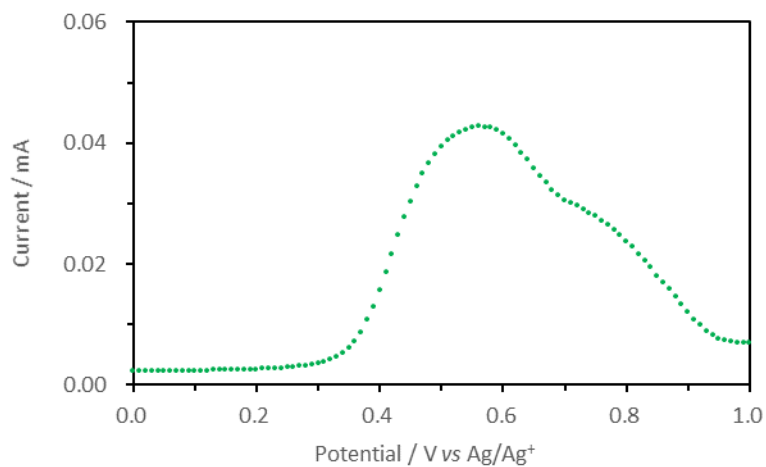
$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +1.122 \text{ V vs SCE}$$

### Luminescence Intensity of Photocatalyst 96:



$$\lambda_{\text{max}} = 451 \text{ nm}$$

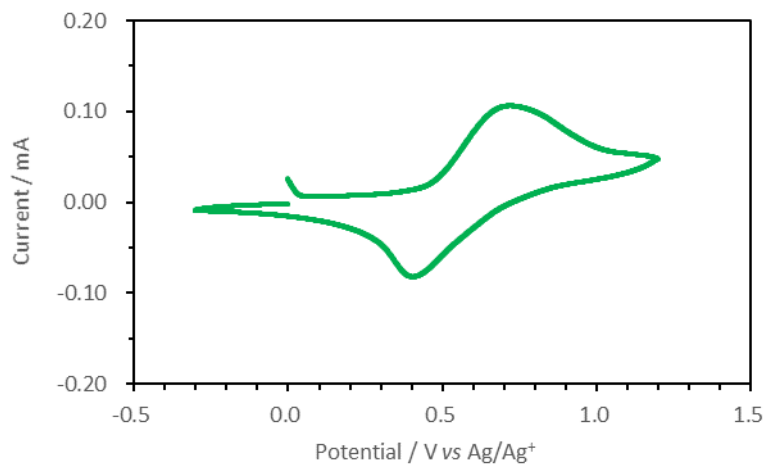
### DPV Analysis of Photocatalyst 126:



$$E(\text{PC}^{+}/\text{PC}) = +0.56 \text{ V vs Ag/Ag}^{+}$$

$$E(\text{PC}^{+}/\text{PC}) = +0.89 \text{ V vs SCE}$$

### CV Analysis of Photocatalyst 126:



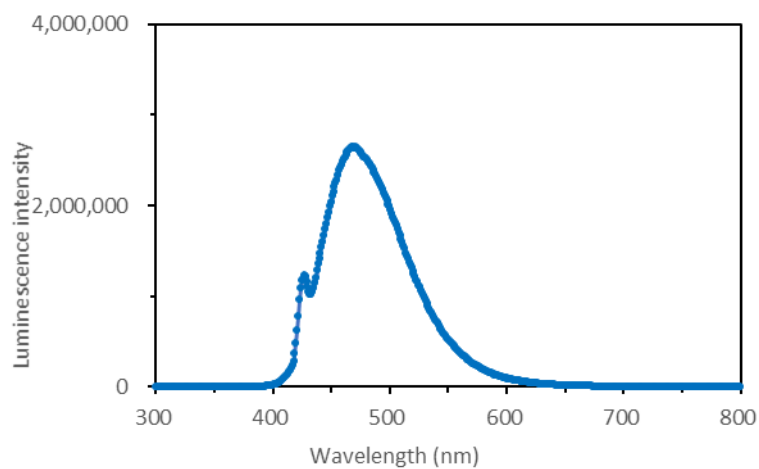
$$E_{pc} = +0.721 \text{ V vs Ag/Ag}^{+}$$

$$E_{pa} = +0.407 \text{ V vs Ag/Ag}^{+}$$

$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.564 \text{ V vs Ag/Ag}^{+}$$

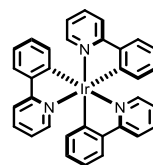
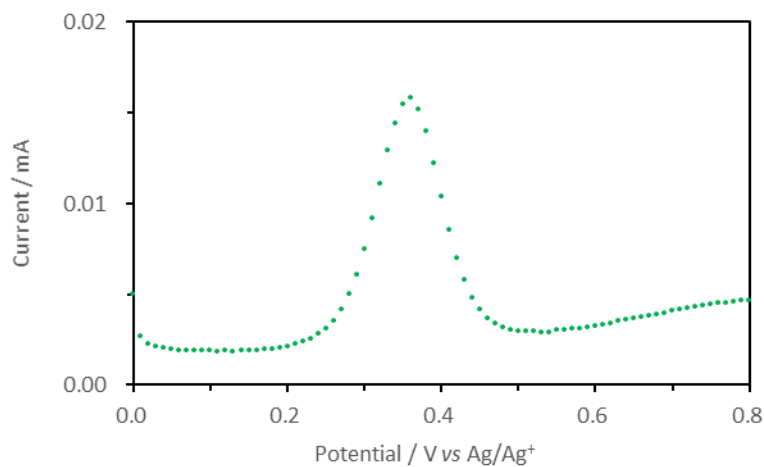
$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.891 \text{ V vs SCE}$$

### Luminescence Intensity of Photocatalyst 126:



$$\lambda_{\text{max}} = 468 \text{ nm}$$

### DPV Analysis of *fac*-Ir(ppy)<sub>3</sub>:

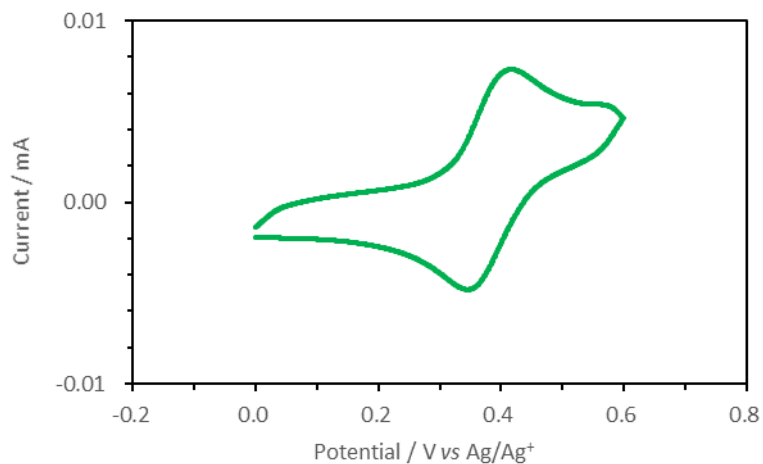


*fac*-Ir(ppy)<sub>3</sub>

$$E(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = +0.36 \text{ V vs Ag/Ag}^+$$

$$E(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = +0.69 \text{ V vs SCE}$$

### CV Analysis of *fac*-Ir(ppy)<sub>3</sub>:



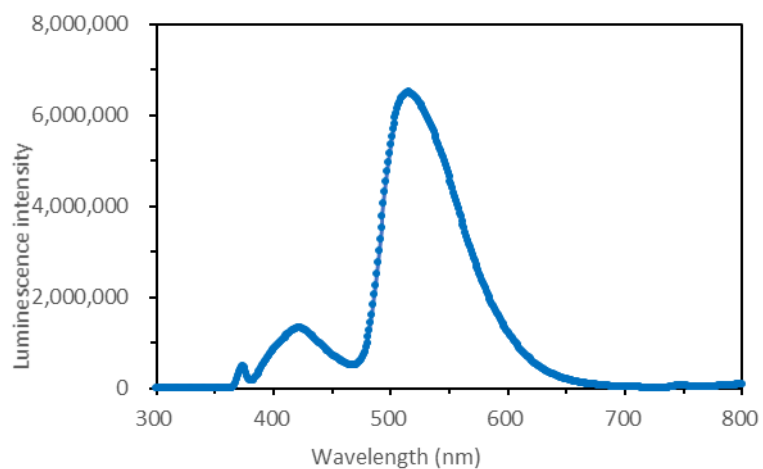
$$E_{pc} = +0.418 \text{ V vs Ag/Ag}^+$$

$$E_{pa} = +0.346 \text{ V vs Ag/Ag}^+$$

$$E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = +0.382 \text{ V vs Ag/Ag}^+$$

$$E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = +0.709 \text{ V vs SCE}$$

### Luminescence Intensity of *fac*-Ir(ppy)<sub>3</sub>:

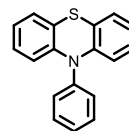
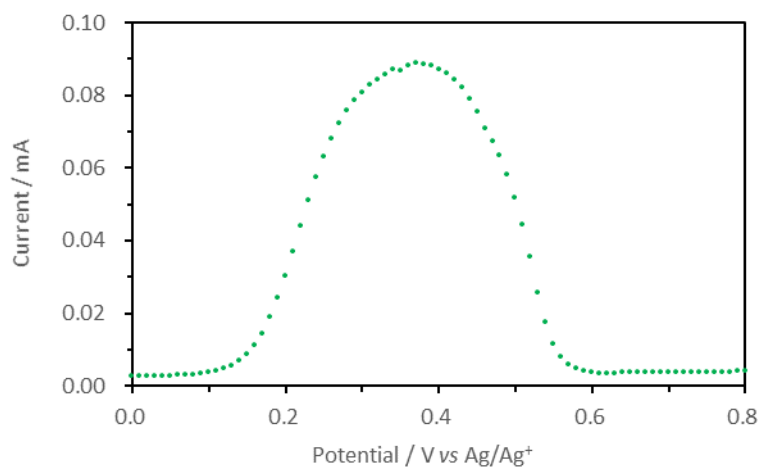


$$\lambda_{\text{max}} = 515 \text{ nm}$$

$$10\% \lambda_{\text{max}} = 476 \text{ nm}$$



### DPV Analysis of PTZ:

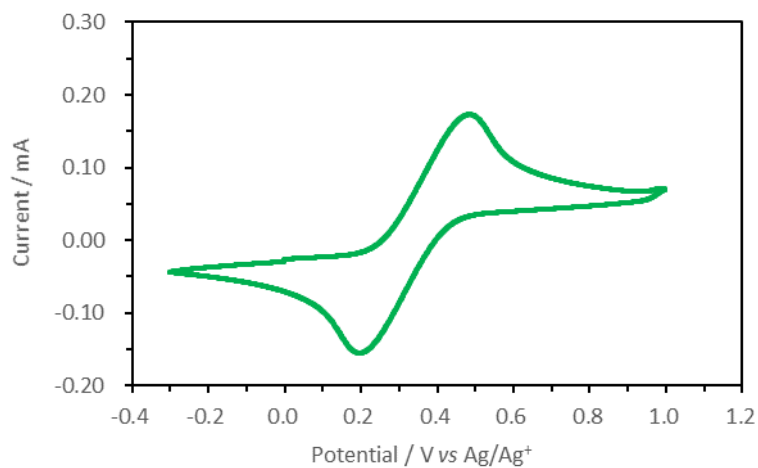


PTZ

$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.37 \text{ V vs Ag/Ag}^{+}$$

$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.70 \text{ V vs SCE}$$

### CV Analysis of PTZ:



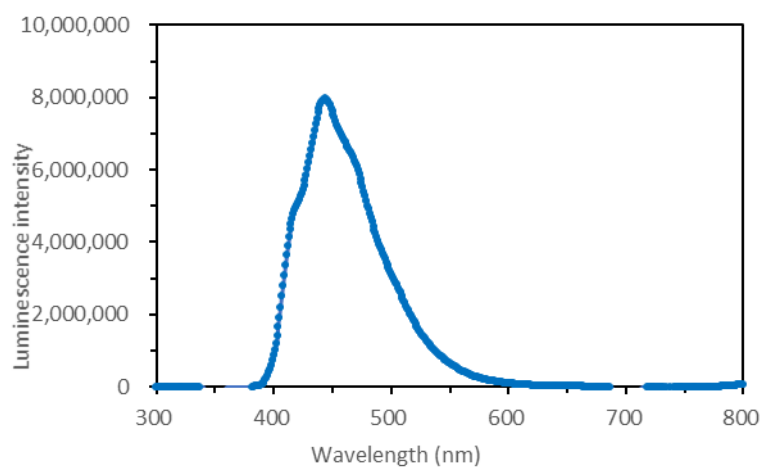
$$E_{pc} = +0.486 \text{ V vs Ag/Ag}^{+}$$

$$E_{pa} = +0.198 \text{ V vs Ag/Ag}^{+}$$

$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.342 \text{ V vs Ag/Ag}^{+}$$

$$E_{1/2}(\text{PC}^{+}/\text{PC}) = +0.669 \text{ V vs SCE}$$

### Luminescence Intensity of PTZ:



$$\lambda_{\text{max}} = 444 \text{ nm}$$

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## 論文目録

### 第二章

1. “Oxidative Decarboxylation Enables Chemoselective, Racemization-free Esterification: Coupling of  $\alpha$ -Ketoacids and Alcohols Mediated by Hypervalent Iodine(III)”  
Takeshi Nanjo, Natsuki Kato, Yoshiji Takemoto  
*Org. Lett.* **2018**, *20*, 5766–5769.
2. “A Hydroperoxide-Mediated Decarboxylation of  $\alpha$ -Ketoacids Enables the Chemoselective Acylation of Amines”  
Takeshi Nanjo, Natsuki Kato, Xuan, Zhang, Yoshiji Takemoto  
*Chem. Eur. J.* **2019**, *25*, 15504–15507.

### 第三章

3. “A Pyridine-based Donor–Acceptor Molecule: A Highly Reactive Organophotocatalyst That Enables the Reductive Cleavage of C–Br Bonds through Halogen Bonding”  
Natsuki Kato, Takeshi Nanjo, Yoshiji Takemoto  
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