銀触媒によるアルキンの活性化を基軸とする
二酸化炭素利用法の開発

平成２７年度

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学位論文　博士（理学）

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二酸化炭素利用法の開発

Incorporation of Carbon Dioxide
based on Alkyne Activation by Silver Catalysts

平成２７年度

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序論

　私たちの豊かな生活は化石資源に大きく依存している。2008 年のデータによれば、世界で利用しているエネルギーは、主に石炭（26%）、石油（34%）、天然ガス（34%）により得られている[1]。しかし、長い年月を経て大地に蓄積した化石資源は、有限である以上、枯渇する可能性をはらんでいる。現在の快適な生活を続けるためには、化石資源に代わる新たなエネルギー源や炭素資源を求める必要性がある。このような状況下で、これまで厄介な廃棄物として大気中に大量に放出されてきた二酸化炭素が炭素資源として注目されている。ノーベル化学賞受賞者のオラーらは炭素循環型社会を提唱し、二酸化炭素をメタノールへ変換することで、化石資源由来の炭素を循環させる社会の構築を目指している（Figure 0.1）[2]。しかし、二酸化炭素をメタノールに還元するには一つの酸素原子を取り除かなければならず、多くの外部エネルギーが必要となるため、どのようなエネルギー源を還元反応に用いるかが鍵となっている。
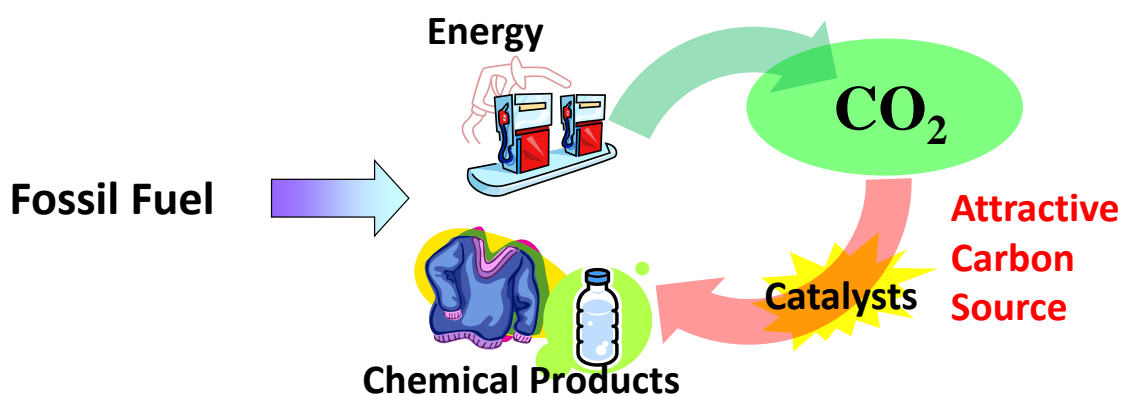

Figure 0.1. Carbon cycle.

　有機化学は炭素原子からなる化合物に関する化学である。炭素原子は互いに結合して主要な骨格を形成するのに加えて、主に水素、酸素、窒素原子と結合することで小さく単純な分子から大きく複雑な分子まで形成することができる。有機化学は、私たちの生活に密着しており、高分子、プラスチック、合成繊維、洗剤、医薬品等を開発するのに不可欠な学問である。

自然界に目を向ければ、二酸化炭素が炭素資源として固定化されていることはごく当然である。多くの植物は光合成により、二酸化炭素と水から糖を合成している。炭素原子を取り扱う有機化学にとって、二酸化炭素分子を利用することは格好の研究課題である。半世紀前には、二酸化炭素分子は最高酸化状態で熱力学的に安定なため、窒素分子と並んで不活性分子の代表であると認識されていただろう。しかし、この当時、反応例は限られていたものの二酸化炭素を有機合成反応に利用することにすでに成功していた。例えば、有機化学の教科書で取り上げられているように、有機リチウム試薬やグリニャール試薬は二酸化炭素と反応して対応するカルボン酸を与える。また、工業的な二酸化炭素の利用も進められ、コルベ・シュミット反応は鎮痛作用のあるサリチル酸誘導体の合成に用いられてきた（Scheme 0.1）。しかし、反応性の高い求核剤や高温高圧の厳しい反応条件が必要であった。その後、1970年代に出版された「炭酸ガスの化学」[3]や1994年に刊行された「二酸化炭素」[4]で取り上げられているように、日本人を含む多くの研究者がさまざまな切り口から二酸化炭素分子の反応性や利用法について研究を進めた結果、金属塩やルイス塩基により二酸化炭素分子が活性化されることが明らかとなった。そのため、二酸化炭素が不活性分子であるという認識が徐々に薄まっていった。
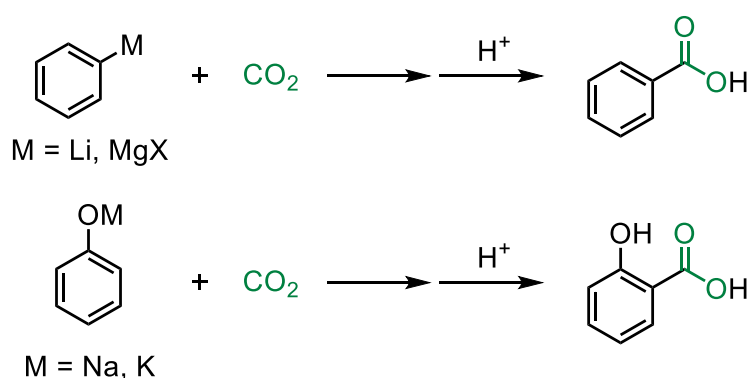

Scheme 0.1. Synthesis of Carboxylic Acids from CO_2

　近年では、炭素資源の有効利用の観点から、二酸化炭素からの高機能・高付加価値な化合物の合成研究が盛んに行われている[5]。アルコールと二酸化炭素から合成される炭酸エステルはリチウムイオン電池の電解液としても用いられ有用性が高い。また、アミンと二酸化炭素から生じるカルバミン酸エステルは医薬品や機能性材料のビルディングブロックとなる。

高分子化学分野においても二酸化炭素が有効利用されており、亜鉛錯体、アルミニウム錯体、コバルト錯体といった様々な高機能な触媒により二酸化炭素とエポキシドとの交互共重合が進行し、ポリエチレンカーボナートが得られる。

　有機金属化学のめまぐるしい発展とともに、遷移金属触媒を用いる炭素‐炭素結合形成を経るカルボキシル化反応が、最近、精力的に研究されている。例えば、岩澤らは 2006 年にアリールボロン酸を出発物質とするカルボキシル化反応がロジウム触媒を用いると、トランスメタル化および二酸化炭素の挿入反応を経て対応するカルボン酸が得られることを見出した（Scheme 0.2(a)）[6]。それ以後、ニッケル、銅、銀触媒を用いても同様の反応が進行することが報告された[7]。また、ハロゲン化アリールやハロゲン化ビニルに対して、パラジウム触媒あるいはニッケル触媒と還元剤を併せ用いると、酸化的付加、カルボキシル化、還元的脱離を含む触媒サイクルによって、対応するカルボン酸が得られることが報告されている（Scheme 0.2(b)）[8]。辻らは、アルキン[9]やアレン[10]化合物へのヒドロカルボキシル化反応およびシラカルボキシル化反応がパラジウムや銅触媒により円滑に進行することを見出した（Scheme 0.2(c)）。とくに銅触媒によるアレン化合物へのシラカルボキシル化反応では、単座ホスフィン配位子および二座ホスフィン配位子により位置選択性が巧みに制御されている（Scheme 0.2(d)）。オレフィンのカルボキシル化反応では、①鉄触媒とグリニャール試薬を組み合わせた反応系と（Scheme 0.2(e)）、②ヒドロホウ素化を経由する銅触媒によるカルボキシル化反応が報告されている（Scheme 0.2(f)）。最近では、辻らによってコバルト触媒を用いるプロパルギル位アセタートのカルボキシル化反応（Scheme 0.2(g)）[11]が、Martinらによってニッケル触媒を用いるアリル位やベンジル位のハロゲン基等のカルボキシル化反応（Scheme 0.2(h) and (i)）[12]が開発された。ハロゲン化アリール等の前駆体を必要としない環境低負荷型な反応を指向した直截的な芳香環のカルボキシル化も報告されている[13]。岩澤らは、ロジウム触媒を用いる炭素‐水素結合活性化を経由するカルボキシル化反応（Scheme 0.3(a)）や、パラジウム触媒を用いるアルケニル炭素‐水素結合の直接的カルボキシル化反応を報告した（Scheme 0.3(b)）。

以上で述べてきたように、遷移金属触媒を用いる炭素－炭素結合形成を伴うカルボキシル化反応が目覚ましく開発されてきた。しかしながら、二酸化炭素への求核付加過程は遷移金属－炭素結合の反応性に起因しているため高温条件が必要である。また、再還元剤として原理的に化学量論量以上の金属を要するという課題が残っている。有機合成化学分野において、温和な反応条件での二酸化炭素との炭素－炭素結合形成反応の開発は依然として重要な研究課題の一つである。
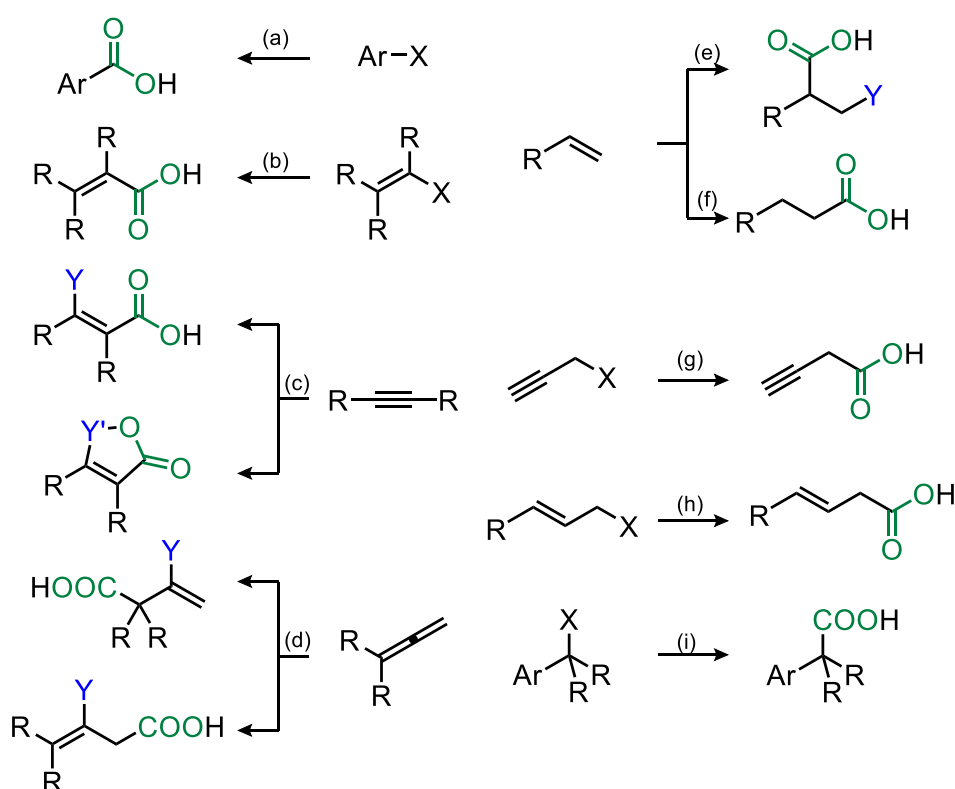

Scheme 0.2. Recent Developments of Transition Metal-catalyzed C-C Bond Formation with CO_2
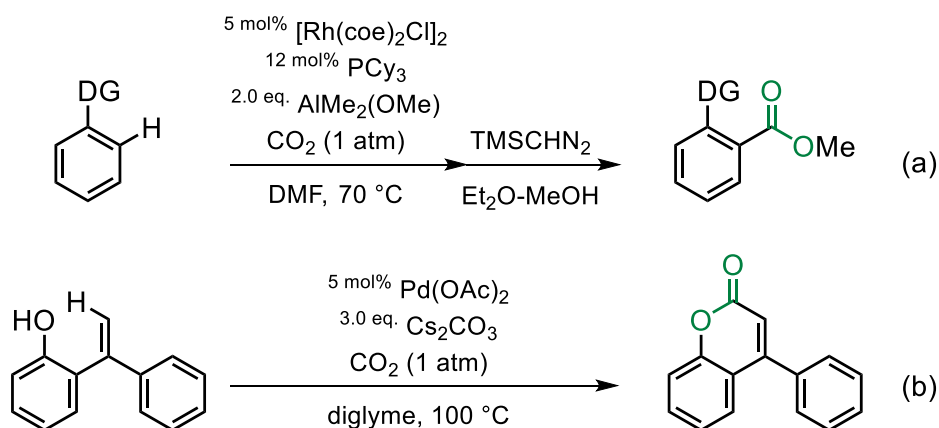
Scheme 0.3. Direct Carboxylation via C-H Activation

　筆者が所属する研究グループは、プロパルギルアルコールと二酸化炭素との反応が銀触媒により温和な反応条件で進行し、対応する環状炭酸エステルが高収率で得られることを2007 年に見出した（Scheme 0.4）[14]。最適な反応条件は、内部アルキンに対しても室温付近で反応が進行し、定量的に生成物を与えた。アルコールと二酸化炭素との反応は可逆的であり、カーボナートは容易に二酸化炭素を放出しアルコールへと戻ってしまう。本反応は、不安定な中間体であるカーボナートを銀触媒により活性化されたアルキンで捕捉し、安定な化合物へ誘導している点が特徴的である。

Ag$^+$
DBU
r.t.
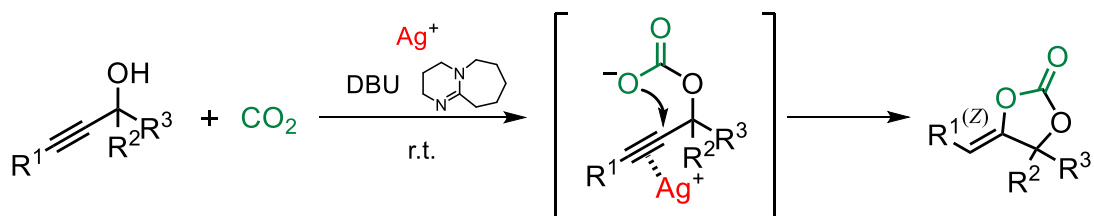
Scheme 0.4. CO$_2$ Incorporation into Propargylic Alcohols

　以上で述べてきたことを研究背景とし、筆者は、有機合成化学における温和な反応条件での二酸化炭素利用法の構築を目指して、銀触媒によるアルキンの活性化を基軸とする二酸化炭素との炭素‐炭素結合形成反応に引き続く環化反応およびプロパルギルアミンへの二酸化炭素と官能基の連続的導入反応の開発に着手した。

　第 1 章では、エノラートを求核剤とする二酸化炭素との反応の開発について述べる。銀触媒を用いる環化反応を適用すれば、熱的に不安定な β‐ケトカルボン酸をより安定なラクトン誘導体へワンポットで誘導できると考えた。触媒量の安息香酸銀、塩基に 7‐メチル‐ト

リアザビシクロ[4.4.0]‐5‐デカエンを用いると、望みの反応が種々の基質に対して進行し、対応する5員環ラクトンが高収率で得られることを見出した。また、銀触媒はアルキンを活性化するだけではなく、カルボニル基を活性化する Lewis 酸としても機能していることが示唆された（第1節）。上述の反応における副生成物を解析することにより、オルト位にアルキンをもつアセトフェノンを出発原料とすれば、カルボキシル基をもつジヒドロイソベンゾフラン誘導体が得られると想定した。二酸化炭素雰囲気下、触媒量の酢酸銀と1,8‐ジアザビシクロ[5.4.0]‐7‐ウンデセンを作用させると、カルボキシル基をもつジヒドロイソベンゾフランが高収率で生成することを明らかにした（第2節）。

第2章では、高付加価値な化合物合成を目指し、銀触媒によるプロパルギルアミンへの二酸化炭素とヨード基の連続的導入反応の開発について述べる。この反応では、カーバメートの環化反応後に生成するビニル銀中間体がヨウ素カチオンにより捕捉され、(*E*)‐ヨードビニルオキサゾリジノンが得られることが示唆された。最適化した反応条件は、様々な第一級および第二級アミンに対して適用可能であることを示した。

第3章では、さらなる炭素‐炭素結合形成反応の構築を目指し、アリル位にトリメチルシリル基をもつ共役エンイン化合物を出発原料として、ラクトン誘導体が得られる反応の開発について述べる。この反応では、これまでの反応とは異なり、アルキンへの環化過程において位置選択性が生じ、5員環の2‐フラノンと6員環の2‐ピロンが得られた。位置選択性はアルキン末端の置換基により変化し、芳香環を有している場合は2‐フラノンへ高い選択性を示し、アルキル鎖を有している場合は2‐ピロンが優先的に得られることを明らかにした。

本論文は、銀触媒によるアルキンの活性化を基軸として、二酸化炭素との炭素‐炭素結合形成反応に引き続く環化反応およびプロパルギルアミンへの二酸化炭素と官能基の連続的導入反応について3章8節にわたって述べたものである。

本論　銀触媒によるアルキンの活性化を基軸とする二酸化炭素分子利用法の開発

第1章　銀触媒によるエノラートを求核種とする二酸化炭素固定化反応

緒言

　序論で述べたように、筆者の所属する研究グループでは、プロパルギルアルコールやプロパルギルアミンに対する二酸化炭素固定化反応が、銀触媒存在下、温和な反応条件で進行し、対応する環状炭酸エステルやオキサゾリジノン誘導体が高収率で得られることを報告した（Scheme 1.1(a)）[14,15]。また、対称なビスプロパルギルアルコールに対して、光学活性な Schiff 塩基配位子を有する銀触媒を用いると、非対称化を伴いながら二酸化炭素との反応が進行し、対応する環状炭酸エステルが高収率・高エナンチオ選択的に得られることを報告した（Scheme 1.1(b)）[16]。X 線結晶構造解析や計算化学的な考察から、銀触媒がアルキンを活性化し、カーボナートのアルキンへの環化反応を効果的に促進する反応機構が提案された[17]。これらの反応は、不安定な中間体であるカーボナートやカーバメートを、銀触媒により活性化されたアルキンで捕捉し、安定な化合物へ誘導している点が特徴的である。
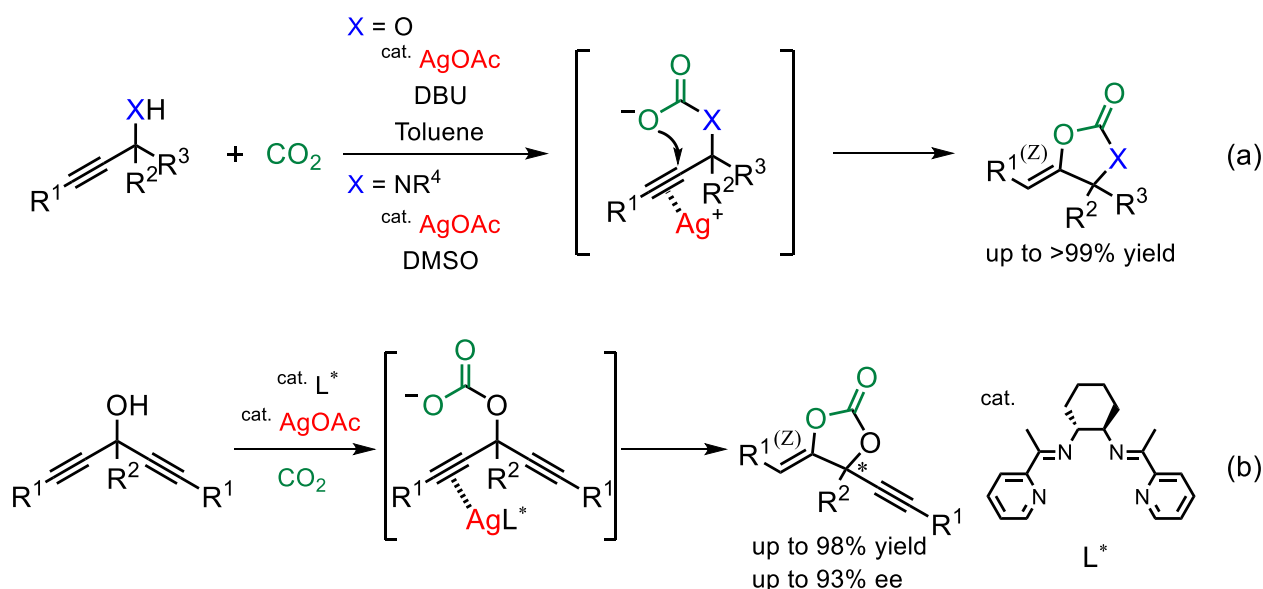
Scheme 1.1. Silver-catalyzed Incorporation of CO_2 into Alkyne Derivatives

　上述の反応では、アルコール性水酸基の酸素原子ないしアミノ基の窒素原子による求核反応で二酸化炭素が捕捉され、環状炭酸エステルやオキサゾリジノン誘導体が生成する。これ

らの生成物はリチウム電池の電解液や医薬品の重要な基本骨格であるが、水和反応により脱炭酸を引き起こす潜在的な可能性がある。また、現在までに、二酸化炭素と酸素‐炭素結合[18] あるいは窒素‐炭素結合 [19] 形成に続くアルキンへの環化反応ついては多数報告例がある（Scheme 1.2(a)）。一方で、有機合成上有用な炭素‐炭素結合形成に続くアルキンへの環化反応に関する報告例は少ない（Scheme 1.2(b)）[20]。そこで、炭素アニオンを求核剤として、二酸化炭素との炭素‐炭素結合形成反応へ展開することとした。
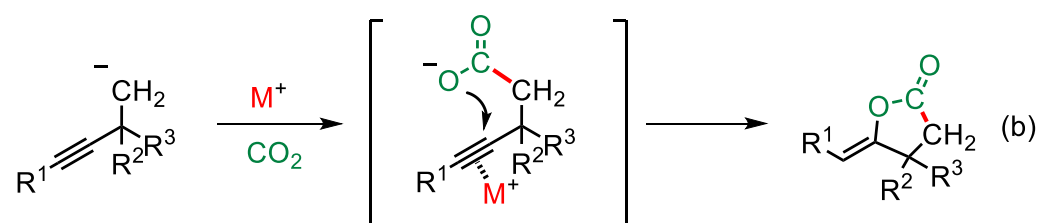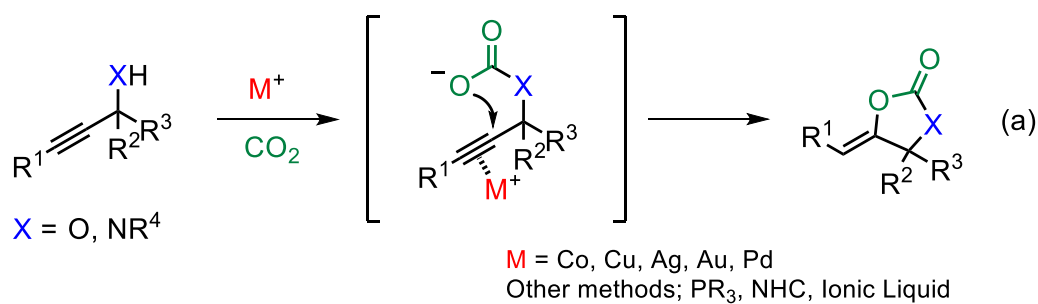
Scheme 1.2. (a) CO_2 Incorporation into Propargylic Alcohols and Amines (b) Cyclization following the C-C Bond Formation with CO_2

　カルボニル化合物と塩基から生成するエノラートは、炭素‐炭素結合形成反応に広く用いられる求核剤の一つである。エノラートと二酸化炭素の反応はいくつか報告例があり、トリエチルアミンや 1,8‐ジアザビシクロ[5.4.0]‐7‐ウンデセン（DBU）等の塩基存在下、カルボニル化合物の二酸化炭素に対する求核付加反応が進行し、酸性条件での反応停止によって、対応する β‐ケトカルボン酸が得られる [21]。しかし、β‐ケトカルボン酸は熱的に不安定であり、容易に脱炭酸反応が生じ、出発物質と二酸化炭素に戻る（Scheme 1.3）。そのため、対応するカルボン酸を高収率で得るためには、脱炭酸を抑制する工夫が必要であった。例えば、β‐ケトカルボン酸をマグネシウム塩として安定化し、低温下で後処理を行うことで生成物を得ているが、化学量論量のマグネシウム塩が必須である（Scheme 1.4(a)）[22]。また、Jessop らは、連続した還元処理により、β‐ヒドロキシカルボン酸を高収率で得ている（Scheme 1.4(b)）[23]。
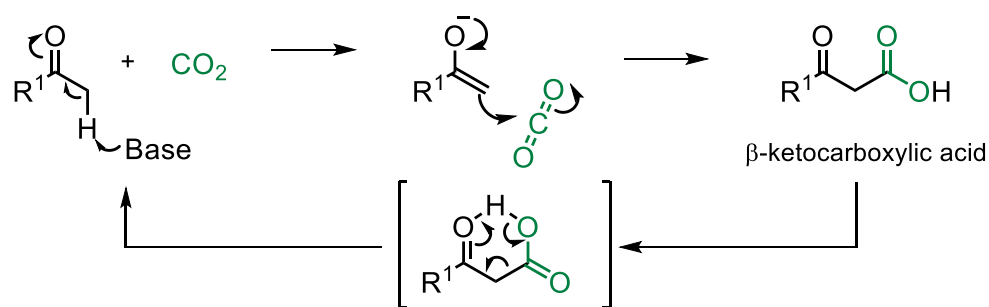
Scheme 1.3. Carboxylation of Ketone Derivatives (1)
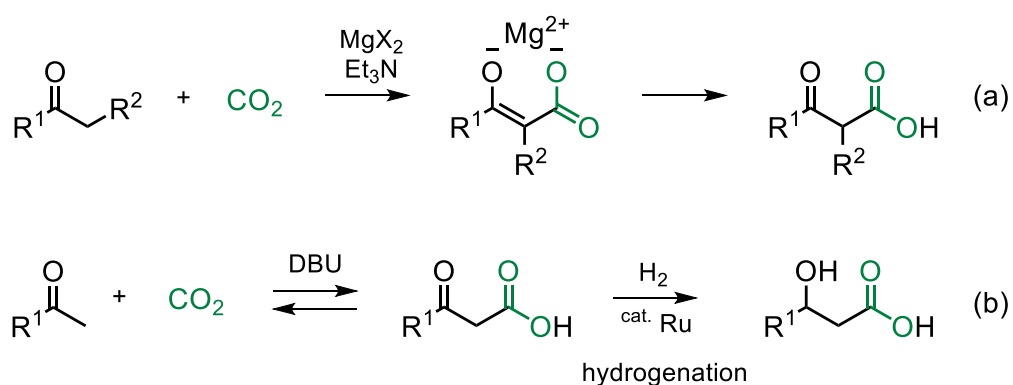
Scheme 1.4. Carboxylation of Ketone Derivatives (2)

　筆者は、銀触媒によるアルキンの活性化を基軸とする環化反応を適用すれば、熱的に不安定なβ‐ケトカルボン酸をより安定な化合物へ誘導できると考えた。本章では、銀触媒を用いるエノラートを求核剤とするラクトン誘導体およびジヒドロイソベンゾフラン誘導体の合成について述べる。

第1節　エノラートを求核種とするラクトン誘導体合成

　二酸化炭素を炭素源とするラクトン合成法については、1970 年代から数例が報告されている。ブタジエン[24]やメトキシアレン[25]に対して、二酸化炭素雰囲気下、パラジウム触媒を作用させると 3 成分による環化反応が進行し、対応する 6 員環ラクトン誘導体が得られる（Scheme 1.5(a)）。また、パラジウム触媒と 2 - トリメチルシリルメチル - 2 - プロペニルアセタートから生じるトリメチレンメタンパラジウム錯体は、二酸化炭素との[3+2]付加環化反応により、γ - ブチロラクトンを温和な反応条件で与える（Scheme 1.5(b)）[26]。

　ホスフィン配位子を有するニッケル触媒により、アルキンと二酸化炭素との環化三量化反応が進行し、対応するラクトン誘導体が得られることが報告された（Scheme 1.5(c)）[20b,c]。ジイン化合物に対する環化三量化反応も同様な反応条件で進行するが、ホスフィン配位子を用いる場合は 50 bar、120℃の苛酷な条件が必要であるのに対して[20d,e]、N - ヘテロサイクリックカルベン配位子を用いると 1 atm、60℃の温和な反応条件で同様の環化三量化反応が進行することが見出されている（Scheme 1.5(d)）[20f]。
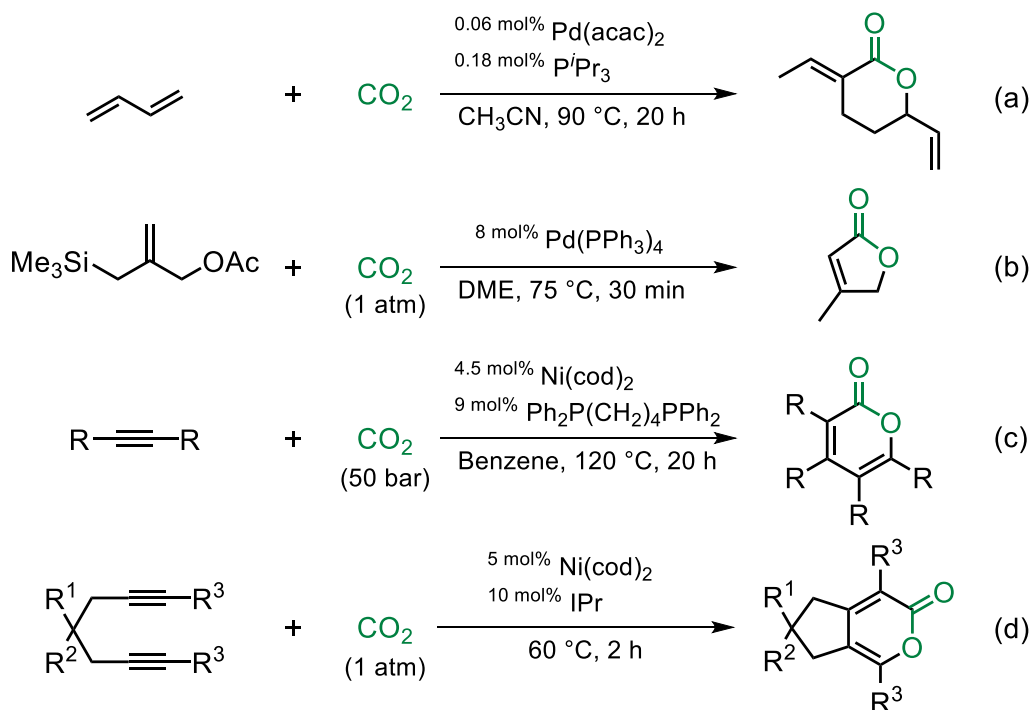
Scheme 1.5. Syntheses of Lactone Derivatives Using CO_2

　今回、アルキンを適切な位置に配置したケトン化合物に対して、塩基によるエノラートの生成、それに続く二酸化炭素への求核付加、また銀イオンによるアルキンの活性化およびカ

ルボキシラートのアルキンへの環化反応を経て、ラクトン誘導体がワンポットで得られる反応系の構築を目指した（Scheme 1.6）。
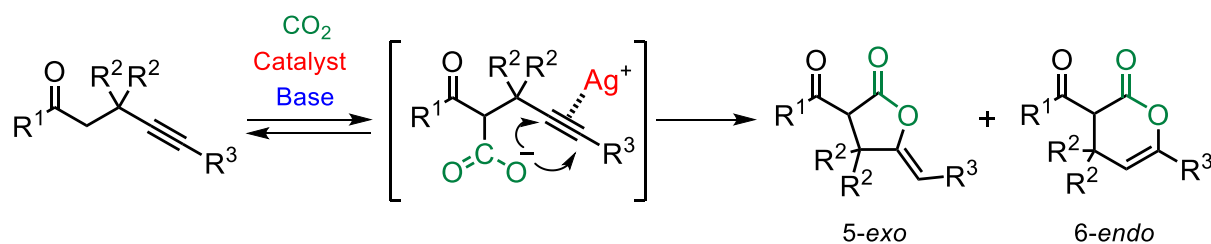
Scheme 1.6. Silver-catalyzed Cyclization following the C-C Bond Formation with CO_2

1-1. 金属触媒の検討

　アルキンとケトンを適切に配置した化合物 **1a** をモデル基質として、1.0 MPa の二酸化炭素雰囲気下、2.0 当量の DBU を用いて、アルキンを活性化すると期待される種々の金属塩を検討した（Table 1.1）。その結果、パラジウム塩、銅塩および金塩を用いた場合には、目的の反応は全く進行しないあるいは痕跡量の生成物を与えるのみであった（Entries 1-7）。一方で、銀塩を用いた場合には目的の反応が進行した。酢酸銀を用いた場合、対応する 5 員環ラクトン **2a** が収率 22％で得られ（Entry 8）、安息香酸銀を用いた場合は収率 40％で得られた（Entry 9）。本反応においても、銀触媒が特異的に環化反応を促進することが明らかとなった。環化反応における位置選択性を考察するにあたって、Baldwin 経験則[27] が用いられる。この経験則では、sp 混成軌道の三重結合に対する環化反応において 5-*exo* および 6-*endo* は許容される。また、環化反応の進行のしやすさは 5 員環＞6 員環であると言われている。本反応では、Baldwin 経験則に則って、5 員環を形成する反応経路が優先したものと考えられる。

Table 1.1. Examination of Various Metal Catalysts
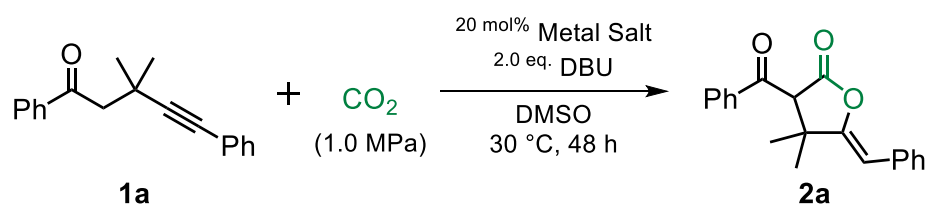
Entry	Metal Salt	Yield / %^{a}
1	none	0
2	Pd(OAc)$_2$	trace
3	Cu(OTf)$_2$	0
4	CuBr	0
5	AuCl	0
6	(PPh$_3$)AuCl	trace
7	AuCl$_3$	trace
8	AgOAc	22
9	AgOBz	40

a) Isolated yield.

　銀塩がπ‐Lweis 酸として働き、アルキンを活性化するという仮説から、カチオン性の銀イオンを用いればアルキンの電子密度が減少し、環化反応が促進され、生成物の収率が向上すると考えた。そこで、種々の銀塩を用いて 50℃の条件下で検討した（Table 1.2）。しかしながら、予想に反して、共役酸の酸性が強いアンチモナートやトリフラートを用いると収率が低下した。中程度の酸性度をもつ安息香酸を対アニオンとする安息香酸銀が最適な触媒であることがわかった。安息香酸銀を最適な触媒として塩基および溶媒に関して検討することにした。

Table 1.2. Screening of Various Silver Salts
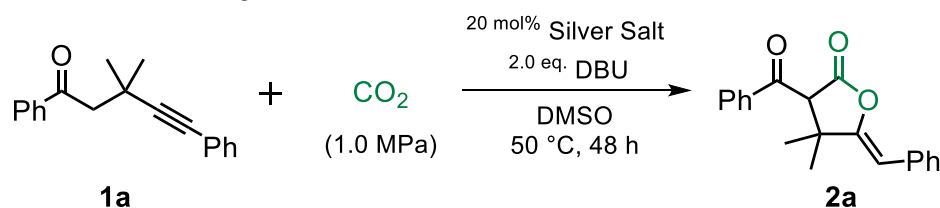
Entry	AgX	Yield / %[a]	Entry	AgX	Yield / %[a]
1	$AgSbF_6$	19	7	AgBr	34
2	$AgClO_4$	27	8	$Ag(OCOCF_3)$	25
3	AgOTf	36	9	AgOAc	34
4	$AgBF_4$	35	10	AgOBz	48
5	AgOTs	23	11	Ag_2CO_3	26
6	AgOMs	17			

a) Isolated yield.

1-2. 反応条件の最適化

　銀塩の検討結果から、カルボキシラートアニオンのアルキンへの環化反応は十分に進行していると考えられる。アセトフェノンの α プロトンの pK_a[28] が 19.2 であり、DBU の共役酸の pK_a[29] が 11.9 であることを考慮すると、エノラートの生成が不十分であると考えられ、エノラートの生成促進を期待して種々の塩基を検討した（Table 1.3）。その結果、DBU より塩基性の弱いトリエチルアミン（Entry 1）やジイソプロピルエチルアミン（Entry 2）を用いた場合には反応が進行しなかったが、ジメチルアミノピリジン（Entry 3）を用いた場合には少量の生成物が確認された。DBU より塩基性が強いグアニジン骨格を有するトリアザビシクロ[4.4.0] - 5 - デセン（TBD, pK_a(TBD-H$^+$) = 14.5[30]）やテトラメチルグアニジン（TMG, pK_a(TMG-H$^+$) = 13.6）を用いた場合にも低収率にとどまった（Entries 5 and 7）。これに対して、^{n}Bu-TMG を用いると DBU の場合と同程度の収率 39%で生成物が得られ（Entry 6）、TBD の 7 位にメチル基をもつ 7 - メチル - トリアザビシクロ[4.4.0] - 5 - デセン（MTBD, pK_a(MTBD-H$^+$) = 13.0[29]）を用いると収率が 48%に向上した（Entry 8）。これらの結果は、塩基の強さ（TBD>TMG>MTBD）とは一致していない。理由として、二酸化

炭素雰囲気下では TBD はアミノ基のプロトンにより二酸化炭素との付加体が安定化される[31]ため、TBD が塩基として十分に機能しなかったと考えらえる。

Table 1.3. Examination of Bases
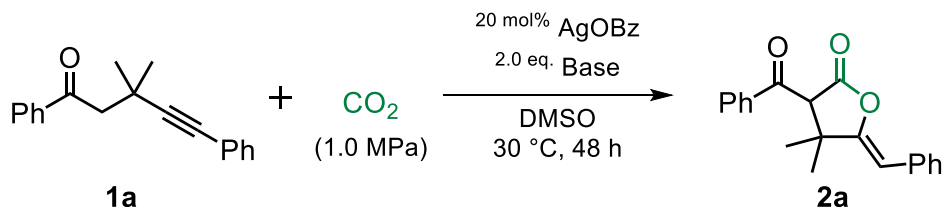
Entry	Base	Yield / %[a]
1	Et$_3$N	NR[b]
2	^{i}Pr$_2$NEt	NR[b]
3	DMAP	6
4	DBU	40
5	TMG	13
6	^{n}Bu-TMG	39
7	TBD	7
8	MTBD	48
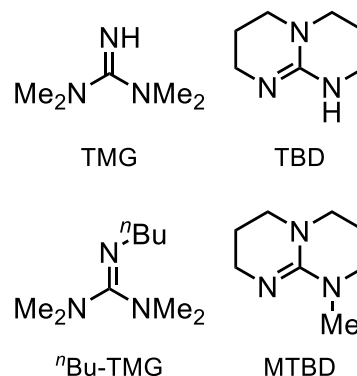
a) Isolated yield. b) No reaction.

　非プロトン性極性溶媒は、双極子‐双極子相互作用によりエノラートが安定化するため、エノラートの生成に有利であると報告されており[32]、反応の促進を期待して非プロトン性極性溶媒を用いて検討した（Table 1.4）。実験の結果、アセトニトリルやジメチルイミダゾリジノン（DMI）を用いた場合には収率が低下することがわかった（Entries 2 and 3）。一方、ジメチルアセトアミド（DMA）やジメチルホルムアミド（DMF）を用いるとそれぞれ収率59%、72%で目的のラクトンが得られた（Entries 4 and 5）。このとき、副生成物として、出発物質のカルボニルがアルキンに対して環化して生成したと考えられるフラン **3a** が収率5%で得られた（Entry 5）。

　さらなる収率向上をめざし、塩基の当量検討を行った（Entries 6-9）。その結果、塩基を4 等量の MTBD を用いると収率が 89%に向上した（Entry 8）。さらに、反応温度が 25℃のとき、目的のラクトンが収率91%で得られることが明かとなった（Entry 10）。生成物には出発物質の α プロトンより酸性度が高い二重にカルボニル基の α 位にあるプロトンが存在し、反応が進行するとともに塩基は出発物質ではなく生成物の α プロトンを引き抜くこと

を考慮しても、原理的には 1 当量強の塩基で十分のはずであるが、本反応では 4 等量の塩基が必要であることが実験的に明らかとなった。

Table 1.4. Examination of Various Conditions

Entry	Solvent	X / eq.	Time / h	Yield /%[a]
1	DMSO	2	48	48
2	CH_3CN	2	48	13
3	DMI	2	48	10
4	DMA	2	48	59
5	DMF	2	48	72
6	DMF	1.5	72	58
7	DMF	3	48	83
8	DMF	4	48	89
9	DMF	5	24	89
10[b]	DMF	4	48	91

a) Isolated yield. b) 25°C.

　次に、触媒量の低減を目指した（Table 1.5）。5 mol%の場合、15 日間反応させたが、ラクトン誘導体が収率 61%と未反応の出発物質が収率 32%で得られる結果となった（Entry 1）。また、10 mol%の安息香酸銀を用いるとラクトン **2a** の収率は 85%であり、20 mol%の場合と同程度の収率を与えたが長い反応時間を要した（Entry 2）。これらの結果から、本反応には 20 mol%の安息香酸銀が必要であることがわかった。

Table 1.5. Examination of the Amount of Catalysts
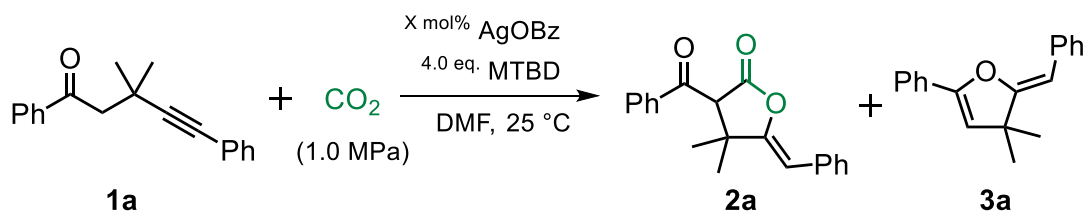
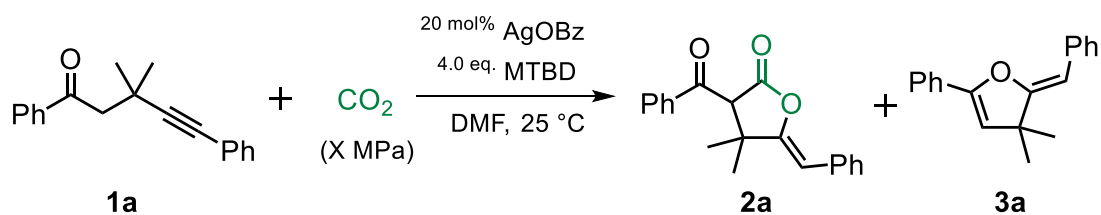| Entry	X / mol%	Time / h	Yields / %[a]		
			2a	**3a**	**1a**
1	5	360	61	trace	32
2	10	240	85	6	1
3	20	48	91	4	2
4	40	26	85	9	1

a) Isolated yield.

　続いて、二酸化炭素の圧力の低減を試みた（Table 1.6）。窒素雰囲気下で反応を行うとフラン **3a** が収率92％で得られた（Entry 1）。圧力を 0.5 MPa に下げるとラクトンは収率79％で得られたが、フランの生成が 14％に増加した（Entry 2）。0.7 MPa の二酸化炭素雰囲気下では、収率85％と 1.0 MPa と同程度の収率であった（Entry 3）。これらの結果から、エノラートがアルキンへ直接環化するのに優先して、二酸化炭素と反応するためには少なくとも 1 MPa の圧力が必要であることがわかった。

Table 1.6. Examination of the Pressure of CO_2

Entry	X	Time / h	Yields / %[a]		
			2a	**3a**	**1a**
1	in N_2	48	0	92	NA[b]
2	0.5	216	79	14	6
3	0.7	96	85	7	1
4	1.0	48	91	4	2

a) Isolated yield. b) Not analysed.

1-3. 基質適用範囲

　安息香酸銀存在下、塩基に 4 当量の MTBD を用いて、25℃の DMF 溶媒中で反応を行う最適条件において、一連のケトン化合物への適用を試みた（Table 1.7）。アルキン末端に電子供与基の p-メチル基や p-メトキシ基をもつ芳香環が置換した基質から、高収率で目的のラクトン誘導体が得られた（Entries 2 and 3）。電子求引基の p-フルオロ基や p-トリフルオロメチル基をもつ芳香環が置換した基質を用いると、ラクトン誘導体がそれぞれ収率 79％および 90％で得られた（Entries 4 and 5）。また、アルキン末端にアルキル鎖を有する場合も反応が進行し、目的の生成物が高収率で得られた（Entries 6 and 7）。ベンゾイル基に p-メチル基が導入された基質を用いた場合、対応するラクトンが収率 84％で得られた（Entry 8）。一方で、p-トリフルオロメチル基やメトキシ基を有する基質を用いると、10％ほどのフランの生成が確認されるものの、良好な収率で目的物が得られた（Entries 9-12）。メトキシ基の場合、オルト、メタ、パラのいずれの異性体においても、反応時間を要するものの高収率で対応するラクトン誘導体が得られることがわかった。

　脂肪族ケトンの反応性と生成物の選択性の二つの点において、脂肪族ケトンへの適用は困難であると予想された（Entries 14-16）。メチルケトン部位をもつ基質（**1n**）を用いたところ、反応温度を 25℃から 50℃にすることで、5 員環ラクトンのみが収率 58％で得られることがわかった。n-プロピルケトン部位をもつ基質（**1o**）および 1-フェニルエチルケトン部位を有する基質（**1p**）に対しても、それぞれ収率 31％および 59％で 5 員環ラクトンが得られた。

　カルボニル基の β 位にシクロアルキル基を有する基質について検討した（Entries 17-21）。シクロブチル基（**1q**）の場合、対応するラクトン **2q** が収率 74％で得られた。シクロペンチル基（**1r**）の場合、目的の生成物が収率 36％で得られ、47％の原料が回収された。一方、シクロヘキシル基の場合には生成物は痕跡量しか得られなかった（Entry 19）。シクロヘキシル基により、銀触媒のアルキンへの接近が困難となり反応が進行しなかったと考えられる。続いて、フェニル基が置換した基質 **1s** を用いると、出発物質が 74％転化され、対応するラ

クトン **2s** が収率 19%、フランが 25%で得られた。一方、置換基のない基質を用いると出発物質は 82%転化されたが、複雑な混合物を与えるのみであった（Entry 21）。

Table 1.7. Lactone Derivatives Obtained from Various Substrates

Entry[a]	Product		Time / h	Yield / %[b]
1		R^1 = H (**2a**)	48	91
2		*p*-Me (**2b**)	96	90
3		*m*-MeO (**2c**)	96	87
4		*p*-F (**2d**)	72	79
5		*p*-CF$_3$ (**2e**)	48	90
6[c]		R^2 = Ph (**2f**)	70	77
7[c]		CH$_2$CH$_3$ (**2g**)	72	83
8		R^3 = *p*-Me (**2h**)	72	84
9[d]		*p*-CF$_3$ (**2i**)	192	79
10[e]		*p*-MeO (**2j**)	144	69
11[e, f]		*m*-MeO (**2k**)	144	77
12[e, f]		*o*-MeO (**2l**)	220	76
13[c]		(**2m**)	120	77
14[g]		R^4 = Me (**2n**)	48	58
15[g]		^{n}Pr (**2o**)	48	31
16[g]		CH$_2$CH$_2$Ph (**2p**)	48	59
17[h]		R^5, R^6 = -(CH$_2$)$_4$- (**2q**)	120	74
18[h, i]		R^5, R^6 = -(CH$_2$)$_5$- (**2r**)	48	36[j]
19		R^5, R^6 = -(CH$_2$)$_6$-	48	trace
20		R^5 = H, R^6 = Ph (**2s**)	48	19[k]
21		R^5, R^6 = H	48	—[l]

a) The reaction was performed by AgOBz (20 mol%) with MTBD (4.0 equiv.) in 1.0 mL of DMF with 0.125 mmol of substrate **1** at 25 °C under 1.0 MPa CO$_2$ pressure. b) Isolated yield. c) 6.0 equivalent of MTBD under 2.0 MPa CO$_2$ pressure. d) 5 °C. e) 10 °C under 2.0 MPa CO$_2$ pressure. f) AgOBz (40 mol%) was used. g) 50 °C under 2.0 MPa CO$_2$ pressure. h) 2.0 MPa CO$_2$ pressure. i) AgOAc (40 mol%) was used instead of AgOBz at 60 °C. j) **1r** was recovered in 47% and the corresponding furan was obtained in 6%. k) **1s** was recovered in 26% and the corresponding furan was obtained in 25%. l) Complex mixture including the desired compound. Starting material was consumed in 82%.

1-4. 反応機構に関する考察

　得られた生成物 **2h** はエキソオレフィンの幾何異性に関して単一化合物であり、X 線結晶構造解析により *Z* 体であることがわかった（Figure 1.1）[33]。その他の生成物 **2a-2g**、**2i-2s** については、核オーバーハウザー効果（NOE）によって、ビニル位のプロトンとジメチル部位の水素間での相関をもとに、*Z* 体であることを確認した。これらのことから、立体選択的に環化反応が進行し、ビニル銀中間体が生成し、その後、立体を保持したままプロトン交換が進行し、*Z* 体の生成物のみを与えたものと推定している。
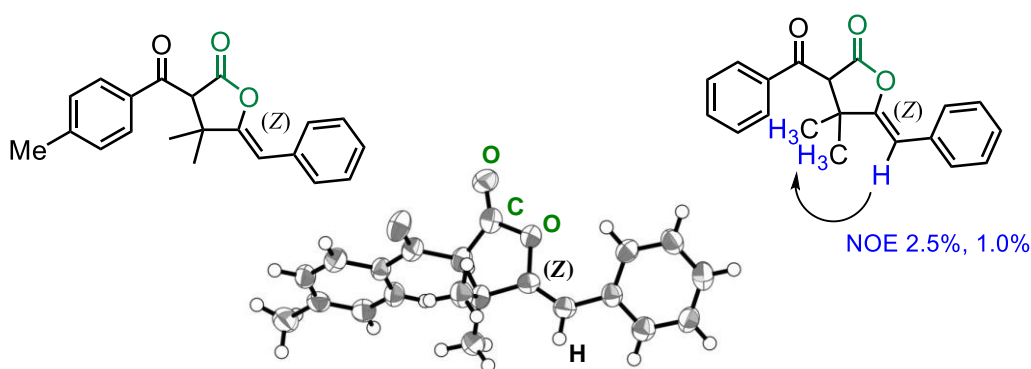

Figure 1.1. The structure of **2h.**

　水中での MTBD-H^{+}の pK_a[29]が 13.0 であり、アセトフェノンの pK_a[28]が 19.2 であることから、MTBD のみでは十分なエノラートが生成していないと考えた。実際に、重ジメチルスルホキシド溶媒中で、基質 **1a** に対して 1 当量の MTBD を作用させたが、^{1}H NMR においてエノラートの生成はほぼ確認されなかった。銀イオンは、カルボニル基およびアルキンのどちらに対しても Lweis 酸として作用することが ^{13}C NMR[34]や計算化学的 [35]に示唆されている。このことから、基質のカルボニル基が銀イオンに配位して、α 位のプロトンが活性化され、エノラートの生成が促進されていると推定した。本反応におけるカルボニル基の銀イオンへの配位を実験的に検証するため、基質 **1a** に対して銀塩の当量を変化させながら、テトラメチルシランを内部標準として重ジメチルスルホキシド中での ^{13}C NMR におけるカルボニル基の炭素の化学シフト値の変化を観測した（Figures 1.2 and 1.3）。銀塩の溶媒への溶解度を考慮してトリフルオロ酢酸銀を用いた。実験の結果、1 当量のトリフルオロ酢酸銀を加えたとき、カルボニルの炭素 C[1]に関して化学シフト値がδ 0.03 変化したのに対し、

アルキンの炭素に関してはほとんど変化しなかった。また、3 当量、5 当量と銀塩を加える
と、アルキンの炭素に関しても化学シフト値の変化が観測された。このとき、トリフルオロ
酢酸由来のピークも観測された。銀イオンに対しては、アルケンやアルキンの不飽和結合の
π 配位に比べ、カルボニル基やイミノ基の σ 配位の方がわずかに優位であるという計算化学
的な結果 [35] と今回の実験結果にもとづくと、銀イオンがカルボニル基を活性化した後に、
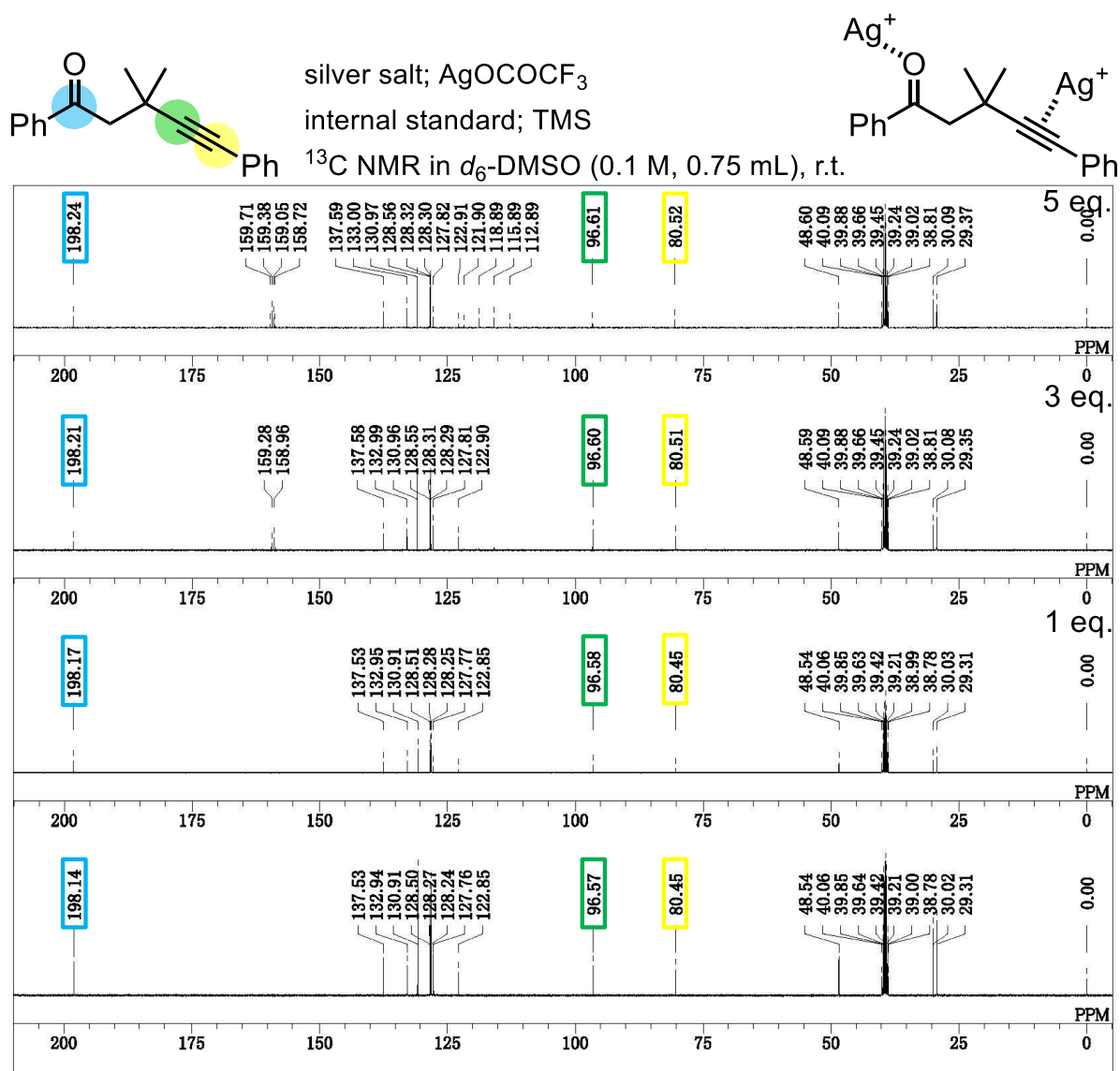アルキンを活性化し、環化反応を促進していると考えられる。

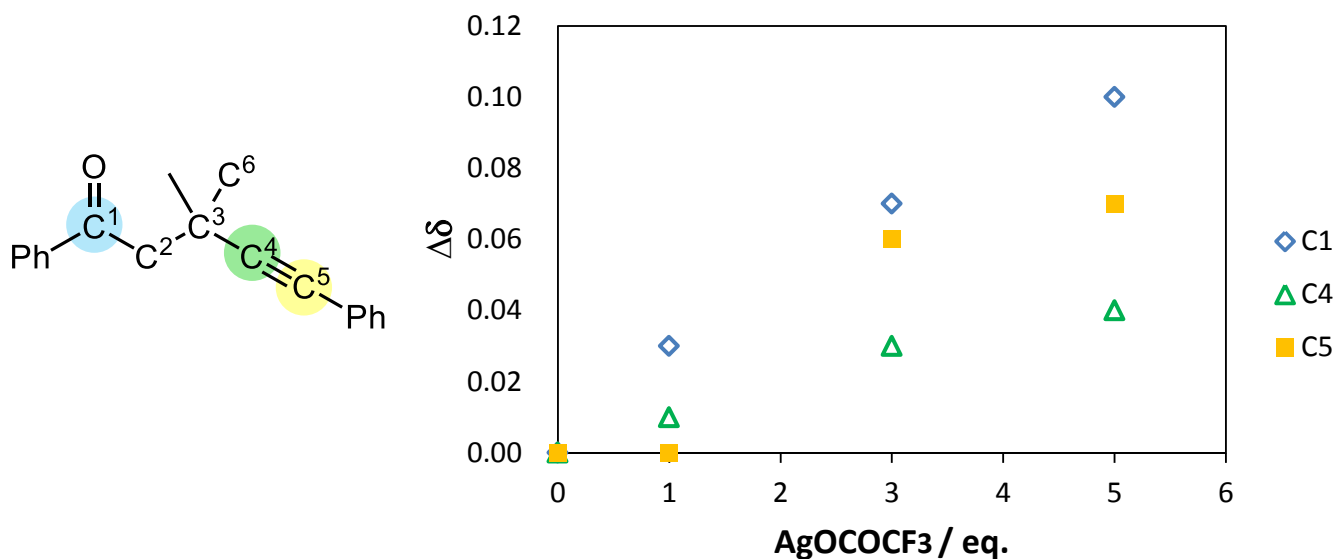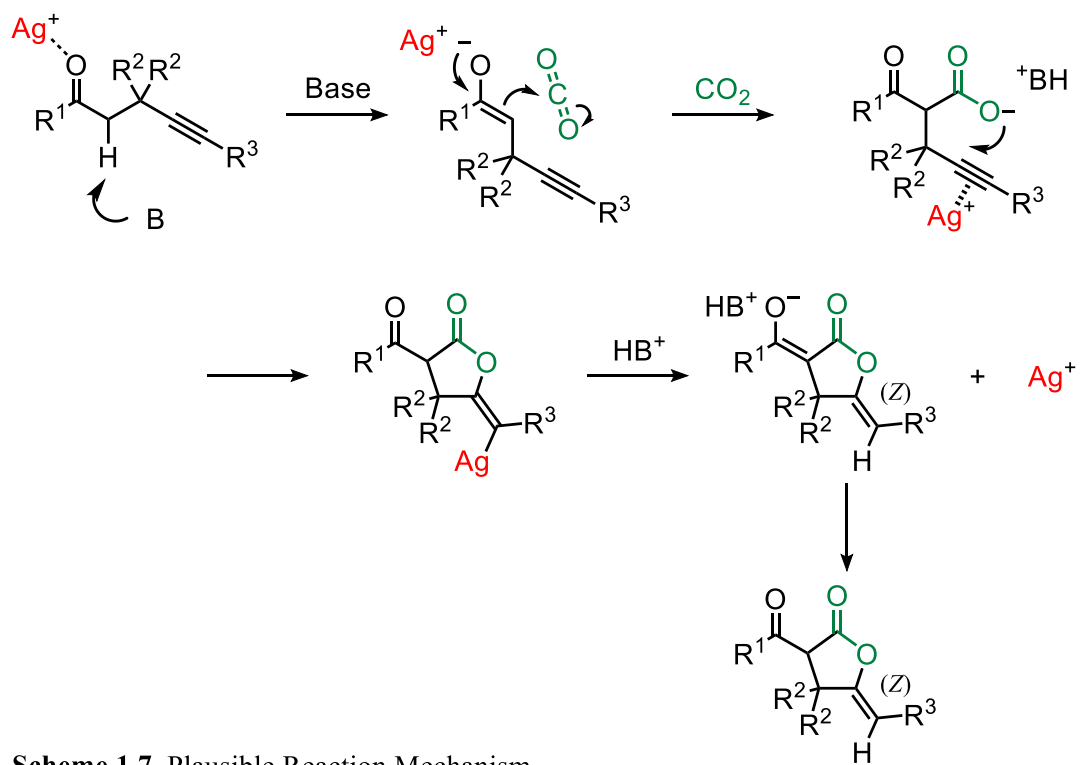**Figure 1.2.** ^{13}C NMR in the titration experiment.

Figure 1.3. Peak shift in carbonyl group and alkyne.

　以上の結果をもとに、反応メカニズムを次のように推定している（Scheme 1.7）。まず、カルボニル基が銀イオンに配位し、α位のプロトンが活性化する。グアニジン塩基によるα位のプロトンの引き抜きによりエノラートが生成し、二酸化炭素へ求核付加する。続いて、カルボキシラートが銀塩により活性化されたアルキンに捕捉され、立体選択的にビニル銀中間体が生成し、立体を保持したままプロトンと交換することで Z 体のラクトン誘導体が得られると考えている。

**Scheme 1.7.** Plausible Reaction Mechanism

第２節　エノラートを求核種とするジヒドロイソベンゾフラン誘導体合成

　前節で述べた反応は、種々の芳香族ケトンと脂肪族ケトンに適用可能であった。興味深いことに、脂肪族ケトンを用いた場合、目的のラクトン誘導体とは別に副生成物が得られることがわかった。ESI‐MS スペクトルから分子量が出発物質より 44 大きいピークが観測され、二酸化炭素が取り込まれて生成した化合物であると推定した。また、IR スペクトルではカルボン酸に特有の 2500-3000 cm^{-1} に幅広い吸収を示したことから、カルボキシル基をもつ化合物であると予想した。さらに NMR による構造解析の結果、得られた副生成物はカルボキシル基を有するフラン誘導体であることがわかった（Scheme 1.8）。
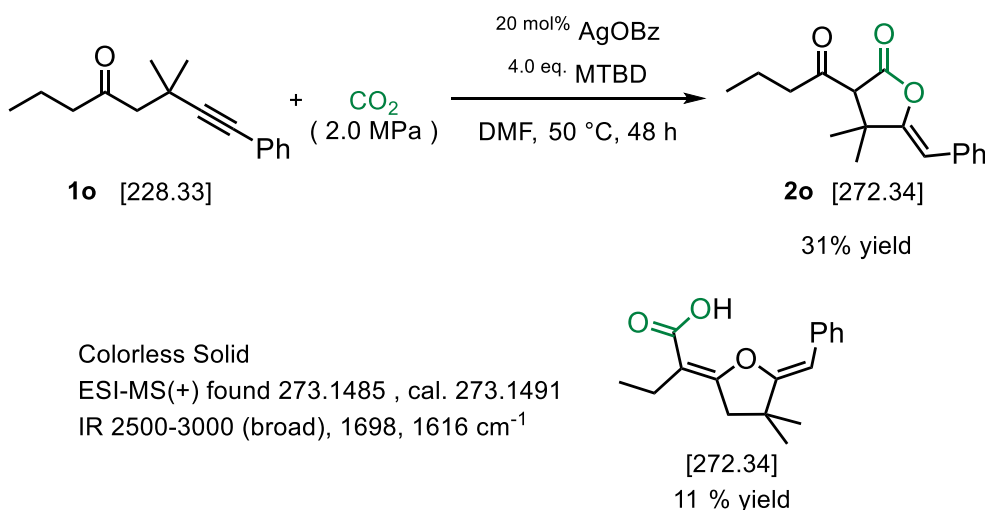

Scheme 1.8. Side-product Obtained by the Silver-catalyzed Reaction of Aliphatic Ketones

　フラン誘導体の生成メカニズムを考察したところ、望みの α プロトン H_a ではない反対側の α'プロトン H_b が塩基により引き抜かれ、二酸化炭素と反応してカルボキシラートアニオンが生成し、その後、ケトンカルボニルが直接環化して得られる生成物であると考えた（Scheme 1.9）。ラクトン誘導体はカルボキシラートアニオンがアルキンにより捕捉されて得られるのに対して、フラン誘導体は反対側の α プロトンが引き抜かれて生成する β‐ケトカルボン酸のケトカルボニルがアルキンにより捕捉されて得られたと想定した。今回、カルボキシル基をもつフラン誘導体が選択的に得られる反応系の開発を目指した。
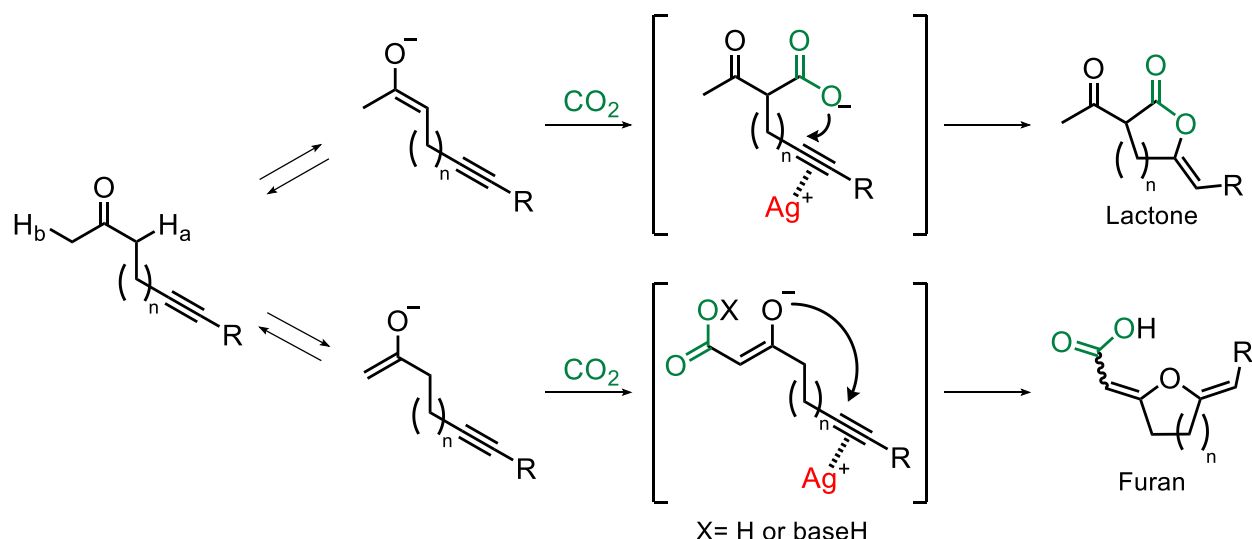
Scheme 1.9. Postulated Reaction Pathways for Lactone and Furan

　銀触媒によるアルキンの活性化を用いることで二酸化炭素を取り込みながらジヒドロイ
ソベンゾフランが得られると想定した。すなわち、オルト位にアルキンをもつアセトフェノ
ンを用いれば、二酸化炭素と炭素 - 炭素結合を形成した後に生成するβ - ケトカルボン酸の
ケトンカルボニルが銀塩により活性化されたアルキンで捕捉され、カルボキシル基をもつジ
ヒドロイソベンゾフランが生成すると期待した（Scheme 1.10）。
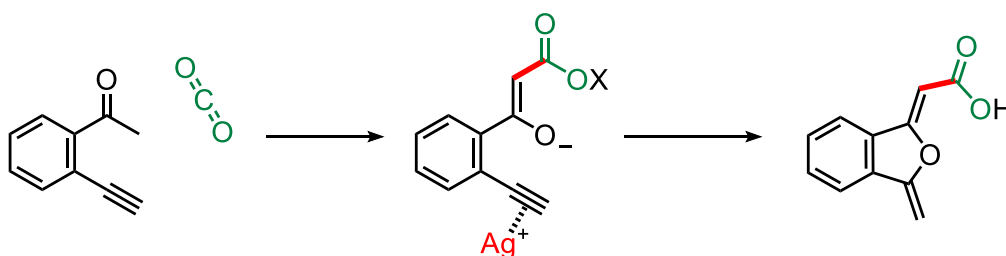
Scheme 1.10. Silver-catalyzed Cyclization for Dihydroisobenzofurans

2-1. 反応条件の最適化

　オルト位にアルキンを有するアセトフェノン **4a** をモデル基質として、1.0 MPa の二酸化
炭素雰囲気下、2 当量の DBU を用いて、種々の金属塩を用いて検討を行った（Table 1.8）。
その結果、金塩（Entry 2）、銅塩（Entry 3）およびパラジウム塩（Entry 4）を用いた場
合には、目的の反応は全く進行しないあるいは痕跡量の生成物を与えるのみであった。一方
で、銀塩を用いた場合には望みの反応が円滑に進行することがわかった。銀の対アニオンを

検討した結果、酢酸銀を用いた場合に目的のジヒドロイソベンゾフラン **5a** が NMR 収率99%で得られた（Entry 7）。非プロトン性極性溶媒であるジメチルホルムアミド（DMF）およびジメチルスルホキシド（DMSO）を用いた場合にも反応は円滑に進行し、ジヒドロイソベンゾフランが高収率で得られることがわかった（Entries 8 and 9）。大気圧（風船圧）雰囲気下においても対応する生成物が高収率で得られたが、長い反応時間を要することがわかった（Entry 10）。

Table 1.8. Screening of Various Conditions
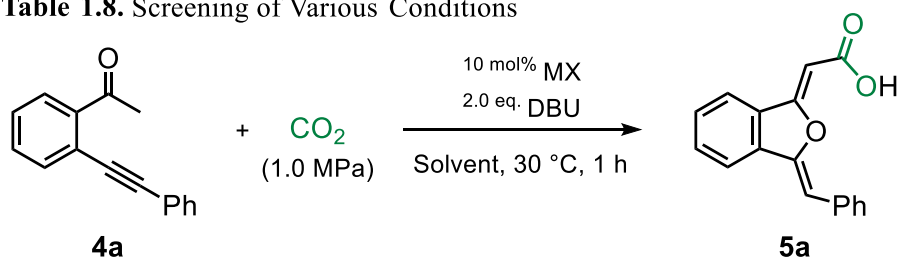
Entry[a]	MX	Solvent	Yield / %[b]
1	None	CH_3CN	<1
2	(PPh$_3$)AuCl	CH_3CN	ND[c]
3[d]	CuBr	CH_3CN	7
4	Pd(OAc)$_2$	CH_3CN	3
5	AgNO$_3$	CH_3CN	91
6	AgBr	CH_3CN	89
7	AgOAc	CH_3CN	99
8	AgOAc	DMF	94
9	AgOAc	DMSO	91
10[e]	AgOAc	CH_3CN	98

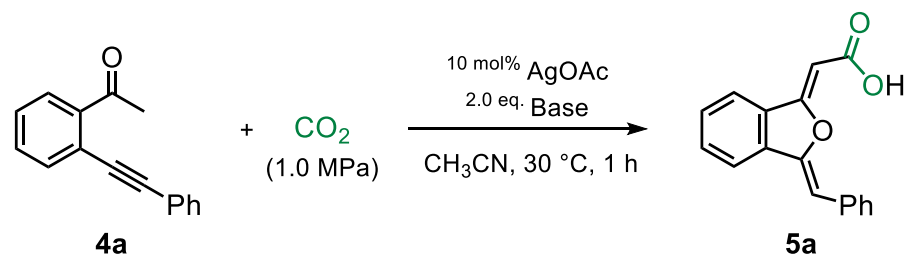a) The reaction was carried out with 0.15 mmol of substrate.
b) Determined by ^{1}H NMR with an internal standard. c) Not detected. d) 21 h. e) 1 atm CO_2. 24 h.
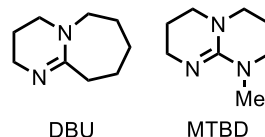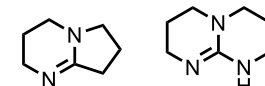
　適用可能な塩基を探索した（Table 1.9）。炭酸カリウムやジイソプロピルエチルアミンを用いた場合は、目的のジヒドロイソベンゾフランを与えなかった（Entries 1 and 2）。第二級アミン部位をもつ TBD を用いた場合は収率が 14%にとどまった（Entry 3）。一方で、DBN、DBU や MTBD といった比較的強い有機塩基は望みの反応を促進し、目的の生成物を与えた（Entries 4-6）。1 当量の DBU を用いた場合、反応時間を 25 時間に伸ばしても、

収率が 72%にとどまることがわかった（Entry 7）。反応の最終段階で、DBU と生成物のカルボン酸が塩を形成するため、反応の進行とともに著しく反応速度が低下するものと考えられる。

Table 1.9. Examination of Various Bases

Entry[a]	Base	Yield / %[b]
1[c]	K_2CO_3	ND[d]
2	[i]Pr_2NEt	ND[d]
3	TBD	14
4	DBN	41
5	MTBD	82
6	DBU	99
7	DBU[e]	72

a) The reaction was carried out with 0.15 mmol of substrate. b) Determined by ^{1}H NMR with an internal standard. c) In DMF. d) Not detected. e) 1 eq. DBU. 25 h.

カルボン酸の精製に通常用いられる逆相シリカゲルカラムクロマトグラフィーや逆抽出では、得られたジヒドロイソベンゾフランの精製は困難であった。一つの原因として、カルボニル基に隣接する二重結合の幾何異性に関して、精製中に *Z* 体が *E* 体に異性化することが考えられた。実際、わずかに酸性である重クロロホルム溶媒中でも、^{1}H NMR によって異性化が確認された。リン酸緩衝液（pH = 6）による反応停止および分液、溶媒除去、THFからの再結晶により *Z* 体の生成物が単体として得られるものの、収率は 66%と中程度にとどまった（Scheme 1.11）。そこで、カルボン酸をエステル化した後に、生成物を得ることを試みた。反応終了後に、オートクレーブから二酸化炭素を放出したのち、4 当量のヨードメタンを加え撹拌し、分液処理、シリカゲルカラムクロマトグラフィーによる精製を経て、

Z 体のメチルエステル体 **6a** が収率 92％で単離できることがわかった。NOE 測定により、生成物の有する 2 つの二重結合の幾何異性は、ともに Z 体であることが示唆された。
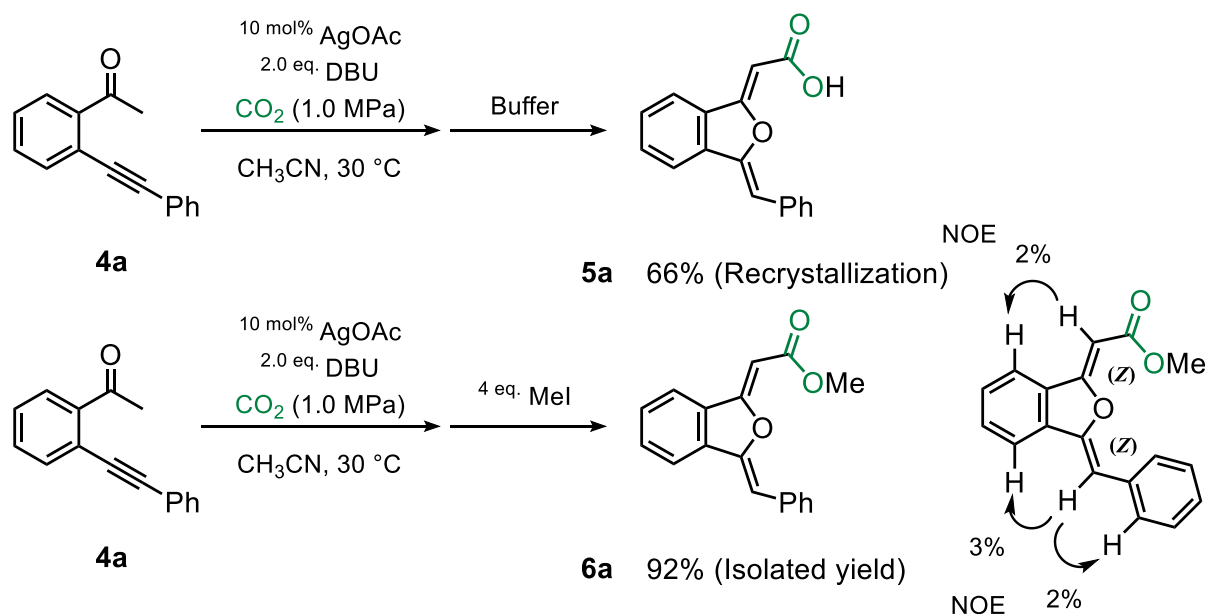
Scheme 1.11. Esterification of **5a** in One Pot Synthesis

2-2. 基質適用範囲

二酸化炭素雰囲気下、10 mol％の酢酸銀、2 当量の DBU、アセトニトリルを溶媒とする最適条件において、基質の適用範囲を調べた（Table 1.10）。芳香環上にメトキシ基（**4b**）、フルオロ基（**4c**）やクロロ基（**4d**）をもつアセトフェノン誘導体に対しても、円滑に反応が進行し、対応するジヒドロイソベンゾフランがそれぞれ収率 91％、90％、95％で得られた。2‐アセチルナフタレン骨格をもつ基質 **4e** は生成物 **5e** を収率 69％で与えた。アルキン末端の芳香環上に、p‐メチル基（**4f**）や p‐トリフルオロメチル基（**4g**）が置換した基質を用いても反応が円滑に進行した。また、カルボニル基を有する基質にも適用可能であり、p‐アセチル基（**4h**）や p‐ホルミル基（**4i**）が置換した基質から対応する化合物がそれぞれ収率 89％および 70％で得られた。さらに、o‐メトキシカルボニル基が置換した基質 **4j** の場合も、対応するジヒドロイソベンゾフラン **6j** を良好な収率で与えることがわかった。アルキル鎖がアルキン末端に置換した場合（**4k-l**）にも、対応するジヒドロイソベンゾフランが高い収率で得られたが、カルボニル基に隣接する二重結合の幾何異性に関して、Z 体と

Table 1.10. Silver-catalyzed Cyclization of Various Substrates[a]
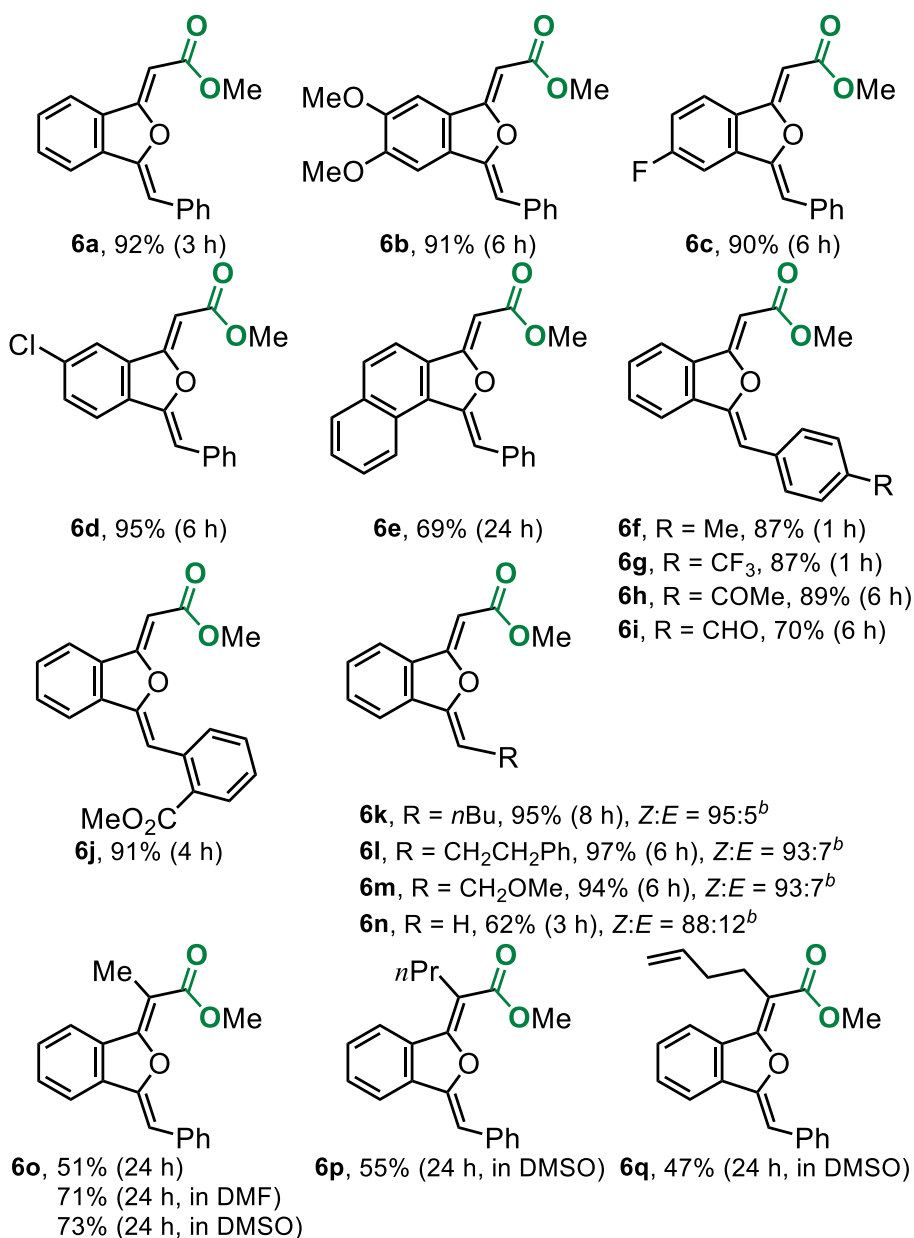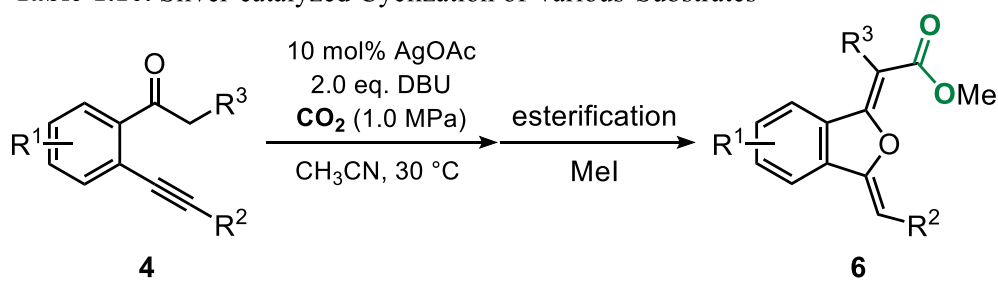
10 mol% AgOAc
2.0 eq. DBU
CO_2 (1.0 MPa)

CH_3CN, 30 °C

esterification
MeI

6a, 92% (3 h)

6b, 91% (6 h)

6c, 90% (6 h)

6d, 95% (6 h)

6e, 69% (24 h)

6f, R = Me, 87% (1 h)
6g, R = CF_3, 87% (1 h)
6h, R = COMe, 89% (6 h)
6i, R = CHO, 70% (6 h)

6j, 91% (4 h)

6k, R = nBu, 95% (8 h), Z:E = 95:5[b]
6l, R = CH_2CH_2Ph, 97% (6 h), Z:E = 93:7[b]
6m, R = CH_2OMe, 94% (6 h), Z:E = 93:7[b]
6n, R = H, 62% (3 h), Z:E = 88:12[b]

6o, 51% (24 h)
71% (24 h, in DMF)
73% (24 h, in DMSO)

6p, 55% (24 h, in DMSO)

6q, 47% (24 h, in DMSO)

a) Isolated yield. b) The ratio of Z and E isomers about the C-C double bond adjacent to the carbonyl group. Determined by ^{1}H NMR.

E 体の混合物として生成物が得られた。また、末端アルキンの基質 **4n** を用いた場合には、

収率 62%、異性体比 Z: E = 88:12 で目的の化合物が得られた。ケトンの α 位にアルキル鎖

を有する基質 **4o** においては、反応時間を要するものの、目的化合物が中程度の収率で得られた。エノラート生成の促進を期待して、DMSO を溶媒として用いたところ、収率が 73% に向上することがわかった。すべての生成物の 2 つのエキソオレフィンに関する幾何異性が *Z* 体であることを、NOE 測定により確認した。

アルキン末端に芳香環をもたない基質に対応する生成物（**6k, 6l, 6m, 6n**）で *E* 体の存在が確認された。類似した化合物において、クロロホルム中やシリカゲルの弱い酸性条件での *Z* 体から *E* 体への異性化が観測されている [36]。本反応において、電子密度豊富なオレフィン部位を有している生成物で顕著に *E* 体が観測されたことから、次のような *Z* 体から *E* 体への異性化が進行したものと考えられる（Scheme 1.12）。
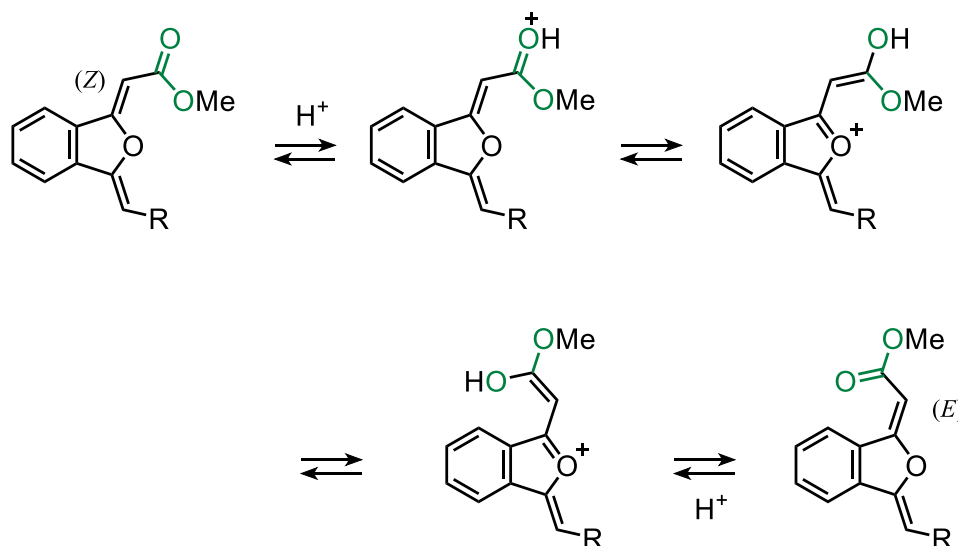

Scheme 1.12. Isomerization from *Z*-isomer to *E*-isomer

第 2 章　プロパルギルアミンに対する二酸化炭素およびヨード基の連続的導入反応

緒言

　3 種類以上の反応剤をひとつの反応で用いる多成分合成反応は、医薬品や材料科学分野において標的の化合物を短工程で得るのに有用な手段のひとつである。二酸化炭素を反応剤として用いる多成分合成反応では、カルボン酸、ラクトン、環状炭酸エステル、カルバミン酸エステルと様々な基本骨格を形成することが可能である[37]。第 1 章の緒言で述べたように、プロパルギルアミンと二酸化炭素との反応は、銀触媒を用いると円滑に進行し、対応するオキサゾリジノン誘導体が高収率で得られた。この反応では、カーバメートがアルキンに対してアンチ付加することにより、ビニル銀中間体が立体選択的に生成していると推定した。ビニル銀中間体が立体を保持したままプロトンと交換することにより、銀触媒が再生するとともに、Z 体のオキサゾリジノンが選択的に得られたと考えた（Scheme 2.1）[16]。この推定反応機構から、適切な求電子剤（E+）存在下では炭素 - 銀結合が立体特異的に求電子剤により捕捉され、炭素 - E 結合をもつオキサゾリジノンが高い立体選択性で得られると想定した。銀イオンと求電子剤の交換反応は、ビニル銀中間体が反応系中で生成している根拠のひとつとなりうる。
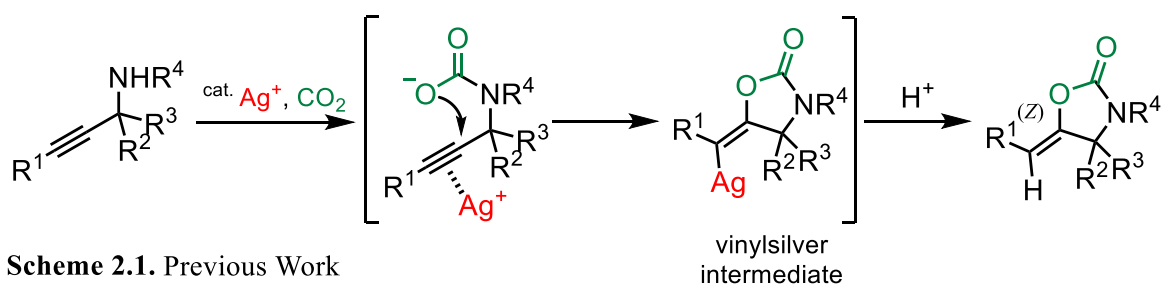
Scheme 2.1. Previous Work

　近年、ビニル - 銀結合の銀イオンと求電子剤の交換反応によるハロゲン化ビニル化合物やビニルスズ化合物の合成が報告された（Scheme 2.2）[38]。Y. Liu らや松原らはほぼ同時期に、銀触媒によるアレニルアミンの環化反応に引き続き、ビニル - 銀結合が適切な求電子剤と置き換わり、3 位にフッ素あるいは塩素が導入されたピロリジンの合成に成功した（Scheme 2.2(a) and (b)）。また、Y. Liu らはオルトアルキニルアニリンに対して、銀触媒とスズ試薬を作用させると、3 位にトリブチルスズ基が導入されたインドールが得られることを報告し

た（Scheme 2.2(c)）。銀触媒および *N*‑ヨードスクシイミドを用いると、アルキンを適切な位置にもつシリルエノールエーテルの環化反応が進行し、ヨードビニル部位をもつスピロ化合物が得られることが報告されている（Scheme 2.2(d)）。
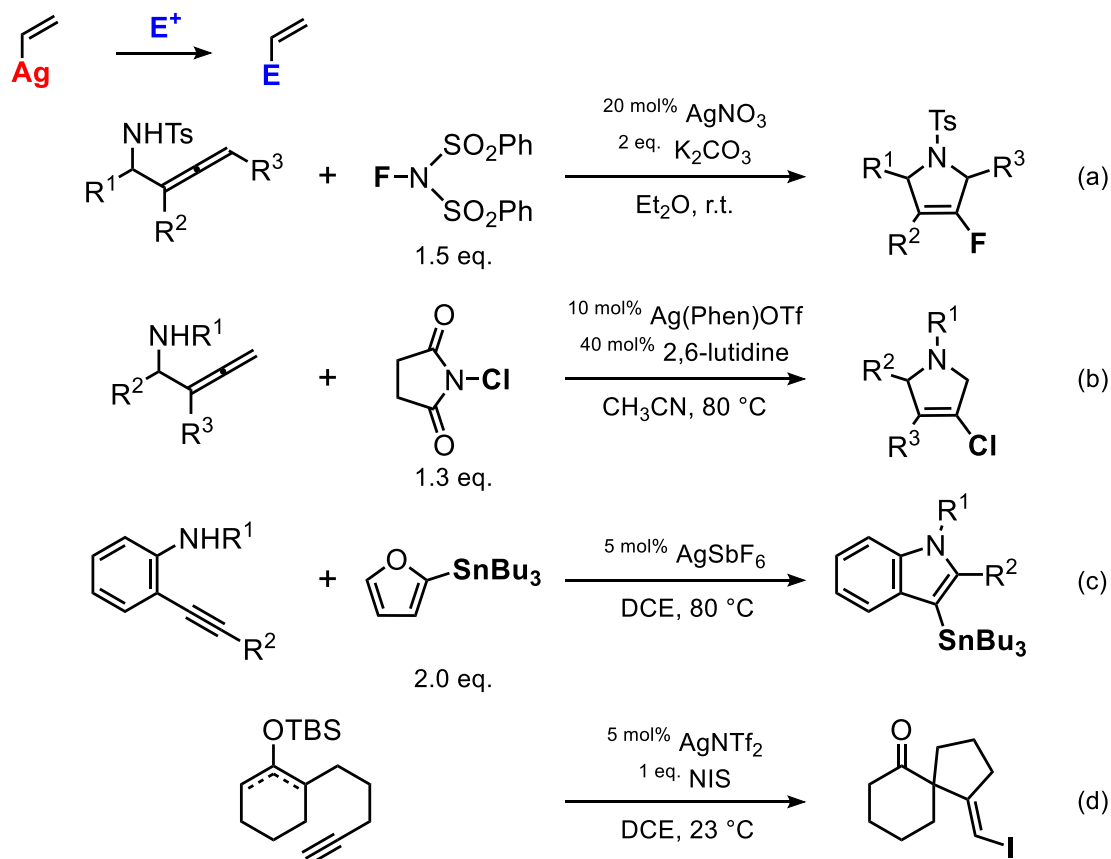
Scheme 2.2. Transformation of Vinylsilver Intermediates

ハロゲン化ビニル化合物は、金属触媒によるカップリング反応において有用性の高い反応剤の一つである。そこで、プロパルギルアミンへの二酸化炭素とハロゲン基の連続的導入反応の開発に取り組んだ。この反応では、ハロゲン化ビニル部位をもつオキサゾリジノン誘導体が得られる。*t*‑ブトキシヨージドによるハロ環化反応を鍵としたプロパルギルアミンに対する二酸化炭素とヨード基の連続的導入反応はすでに報告されているが、末端アルキンあるいはトリメチルシリル基をもつ基質に限定されており、収率も十分ではなかった（Scheme 2.3）[39]。

Scheme 2.3. Previously Reported Study
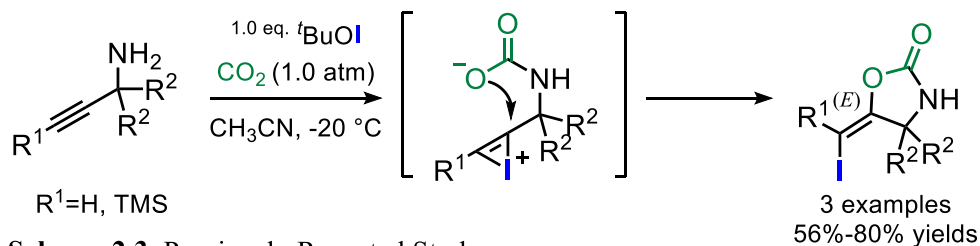
　すでに報告したプロパルギルアミンへの二酸化炭素固定化反応にもとづくと、銀触媒を用いれば室温付近で種々のプロパルギルアミン、特に内部アルキンを有するプロパルギルアミンに対して、二酸化炭素とハロゲン基を導入できると期待した（Scheme 2.4）。本章では、銀触媒によるプロパルギルアミンへの二酸化炭素とヨード基の連続的導入反応について述べる。

Scheme 2.4. This Work
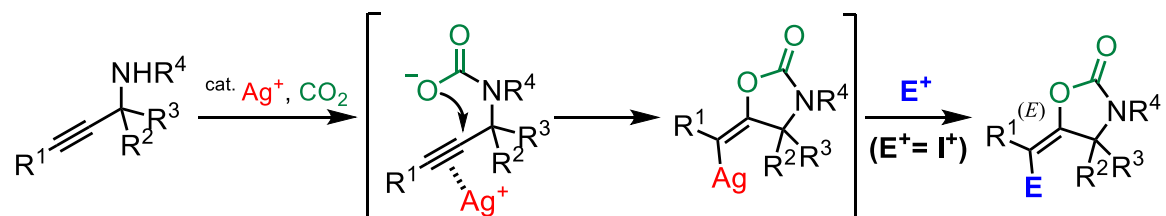
第 1 節 反応条件の最適化

まず、プロパルギルアミン **7a** を出発物質として、2.0 MPa の二酸化炭素雰囲気下、ジメ
チルスルホキシド（DMSO）溶媒中、10 mol%の酢酸銀存在下、N-スクシイミド誘導体を
用いてハロゲン化剤の検討を行った（Table 2.1）。N-クロロスクシイミド（NCS）を用い
た場合、二酸化炭素を取り込んだのちに生成するオキサゾリジノン **9a** が収率 15%で得られ
たが、望みのクロロビニル部位をもつオキサゾリジノン **8a** は得られなかった（Entry 1）。
N-ブロモスクシイミド（NBS）を用いた場合も目的のオキサゾリジノン **8a** は得られなか
った（Entry 2）。

Table 2.1. Examination of Electorophile Sources

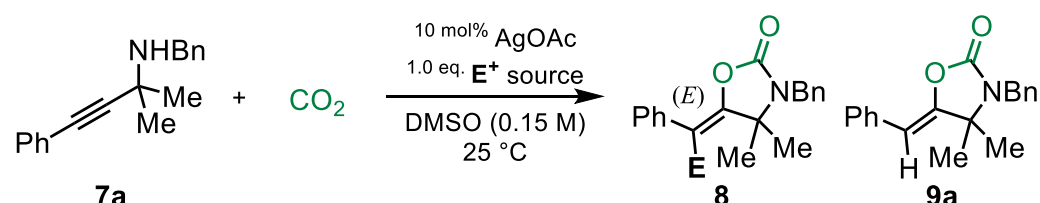| Entry	E^+ source	CO_2 pressure / MPa	Time / h	Yield **8** / %[a]
1	NCS	2.0	24	0[b]
2	NBS	2.0	24	0
3	NIS	2.0	24	92 (**8a**)
4	I_2	2.0	24	trace
5	I-Cl	2.0	24	0
6	I^+ [c]	2.0	24	0
7	NIS	1.0	60	92 (**8a**)

[a] Isolated yield. [b] The corresponding oxazolidinone **9a** was obtained in 15% yield.
[c] Bis(2,4,6-trimethylpyridine)iodonium hexafluorophosphate was employed.
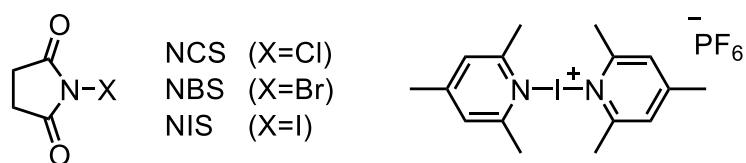
一方で、N-ヨードスクシイミド（NIS）を用いると反応が円滑に進行し、24 時間後で反
応が終了し、ヨードビニル部位を有するオキサゾリジノン **8a** が収率 92%で得られることが
わかった（Entry 3）。他のヨウ素源を検討した結果、ヨウ素、ヨードモノクロリド、ビス（2，
4，6-トリメチルピリジン）ヨードニウムヘキサフルオロホスフェートは本反応において

効果的でないことがわかった（Entries 4-6）。二酸化炭素の圧力を 1.0 MPa に低減したところ、目的のヨードビニルオキサゾリジノン **8a** が収率 92％で得られたものの、反応終了までに 60 時間を要した（Entry 7）。

　つづいて、適用可能な溶媒を探索したところ、低極性のトルエンや塩化メチレン溶媒中では痕跡量か数％の目的物のみを与えるのに対して、非プロトン性極性溶媒であるアセトニトリル、*N, N* - ジメチルホルムアミド（DMF）やジメチルスルホキシド（DMSO）が本反応において適切な溶媒であり、中程度から高い収率でオキサゾリジノン **8a** が得られることがわかった（Table 2.2）。

Table 2.2. Examination of Solvents
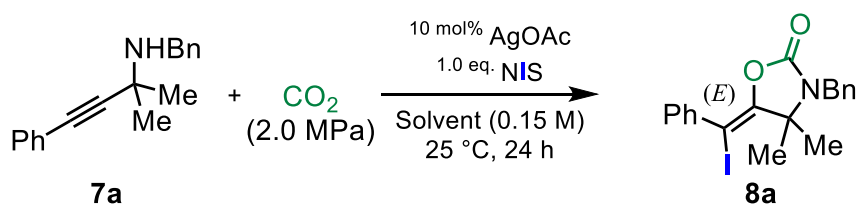
Entry	Solvent	Yield **8a** / %[a]
1	Toluene	trace
2	CH_2Cl_2	3
3	CH_3CN	57
4	DMF	71
5	DMSO	92

[a] Isolated yield.

　得られた生成物 **8a** は、¹H NMR からエキソオレフィンの幾何異性に関して単一化合物であることを確認した。また、単結晶 X 線構造解析を行ったところ、確かにヨードビニル部位をもつオキサゾリジノンであり、*E* 体のエキソオレフィンを有していることが明らかとなった（Figure 2.1）。
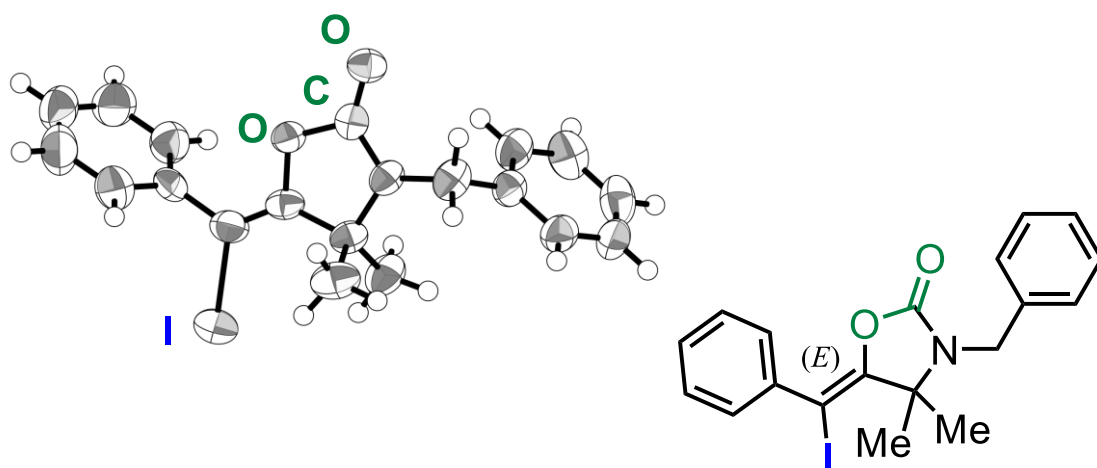
Figure 2.1. The structure of **8a**.

第 2 節　種々のプロパルギルアミンへの適用

　ジメチルスルホキシド溶媒中、10 mol%の酢酸銀、2.0 MPa 二酸化炭素雰囲気下の最適な反応条件を種々のプロパルギル第二級アミンへ適用した（Scheme 2.5）。まず、アルキン末端に置換した芳香環上の置換基について検討した。電子求引基である *p* - トリフルオロメチル基や *p* - アセチル基を有する基質では、対応するヨードビニルオキサゾリジノン **8b** と **8c** がそれぞれ収率 89%、82%で得られた。電子供与基である *p* - メチル基（**7d**）や *p* - メトキシ基（**7e**）をもつプロパルギルアミンも本反応において適切な基質であった。また、アルキンの末端に 1 - ナフチル基あるいは 2 - ナフチル基が置換した 2 つの位置異性体は同様の反応性を示し、それぞれ収率 96%、95%でオキサゾリジノン **8f** と **8g** が得られた。アルキンの末端に 2 - チエニル基が置換した基質を用いた場合も反応が円滑に進行し、オキサゾリジノン **8h** が高収率で得られた。アルキンの末端にアルキル鎖が置換したプロパルギルアミン **7i** に対しても本反応条件は適用可能であることがわかった。窒素上の置換基をベンジル
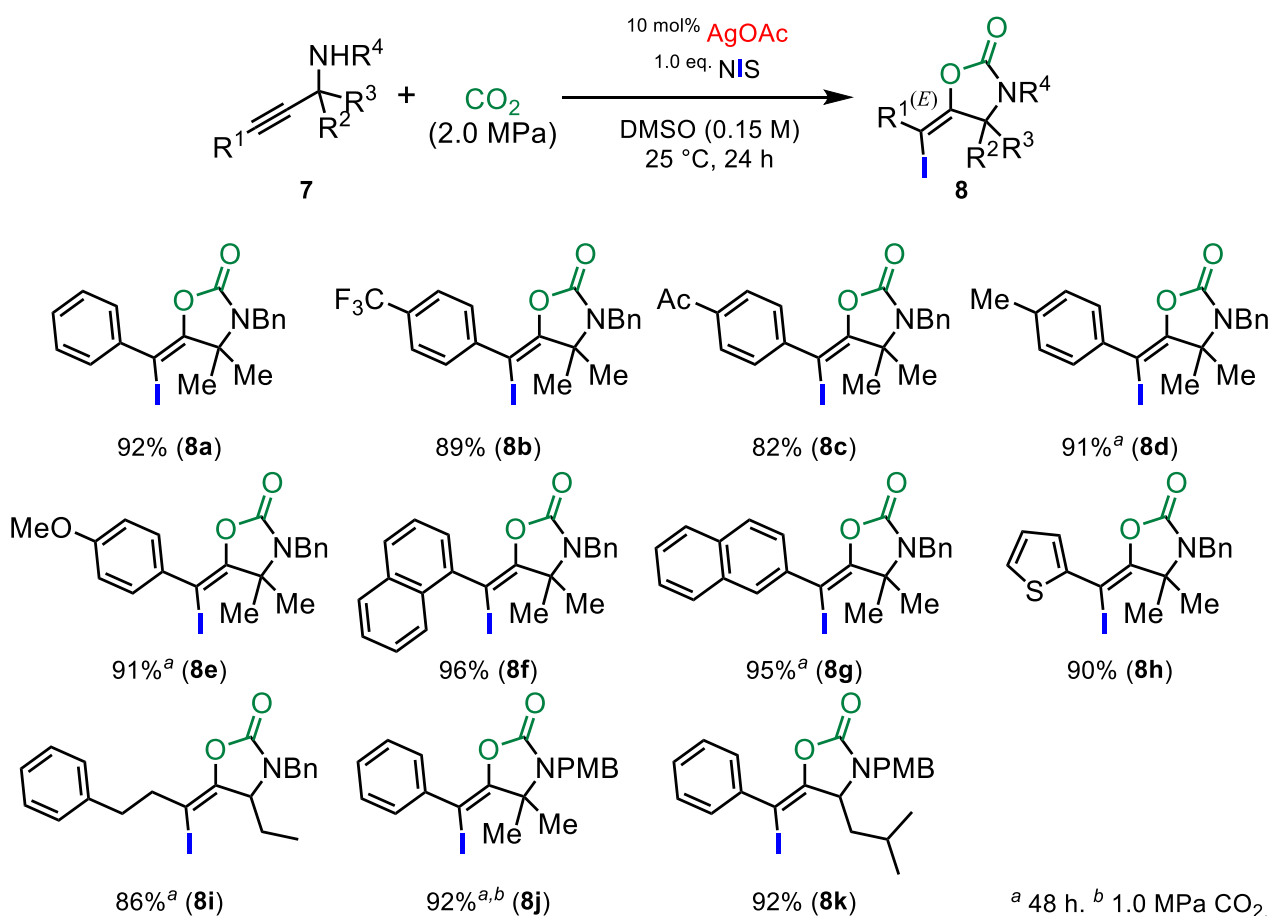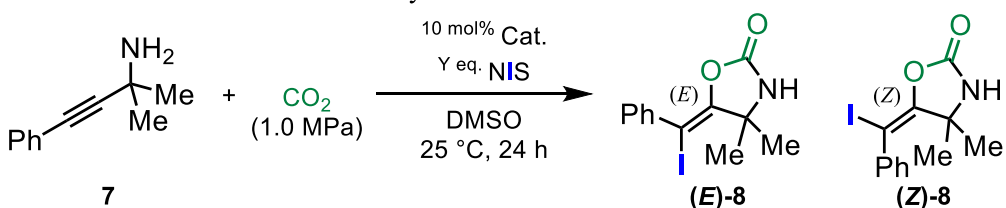
Scheme 2.5. Various Substituents on Alkynes

- 37 -

基から p - メトキシベンジル基とした場合、対応する目的生成物 **8j** が収率 92% で得られた。プロパルギル位にプロトンをもつ基質 **7k** を用いても反応が進行し、収率 92% でヨードビニルオキサゾリジノンを与えた。すべての場合において、E 体のヨードビニルオキサゾリジノンが単一化合物として得られた。

　触媒量の酢酸銀、1.2 当量の NIS、溶媒に DMSO を用いる条件を第一級アミンに適用した（Table 2.3）。第二級アミンの場合と同様に反応は進行したが、対応するヨードビニルオキサゾリジノンは E 体と Z 体の混合物として収率 86% で得られ、その混合比は 58 : 42 であった（Entry 1）。臭素カチオンやヨウ素カチオンはアルケンやアルキンへの環化付加反応、例えばハロラクトン化反応においてよく用いられる反応剤の一つである。そのため、NIS 由来のヨウ素カチオンによる環化反応が進行し、Z 体の生成物を与え、全体として低い立体選択性として観測されたと考えた。実際、銀触媒を用いない場合にも反応は進行し、E 体と Z 体が 22 : 78 で得られ、Z 体の生成物を優先的に与えることがわかった（Entry 2）。Peng らの報告によれば、アルキンを有するホスホリル酸に対するブロモ環化反応では、ピリジン存在下で 2 種類の三員環ブロモニウム中間体が平衡状態にあり、Z 体の環状化合物を優先的に与える [40]。詳細は明らかではないが、本反応においても、ヨードニウム中間体において 2 つの平衡状態が存在し、熱力学的に安定な Z 体が得られたと考えられる（Scheme 2.6）。この結果より、ヨウ素カチオンによる環化反応が低い立体選択性の原因の一つであると示唆された。

　そこで、筆者は、銀触媒による環化反応を促進すれば、相対的にヨード環化反応が遅くなり、高い選択性で E 体のオキサゾリジノンが得られると考えた。銀の対イオンについて検討したところ、よりカチオン性の高い AgBF$_4$ や AgSbF$_6$ を用いたときに選択性が向上することがわかり、特に AgNO$_3$ の場合に、収率 90%、91 : 9（E : Z）の選択性でオキサゾリジノンが得られた（Entries 4-6）。反応濃度を 0.15 M から 0.05 M にすると、さらに選択性が向上し、収率 94%、95 : 5（E : Z）の高い選択性でオキサゾリジノンが得られることがわかった（Entry 7）。

Table 2.3. Examination of Primary Amines

Entry	Cat.	Y / eq.	Conc. / M	Yield / %[a]	E : Z [b]
1	AgOAc	1.2	0.30	86	58 : 42
2	none	1.2	0.30	79[c]	22 : 78
3	AgOAc	1.0	0.15	95	83 : 17
4	$AgBF_4$	1.0	0.15	93	88 : 12
5	$AgSbF_6$	1.0	0.15	95	88 : 12
6	$AgNO_3$	1.0	0.15	90	91 : 9
7	$AgNO_3$	1.0	0.05	94	95 : 5

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Undesired and unseparated compound was detected by ^{1}H NMR.
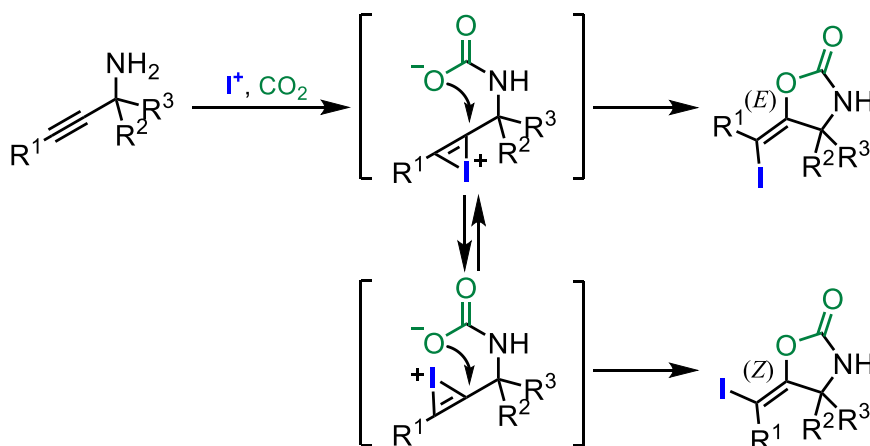
Scheme 2.6. Iodocyclization

　触媒量の硝酸銀、1 当量の NIS、反応濃度を 0.05 M とする反応条件は、電子供与基である *p* - メチル基（**8m**）や電子求引基である *p* - トリフルオロメチル基（**8n**）にも適用可能で、それぞれ *E* : *Z* の比が 96 : 4、97 : 3 と高い選択性で対応するオキサゾリジノン誘導体が得られた（Scheme 2.7）。
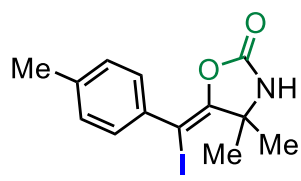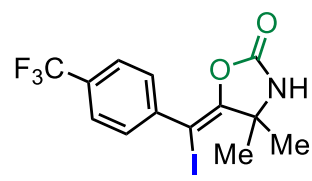
Scheme 2.7. Primary Amines

^{a} 2.0 MPa CO_2.

94%(95:5) (**8l**)

91% (96:4) (**8m**)

98% (97:3)^a (**8n**)

<u>第 3 節　反応に関する考察</u>

　前節で述べたように、第一級プロパルギルアミンを用いた場合に、ヨウ素カチオンによる
ヨード環化反応が確認された。第二級プロパルギルアミンに関しては、オキサゾリジノン誘
導体が *E* 体選択的に得られたことから、ヨード環化反応によるオキサゾリジノンの生成の
可能性は低いと考えられたが、反応に関して考察するため、第二級プロパルギルアミンを用
いて対照実験を行った（Table 2.4）。まず、銀触媒の有無による反応の変化を確認した。酢
酸銀を用いない場合、オキサゾリジノン **8a** が収率 10％で得られ、それとともにイミン **10a**
が収率 20％で得られた（Entry 2）。イミン **10a** はベンジルアミン部位がヨウ素カチオンに
よって酸化されて生成したと考えられる（Scheme 2.8）[41]。ヨウ素カチオン源として、NIS
の代わりにヨウ素を用いたところ、オキサゾリジノン **8a** は得られず、イミン **10a** が収率 5％
で確認されるのみであった（Entry 3）。以上の結果より、本反応において、ヨウ素カチオン
による環化反応が支配的でないと結論付けられる。

Table 2.4. Control Experiments

Entry	Cat.	I$^+$ source	Yields / %[a]		
			8a	**10a**	**7a**
1	AgOAc	NIS	92	trace	0
2	none	NIS	10	20	26
3	none	I$_2$	0	5	71

[a] Isolated yield.
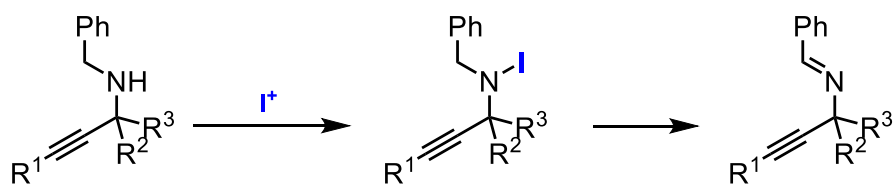
Scheme 2.8. Oxidation of Benzyl Amine by NIS

しかしながら、銀触媒が NIS のカルボニル基に配位子して NIS を活性化することで、ヨウ素カチオンによる環化反応が促進される可能性が考えられた [42]。銀触媒により NIS が活性化されるとすれば、ヨウ素カチオンにより生じるベンジルアミン部位の酸化反応も促進しうると想定された。そこで、プロパルギルアミン **7a** の酸化反応により、NIS の活性化の有無を評価することとした（Table 2.5）。プロパルギルアミン **7a** を NIS 存在下、窒素雰囲気下で 24 時間反応させたところ、イミン **10a** が収率 30%で得られた（Entry 1）。一方で、10 mol%の酢酸銀を加えた条件でも、銀触媒を添加しない場合とほぼ同等の収率 27%でイミン **10a** が得られることがわかった（Entry 2）。この結果より、ベンジルアミン部位の酸化反応は銀触媒により促進されていないことが明らかになった。銀触媒による NIS の活性化によって、プロパルギルアミンへ連続的に二酸化炭素とヨード基が導入される可能性は低いと考えらえる。

Table 2.5. Control Experiments

Entry	Cat.	Yield[a] **10a** / %	**7a** / %
1	none	30	34
2	AgOAc	27	27
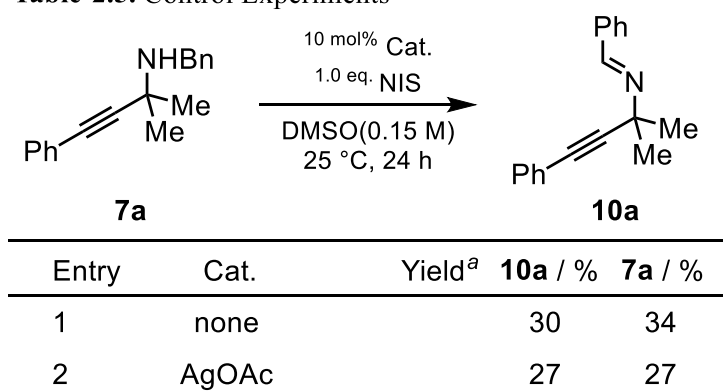
[a] Isolated yield.

次に、オキサゾリジノン **9a** が生成後にヨードビニルオキサゾリジノン **8a** が生成しているか確認した（Scheme 2.9）。報告論文 [16] に従って、プロパルギルアミン **7a** からオキサゾリジノン **9a** を合成し、本反応の最適な反応条件下にさらした。その結果、ヨードビニルオキサゾリジノン **8a** は全く確認されず、出発物質のオキサゾリジノン **9a** がほぼ定量的に得られた。したがって、ヨードビニルオキサゾリジノン **8a** はオキサゾリジノン **9a** から生成していないことがわかった。
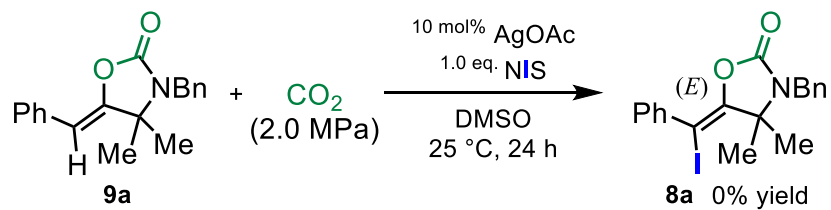
Scheme 2.9. Reaction of **9a** under the Optimized Conditions

　以上の実験により、銀触媒による環化反応後に生成すると考えられるビニル銀中間体がヨウ素カチオンにより立体特異的に捕捉され、*E*体のオキサゾリジノンが得られると示唆される。

第 3 章　銀触媒を用いるアリルケイ素化合物を求核種とする二酸化炭素固定化反応

緒言

　第 1 章では、二酸化炭素を反応剤とする炭素 - 炭素結合形成反応を伴うラクトン誘導体の合成反応について述べた。この反応と同様に、二酸化炭素由来のカルボキシラートがアルキンに対して環化し、ラクトン誘導体が得られる反応が 2 例報告された。2014 年に小林らのグループはアルキン、アライン、二酸化炭素を用いる三成分カップリング反応が銅触媒により進行し、対応するクマリン誘導体が得られることを報告した（Scheme 3.1(a)）[37d]。また、2015 年に Skrydstrup らは適切な位置にアルキンを有するインドール化合物に対して、3 当量の二酸化炭素雰囲気下、触媒量のトリアザビシクロ[4.4.0] - 5 - デセン（TBD）を作用させると、二酸化炭素への求核付加に続く環化付加が進行することを見出した（Scheme 3.1(b)）[20h]。筆者は他の炭素 - 炭素結合形成反応へ展開することを目的として、求核剤として有機ケイ素化合物に注目した。
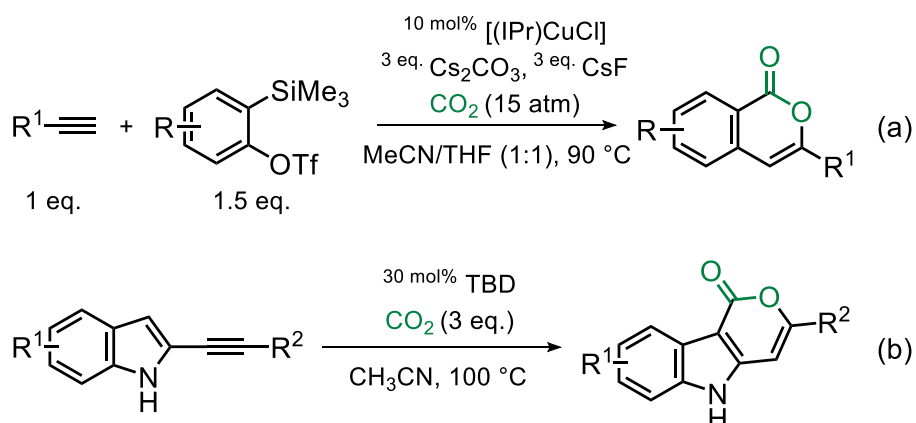
Scheme 3.1. Cyclization Following C-C Bond Fromation with CO_2

　アリルケイ素、アリールケイ素やビニルケイ素などの有機ケイ素化合物は、有機合成上有用な炭素 - 炭素結合形成反応に用いられる反応剤である。例えば、細見 - 櫻井アリル化反応では、Lweis 酸触媒存在下、アリルシラン化合物とアルデヒドあるいはケトン化合物が反応し、対応するホモアリルアルコールが得られる[43]。不斉合成反応にも展開され、天然物化合物の全合成や医薬品合成の分野で広く用いられている。また、ビニルケイ素化合物とハロゲン化アリール化合物とのクロスカップリング反応は、パラジウム触媒存在下、フッ素化物イ

オンによる活性化により促進されることが見出されている[44]。

　有機ケイ素化合物を求核種とする二酸化炭素への付加反応に関する研究は報告されており、対応するカルボン酸誘導体が得られている。例えば、sp³炭素‐ケイ素結合を有する化合物に対して、高温条件が必要であるけれども、二酸化炭素雰囲気下でフッ化物イオンを作用させると対応するカルボン酸誘導体が高い収率で得られる（Scheme 3.2）[45]。また、sp炭素‐ケイ素結合からも対応するカルボン酸が高収率で得られることが報告されている[46]。
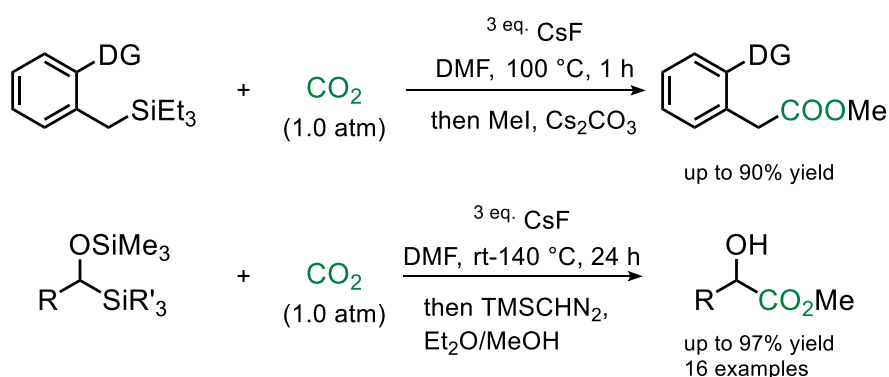
Scheme 3.2. Carboxylation of C(sp³)-SiR₃ Bond

　二酸化炭素、イミン、2‐トリメチルシリルフェニルトリフラートの三成分カップリング反応は、フッ化物イオンによるアライン中間体を経て、対応するベンゾオキサジノンが生成する（Scheme 3.3(a)）[37a]。また、イミンに替えてアミンを用いることでアントラニル酸が得られることが報告されている（Scheme 3.3(b)）[37b]。これらの反応ではアラインが求電子的に働き、求核種が付加した両性イオン中間体が鍵となり、二酸化炭素との反応が進行している。
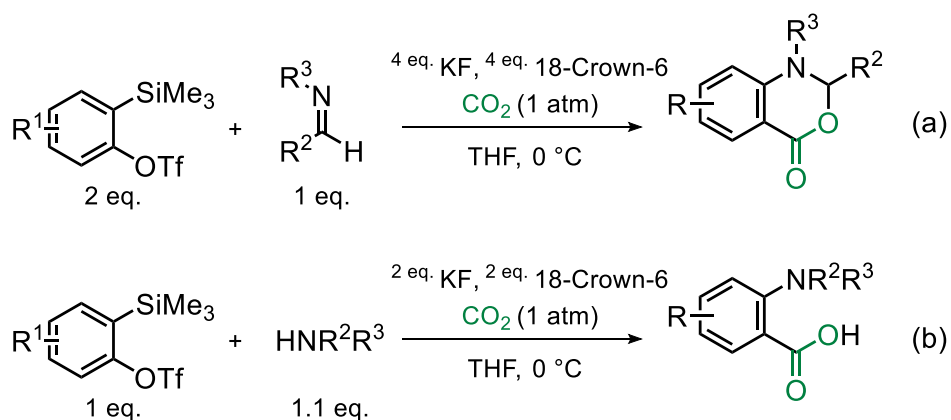
Scheme 3.3. Three-component Reactions Using Aryne Precursor

　一方で、アリルケイ素化合物を求核剤とするカルボキシル化反応に関して、アルミニウム

試薬を用いる反応が報告されているが、化学量論量の金属試薬が必要であるうえに、対応するカルボン酸やラクトン誘導体の生成は低収率にとどまっている（Scheme 3.4(a)）[47]。また、トリメチレンメタンパラジウム錯体を経由する反応が報告されているが、4 例の基質のみであり、収率も中程度であった（Scheme 3.4(b)）[48]。そこで、筆者はアリルケイ素化合物を求核剤とするカルボキシル化とそれに引き続くアルキンへの環化反応の開発に着手した。
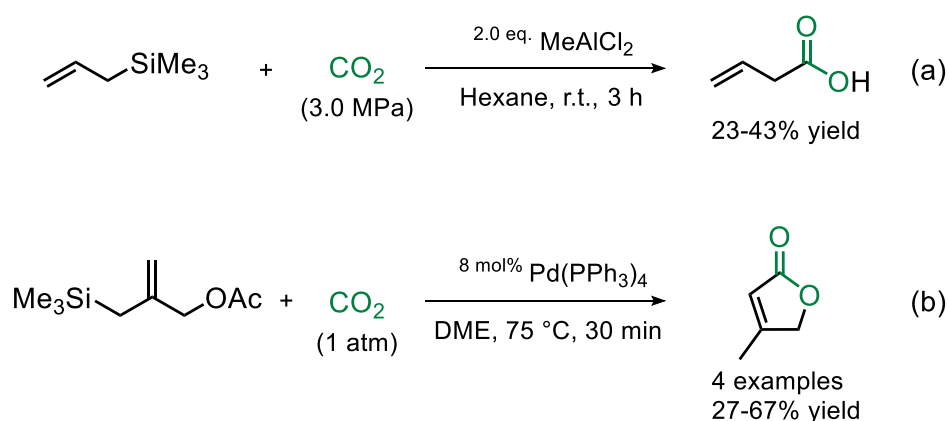
Scheme 3.4. Carboxylation of Allylsilane Compounds

本章では、トリメチル（2 - メチレンブチン）シランを出発物質として、二酸化炭素への求核付加により生成するカルボキシラートが銀触媒により活性化されたアルキンにより捕捉され、5 員環ラクトンあるいは 6 員環ラクトンが得られる反応について述べる（Scheme 3.5）。また、環化過程における位置選択性について考察する。
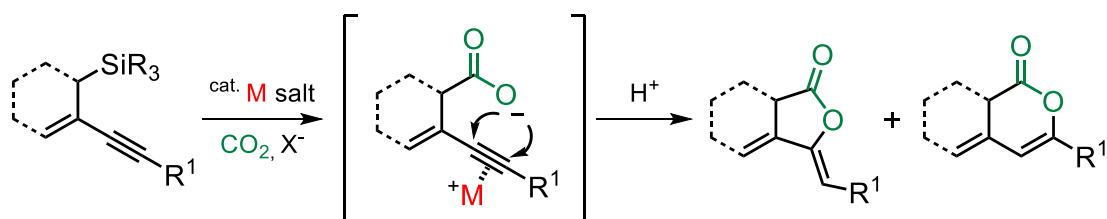
Scheme 3.5. Postulated Reaction Pathway

第1節　反応条件の最適化

　細見‐櫻井アリル化反応では、カルボアニオン等価体が活性種であることが示唆されている。強力なケイ素‐フッ素結合あるいはシラン‐酸素結合形成が駆動力となり、ケイ素‐炭素結合の解裂ともにカルボアニオン等価体が生成する。求核種の生成が必須であることから、適切なフッ素源を探索した。トリメチル（2‐メチレン‐4‐フェニルブチ‐3‐ニル）シラン（**11a**）を出発物質として、1.0 MPa の二酸化炭素雰囲気下、10 mol%のトリフラート銀、1.2 当量のメタノールを用いて、種々のフッ素源を検討した（Table 3.1）。想定反応機構から触媒サイクルを回すためにプロトン源が必須であり、メタノールをプロトン源として加えた。フッ化リチウムとフッ化ナトリウムを用いた場合は、目的の生成物は全く得られず、原料が定量的に回収された（Entries 1 and 2）。フッ化カリウムを用いたところ、目的の反応が進行し、対応する 2‐フラノン **12a** および 2‐ピロン **13a** が合わせて収率 28%、87：13 の割合で得られた（Entry 3）。フッ化カリウムの DMF への溶解度を考慮して、18‐クラウン‐6‐エーテルをフッ化カリウムと併せ用いると、期待通り収率が向上し、フラノンとピロンが収率 78%、70：30 の割合で得られた（Entry 4）。より溶解性が高いフッ化セシウムを用いると、収率 79%、88：12 の割合でフラノンとピロンが得られることがわかった（Entry 5）。化学量論量以上のフッ化銀を用いた場合、目的の反応は進行しなかった（Entry 6）。比較的湿気に強いフッ素アニオン源であるテトラブチルアンモニウムジフルオロトリフェニルシリカート（TBAT）を用いると収率 73%、81：19 の割合で生成物が得られた（Entry 7）。ケイ素‐酸素結合形成によるカルボアニオン等価体の生成を期待して、ナトリウムメトキシドを用いたが、痕跡量の生成物を与えるのみであった（Entry 8）。以上の結果より、収率と選択性の高かったフッ化セシウムを最適なフッ素化物イオン源とした。

CO$_2$ (1.0 MPa)
10 mol% AgOTf
1.5 eq. Activator
1.2 eq. MeOH
DMF, 50 °C

Me$_3$Si — ... — Ph   **11a**   →   **12a**   **13a**
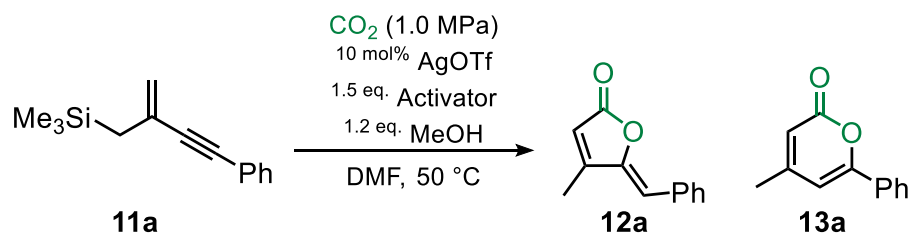
Entry[a]	Activator	Time / h	Yield **12 + 13 (12:13)**[d] / %[b]	**11** / %[c]
1	LiF	24	0	>99
2	NaF	24	0	>99
3	KF	12	28 (87:13)	57
4	KF, 18-crown-6	12	78 (70:30)	<1
5	CsF	12	79 (88:12)	1
6[e]	AgF	36	0	>99
7	TBAT	12	73 (81:19)	<1
8	NaOMe	12	trace	96

a) The reaction was carried out with 0.15 mmol of substrate. b) Isolated yield.
c) GC yield. d) Determined by ^{1}H NMR. e) Without AgOTf.

　カルボキシラートが炭素－炭素三重結合に対して環化する過程が、収率および選択性に影響を及ぼしていると考えられ、π－Lweis 酸としてアルキンの活性化に大きく寄与している金属触媒を検討した（Table 3.2）。金属塩を用いない場合やヨウ化銅を用いた場合、目的のラクトン誘導体が痕跡量のみ得られた（Entries 1 and 2）。トリメチルシリルジアゾメタンによるメチル化を行うと、メチルエステル **14a** がそれぞれの場合に収率 54%、63% で得られることがわかった。金属触媒が存在しない場合でも、二酸化炭素への求核付加反応は進行しカルボキシラートは生成するが、カルボキシラートの環化反応がほとんど進行していないことがわかった。クロロ（トリフェニルホスフィン）金を用いると、収率 17% と低収率であったものの、95：5 の高い選択性でフラノン **12a** とピロン **13a** が得られた（Entry 3）。酢酸パラジウムの場合、収率 49%、89：11 の割合で対応するラクトン誘導体が得られた（Entry 4）。一方で、銀触媒を用いると良好な収率で目的生成物を与えた（Entries 5-13）。塩化銀（Ⅰ）を用いた場合、収率 77%、81：19 の割合でフラノン **12a** とピロン **13a** が得られた。なかでも、銀カルベン錯体は良好な収率とフラノンへの高い選択性を示した

（Entries 10-13）。1,3‐ビス（2,6‐ジイソプロピルビフェニル）イミダゾール‐2‐イリデン（IPr）を配位子とする(IPr)AgCl を用いた場合には、収率80%、94：6 の高い選択性でフラノン **12a** が得られることがわかった。

Table 3.2. Examination of Various Metal Salts

Entry[a]	MX	Yield[b] **12 + 13** / %	**12 : 13**[c]
1	none	trace[d]	—
2	CuI	trace[e]	—
3	(PPh$_3$)AuCl	17	95: 5
4	Pd(OAc)$_2$	49	89:11
5	AgF	70	77:23
6	AgCl	77	81:19
7	AgOTf	79	88:12
8	AgOAc	73	89:11
9	AgBF$_4$	73	91: 9
10	(SIMes)AgCl	83	91: 9
11	(IMes)AgCl	80	93: 7
12	(SIPr)AgCl	83	93: 7
13	(IPr)AgCl	80	94: 6
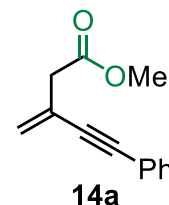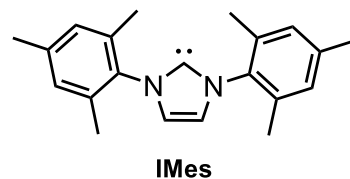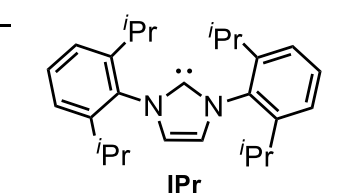
a) The reaction was carried out with 0.15 mmol of substrate. b) Isolated yield.
c) Determined by ^{1}H NMR. d) **14a** was obtained in 54% yield after methylation.
e) **14a** was produced in 63% yield after methylation.

さらなる位置選択性向上を目指して反応温度の検討を行った結果、反応温度の低下とともに生成物の選択性が向上することがわかった（Table 3.3）。20℃、30℃の条件下では98：2 の高い選択性でフラノン **12a** とピロン **13a** が得られたものの、反応は完結せず未反応の出発物質 **11a** が残った（Entries 1 and 2）。40℃、24 時間の条件では、反応が完結し、収率78%、97：3 の選択性でフラノン **12a** とピロン **13a** が得られた（Entry 4）。50℃および60℃では選択性の低下がみられた（Entries 5 and 6）。温度検討の結果より、40℃、24 時間の条件を最適とした。

二酸化炭素への求核付加反応を十分に促すための二酸化炭素の圧力を調べた（Table 3.4）

二酸化炭素圧力の低下に伴い、カルボアニオン等価体がメタノール由来であるプロトンを捕捉して生成したと考えられる（3‐メチルブチ‐3‐エン‐1‐イン‐1‐イル）ベンゼン（**15a**）の収率が増加することがわかった。実際、0.2 MPa 二酸化炭素雰囲気下ではフラノン **12a** とピロン **13a** が合わせて収率35％で得られ、化合物 **15a** が収率35％で得られた（Entry 1）。カルボアニオン等価体が優先して二酸化炭素と反応するには、少なくとも 0.5 MPa 二酸化炭素が必要であり、1.0 MPa の二酸化炭素雰囲気下で、最もよい収率を示した。

Table 3.3. Examination of Reaction Temperatures

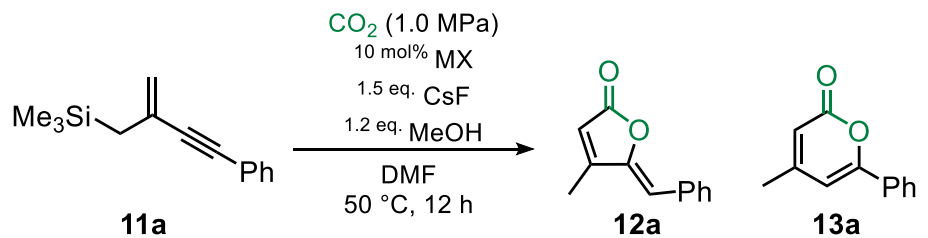| Entry[a]	Temp. / °C	Time / h	12 + 13 (12:13)[d] / %[b]	11 / %[c]
			Yields	
1	20	48	50 (98:2)	14
2	30	24	69 (98:2)	5
3	40	12	71 (97:3)	<1
4	40	24	78 (97:3)	<1
5	50	12	80 (94:6)	<1
6	60	12	80 (93:7)	<1

a) The reaction was carried out with 0.15 mmol of substrate. b) Isolated yield.
c) GC yield. d) Determined by ^{1}H NMR.

Table 3.4. Examination of CO_2 Pressure
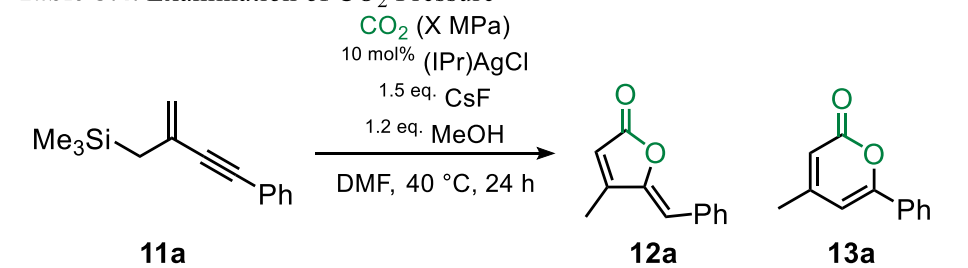

Entry[a]	X	12 + 13 (12:13)[d] / %[b]	11 / %[c]	15 / %[c]
		Yields		
1	0.2	35 (96:4)	<1	35
2	0.5	74 (96:4)	<1	8
3	1.0	78 (97:3)	<1	5
4	2.0	77 (98:2)	1	3

a) The reaction was carried out with 0.15 mmol of substrate.
b) Isolated yield. c) GC yield. d) Determined by ^{1}H NMR.

15a
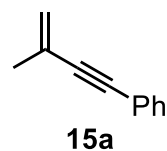
第 2 節　基質適用範囲

　最適化した反応条件を種々の出発物質に対して適用した（Table 3.5）。まず、アルキン末端の芳香環上の置換基を検討した。電子供与基はピロン **13a** の生成を促進することがわかった。*p*‐メチル基（**11b**）、*m*‐メチル基（**11c**）、*p*‐メトキシ基（**11e**）が置換した基質の場合、対応するフラノン **12** およびピロン **13** が 94：6、95：5、88：12 の割合で得られた（Entries 2, 3 and 5）。*o*‐メチル基の場合、反応温度を 50℃にすると収率が向上し、対応するフラノン **12d** およびピロン **13d** がそれぞれ収率 43%、29%で得られた（Entry 4）。オルト位のメチル基により銀イオンの接近が妨げられているため、高温や長い反応時間が必要であると考えられる。一方、*p*‐エトキシカルボニル基（**11f**）、*p*‐アセチル基（**11g**）、*p*‐シアノ基（**11h**）や *p*‐トリフルオロメチル基（**11i**）といった電子求引基が置換した芳香環の場合、ピロン誘導体は観測されず、フラノン誘導体のみが選択的に得られることがわかった（Entries 6-9）。位置異性体である 1‐ナフチル基（**11j**）と 2‐ナフチル基（**11k**）の場合、収率と選択性に大きな影響を与えることわかった。1‐ナフチル基の場合、対応するフラノン **12j** とピロン **13j** がそれぞれ収率 18%および 15%で得られた（Entry 10）。一方、2‐ナフチル基の場合、フラノン **12k** が収率 80%で選択的に得られた（Entry 11）。*p*‐メチル基、*m*‐メチル基、*o*‐メチル基、1‐ナフチル基、2‐ナフチル基に対する位置選択性の違いは、オルト位の置換基の立体反発によるものと考えられる。すなわち、オルト位の立体反発により銀イオンが 5‐エキソ環化に適した位置を占めることができず、6‐エンド環化が進行しピロンが生成したと考えられる（Figure 3.1）。また、2‐ピリジル基が置換した出発物質の場合、フラノン **12l** のみが収率 73%で得られた（Entry 12）。

　一方、アルキル鎖が置換したアルキンをもつ基質にも適用可能であることがわかった。興味深いことに、*n*‐ブチル基（**11m**）や 1‐フェニルエチル基（**11n**）の場合、6 員環のピロン誘導体が選択的に得られ、収率はそれぞれ 77%、65%であった（Entries 13 and 14）。*t*‐ブチル基（**11o**）の場合も、ピロン **13o** がフラノン **12o** より優位に得られることがわかった（Entry 15）。アルキル鎖が置
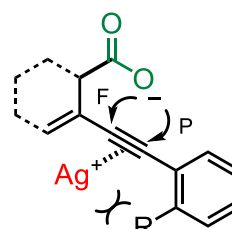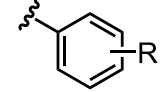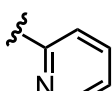
Figure 3.1.

換した基質におけるピロンへの選択性は、アルキル鎖のもつ電子供与性に起因していると考えられる。これは電子供与基であるメチル基やメトキシ基が置換した芳香環の場合と同様の傾向を示している。

Table 3.5. Silver-catalyzed Cyclization of Various Substrates

Entry[a]	Substrate		12 / %	13 / %	(12 : 13)[c]
1	R = aryl-R^1	R^1 = H(**11a**)	78	trace	
2		p-Me(**11b**)	76	5	(94: 6)
3		m-Me(**11c**)	78	4	(95: 5)
4[d,e]		o-Me(**11d**)	43	29	(60:40)
5		p-OMe(**11e**)	66	9	(88:12)
6[d]		p-COOEt(**11f**)	74	ND[f]	
7		p-Ac(**11g**)	72	ND[f]	
8		p-CN(**11h**)	92	ND[f]	
9		p-CF$_3$(**11i**)	78	ND[f]	
10	R = 1-naphthyl (**11j**)		18	15	(56:44)
11	2-naphthyl (**11k**)		80	trace	
12	pyridine (**11l**)		73	ND[f]	
13[d]	^{n}Bu (**11m**)		ND[f]	77	
14[d,g]	CH$_2$CH$_2$Ph (**11n**)		ND[f]	65	
15[d]	^{t}Bu (**11o**)		14	43	(25:75)

a) The reaction was carried out with 0.15 mmol of substrate in 1.5 mL of DMF.
b) Isolated yield. c) The ratio was calculated based on isolated yields.
d) 50 °C. e) 20 mol% (IPr)AgCl was employed. 48 h. f) Not detected. g) Using AgOTf instead of (IPr)AgCl.

　シランの α 位に置換基をもつ基質 **11p** に対して最適化した反応条件を適用したが、目的生成物を痕跡量与えるのみであった。反応温度を上げると、反応が進行し、60℃の条件下では、フラノン **12p** とピロン **13p** がそれぞれ収率 52%、11%で得られることがわかった（Scheme 3.6）。

Scheme 3.6. Cyclohexyl Substrate
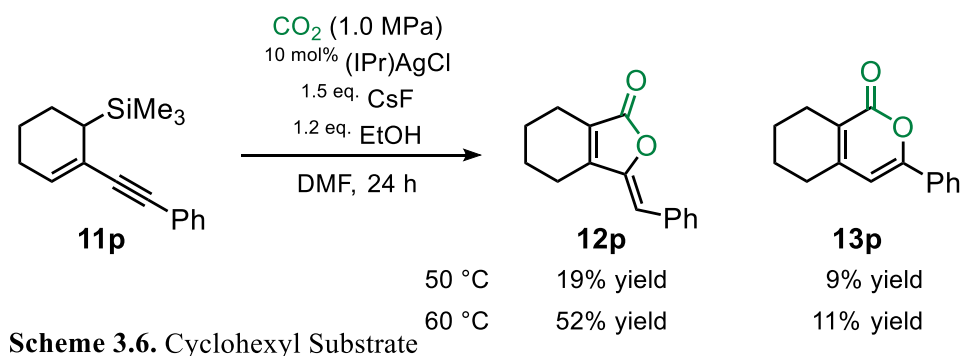
5 員環のフラノンと 6 員環のピロンは HMQC（Heteronuclear Multiple Quantum Coherence）および HMBC（Heteronuclear Multiple Bond Coherence）を用いて識別した。HMBC はあるプロトンに対して、3 結合以内にある炭素との相関を示す二次元 NMR である。HMBC スペクトルの相違点として考えられるのは、ビニル位のプロトン H_b とメチル基の C^1 炭素との相関である。すなわち、フラノンでは H_b と C^1 の相関は観測されないが、ピロンでは相関が観測されると想定した。^{13}C NMR スペクトルにおいて 5 員環のフラノンでは、メチル基の C^1 炭素は δ 12.0 に観測され、6 員環のピロンでは C^1 炭素は δ 21.6 に表れた。実際に、モデル基質 **11a** 由来の 2 つの生成物の HMBC を測定した結果、想定通りにフラノンでは H_b と C^1 の相関は確認されなかったのに対して、ピロンでは対応する相関関係が観測された（Figure 3.2）。
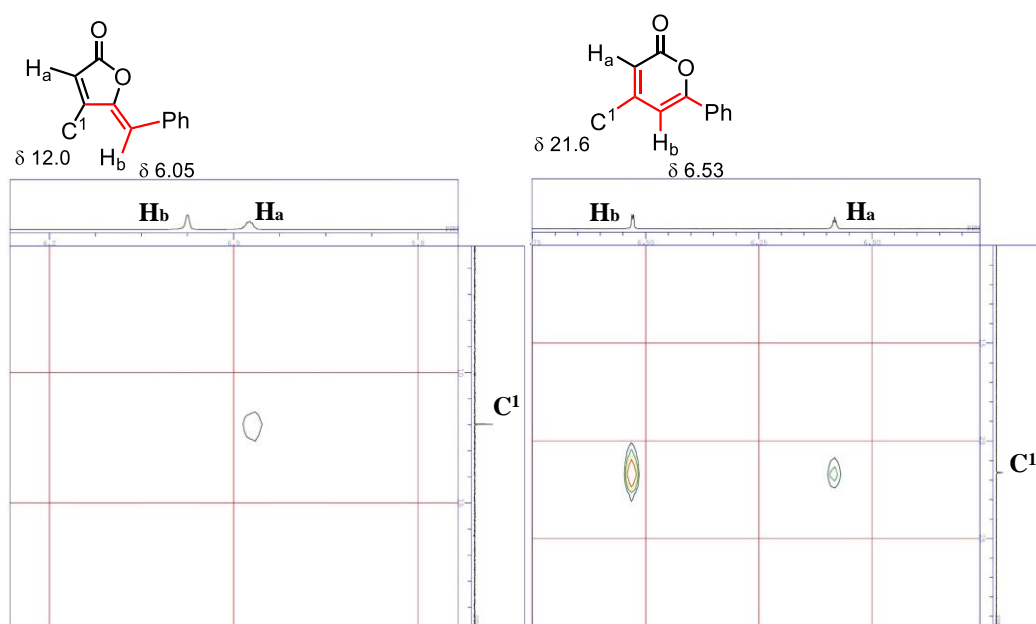
Figure 3.2. HMBC of **12a** and **13a**.

アルキン末端の芳香環上に *o* - メチル基を導入した基質 **11d** の場合にも、生成物 **12d** と **13d** では基質 **11a** の場合と同様の HMBC 相関が観測された。すなわち、フラノンでは H_b と C^1 の相関がみられなかったのに対して、ピロンでは H_b と C^1 の相関が確認された（Figure 3.3）。さらに、フラノンに関しては単結晶が得られたので、X 線結晶構造解析をしたところ、確かに 5 員環のラクトン構造を有しており、HMBC により推定した構造と一致することがわかった（Figure 3.4）[49]。また、得られたフラノンのエキソオレフィンに関する幾何異性は *Z* 体であることが X 線結晶構造解析により決定された。
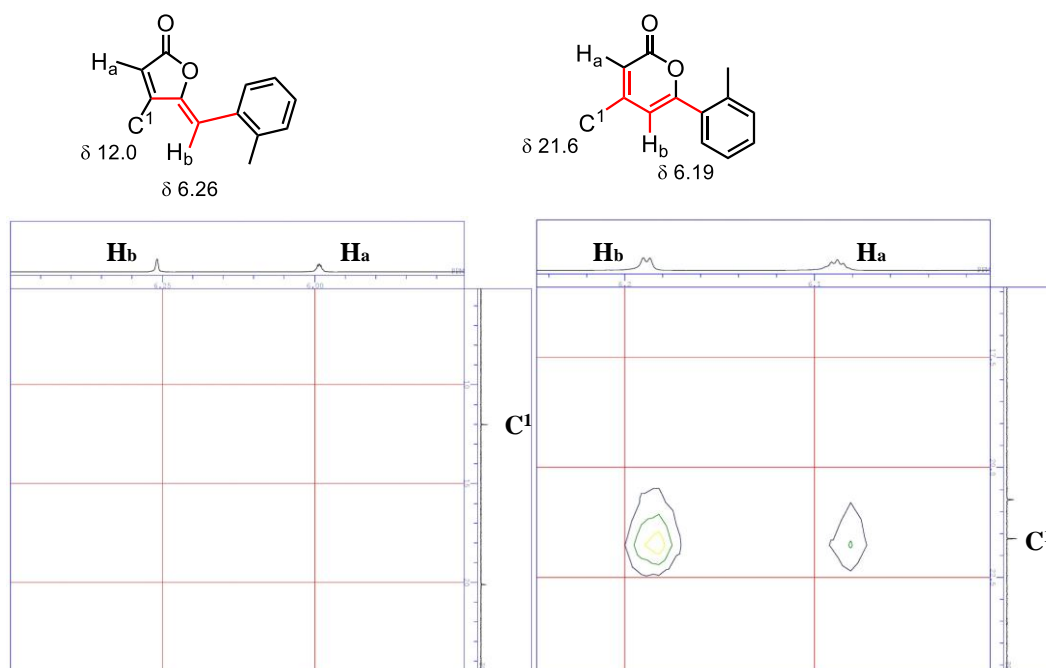
Figure 3.3. HMBC of **12d** and **13d**.
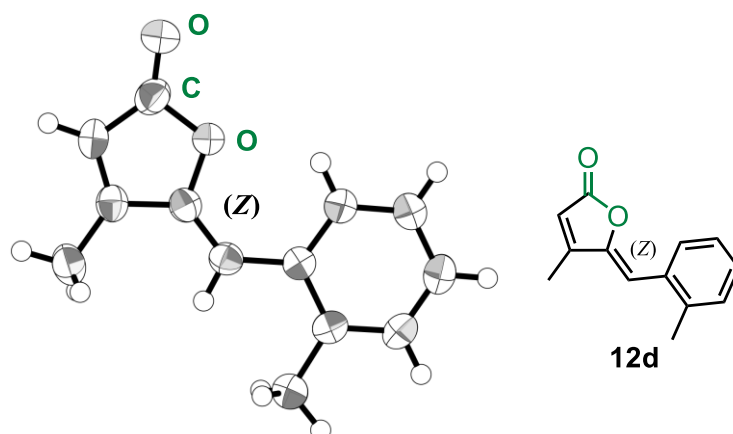
Figure 3.4. The structure of **12d**.

第3節　反応機構に関する考察

　求核種に関する知見を得るため、三置換オレフィン部位をもつ出発物質を用いて検討を行った。カルボニル化合物存在下、アリルシランにフッ化セシウムを作用させると、ホモアリルアルコールが得られることが報告されている。ケイ素－フッ素結合形成を駆動力として、カルボアニオン等価体が生成することが示唆されている。3置換オレフィンをもつアリルシランを出発物質として用いた場合、置換基の少ない側から求核付加反応が進行し、反応前後で出発物質の位置選択性が失われるため、共鳴構造をもつカルボアニオン等価体が求核種として存在していると結論付けている（Scheme 3.7）[43c]。
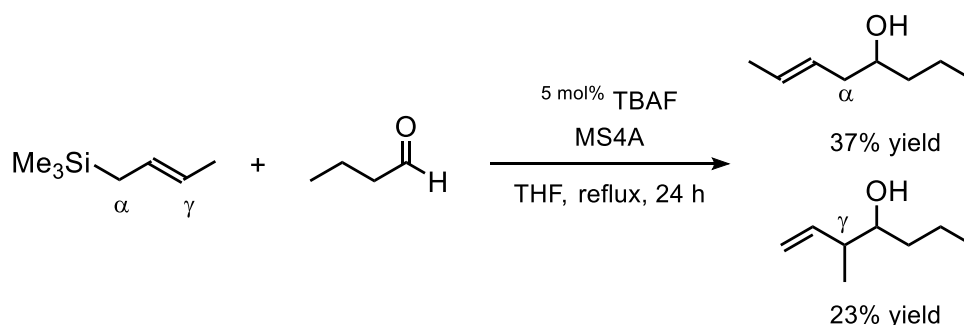
Scheme 3.7. Allylation with Alkyl-substituted Allylsilane

　本反応におけるカルボアニオン等価体の存在を確認するために以下の実験を行った。3置換オレフィン部位をもつ化合物 **11q** を出発物質とすれば、トリメチルシリル基のα位あるいはγ位から二酸化炭素へ求核付加を起こし、カルボキシラートがアルキンに捕捉されてフラノンおよびピロンが生成し、計4種類の異性体が得られると想定した。実際に、下記の反応条件に化合物 **11q** をさらしたところ、3つの異性体 **12q-γ**、**12q-α**、**13q-α**が得られた。α位からの求核攻撃により生成する化合物が確認されたことから、カルボアニオン等価体が反応途中で生成し、二酸化炭素へ求核付加していることが示唆された（Scheme 3.8）。
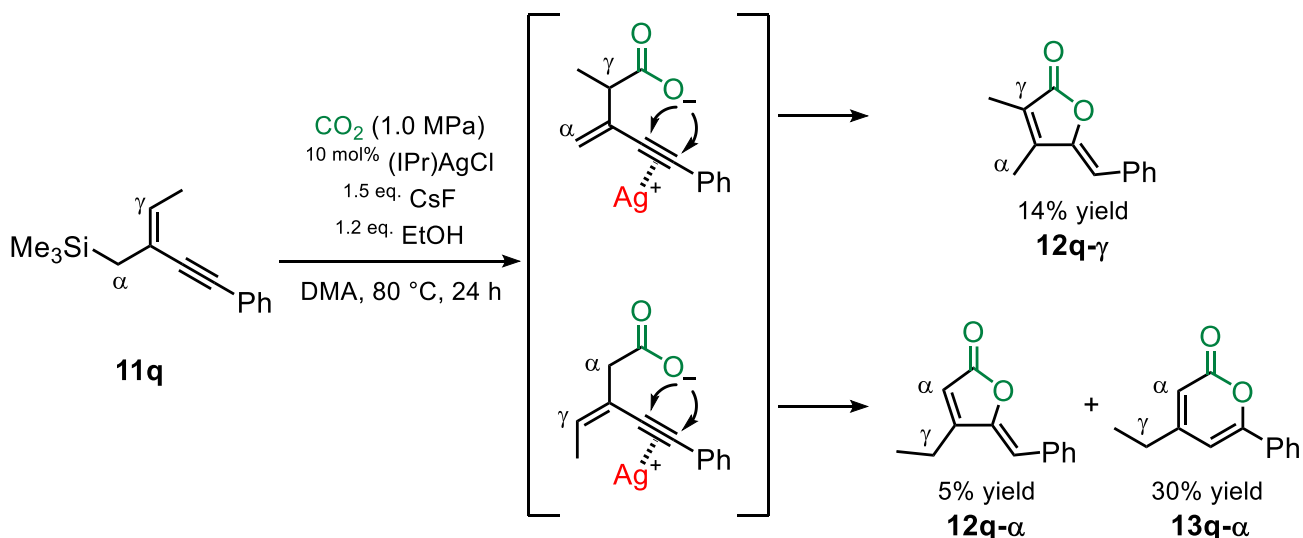
Scheme 3.8. Carboxylation with Alkyl-substituted Allylsilane **11q**

　以下のような反応機構であると推定した。強いシラン‐フッ素結合形成を足掛かりとして、カルボアニオン等価体が生成する。次に、二酸化炭素への求核付加反応によりカルボキシラートが生成する。カルボキシラートが、銀触媒により活性化されたアルキンにより、立体選択的に捕捉される。それに引き続き、メタノールとのプロトン交換により、ラクトンが生成したのち、異性化を経てフラノンおよびピロンが得られると考えられる（Scheme 3. 9）。
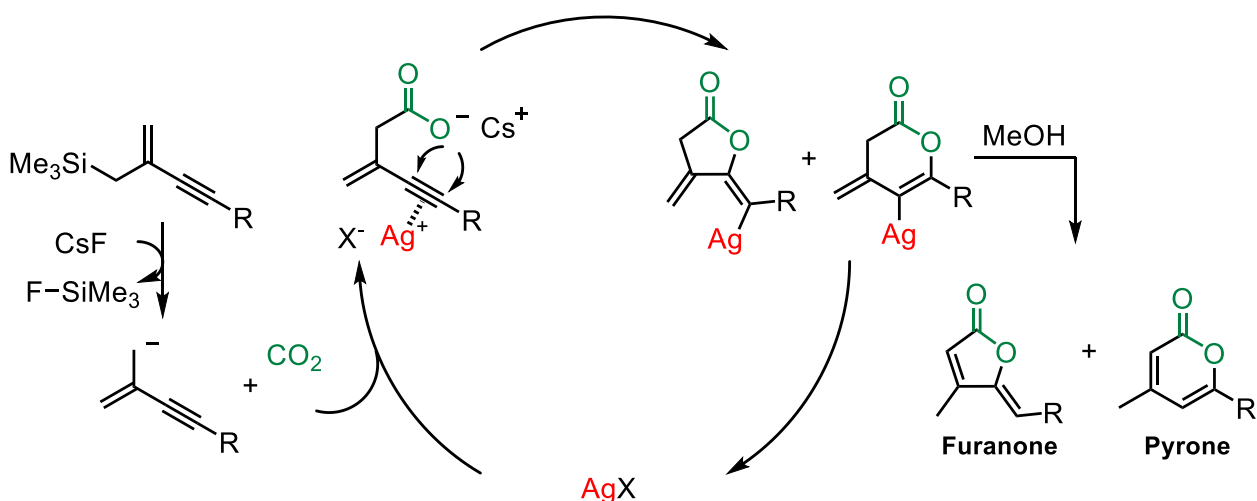
Scheme 3.9. Proposed Reaction Mechanism

　本反応では、第 1 章および第 2 章で述べた反応とは異なり、カルボキシラートのアルキンへの環化反応過程において、5‐エキソ環化および 6‐エンド環化の位置選択性が生じ、5 員環の 2‐フラノンおよび 6 員環の 2‐ピロンが生成した。基質適用範囲の検討結果から、アルキン末端に電子求引基を有する芳香環が置換した場合、フラノンが優先的に得られた一

方で、電子供与基を有する芳香環が置換した場合はピロンの生成比が増加し、アルキン末端にアルキル鎖が置換した場合にピロンが優先的に得られた。位置選択性がアルキン末端の置換基の電子効果に強く影響を受けることから、出発物質のアルキンの電子状態と位置選択性に相関があると考え、炭素 - 炭素三重結合の 2 つの炭素の ^{13}C NMR の化学シフト値に注目した。^{13}C NMR では、炭素上の電子密度と化学シフト値に直接的な相関関係があるので、電荷状態を評価するための手段の一つとなる。6 つの出発物質（**11a, 11b, 11e, 11h, 11m, 11n**）のアルキン炭素の化学シフト値とそれらの差（$\Delta\delta = \delta C^5 - \delta C^6$）および生成物の生成比を Figure 3.4 に示した。3 つの出発物質 **11a**、**11b**、**11e** について、アルキンの二つの炭素（C^5, C^6）の化学シフト値の差$\Delta\delta$と位置選択性との関係に注目すると、$\Delta\delta$が小さくなるにつれてピロンの生成が増加することがわかった。また、出発物質 **11a, 11b, 11e, 11h** では 5 員環のフラノンが優先的に得られ、出発物質（**11m, 11n**）ではピロンが優先的に得られたことから、δC^5 と δC^6 の大小が逆転すると生成物の生成比も逆転することがわかった。出発物質（**11a-11o**）に関して縦軸を位置選択性、横軸を$\Delta\delta$としたグラフ（Figure 3.5）からも同様の傾向があることがわかった。傾向から大きく外れている *o* - トリル基（**11d**）と 1 - ナフチル基（**11j**）が置換した基質に関しては、置換基による立体反発が強く反映され、6 - エンド環化反応によりピロンの生成が増加したと考えられる。以上の考察から、位置選択性が出発物質のアルキンの電子状態の違いに起因していることが示唆される。

$\Delta\delta = 3.1$

Me₃Si... δ 88.4 / δ 91.5 C≡C—phenyl

11a   97:3

$\Delta\delta = 9.2$

Me₃Si... δ 86.7 / δ 95.9 C≡C—Ar(CN)

11h   100:0

$\Delta\delta = 2.3$

Me₃Si... δ 88.6 / δ 90.9 C≡C—Ar(CH₃)

11b   94:6

$\Delta\delta = 1.8$

Me₃Si... δ 88.4 / δ 90.2 C≡C—Ar(OMe)

11e   88:12

$\Delta\delta = -6.8$

Me₃Si... δ 89.4 / δ 82.6 C≡C—butyl

11m   0:100

$\Delta\delta = -5.1$

Me₃Si... δ 88.4 / δ 83.3 C≡C—CH₂CH₂Ph

11n   0:100

Me₃Si... $C^5 \equiv C^6$—Ar

5-membered:6-membered, $\Delta\delta = \delta C^5 - \delta C^6$
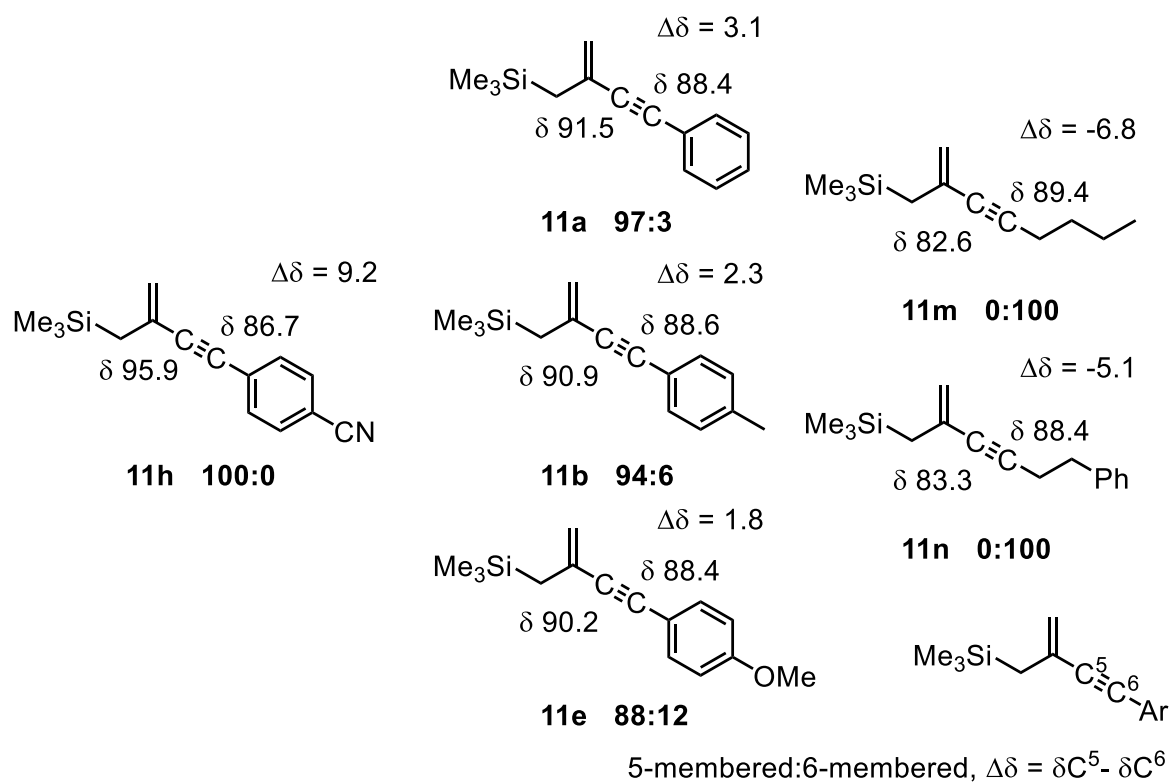
Figure 3.4. Consideration of Regioselectivity
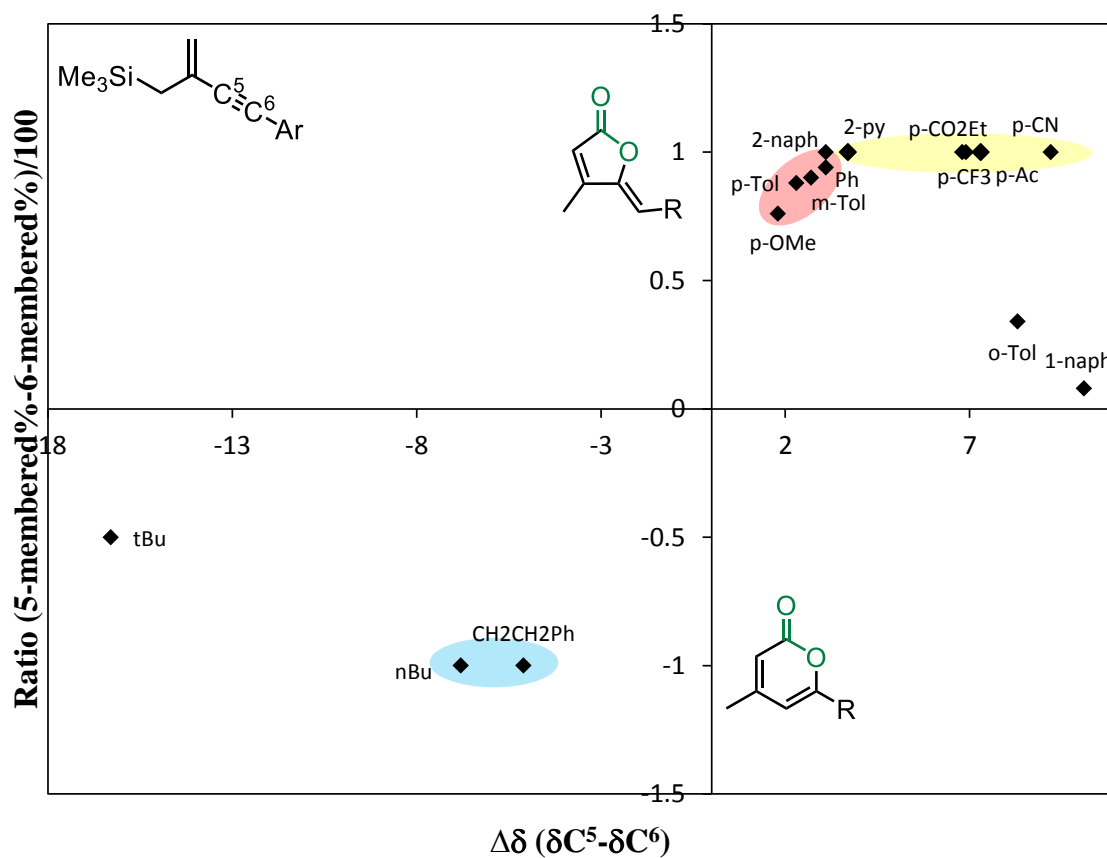
Figure 3.5. Correlation of Δδ and regioselectivity.

<u>総括</u>

　本論文では、銀触媒によるアルキンの活性化を基軸とする二酸化炭素との炭素‐炭素結合形成反応に引き続く環化反応およびプロパルギルアミンへの二酸化炭素と官能基の連続的導入反応について報告した。

　第1章では、エノラートを求核剤としてラクトン誘導体およびジヒドロイソベンゾフラン誘導体の合成反応について述べた。筆者は、熱的に不安定な β ‐ケトカルボン酸をアルキンへの環化反応を連続させれば、より安定なラクトン誘導体へワンポットで誘導できると考えた。反応条件を検討した結果、触媒量の安息香酸銀、塩基に7‐メチル‐トリアザビシクロ[4.4.0]‐5‐デカエンを用いると、目的とする反応が種々の基質に対して円滑に進行し、対応する5員環ラクトンが高収率で得られることを見出した。また、^{13}C NMR による実験から、銀触媒はアルキンを活性化するだけではなく、カルボニル基を活性化する Lweis 酸としても機能していることが示唆された（第1節）。上述の反応において脂肪族ケトンを用いた場合、副生成物としてカルボキシル基を有するフラン誘導体が得られることがわかった。フラン誘導体の生成機構の考察から、オルト位にアルキンをもつアセトフェノンを出発原料とすれば、カルボキシル基をもつジヒドロイソベンゾフラン誘導体が得られると想定した。二酸化炭素雰囲気下、触媒量の酢酸銀と1,8‐ジアザビシクロ[5.4.0]‐7‐ウンデセンを作用させると、カルボキシル基をもつジヒドロイソベンゾフランが高収率で生成することを明らかにした（第2節）。

　第2章では、銀触媒によるプロパルギルアミンへの二酸化炭素とヨード基の連続的導入反応について述べた。この反応では、カーバメートの環化反応後に生成するビニル銀中間体がヨウ素カチオンにより捕捉され、(*E*)‐ヨードビニルオキサゾリジノンが得られると期待した。最適化した反応条件は、様々な第一級および第二級アミンに対して適用可能であることを示した。

　第3章では、アリル位にトリメチルシリル基をもつ共役エンイン化合物を出発原料として、カルボアニオン等価体の二酸化炭素への求核付加により生成するカルボキシラートが銀触

媒により活性化されたアルキンにより捕捉され、5員環の 2‐フラノンおよび 6員環の 2‐ピロンが得られる反応について述べた。アルキン末端の置換基により生成物の選択性が変化し、芳香環置換の場合は 2‐フラノンに高い選択性を示し、アルキル置換の場合は 2‐ピロンが優先的に得られることを明らかにした。この位置選択性は出発原料のアルキン炭素の電子状態に由来すると考えられる。

実験の部

1. 測定装置

核磁気共鳴スペクトル（NMR）：ECX-400, JEOL AL-400 または Alpha-400

ESI 質量分析（ESI-MS）：Waters LCT Premier XE

赤外吸収スペクトル（IR）：JASCO FT/IR-410

融点測定：Stanford Research Systems MPA100

2. クロマトグラフィー

薄層クロマトグラフィー（TLC）：Merck 社（silica gel 60 F254）

カラムクロマトグラフィー：関東化学社（silica gel 60N）

3. 二酸化炭素ガス

二酸化炭素は、東横化学社から純度 99.9%の液化二酸化炭素を購入してそのまま用いた。
なお、本論文では二酸化炭素のゲージ圧を示した。

4. 銀触媒によるエノラートを求核種とする二酸化炭素固定化反応（第 1 章）

4-1. 溶媒

テトラヒドロフランおよびジクロロメタンは関東化学社から購入した有機合成用安定化
剤無添加脱水溶媒をそのまま用いた（製品番号：THF 41001-85, CH$_2$Cl$_2$ 11338-85）。アセ
トニトリル、*N, N* - ジメチルホルムアミドおよびジメチルスルホキシドは和光純薬社から
購入した有機合成用脱水溶媒をそのまま用いた（製品番号：CH$_3$CN 018-22901, DMF
046-26023, DMSO 041-25473）。

4-2. 試薬

安息香酸銀は関東化学社から購入した市販品をそのまま用いた（製品番号：37001-31）。
トリアザビシクロ[4.4.0] - 5 - デセン（TBD）は Aldrich 社（製品番号：345571）、7 - メチ
ル - トリアザビシクロ[4.4.0] - 5 - デセン（MTBD）は東京化成工業社（製品番号：M1443）
から購入した市販品をそのまま用いた。

4-3. 出発原料 1 の合成 [50]
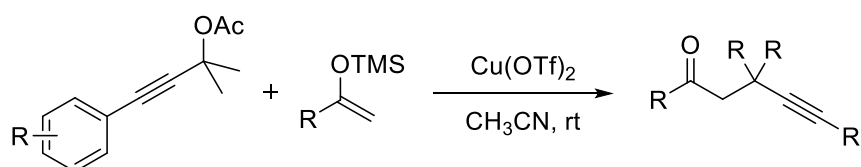
Under nitrogen, a solution of silyl enol ether (10 mmol) and propargylic acetate (5 mmol) in
MeCN (8 mL)was added to a solution of Cu(OTf)$_2$ (2 mol%) in MeCN (2 mL) at room temperature.
After 1 day, the solvent was evaporated under reduced pressure and the residue was purified by
column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the desired starting material **1**.

4-4. 出発原料 1 の化合物データ

3,3-Dimethyl-1,5-diphenyl-4-pentyne-1-one (1a)
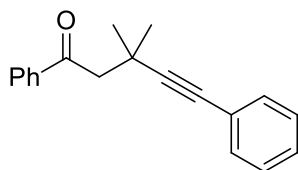
Colorless solid; m.p. 46 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.49 (s, 6H), 3.18 (s, 2H), 7.13-7.21 (m, 5H), 7.43-7.47 (m, 2H), 7.52-7.56 (m, 1H), 8.01-8.03 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 30.7, 49.4, 81.3, 96.1, 123.5, 127.5, 128.0, 128.4, 128.6, 131.4, 132.8, 138.0, 198.4; IR (KBr): 2968, 2867, 1687, 1596, 1581, 1488, 1360, 1241, 1217, 1183, 915, 754, 692; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{19}$O$^+$, 263.1436; found, m/z 263.1434.

3,3-Dimethyl-1-phenyl-5-(4-methylphenyl)-4-pentyne-1-one (1b)
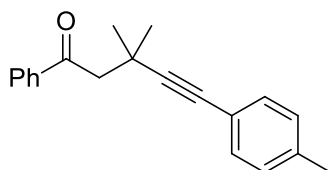
Pale yellow solid; m.p. 62 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.48 (s, 6H), 2.29 (s, 3H), 3.17 (s, 2H), 7.01 (dd, J = 14.6 Hz, 8.3 Hz, 4H), 7.44 (t, J = 7.6 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 8.02 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 29.7, 30.7, 49.5, 81.3, 95.3, 120.4, 128.4, 128.6, 128.7, 131.3, 132.8, 137.5, 138.0, 198.5; IR (KBr): 2966, 2920, 1670, 1598, 1471, 1448, 1359, 1305, 1219, 756, 692; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$O$^+$, 277.1592; found, m/z 277.1592.

3,3-Dimethyl-5-(3-methoxyphenyl)-1-phenyl-4-pentyne-1-one (1c)
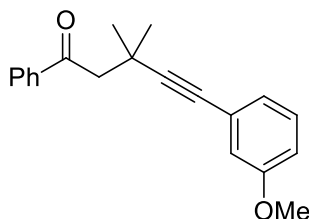
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.49 (s, 6H), 3.18 (s, 2H), 3.73 (s, 3H), 6.67 (t, J = 2.4 Hz, 1H), 6.76 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.53 (t, J = 6.4 Hz, 1H), 8.02 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 30.7, 49.4, 55.2, 81.2, 95.8, 114.4, 116.1, 124.1, 128.4, 128.6, 129.0, 132.8, 138.0, 159.2, 198.3; IR (KBr): 2969, 2937, 1713, 1676, 1693, 1449, 1429, 1356, 1319, 1283, 1178, 1021, 1045, 860, 786, 752, 689; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$O$_2^+$, 293.1542; found, m/z 293.1542.

3,3-Dimethyl-5-(4-fluorophenyl)-1-phenyl-4-pentyne-1-one (1d)
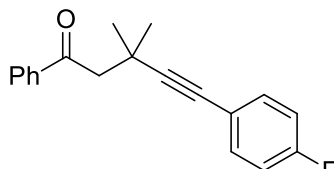
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.48 (s, 2H), 6.88 (t, J = 8.4 Hz, 2H), 7.11 (dd, J = 5.6 Hz, 2.8 Hz, 2H), 7.43 (t, J = 8.4 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 8.01 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 30.6, 49.4, 80.2, 95.6, 115.0, 115.3, 128.4, 128.5, 128.6, 132.8, 133.2, 133.3, 138.0, 160.8, 163.3, 198.3; IR (KBr): 2979, 2934, 1676, 1600, 1581, 1507, 1449, 1354, 1222, 1181, 1156, 1092, 1037, 1021, 752, 692, 622; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{18}$FO$^+$, 281.1342; found, m/z 281.1343.

3,3-Dimethyl-5-(4-trifluoromethylphenyl)-1-phenyl-4-pentyne-1-one (1e)
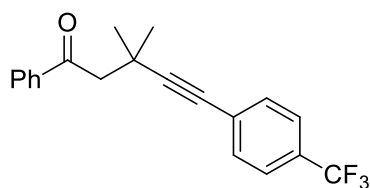
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.50 (s, 6H), 3.19 (s, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.44-7.56 (m, 5H), 8.01 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 29.5, 30.7, 49.3, 80.2, 98.7, 124.8 (q), 128.5, 131.6, 132.9, 137.9, 198.1; IR (KBr): 2973, 2934, 1694, 1678, 1615, 1598, 1449, 1404, 1166, 1123, 1105, 1066, 1016, 843, 689; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{18}$F$_3$O$^+$, 331.1304; found, m/z 331.1310.

3,3-Dimethyl-1,7-diphenyl-4-heptyne-1-one (1f)
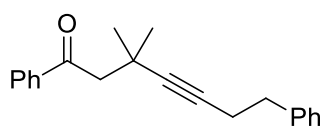
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.35 (s, 6H), 2.26 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 3.04 (s, 2H), 7.12-7.27 (m, 5H), 7.42-7.46 (m, 2H), 7.52-7.56 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.0, 30.0, 30.2, 35.2, 49.6, 80.4, 87.4, 126.1, 128.2, 128.3, 128.5, 128.6, 132.7, 138.1, 141.0, 198.7; IR (KBr): 3062, 2969, 2929, 1675, 1598, 1449, 1355, 1243, 1181, 750, 699; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{23}$O$^+$, 291.1749; found, m/z 291.1750.

3,3-Dimethyl-1-phenyl-4-nonyne-1-one (1g)
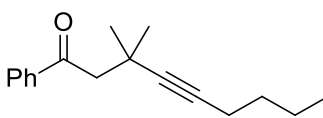
Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.82 (t, J = 6.8 Hz, 3H), 1.22-1.27 (m, 2H), 1.36 (s, 6H), 1.97 (t, J = 6.8 Hz, 3H), 3.05 (s, 2H), 7.43-7.46 (m, 2H), 7.52-7.56 (m, 1H), 7.98-8.00 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.6, 18.2, 21.8, 30.0, 30.2, 30.9, 49.6, 81.1, 86.5, 128.2, 128.4, 128.6, 132.7, 138.1, 198.8; IR (KBr): 2963, 2932, 2872, 1677, 1598, 1449, 1354, 1323, 1182, 1021, 751, 691; HRMS (ESI): [M+H]$^+$ calcd for C$_{17}$H$_{23}$O$^+$, 243.1749; found, m/z 243.1747.

3,3-Dimethyl-5-phenyl-1-(4-methylphenyl)-4-pentyne-1-one (1h)
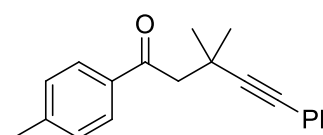
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.48 (s, 6H), 2.39 (s, 3H), 3.17 (s, 2H), 6.99-7.04 (m, 4H), 7.42-7.46 (m, 2H), 7.53 (m, 1H), 8.02 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 29.7, 30.7, 49.5, 81.3, 95.2, 120.3, 128.4, 128.6, 128.7, 131.2, 132.9, 137.5, 138.0, 198.2; IR (KBr): 3033, 2970, 2926, 1737, 1671, 1607, 1443, 1239, 1182, 757, 693; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$O$^+$, 277.1592; found, m/z 277.1592.

3,3-Dimethyl-1-(4-trifluoromethylphenyl)-5-phenyl-4-pentyne-1-one (1i)
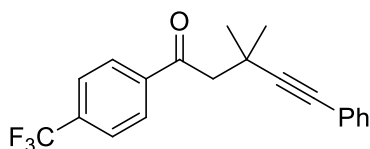
Colorless solid; m.p. 39 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.49 (s, 6H), 3.19 (s, 2H), 7.04 (d, J = 7.0 Hz, 2H), 7.18 (d, J = 7.0 Hz, 3H), 7.69 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 30.8, 49.9, 81.9, 95.5, 123,1, 125.4(q), 127.7, 128.0, 128.9, 131.3, 140.7, 197.7; IR (KBr): 2980, 2931, 1686, 1489, 1331, 1161, 1127, 1067, 758,

693; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{18}$F$_3$O$^+$, 331.1310; found, m/z 331.1312.

3,3-Dimethyl-1-(4-methoxyphenyl)-5-phenyl-4-pentyne-1-one (1j)
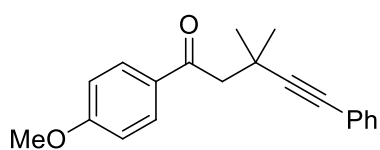
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.47 (s, 6H), 3.11 (s, 2H), 3.83 (s, 3H), 6.90 (d, J = 8.0 Hz, 2H), 7.16-7.20 (m, 5H), 8.00 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.6, 29.7, 30.8, 49.2, 55.4, 81.3, 96.3, 113.4, 113.5, 123.6, 125.8, 127.5, 127.9, 130.9, 131.1, 131.4, 163.3, 196.9; IR (KBr): 2969, 2935, 1667, 1601, 1575, 1510, 1490, 1464, 1443, 1419, 1353, 1315, 1219, 1172, 1111, 1027, 962, 916, 850, 833, 809, 757, 693; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$O$_2^+$, 293.1542; found, m/z 293.1542.

3,3-Dimethyl-1-(3-methoxyphenyl)-5-phenyl-4-pentyne-1-one (1k)
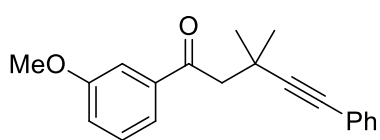
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.48 (s, 6H), 3.16 (s, 2H), 3.81 (s, 3H), 7.08 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.19 (m, 5H), 7.34 (t, J = 8.4 Hz, 1H), 7.54 (t, J = 2.2 Hz, 1H), 7.60 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 1H ; ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.6, 29.6, 30.7, 41.4, 49.5, 55.3, 81.2, 96.0, 112.6, 112.7, 119.3, 119.4, 121.3, 123.5, 127.5, 127.9, 129.3, 131.4, 139.3, 159.7, 198.1; IR (KBr): 2969, 2937, 1676, 1597, 1582, 1488, 1464, 1451, 1431, 1288, 1261, 1205, 1178, 1032, 866, 785, 758, 692; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$O$_2^+$, 293.1542; found, m/z 293.1537.

3,3-Dimethyl-1-(2-methoxyphenyl)-5-phenyl-4-pentyne-1-one (1l)
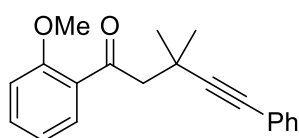
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.39 (s, 6H), 3.19 (s, 2H), 3.82 (s, 3H), 6.85 (d, J = 8.4 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 7.18 (m, 5H), 7.36 (t, J = 8.4 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.8, 29.6, 30.6, 54.6, 55.4, 55.5, 80.4, 96.3, 111.3, 111.4, 120.6, 123.7, 125.8, 127.4, 127.9, 130.0, 131.5, 132.9, 158.1, 201.3; IR (KBr): 2969, 2939, 2870, 2839, 1678, 1597, 1579, 1486, 1465, 1437, 1350, 1284, 1244, 1210, 1180, 1163, 1024, 917, 754, 693; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$O$_2^+$, 293.1542; found, m/z 293.1535.

3,3-Dimethyl-1-(1-naphthyl)-5-phenyl-4-pentyne-1-one (1m)
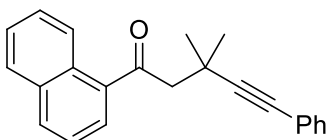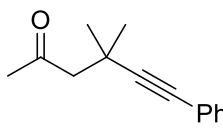
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.51 (s, 6H), 3.28 (s, 2H), 7.01 (d, J = 7.8 Hz, 2H), 7.12-7.20 (m, 3H), 7.44-7.56 (m, 3H), 7.85 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.94 (d, J = 8.3 Hz, 1H) , 8.55 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.88, 31.14, 53.54, 81.55, 95.62, 123.314, 124.22, 125.87, 126.33, 127.46, 127.54, 127.74, 127.86, 128.32, 130.06, 131.36, 132.17, 133.99, 137.557, 203.09; IR (KBr): 3052, 2970, 2930, 1678, 1508, 1443, 1236, 1182, 1070, 791, 777, 757, 692; HRMS (ESI): [M+H]$^+$ calcd for C$_{23}$H$_{21}$O$^+$, 313.1592; found,
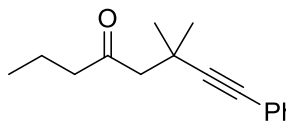
m/z 313.1591.
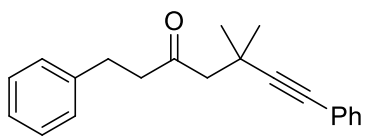
4,4-Dimethyl-6-phenyl-5-hexyne-2-one (1n)

Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.39 (s, 6H), 2.30 (s, 3H), 2.61 (s, 2H), 7.27-7.28 (m, 3H), 7.37-7.39 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.5, 30.1, 31.8, 55.5, 81.2, 95.7, 123.4, 127.8, 128.2, 131.5, 207.3; IR (KBr): 2971, 2929, 1708, 1598, 1491, 1468, 1443, 1360, 1309, 1203, 1184, 757, 693, 544; HRMS (ESI): [M+H]$^+$ calcd for C$_{14}$H$_{17}$O$^+$, 201.1279; found, m/z 201.1274.
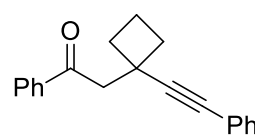
6,6-Dimethyl-8-phenyl-7-octyne-2-one (1o)

Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.91 (t, J = 7.6 Hz, 3H), 1.39 (s, 6H), 1.62 (td, J = 14.6, 7.3 Hz, 2H), 2.58 (t, J = 7.3 Hz, 2H), 2.59 (s, 2H), 7.27-7.29 (m, 3H), 7.35-7.39 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.7, 17.1, 29.6, 30.2, 46.4, 54.4, 81.0, 95.9, 123.5, 127.7, 128.2, 131.5, 209.3; IR (KBr): 2966, 2934, 2875, 1712, 1491, 1466, 1443, 1364, 1301, 757, 692; HRMS (ESI): [M+H]$^+$ calcd for C$_{16}$H$_{21}$O$^+$, 229.1592; found, m/z 229.1590.
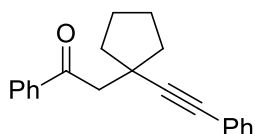
5,5-Dimethyl-1, 7-phenyl-6pentyne-3-one (1p)

Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.38 (s, 6H), 2.58 (s, 2H), 2.93 (m, 4H), 7.13-7.37 (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.6, 30.3, 46.1, 81.3, 95.7, 123.4, 125.9, 126.0, 127.6, 127.8, 128.2, 128.4, 128.41, 128.43, 128.5, 129.5, 131.5, 141.1, 208.3; IR (KBr): 3028, 2969, 2926, 2868, 1709, 1599, 1496, 1466, 1443, 1364, 757, 693, 549; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{23}$O$^+$, 291.1749; found, m/z 291.1747.

1-phenyl-2-(1-(phenylethynyl)cyclobutyl)ethanone (1q)

Pale yellow solid; m.p. 67 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.96-2.08 (m, 1H), 2.13-2.24 (m, 1H), 2.29-2.36 (m, 2H), 2.48-2.55 (m, 2H), 3.41 (s, 1H), 7.21 (s, 6H), 7.44-7.88 (m, 2H), 7.53-7.57 (m, 1H), 8.00-8.03 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.8, 34.9, 35.0, 47.5, 82.1, 95.6, 123.7, 127.4, 127.9, 128.36, 128.43, 131.4, 132.9, 137.5, 197.9; IR (KBr): 3005, 2982, 2895, 1686, 1595, 1492, 1352, 1323, 1216, 1072, 756, 692, 622; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{19}$O$^+$, 275.1436; found, m/z 275.1435.

1-phenyl-2-(1-(phenylethynyl)cyclopentyl)ethanone (1r)

Pale yellow solid; m.p. 54 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.74-1.85 (m, 4H), 1.87-1.93 (m, 2H), 2.12-2.19 (m, 2H), 3.27 (s, 2H), 7.11-7.15 (m, 2H), 7.17-7.20 (m, 3H), 7.43-7.47 (m, 2H), 7.52-7.57 (m, 1H), 8.02-8.05 (m, 2H);
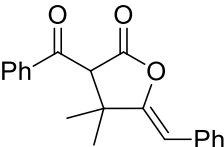
^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.9, 40.4, 41.1, 47.4, 81.7, 95.7, 123.7, 127.4, 127.9, 128.4, 128.5, 131.4, 132.8, 137.9, 198.6; IR (KBr): 3027, 2956, 2905. 2217, 1687, 1597, 1579, 1493, 1448, 1403, 1366, 1218, 995, 753, 6889, 626; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{21}$O$^+$, 289.1592; found, m/z 289.1592.

4-5. ラクトン誘導体 2 の合成反応
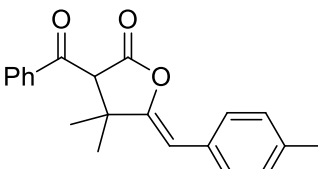
The reaction was performed using a pressure test-tube equipped with a stirring bar in a 30 mL autoclave. To a mixture of AgOBz (5.7 mg, 0.025 mmol) and **1a** (32.8 mg, 0.125 mmol) in 0.5 mL DMF in a pressure test-tube was added a solution of MTBD (72 mL, 0.50 mmol) in DMF (0.5 mL). The pressure test-tube containing the reaction mixture was placed in the autoclave. CO$_2$ (1.0 MPa) was purged and the reaction mixture was stirred at 25 °C for 48 h. After the CO$_2$ was vented, the reaction mixture was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc 40/1, 20/1 then 4/1) to afford the corresponding lactone **2a** in 91% yield (34.6 mg) as a colorless solid.

4-6. ラクトン誘導体 2 の化合物データ
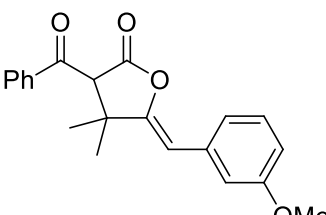
(Z)-3-Benzoyl-5-benzylidene-4,4-dimethyldihydrofuran-2(3H)-one (2a)

Colorless solid; m.p. 88 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.26 (s, 3H), 1.58 (s, 3H), 4.51 (s, 1H), 5.57 (s, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.54 (t, J = 8.0 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.94 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.1, 29.8, 44.8, 58.3, 103.0, 127.0, 128.4, 128.7, 128.8, 129.1, 133.5, 134.3, 136.5, 170.3, 193.3; IR (KBr): 3057, 2972, 2929, 1805, 1671, 1597, 1449, 1328, 1303, 1196, 1061, 918, 755, 691; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{19}$O$_3$$^+$, 307.1348; found, m/z 307.1334; NOE 2.5%, 1.0%.

(Z)-3-Benzoyl-4,4-dimethyl-5-(4-methylbenzylidene)dihydrofuran-2(3H)-one (2b)

Colorless solid; m.p. 127 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.23 (s, 3H), 1.55 (s, 3H), 2.34 (s, 3H), 4.50 (s, 1H), 5.53 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.49-7.56 (m, 4H), 7.65 (t, J = 8.0 Hz, 1H), 7.93 (d, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.2, 23.2, 29.7, 44.7, 58.3, 102.9, 128.5, 128.7, 129.0, 129.1, 130.6, 134.3, 136.5, 136.8, 155.4, 170.4, 193.4; IR (KBr): 2974, 2921, 1815, 1679, 1595, 1327, 1304, 1194, 1185, 1072, 920, 799, 706; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{21}$O$_3$$^+$, 321.1491; found, m/z 321.1493; NOE 1.8%, 0.2%.

(Z)-3-Benzoyl-4,4-dimethyl-5-(3-methoxybenzylidene)dihydrofuran-2(3H)-one (2c)

Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.24 (s, 3H), 1.56 (s, 3H), 3.83 (s, 3H), 4.50 (s, 1H), 5.54 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 7.23-7.27 (m, 3H), 7.53 (t, J = 7.2, 7.6 Hz, 2H), 7.65 (t, J = 7.2, 7.6 Hz, 1H), 7.94 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.1,

29.8, 44.8, 55.2, 58.2, 102.8, 113.0, 113.8, 121.3, 128.7, 128.8, 129.1, 129.3, 134.3, 134.8, 136.5, 156.4, 159.6, 170.1, 193.3; IR (KBr): 2971, 2934, 1808, 1673, 1598, 1578, 1492, 1434, 1326, 1302, 1194, 1061, 809, 690; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{21}$O$_4^+$, 337.1440; found, m/z 337.1439; NOE 1.1%, 2.3%.

(Z)-3-Benzoyl-4,4-dimethyl-5-(4-fluorobenzylidene)dihydrofuran-2(3H)-one (2d)
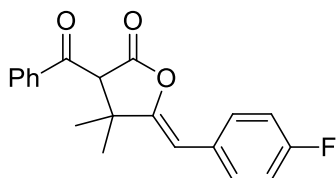
Colorless solid; m.p. 117 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.24 (s, 3H), 1.56 (s, 3H), 4.51 (s, 1H), 5.52 (s, 1H), 7.02 (t, J = 8.5 Hz, 2H), 7.47-7.62 (m, 5H), 7.94 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.0, 29.9, 44.8, 58.3, 101.9, 115.3, 115.4, 128.76, 128.79, 129.1, 130.25, 130.33, 136.5, 155.8 (d), 160.4, 162.9, 170.2, 193.3; IR (KBr): 2980, 2962, 1804, 1667, 1509, 1227, 1201, 1069, 708, 690; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{18}$FO$_3^+$, 325.1240; found, m/z 325.1242; NOE 0.9%, 2.3%.

(Z)-3-Benzoyl-4,4-dimethyl-5-(4-(trifluoromethyl)benzylidene)dihydrofuran-2(3H)-one (2e)
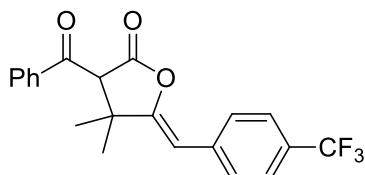
Colorless solid; m.p. 82 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.26 (s, 3H), 1.58 (s, 3H), 4.54 (s, 1H), 5.60 (s, 1H), 7.51-7.70 (m, 7H), 7.94 (d, J = 7.3 Hz, 2H), 11.65 (enol form); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 22.8, 29.9, 44.9, 58.1, 101.6, 125.2 (q), 128.5, 128.7, 128.8, 129.1, 134.5, 136.3, 137.1, 158.3, 169.9, 193.2 IR (KBr): 2975, 2932, 1813, 1674, 1617, 1597, 1450, 1325, 1166, 1117, 1066, 1017, 1001, 920, 861, 689; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{18}$F$_3$O$_3^+$, 375.1208; found, m/z 375.1204; NOE 0.8%, 2.1%.

(Z)-3-Benzoyl-4,4-dimethyl-5-(3-phenylpropylidene)dihydrofuran-2(3H)-one (2f)
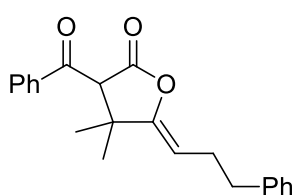
Pale brown solid; m.p. 86 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.08 (s, 3H), 1.40 (s, 3H), 2.46-2.56 (m, 2H), 2.64-2.81 (m, 2H), 4.40 (s, 1H), 4.63 (t, J = 7.4 Hz, 1H), 7.14-7.32 (m, 5H), 7.48-7.55 (m, 2H), 7.60-7.67 (m, 1H), 7.88-7.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.0, 26.8, 29.8, 35.7, 43.7, 59.3, 102.4, 126.0, 128.4, 128.7, 128.8, 129.1, 134.3, 136.7, 141.5, 156.5, 170.7, 193.7; IR (KBr): 2964, 2927, 1798, 1701, 1675, 1449, 1333, 1071, 1047, 916, 712, 691; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{23}$O$_3^+$, 335.1647; found, m/z 335.1643; NOE 1.9%, 0.3%.

(Z)-3-Benzoyl-4,4-dimethyl-5-(pentylidene)dihydrofuran-2(3H)-one (2g)
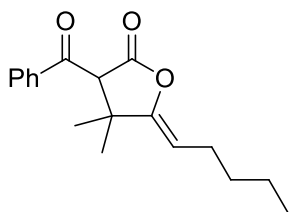
Pale green oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.92 (t, 3H), 1.11 (s, 3H), 1.31-1.41 (m, 4H), 1.45 (s, 3H), 2.13-2.23 (m, 2H), 4.42 (s, 1H), 4.63 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.92 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.9, 22.2, 22.9, 24.8, 29.8, 31.6, 43.6, 59.3, 103.4, 128.7, 129.0, 134.1, 136.7, 155.9, 170.7, 193.6; IR

(KBr): 2960, 2872, 1801, 1674, 1597, 1581, 1449, 1330, 1214, 1053, 1001, 975, 947, 780, 710, 689; HRMS (ESI): [M+H]$^+$ calcd for $C_{18}H_{23}O_3^+$, 287.1647; found, m/z 287.1650; NOE 1.7%, 0.7%.

### (Z)-5-Benzylidene-4,4-dimethyl-3-(4-methylbenzoyl)dihydrofuran-2(3H)-one (2h)
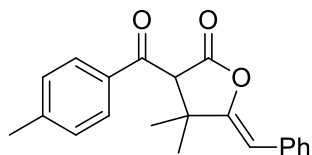
Colorless solid; m.p. 112 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.23 (s, 3H), 1.55 (s, 3H), 2.44 (s, 3H), 4.48 (s, 1H), 5.55 (s, 1H), 7.19-7.25 (m, 1H), 7.29-7.37 (m, 4H), 7.60 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 11.70 (enol form); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.9, 23.3, 44.8, 58.3, 103.0, 127.1, 128.5, 128.8, 129.0, 129.9, 145.6, 156.4, 170.6, 193.0; IR (KBr): 2971, 2926, 1806, 1667, 1603, 1346, 1186, 1055, 911, 738, 692; HRMS (ESI): [M+H]$^+$ calcd for $C_{21}H_{21}O_3^+$, 321.1491; found, m/z 321.1492; NOE 2.0%, 0.3%.

(Z)-5-Benzylidene-4,4-dimethyl-3-(4-(trifluoromethyl)benzoyl)dihydrofuran-2(3H)-one (2i)
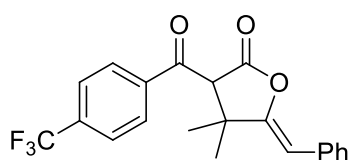
Colorless solid; m.p. 111 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.26 (s, 3H), 1.58 (s, 3H), 4.50 (s, 1H), 5.58 (s, 1H), 7.20-7.29 (m, 2H), 7.30-7.40 (m, 2H), 7.56-7.64 (m, 2H), 7.79-7.82 (m, 2H), 8.05 (d, J = 8.3 Hz, 2H), 11.70 (enol form); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.3, 29.8, 45.1, 58.7, 103.4, 126.3, 127.3, 128.6, 128.8, 129.2, 133.4, 139.1, 155.8, 169.7, 192.6; IR (KBr): 2976, 2929, 1812, 1684, 1315, 1302, 1142, 1066, 756, 695; HRMS (ESI): [M+H]$^+$ calcd for $C_{21}H_{18}F_3O_3^+$, 375.1208; found, m/z 375.1205; NOE 2.0%, 0.5%.

(Z)-5-Benzylidene-4,4-dimethyl-3-(4-methoxbenzoyl)dihydrofuran-2(3H)-one (2j)
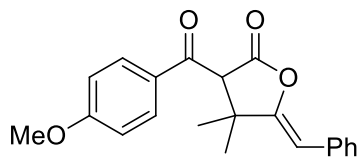
Colorless solid; m.p. 141 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.24 (s, 3H), 1.56 (s, 3H), 3.89 (s, 3H), 4.44 (s, 1H), 5.55 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H) , 7.22 (t, J = 7.1 Hz, 2H), 7.33 (t, J = 7.6 Hz, 3H), 7.60 (d, J = 7.3 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 22.8, 30.4, 45.0, 55.4, 62.1, 102.4, 11.8, 121.3, 126.8, 128.4, 128.6, 131.5, 133.9, 157.1, 158.6, 170.6, 194.4; IR (KBr): 2974, 1810, 1684, 1657, 1601, 1573, 1356, 1264, 1237, 1186, 1053, 911, 844; HRMS (ESI): [M+H]$^+$ calcd for $C_{21}H_{21}O_4^+$, 337.1440; found, m/z 337.1440; NOE 2.3%, 1.1%.

(Z)-5-Benzylidene-4,4-dimethyl-3-(3-methoxybenzoyl)dihydrofuran-2(3H)-one (2k)
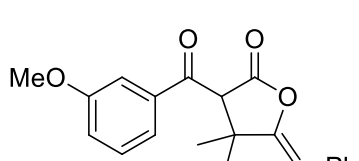
Colorless solid; m.p. 91 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.25 (s, 3H), 1.57 (s, 3H), 3.86 (s, 3H), 4.47 (s, 1H), 5.56 (s, 1H), 7.18-7.2 (m, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.49-7.47 (m, 2H), 7.60 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.1, 29.8, 44.8, 55.5, 58.5, 103.0, 112.6, 120.9, 121.4, 127.0, 128.4, 128.6, 130.0, 133.5, 137.9, 156.2, 160.2, 170.3, 193.2; IR (KBr): 2973, 1804, 1669, 1594, 1317, 1203, 1187, 1173, 1066, 774, 697;

HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{21}$O$_4^+$, 337.1440; found, m/z 337.1442; NOE 0.3%, 2.4%.

(Z)-5-Benzylidene-4,4-dimethyl-3-(2-methoxybenzoyl)dihydrofuran-2(3H)-one (2l)
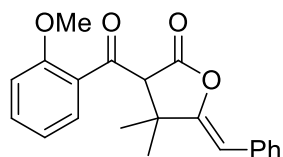
Pale yellow solid; m.p. 109 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ =1.30 (s, 3H), 1.50 (s, 3H), 3.93 (s, 3H), 4.71 (s, 1H), 5.53 (s, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.53-7.57 (m, 1H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.79 (dd, *J* = 7.8, 2.0 Hz, 1H), 11.45 (enol form); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 22.4, 30.4, 45.0, 55.4, 62.1, 102.4, 111.8, 121.3, 126.8, 128.4, 128.6, 131.5, 133.9, 135.3, 157.1, 158.6, 174.6, 194.4; IR (KBr): 2963, 2949, 1813, 1683, 1649, 1593, 1481, 1465, 1179, 1166, 1059, 783, 695, 586; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{21}$O$_4^+$, 337.1440; found, m/z 337.1440; NOE 2.3%, 1.0%.

(Z)- 5-benzylidene-4,4-dimethyl-3-(1-naphtoyl)-dihydrofuran-2(3H)-one (2m)
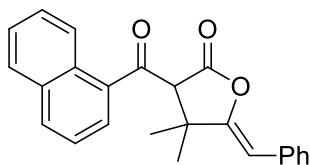
Pale brown oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.25 (enol form), 1.36 (s, 3H), 1.50 (s, 3H), 1.54 (enol form), 4.57 (s, 1H), 5.47 (enol form), 5.59 (s, 1H), 7.22 (enol form), 7.35 (q, 2H), 7.49-7.66 (m, 5H), 7.87 (m, 3H), 8.09 (d, 1H), 8.73 (enol form), 11.75 (enol form); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 22.8, 30.0, 41.8, 45.4, 61.4, 102.2, 102.8, 106.3, 124.2, 124.4, 125.2, 125.6, 126.59, 126.61, 126.7, 126.98, 127.00, 127.2, 128.3, 128.4, 128.7, 128.8, 129.5, 130.1, 130.13, 130.5, 130.6, 133.2, 133.6, 133.8, 134.1, 134.4, 134.7, 156.3, 158.4, 169.6, 170.2, 173.7, 196.3 (including enol form); IR (KBr): 3057, 2972, 2929, 1805, 1727, 1668, 1594, 1508, 1335, 1139, 1086, 1049, 916, 755, 695; HRMS (ESI): [M+H]$^+$ calcd for C$_{24}$H$_{21}$O$_3^+$, 357.1491; found, m/z 357.1492; NOE 2.5%, 1.1%.

(Z)-3-Acetyl-5-benzylidene-4,4-dimethyldihydrofuran-2(3H)-one (2n)
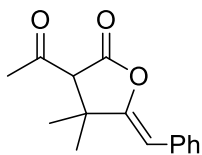
Yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.34 (s, 3H), 1.50 (s, 3H), 2.14 (enol form), 2.35 (s, 3H), 3.46 (s, 1H), 5.55 (s, 1H), 5.57 (enol form), 7.20-7.25 (m, 1H), 7.31-7.36 (m, 2H), 7.56-7.60 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 18.5, 23.2, 28.4, 28.6, 29.7, 31.3, 41.2, 44.2, 62.8, 102.0, 102.9, 103.0, 126.6, 127.1, 128.36, 128.4, 128.6, 133.2, 133.9, 155.7, 158.52, 169.8, 171.0, 173.2, 200.5 (including enol form); IR (KBr): 3057, 3026, 2927, 2930, 1806, 1717, 1682, 1639, 1449, 1362, 1247, 1198, 1053, 966, 755, 696; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{19}$O$_3^+$, 245.1178; found, m/z 245.1177; NOE 2.3%, 0.6%.

(Z)-3-Butyryl-5-benzylidene-4,4-dimethyldihydrofuran-2(3H)-one (2o)
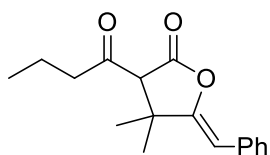
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.94 (t, *J* = 7.4 Hz, 2H), 1.02 (enol form), 1.32 (s, 3H), 1.50 (enol form), 1.51 (s, 3H), 1.64 (td, *J* = 14.6, 7.5 Hz, 2H), 1.74 (enol form), 2.37 (enol form), 2.60 (m, 2H), 3.49 (s, 1H), 5.55 (s, 1H), 7.18-7.25 (m, 1H), 7.31-7.36 (m, 2H), 7.56-7.61 (m, 2H),

11.49 (enol form); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.5, 13.9, 16.4, 20.0, 23.0, 29.1, 29.4, 33.1, 41.4, 44.3, 46.2, 62.6, 101.9, 102.8, 126.6, 127.1, 128.4, 128.5, 128.6, 133.4, 134.0, 156.0, 158.6, 169.9, 174.5, 202.7; IR (KBr): 3057, 3026, 2968, 2933, 2876, 1806, 1763, 1716, 1681, 1630, 1449, 1391, 1323, 1196, 1049, 947, 754, 695; HRMS (ESI): [M+H]$^+$ calcd for C$_{18}$H$_{21}$O$_3^+$, 273.1491; found, m/z 273.1487; NOE 2.2%, 1.1%.

(Z)- 5-Benzylidene-4,4-dimethyl-3-(3-phenylpropionyl)-dihydrofuran-2(3H)-one (2p)
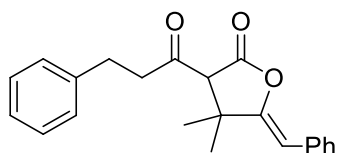
Yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.21 (s, 3H), 1.36 (enol form), 1.47 (s, 3H) 2.67 (enol form), 2.91-2.96 (m, 2H), 3.01 (m, 2H), 3.47 (s, 1H), 5.50 (enol form), 5.52 (s, 1H), 7.18-7.35 (m, 8H), 7.57 (t, J = 7.1 Hz, 2H), 11.57 (enol form); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.0, 28.7, 28.9, 29.2, 32.4, 34.3, 41.3, 44.4, 46.0, 62.4, 102.0, 102.8, 103.4, 126.3, 126.5, 126.7, 127.1, 128.38, 128.43, 128.5, 128.61, 128.65, 133.3, 133.9, 140.2, 155.8, 158.5, 169.7, 172.9, 173.5, 201.8; IR (KBr): 3061, 3027, 2971, 2930, 1805, 1717, 1681, 1632, 1497, 1450, 1243, 1196, 1051, 948, 753, 697; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{23}$O$_3^+$, 335.1647; found, m/z 335.1646; NOE 1.6%, 1.1%.

(Z)-8-benzoyl-5-benzylidene-6-oxaspiro[3.4]octan-7-one (2q)
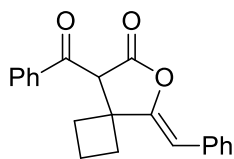
Yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.87-2.00 (m, 2H), 2.06-2.25 (m, 2H), 2.40-2.53 (m, 4H), 4.73 (s, 1H), 5.92 (s, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.8 Hz, 2H), 7.61-7.61 (m, 1H), 7.65-7.71 (m, 2H), 8.06 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.08, 28.27, 37.31, 49.41, 58.33, 102.62, 126.91, 128.40, 128.65, 128.90, 128.95, 128.98, 129.06, 133.67, 134.35, 136.09, 155.92, 169.58, 192.35; IR (KBr): 3059, 3025, 2988, 1801, 1674, 1597, 1449, 1326, 1214, 1182, 1042, 803, 754, 721, 693; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{19}$O$_3^+$, 319.1334; found, m/z 319.1334; NOE 3.5%.

(Z)-4-benzoyl-1-benzylidene-2-oxaspiro[4.4]nonan-3-one (2r)
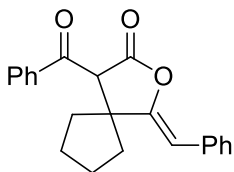
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.53-1.62 (m, 1H), 1.74-2.11 (m, 7H), 4.55 (s, 1H), 5.56 (s, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.53 (t, J = 7.7 Hz, 2H), 7.60-7.67 (m, 3H), 7.98 (d, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 24.0, 24.1, 29.7, 31.9, 42.0, 56.1, 57.9, 103.0, 126.9, 128.4, 128.7, 128.8, 129.1, 133.7, 134.3, 136.4, 156.0, 170.2, 193.4; IR (KBr): 2962, 2876, 1801, 1673, 1596, 1448, 1326, 1213, 1180, 1088, 999, 804, 754, 692; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{21}$O$_3^+$, 333.1491; found, m/z 333.1490; NOE 3.0%.

4-7. オルトアルキニルアセトフェノン **4** の合成
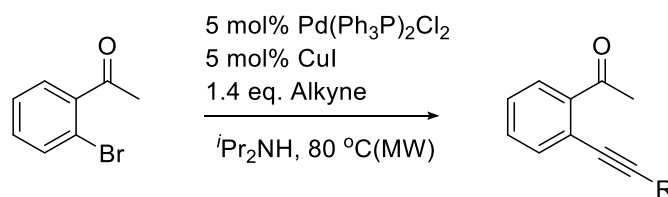
Compound **4a, 4f, 4k-4m** were synthesized by the modified procedure of the literature.[51] The corresponding alkyne (1.4 eq.) was added to the solution of Pd(PPh$_3$)$_2$Cl$_2$ (5 mol%), CuI (5 mol%) and o-bromoacetophenone (1 eq., 5 mmol) in iPr$_2$NH (20 mL) using vial. The solution was heated at 80 °C with microwave. After 4 h, the reactant was filtered, then the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the desired starting material **4a**, **4f**, **4k**-**4m**.

S1
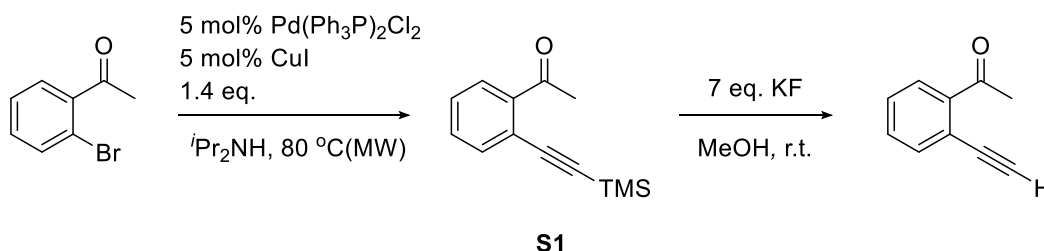
The trimethylsilylacetylene (1.4 eq.) was added to the solution of Pd(PPh$_3$)Cl$_2$ (5 mol%), CuI (5 mol%) and o-bromoacetophenone (1 eq., 5 mmol) in iPr$_2$NH (20 mL) using vial. The solution was heated at 80 °C with microwave. After 4 h, the reactant was filtered, then the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the corresponding o-alkynylacetophenone **S1**.

Desilylation was carried out according to the literature.[51] KF (7 eq.) was added to the solution of compound **S1** in MeOH (0.12 M). After stirring for 2 h, MeOH was removed under reduced pressure, then Et$_2$O and water were added. The organic layer was extracted with Et$_2$O, washed with water, dried with Na$_2$SO$_4$, filtered. After the solvet was removed under reduced pressure, the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford 2`-ethynylacetophenone **4n**.
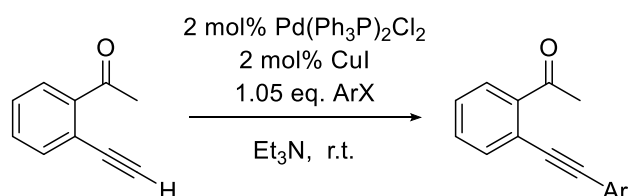
2`-ethynylacetophenone **4n** (1.05 eq.) was added to the solution of Pd(PPh$_3$)$_2$Cl$_2$ (2 mol%), CuI (2 mol%) and the corresponding aryl halide (1 eq.) in Et$_3$N under N$_2$. The solution was stirred at room temperature overnight. After the reactant was filtered, the solvent was removed under reduced

pressure and the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the desired starting material **4g-4j**.
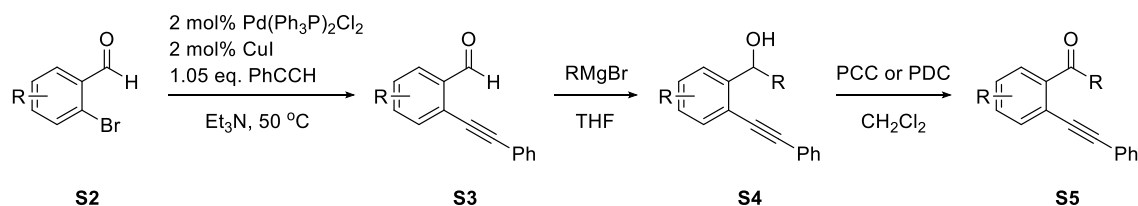
The corresponding alkyne (1.05 eq.) was added to the solution of Pd(PPh$_3$)$_2$Cl$_2$ (2 mol%), and CuI (2 mol%) and *o*-bromobenzaldehyde (1 eq., 10 mmol) in Et$_3$N (20 mL) under N$_2$. The reaction mixture was heated at 50 °C. After 4 h, the reaction mixture was filtered, then removed solvent under reduced pressure and the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the corresponding *o*-alkynylbenzaldehyde **S3**.

Alkylation and oxidation steps were carried out according to the literature.[53] To a solution of the corresponding 2-alkenylbenzaldehyde in dry THF (0.2 M) was added MeMgBr or *n*BuLi at -78 °C under N$_2$. After stirring at -78 °C for 2 hours, the reaction mixture was quenched with sat. NH$_4$Cl aq. then extracted with CH$_2$Cl$_2$. The combined organic layer was dried with NaSO$_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the corresponding alcohol **S4**.

To a solution of the corresponding **S4** in CH$_2$Cl$_2$ (0.1 M) was added PCC (2.5 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. After the reaction was completed, 1.0 g of Celite was added and stirred for 5-10 min. The rection mixture was flitered through Celite and silica gel and concentrated under reduced pressure. The residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the corresponding **4b-4e**, **4o-4q**.

1-(1-phenylethynyl)phenyl)ethan-1-one (4a)
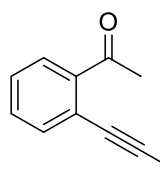
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.80 (s, 3H), 7.35-7.39 (m, 3H), 7.42 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.48 (td, *J* = 1.4, 7.5 Hz, 1H), 7.54-7.57 (m, 2H), 7.64 (dd, *J* = 0.9, 7.7 Hz, 1H), 7.76 (dd, *J* = 1.2, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 30.0, 88.4, 95.0, 121.7, 122.9, 128.3, 128.4, 128.67, 128.74, 131.3, 131.5, 133.9, 140.7, 200.4; IR (KBr): 3061, 2215, 1686, 1592, 1279, 757, 691; HRMS (ESI): [M+H]$^+$ calcd for C$_{16}$H$_{13}$O$^+$, 221.0966; found, m/z 221.0960.

1-(4, 5-dimethoxy-2-(phenylethynyl)phenyl)ethan-1-one (4b)
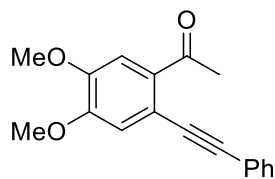
Colorless solid; m.p. 119 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.86 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 7.07 (s, 1H), 7.34-7.41 (m, 3H), 7.43 (s, 1H), 7.51-7.58 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 30.4, 56.1, 56.2, 89. 1, 94.5, 111.3, 115.5, 116.1, 122.9, 128.5, 128.7, 131.2, 133.5, 149.1, 151.5, 198.4; IR (KBr): 2962, 2931, 1659, 1590, 1246, 1053, 756; HRMS (ESI): [M]$^+$ calcd for C$_{18}$H$_{17}$O$_3$$^+$,

281.1178; found, m/z 281.1176.

1-(4-fluoro-2-(1-phenylethynyl)phenyl)ethan-1-one (4c)

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.79 (s, 3H), 7.07-7.12 (m, 1H), 7.32 (dd, J = 2.6, 9.1 Hz, 1H), 7.36-7.41 (m, 3H), 7.53-7.58 (m, 2H), 7.83 (dd, J = 5.8, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.9, 87.5 (d), 96.2, 115.7 (d), 120.3, 121.4 (d), 124.5 (d), 129.1, 131.5, 131.6, 131.6 (d), 136.8 (d), 164.0 (d), 198.5; IR (KBr): 3068, 2214, 1685, 1572, 1239, 1100, 757, 690; HRMS (ESI): [M+H]$^+$ calcd for C$_{16}$H$_{12}$FO$^+$, 239.0872; found, m/z 239.0870.

1-(5-chloro-2-(1-phenylethynyl)phenyl)ethan-1-one (4d)

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.79 (s, 3H), 7.34-7.40 (m, 3H), 7.44 (dd, J = 2.4, 8.3 Hz, 1H), 7.50-7.58 (m, 3H), 7.73 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.9, 87.4, 96.0, 120.1, 122.5, 128.5, 128.8, 129.0, 131.4, 131.5, 134.5, 135.0, 141.8, 198.9; IR (KBr): 3064, 2215, 1686, 1493, 1469, 1356, 1281, 1254, 1102, 828, 690; HRMS (ESI): [M+H]$^+$ calcd for C$_{16}$H$_{12}$ClO$^+$, 255.0572; found, m/z 255.0574.

1-(1-(phenylethynyl)naphthalen-2-yl)ethan-1-one (4e)

Pale yellow solid; m.p. 46 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.92 (s, 3H), 7.38-7.45 (m, 3H), 7.57-7.70 (m, 4H), 7.79 (d, J = 8.8 Hz, 1H), 7.82-7.88 (m, 2H), 78.61 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 30.6, 86.3, 101.5, 119.9, 122.8, 124.5, 127.4, 127.6, 128.1, 128.2, 128.56, 128.61, 129.0, 131.5, 133.2, 134.2, 139.4, 201.4; IR (KBr): 3057, 2993, 2202, 1663, 1264, 1241, 752; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{15}$O$^+$, 271.1118; found, m/z 271.1122.

1-(2-(1-p-tolylethynyl)phenyl)ethan-1-one (4f)

Oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.38 (s, 3H), 2.80 (s, 3H), 7.18 (d, J = 7.9 Hz, 2H), 7.36-7.41 (m, 1H), 7.42-7.50 (m, 3H), 7.62 (dd, J = 1.3, 7.9 Hz, 1H), 7.75 (dd, J = 1.5, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.6, 30.1, 87.9, 95.4, 119.8, 121.9, 128.1, 128.7, 129.2, 131.3, 131.4, 133.8, 139.0, 140.7, 200.5; IR (KBr): 3027, 2873, 2214, 1686, 958, 817, 762; HRMS (ESI): [M+H]$^+$ calcd for C$_{17}$H$_5$O$^+$, 235.1123; found, m/z 235.1121.

1-(2-(1-(4-trifuluoromethylphenyl)ethynyl)phenyl)ethan-1-one (4g)

Oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.76 (s, 3H), 7.45 (td, J = 1.5, 7.6 Hz, 1H), 7.51 (td, J = 1.6, 7.6 Hz, 1H), 7.60-7.69 (m, 5H), 7.79 (dd, J = 1.5, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 90.7, 93.0,

120.9, 123.8 (d), 125.4 (q), 126.7 (d), 128.8, 128.9, 130.3 (d), 131.4, 131.8, 134.1, 140.7, 199.7; IR (KBr): 2220, 1684, 1320, 1123, 957, 843, 762, 598; HRMS (ESI): [M+H]$^+$ calcd for C$_{17}$H$_{12}$F$_3$O$^+$, 289.0835 ; found, m/z 289.0834.

1-(2-(1-(4-acetylphenyl)ethynyl)phenyl)ethan-1-one (4h)

Pale yellow solid; m.p. 62 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.63 (s, 3H), 2.78 (s, 3H), 7.45 (td, J = 1.5, 7.6 Hz, 1H), 7.51 (td, J = 1.6, 7.6 Hz, 1H), 7.62-7.68 (m, 3H), 7.77-7.80 (m, 1H), 7.93-7.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.6, 29.7, 91.6, 93.7, 121.0, 127.7, 128.3, 128.8, 128.9, 131.4, 131.7, 134.1, 136.5, 140.7, 197.2, 199.8; IR (KBr): 2210, 1680, 1602, 1266, 826; HRMS (ESI): [M+H]$^+$ calcd for C$_{18}$H$_{15}$O$_2$$^+$, 263.1067; found, m/z 263.1066.
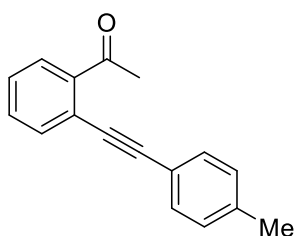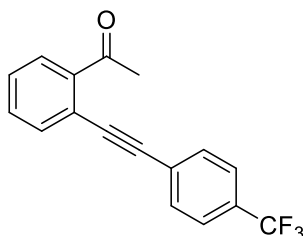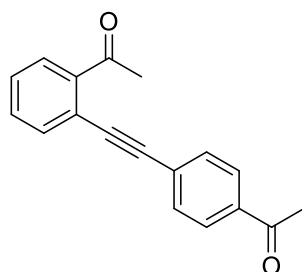
1-(2-(1-(4-formylphenyl)ethynyl)phenyl)ethan-1-one (4i)
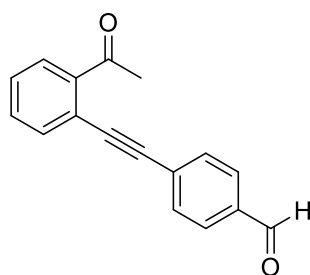
Pale yellow solid; m.p. 53 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.76 (s, 3H), 7.45 (td, J = 1.3, 7.7 Hz, 1H), 7.51 (td, J = 1.5, 7.6 Hz, 1H), 7.64-7.68 (m, 1H), 7.69-7.71 (m, 2H), 7.79 (dd, J = 1.0, 7.8 Hz, 1H), 7.85-7.91 (m, 2H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.6, 92.3, 93.4, 120.8, 128.9, 128.9, 129.1, 129.5, 131.4, 132.0, 134.1, 135.6, 140.5, 191.3, 199.6; IR (KBr): 3064, 2835, 2215, 1697, 1601, 1562, 1207; HRMS (ESI): [M+H]$^+$ calcd for C$_{17}$H$_{13}$O$_2$$^+$, 249.0919; found, m/z 249.0915.

1-(2-(1-(2-methoxycarbonylphenyl)ethynyl)phenyl)ethan-1-one (4j)

Pale yellow solid; m.p. 72 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.81 (s, 3H), 3.96 (s, 3H), 7.42 (td, J = 1.4, 7.6 Hz, 2H), 7.48-7.55 (m, 2H), 7.67-7.73 (m, 2H), 7.76-7.79 (m, 1H), 7.99-8.02 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 30.0, 52.3, 93.2, 93.8, 121.8, 123.4, 128.4, 128.5, 128.7, 130.6, 131.4, 131.7, 131.8, 134.0, 134.2, 140.6, 166.4, 200.3; IR (KBr): 3068, 3002, 2958, 1725, 1670, 1251, 1080, 760; HRMS (ESI): [M+H]$^+$ calcd for C$_{18}$H$_{15}$O$_3$$^+$, 279.1016; found, m/z 279.1013.
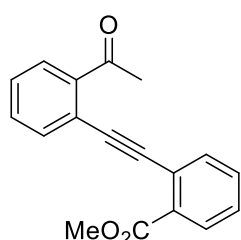
1-(2-hexynylphenyl)ethan-1-one (4k)
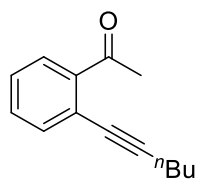
Oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.95 (t, J = 7.3 Hz, 3H), 1.44-1.53 (m, 2H), 1.58-1.65 (m, 2H), 2.47 (t, J = 7.1 Hz, 2H), 2.73 (s, 3H), 7.33 (td, J = 1.3, 7.6 Hz, 1H), 7.40 (td, J = 1.1, 7.6 Hz, 1H), 7.49 (dd, J = 1.0, 7.8 Hz, 1H), 7.66 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.6, 19.4, 22.1, 30.1, 30.5, 79.6, 96.9, 122.5, 127.5, 128.3, 131.1, 134.0, 141.0, 201.2; IR (KBr): 2960, 2932, 2230, 1684, 963, 763; HRMS (ESI): [M+H]$^+$ calcd for C$_{14}$H$_{17}$O$^+$, 201.1279; found, m/z 201.1268.

1-(2-(4-butynylphenly)phenyl)ethan-1-one (4l)
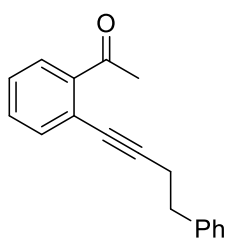
Oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.56 (s, 3H), 2.77 (t, J = 7.4 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 7.20-7.35 (m, 6H), 7.39 (td, J = 1.5, 7.5 Hz, 1H), 7.45 (dd, J = 1.5, 7.7 Hz, 1H), 7.65 (dq, J = 0.7, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.8, 29.9, 34.7, 80.3, 95.7, 122.1, 126.4, 127.6, 128.3, 128.4, 128.5, 131.0, 134.0, 140.4, 141.0, 201.0; IR (KBr): 3028, 2927, 2227, 1688, 1279, 1244, 763, 700;HRMS (ESI): [M+H]$^+$ calcd for C$_{18}$H$_{17}$O$^+$, 249.1274; found, m/z 249.1275.

1-(2-(3-methoxyprop-1-yn-1-yl)phenyl)ethan-1-one (4m)
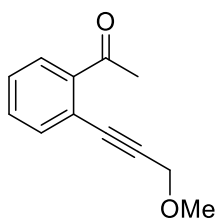
Oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.71 (s, 3H), 3.48 (s, 3H), 4.37 (s, 2H), 7.36-7.48 (m, 2H), 7.55 (d, J = 7.3 Hz, 1H), 7.71 (dd, J = 1.5, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 57.8, 60.4, 85.2, 90.7, 120.9, 128.4, 128.5, 131.2, 134.2, 140.8, 200.1; IR (KBr): 2933, 2823, 1690, 1357, 1246, 1090, 764; HRMS (ESI): [M+H]$^+$ calcd for C$_{12}$H$_{13}$O$_2^+$, 189.0911; found, m/z 189.0903.

1-(2-ethynylphenyl)ethan-1-one (4n)
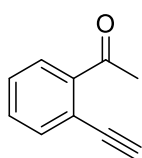
Oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.72 (s, 3H), 3.40 (s, 1H), 7.40-7.48 (m, 2H), 7.59-7.63 (m, 1H), 7.69-7.73 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.8, 82.4, 82.9, 120.3, 128.6, 128.8, 131.2, 134.7, 141.5, 200.1; IR (KBr): 3284, 3065, 2104, 1686, 1593, 1281, 764; HRMS (ESI): [M+H]$^+$ calcd for C$_{10}$H$_9$O$^+$, 145.0563; found, m/z 145.0646.

1-(1-phenylethynyl)phenyl)propanone (4o)
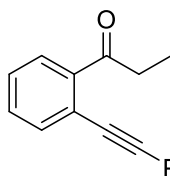
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.25 (t, J = 7.2 Hz, 3H), 3.18 (q, J = 7.3 Hz, 2H), 7.35-7.42 (m, 4H), 7.46 (tq, J = 1.6, 7.5 Hz, 2H),7.51-7.56 (m, 1H), 7.62 (dd, J = 1.2, 7.3 Hz, 1H), 7.66 (d, J = 1.3 Hz, 1H), 7.68 (d, J = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 8.5, 35.3, 88.2, 94.4, 121.1, 122.9, 128.1, 128.3, 128.4, 128.7, 130.8, 131.5, 133.7, 141.3, 204.1; IR (KBr): 2976, 2937, 2215, 1698, 950, 757, 732, 691; HRMS (ESI): [M+H]$^+$ calcd for C$_{17}$H$_{15}$O$^+$, 235.1118; found, m/z 235.1118.

1-(1-phenylethynyl)phenyl)pentanone (4p)
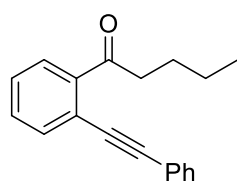
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.92 (t, J = 7.3 Hz, 3H), 1.40 (td, J = 7.3, 14.9 Hz, 2H), 1.69-1.78 (m, 2H), 3.16 (t, J = 7.6 Hz, 2H), 7.35-7.42 (m, 4H), 7.46 (td, J = 1.3, 7.4 Hz, 1H), 7.51-7.56 (m, 2H), 7.62 (dd, J = 1.0, 7.8 Hz, 1H), 7.65 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.9, 22.5, 26.6, 41.9, 88.2, 94.4, 121.1, 122.9, 128.1, 128.3, 128.4, 128.7, 130.8, 131.5, 133.7, 141.5, 203.9; IR (KBr): 3061, 2958, 2872, 2215, 1686, 1493, 1200, 758; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{19}$O$^+$, 263.1436; found, m/z 263.1434.

1-(1-phenylethynyl)phenyl)hex-5-en-1-one (4q)
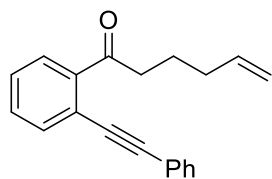
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.83-1.90 (m, 2H), 2.14 (q, J = 7.2 Hz, 2H), 3.16 (t, J = 7.6 Hz, 2H), 4.91-5.03 (m, 2H), 5.73-5.83 (m, 1H), 7.32-7.40 (m, 4H), 7.44 (td, J = 1.5, 7.6 Hz, 1H), 7.61 (dd, J = 1.5, 7.8 Hz, 2H), 7.65 (dd, J = 1.2, 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ =23.5, 33.2, 41.3, 88.2, 94.4, 115.2, 121.08, 122.8, 128.1, 128.2, 128.4, 128.6, 130.8, 131.5, 133.7, 137.9, 141.3, 203.3; IR (KBr):3063, 2933, 2215, 1686, 1474, 1197, 690; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{19}$O$^+$, 275.1430; found, m/z 275.1436.

4-8. ジヒドロイソベンゾフラン誘導体 5a の合成

The reaction was performed using a pressure test-tube equipped with a stirring bar in a 30 mL autoclave. To a mixture of AgOAc (2.5 mg, 0.015 mmol) and **4a** (33.0 mg, 0.15 mmol) in 1.0 mL CH$_3$CN in a pressure test-tube was added DBU (45 μL, 0.30 mmol) with a micro syling. The pressure test-tube containing the reaction mixture was placed in the autoclave. CO$_2$ (1.0 MPa) was purged and the reaction mixture was stirred at 30 °C for 1 h. After the CO$_2$ was vented, the reaction was quenched with buffer (pH = 6) and extracted with EtOAc, then removed solvent to give **5a** (99%) (trimethylphenylsilane (5 μL, 0.029 mmol) was added, then the yield was determined by ^{1}H NMR spectrum). If needed, the product was purified by recrystalization with CH$_3$CN to afford the corresponding dihydroisobenzofuran **5a** (66%) as a yellow solid.

4-9. ジヒドロイソベンゾフラン誘導体 6b の合成

The reaction was performed using a pressure test-tube equipped with a stirring bar in a 30 mL autoclave. To a mixture of AgOAc (2.5 mg, 0.015 mmol) and **5b** (42.0 mg, 0.15 mmol) in 1.0 mL CH$_3$CN in a pressure test-tube was added DBU (45 μL, 0.30 mmol) with a microsyringe. The pressure test-tube containing the reaction mixture was placed in the autoclave. The autoclave was purged with CO$_2$ (1.0 MPa) and the reaction mixture was stirred at 30 °C for 6 h. After the CO$_2$ was released, MeI (37 μL, 0.60 mmol) was added to the reactant. After 3 h, the reaction mixture was purified with column chromatography (SiO$_2$, eluent: hexane/EtOAc 20/1 then 8/1) to produce the corresponding dihydroisobenzofuran **6b** (91%) as a yellow solid.

4-10. ジヒドロイソベンゾフラン誘導体 5 および 6 の化合物データ
(Z)-2-[(Z)-3-Benzylideneisobenzofuran-1(3H)-ylidene]acetic acid (5a):
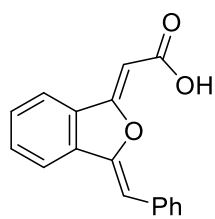
Yellow solid; m.p. 192 °C; ^{1}H NMR (400 MHz, d-DMSO): δ = 5.92 (s, 1H), 6.72 (s, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.52-7.59 (m, 1H), 7.63-7.69 (m, 1H), 7.66 (t, J = 7.5 Hz, 1H), 8.00 (t, J = 6.1 Hz, 1H), 8.01-8.07 (m, 3H), 12.09 (s, 1H); ^{13}C NMR (100 MHz, d-DMSO): δ = 89.8, 103.1, 120.5, 122.1, 127.4, 128.7, 129.3, 129.9, 131.4, 132.0, 134.1, 134.6, 150.3, 150.3, 161.1, 165.9;

IR (KBr): 2584, 1698, 1629, 1462; HRMS (ESI): [M+H]$^+$ calcd for $C_{17}H_{13}O_3^+$, 265.0865; found, m/z 265.0863; NOE (δ = 5.92) 4%, NOE (δ = 6.72) 5 %, 7%.

Methyl (*Z*)-2-[(*Z*)-3-Benzylideneisobenzofuran-1(3*H*)-ylidene]acetate (6a)
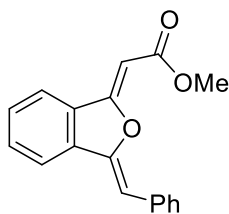
Pale yellow solid; m.p. 96 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.90 (s, 3H), 5.69 (s, 1H), 6.33 (s, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 3H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.4, 88.4, 103.9, 119.9, 121.4, 127.6, 128.7, 129.37, 129.42, 131.6, 131.9, 134.0, 135.5, 150.7, 162.1, 165.9; IR (KBr): 3067, 1686, 1434, 1273, 1150, 1021, 758; HRMS (ESI): [M+H]$^+$ calcd for $C_{18}H_{15}O_3^+$, 279.1016; found, m/z 279.1016; NOE (δ = 5.69) 2.0%, NOE (δ = 6.33) 2.2%, 2.9%.

Methyl (*Z*)-2-[(*Z*)-3-benzylidene-5, 6-dimthoxy-isobenzofuran-1(3*H*)-ylidene]acetate (6b)
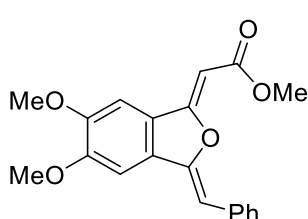
Pale yellow solid; m.p. 194 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.88 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 5.52 (s, 1H), 6.18 (s, 1H), 6.99 (s, 1H), 7.05 (s, 1H), 7.27 (t, *J* = 7.3 Hz, 3H), 7.44 (t, *J* = 7.8 Hz, 2H), 8.00 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.3, 56.2, 56.3, 86.8, 100.9, 102.0, 102.6, 124.8, 127.2, 128.7, 129.2, 129.3, 134.2, 150.8, 151.3, 153.2, 162.2, 166.0; IR (KBr): 3000, 2946, 1686, 1501, 1343, 1263, 1222, 1030, 826; HRMS (ESI): [M+H]$^+$ calcd for $C_{20}H_{19}O_5^+$, 339.1227; found, m/z 339.1230; NOE (δ = 5.50) 3.7%, NOE (δ = 6.15) 4.0 %, 5.2%.

Methyl (*Z*)-2-[(*Z*)-3-benzylidene-5-fluoro-isobenzofuran-1(3*H*)-ylidene]acetate (6c)
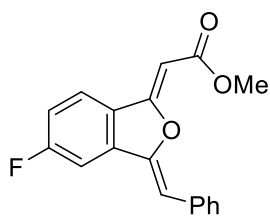
Pale yellow solid; m.p. 162 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.87 (s, 3H), 5.59 (s, 1H), 6.24 (s, 1H), 7.12 (td, *J* = 2.6, 8.6 Hz, 1H), 7.25-7.32 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.57 (dd, *J* = 4.5, 8.5 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.4, 88.2 (d), 104.9, 106.4 (d), 117.7 (d), 123.3 (d), 127.8 (d), 127.9, 128.7, 129.5, 133.6, 137.6 (d), 149.7 (d), 161.1, 163.7, 164.9 (d); IR (KBr): 3067, 2944, 1679, 1480, 1267, 1200, 1026, 810; HRMS (ESI): [M+H]$^+$ calcd for $C_{18}H_{14}FO_3^+$, 297.0922; found, m/z 297.0918; NOE (δ = 5.59) 2.3%, NOE (δ = 6.19) 2.5 %, 3.5%.

Methyl (*Z*)-2-[(*Z*)-3-benzylidene-6-chloro-isobenzofuran-1(3*H*)-ylidene]acetate (6d)
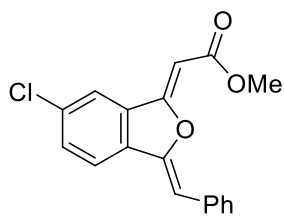
Pale yellow solid; m.p. 172 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.87 (s, 3H), 5.62 (s, 1H), 6.25 (s, 1H), 7.24-7.32 (m, 1H), 7.40-7.50 (m, 3H), 7.53-7.62 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.5, 89.2, 104.5, 121.0, 121.2, 128.8, 127.8, 129.5, 132.0, 133.3, 133.7, 133.8, 135.4, 149.8, 160.6, 165.5; IR (KBr): 3067, 2943, 1698, 1464, 1433,

1317, 1284, 1125, 1026, 815; HRMS (ESI): [M+H]$^+$ calcd for C$_{18}$H$_{14}$ClO$_3$$^+$, 313.0626; found, m/z 313.0626; NOE (δ = 5.62) 2.4%, NOE (δ = 6.25) 2.5 %, 3.7%.

Methyl (*Z*)-2-[(*Z*)-1-benzylidenenaththo[1.2-*c*]furan-3(1*H*)-ylidene]acetate (6e)

Yellow solid; m.p. 164 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.89 (s, 3H), 5.65 (s, 1H), 6.80 (s, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.33-7.43 (m, 3H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 8.13 (d, *J* = 7.6 Hz, 2H), 8.39 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.4, 88.0, 109.2, 117.4, 123.7, 126.5, 127.6, 127.8, 128.4, 128.7, 129.7, 130.0, 130.9, 131.0, 131.3, 134.6, 135.29, 151.8, 161.8, 166.0; IR (KBr): 3079, 2947, 1686, 1431, 1264, 1094, 1038, 819; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{17}$O$_3$$^+$, 329.1173; found, m/z 329.1174; NOE (δ = 5.65) 3.6%, NOE (δ = 6.81) 4.7 %, 12.9%.
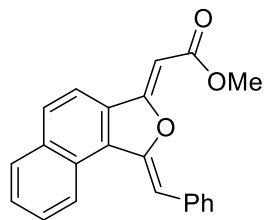
Methyl (*Z*)-2-[(*Z*)-3-(4-methylbenzylidene)isobenzofuran-1(3*H*)-ylidene]acetate (6f)
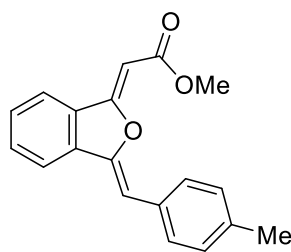
Pale yellow solid; m.p. 119 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.38 (s, 3H), 3.89 (s, 3H), 5.67 (s, 1H), 6.31 (s, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.43(td, *J* = 0.9, 7.5 Hz, 1H), 7.54 (td, *J* = 1.0, 7.5 Hz, 1H), 7.62-7.69 (m, 2H), 7.93 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 51.4, 88.0, 104.0, 119.8, 121.3, 129.1, 129.4, 129.5, 131.2, 131.5, 131.7, 135.6, 137.6, 150.1, 162.1, 166.0; IR (KBr): 3075, 2948, 1697, 1636, 1265, 1035, 848, 754; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{17}$O$_3$$^+$, 293.1173; found, m/z 293.1174; NOE (δ = 5.67) 2.3%, NOE (δ = 6.31) 2.4, 3.4%.

Methyl (*Z*)-2-[(*Z*)-3-(4-trifluoromethylbenzylidene)isobenzofuran-1(3*H*)-ylidene]acetate (6g)

Pale yellow solid; m.p. 135 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.89 (s, 3H), 5.73 (s, 1H), 6.33 (s, 1H), 7.50 (td, *J* = 0.9, 7.5 Hz, 1H), 7.58 (td, *J* = 0.9, 7.5 Hz, 1H), 7.66-7.74 (m, 4H), 8.12 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.5, 89.2, 102.1, 120.2, 121.4, 125.6 (q), 128.6, 128.9, 1289.3, 123.0, 131.8, 132.2, 135.0, 137.6, 152.2, 161.7, 165.6; IR (KBr): 3066, 1682, 1474, 1331, 1267, 1162, 1070, 1026, 874, 760; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{14}$F$_3$O$_3$$^+$, 347.0890; found, m/z 347.0893; NOE (δ = 5.73) 2.3%, NOE (δ = 6.33) 2.9 %, 3.7%.

Methyl (*Z*)-2-[(*Z*)-3-(4-acetylbenzylidene)isobenzofuran-1(3*H*)-ylidene]acetate (6h)
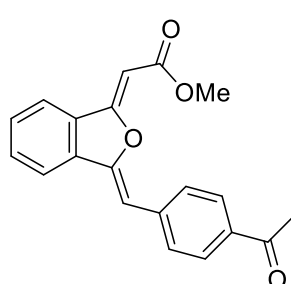
Pale yellow solid; m.p. 194 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.63 (s, 3H), 3.90 (s, 3H), 5.73 (s, 1H), 6.33 (s, 1H), 7.49 (td, *J* = 1.0, 7.6 Hz, 1H), 7.57 (td, *J* = 1.0, 7.6 Hz, 1H), 7.65-7.67 (m, 1H), 7.70-7.72 (m, 1H), 8.01-8.05 (m, 2H), 8.08-8.12 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ =

26.6, 51.5, 89.2, 102.6, 120.2, 121.4, 128.8, 129.2, 130.0, 131.7, 132.1, 135.0, 135.3, 138.8, 152.4, 156.0, 161.6, 165.6, 197.6; IR (KBr): 3085, 2953, 1710, 1668, 1645, 1276, 1154, 856; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{17}$O$_4^+$, 321.1121; found, m/z 321.1129; NOE (δ = 5.69) 8.4%, NOE (δ = 6.31) 10.8 %, 16.3%.

Methyl (Z)-2-[(Z)-3-(4-formylbenzylidene)isobenzofuran-1(3H)-ylidene]acetate (6i)
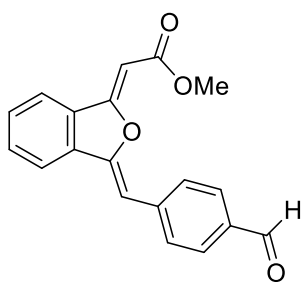
Pale yellow solid; m.p. 144 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.90 (s, 3H), 5.74 (s, 1H), 6.33 (s, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.3 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 8.16 (d, J = 8.3 Hz, 2H), 10.0 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.5, 89.6, 102.4, 120.3, 121.4, 129.6, 130.1, 130.2, 131.8, 132.2, 134.6, 134.8, 140.3, 152.9, 161.5, 165.5, 191.7; IR (KBr): 3025, 2794, 2717, 1721, 1691, 1594, 1151, 1041, 852, 765; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{15}$O$_4^+$, 307.0965; found, m/z 307.0966; NOE (δ = 5.69) 11.2%, NOE (δ = 6.29) 12.3 %, 19.7%.

Methyl (Z)-2-[(Z)-(2-methoxycarbonylbenzylidene)isobenzofuran-1(3H)-ylidene]acetate (6j)
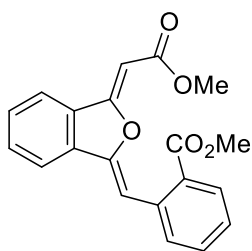
Pale yellow solid; m.p. 139 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.85 (s, 3H), 3.93 (s, 3H), 5.68 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.51-7.57 (m, 2H), 7.60-7.70 (m, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.76 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.3, 52.1, 88.6, 100.2, 120.5, 121.2, 126.8, 128.2, 129.6, 130.7, 131.0, 131.6, 131.8, 132.3, 134.7, 135.6, 151.8, 161.9, 165.7, 167.9; IR (KBr): 2047, 1724, 1684, 1487, 1425, 1265, 1243, 1107, 1034, 759; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{17}$O$_5^+$, 337.1071; found, m/z 337.1073; NOE (δ = 5.67) 2.6%.

Methyl (Z)-2-[(Z)-3-pentylideneisobenzofuran-1(3H)-ylidene]acetate (6k)
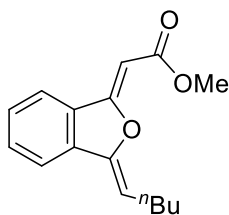
Pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.95 (t, J = 7.2 Hz, 3H), 1.37-1.48 (m, 2H), 1.49-1.58 (m, 2H), 2.56 (q, J = 7.4 Hz, 2H), 3.80 (s, 3H), 5.48 (t, J = 7.7 Hz, 1H), 5.56 (s, 1H), 7.37-7.42 (m, 1H), 7.47-7.52 (m, 1H), 7.56 (dd, J = 0.9, 7.9 Hz, 1H), 7.59 (dd, J = 1.0, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.9, 22.4, 25.4, 31.6, 51.2, 86.6, 105.9, 119.7, 121.2, 128.9, 131.4, 132.5, 134.6, 151.5, 162.6, 166.2; IR (KBr): 2954, 2858, 1868, 1647, 1434, 1270, 1152, 1038, 767; HRMS (ESI): [M+H]$^+$ calcd for C$_{15}$H$_{17}$O$_3^+$, 245.1178; found, m/z 245.1176.

Methyl (Z)-2-[(Z)-3-(3-phenylpropylidene)isobenzofuran-1(3H)-ylidene]acetate (6l)
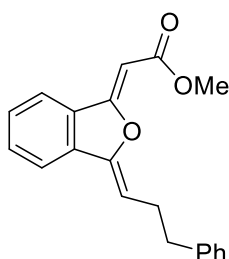
Pale yellow viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.87-2.91 (m, 4H), 3.81 (s, 3H), 5.45-5.50 (m, 1H), 5.57 (s, 1H), 7.17-7.23 (m, 1H), 7.26-7.33 (m, 4H), 7.37-7.42 (m, 1H), 7.45-7.54 (m, 2H), 7.59 (dd, J = 0.7, 8.8 Hz, 1H); ^{13}C

NMR (100 MHz, CDCl$_3$): δ = 27.2, 35.5, 51.2, 86.9, 104.4, 119.8, 121.2, 126.0, 128.4, 128.6, 129.0, 131.4, 132.6, 134.5, 141.4, 151.9, 162.4, 166.1; IR (KBr): 3025, 2947, 1650, 1473, 1270, 1148, 1030; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{19}$O$_3$$^+$, 307.1329; found, m/z 307.1332.

Methyl (*Z*)-2-[(*Z*)-3-(2-methoxyethylidene)isobenzofuran-1(3*H*)-ylidene]acetate (6m)

Colorless viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.44 (s, 3H), 3.80 (s, 3H), 4.47 (d, *J* = 7.0 Hz, 2H), 5.60 (t, *J* = 7.2 Hz, 1H), 5.61 (s, 1H), 7.43-7.48 (m, 1H), 7.50-7.56 (m, 1H), 7.59-7.63 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.2, 58.3, 88.4, 87.9, 100.7, 120.3, 121.1, 129.8, 131.6, 132.9, 133.9, 153.0, 161.9, 165.8; IR (KBr): 2949, 1775, 1686, 1655, 1435, 1273, 1155, 769; HRMS (ESI): [M+H]$^+$ calcd for C$_{14}$H$_{15}$O$_4$$^+$, 247.0965; found, m/z 247.0968.
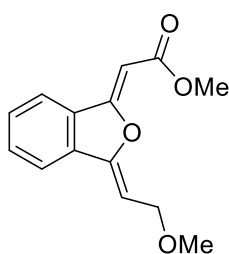
Methyl (*Z*)-2-[(*Z*)-3-methyleneisobenzofuran-1(3*H*)-ylidene]acetate (6n)
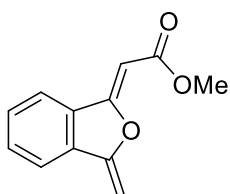
Viscous oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.80 (s, 3H), 5.06 (d, *J* = 3.1 Hz, 1H) 5.20 (d, *J* = 3.1 Hz, 1H), 5.60 (s, 1H), 7.45-7.50 (m, 1H), 7.52-7.57 (m, 1H), 7.59-7.67 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 51.3, 87.6, 87.7, 120.7, 121.1, 129.9, 131.6, 133.2, 134.0, 157.7, 162.0, 165.8; IR (KBr): 2947, 1686, 1638, 1467, 1433, 1152, 1052, 765; HRMS (ESI): [M+H]$^+$ calcd for C$_{12}$H$_{11}$O$_3$$^+$, 203.0703; found, m/z 203.0700.

Methyl (*Z*)-2-[(*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene]propionate (6o)

Pale yellow solid; m.p. 118 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.35 (s, 3H), 3.98 (s, 3H), 6.21 (s, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.38-7.52 (m, 4H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.4, 52.0, 100.9, 101.4, 119.9, 125.3, 127.0, 128.5, 129.0, 129.2, 130.3, 132.5, 134.5, 136.4, 150.4, 157.5, 168.2; IR (KBr): 3050, 1672, 1619, 1128, 1108, 753; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{17}$O$_3$$^+$, 293.1173; found, m/z 293.1177; NOE (δ = 2.35) 4.6%, NOE (δ = 6.22) 2.5 %, 2.8%.

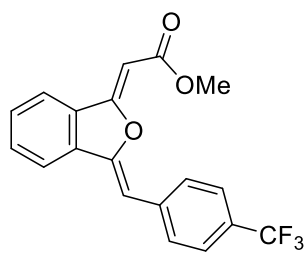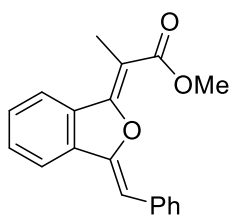### Methyl (*Z*)-2-[(*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene]pentanoate (6p)
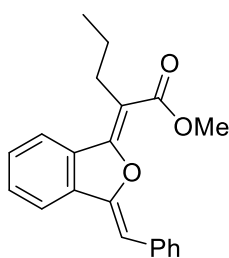
Pale yellow solid; m.p. 93 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.07 (t, *J* = 7.3 Hz, 3H), 1.59-1.69 (m, 2H), 2.77 (t, *J* = 8.0 Hz, 2H), 3.98 (s, 3H), 6.23 (s, 1H), 7.22-7.29 (m, 1H), 7.37-7.54 (m, 4H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.99 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.0, 22.6, 29.0, 51.9, 101.3, 107.0, 120.0, 124.8, 127.0, 128.5, 129.0, 129.4, 130.4, 131.9, 134.5, 136.6, 150.2, 157.5, 168.2; IR (KBr): 2956, 1682, 1618, 1137, 1109, 757; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{21}$O$_3$$^+$, 321.1486; found, m/z 321.1488; NOE (δ = 2.78) 9.9%, NOE (δ = 6.23) 2.7 %, 3.3%.

Methyl (*Z*)-2-[(*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene]hex-5-enoate (6q)

Pale yellow solid; m.p. 89 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.37 (dd, *J* = 6.8, 15.1 Hz, 2H), 2.85-2.94 (m, 2H), 3.99 (s, 3H), 5.04-5.07 (m, 1H), 5.12-5.16 (m, 1H), 5.92-6.04 (m, 1H), 6.24 (s, 1H), 7.22-7.29 (m, 1H), 7.36-7.55 (m, 4H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.4, 33.3, 52.0, 101.5, 106.1, 115.2, 120.0, 124.9, 127.1, 128.5, 129.0, 129.5, 130.5, 131.7, 134.4, 136.6, 137.6, 150.2, 157.8, 167.9; IR (KBr): 3075, 2943, 1675, 1618, 1321, 1108, 764; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{21}$O$_3^+$, 333.1485; found, m/z 333.1482; NOE (δ = 6.22) 13.0%, 16.7%.

5. プロパルギルアミンに対する二酸化炭素およびヨード基の連続的導入反応（第2章）

5-1. 溶媒

　テトラヒドロフランおよびジクロロメタンは関東化学社から購入した有機合成用安定化剤無添加脱水溶媒をそのまま用いた（製品番号：THF 41001-85，CH_2Cl_2 11338-85）。アセトニトリル、N, N - ジメチルホルムアミドおよびジメチルスルホキシドは和光純薬社から購入した有機合成用脱水溶媒をそのまま用いた（製品番号：CH_3CN 018-22901，DMF 046-26023，DMSO 041-25473）。

5-2. 試薬

　N - ヨードスクシイミド（製品番号：095-04312）と酢酸銀（製品番号：197-09842）は和光純薬社から購入した市販品をそのまま用いた。硝酸銀（製品番号：209,39-100G）はAldrich 社から購入した市販品をそのまま用いた。

5-3. プロパルギルアミン 7 の合成

R^1 = Bn, R^2 = Ph(**7a**), 4-CF$_3$C$_6$H$_4$(**7b**), 4-MeC$_6$H$_4$(**7d**), 4-OMeC$_6$H$_4$(**7e**)
　　　　　1-naph(**7f**), 2-naph(**7g**), 2-thienyl(**7h**)
R^1 = PMB, R^2 = Ph(**7j**)

　　　Propargyl amines **7a**-**7h** and **7j** were synthesized by the introduction of acetyl group followed by propargylic substitution reaction and Sonogashira-coupling reaction.

　　　To the solution of DMAP (20 mol%, 4 mmol) and 2-methyl-3-butyn-2-ol (1.0 eq., 20 mmol) in CH_2Cl_2 (40 mL) were added Et$_3$N (3.0 eq., 60 mmol) and Ac$_2$O (1.0 eq., 20 mmol), and the mixture was stirred at room temperature. Upon completion, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO$_2$, eluent: CHCl$_3$) to give 2-methylbut-3-yn-2-yl acetate (92% yield) as a colorless oil.

　　　N-benzyl-2-methylbut-3-yn-2-amine was synthesized according to the literature.[54] To the solution of CuCl (20 mol%, 2 mmol) in THF (20 mL) were added propargyl acetate (1.0 eq., 10 mmol) and benzylamine (2.0 eq., 20 mmol), and the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was diluted with Et$_2$O and acidified with 2 N HCl, and layers were separated. The aqueous layer was basified with 1 N NaOH and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to give *N*-benzyl-2-methylbut-3-yn-2-amine (65% yield) or *N*-(4-methoxybenzyl)-2-methylbut-3-yn-2-amine (60% yield) as a colorless solid.

To the solution of PdCl$_2$(PPh$_3$)$_2$ (2 mol%, 0.02 mmol), CuI (4 mol%, 0.04 mmol), Et$_3$N (2.0 eq., 2 mmol) and the corresponding aryl iodide (1.1 eq., 1.1 mmol) in THF (2 mL), *N*-benzyl-2-methylbut-3-yn-2-amine or *N*-(4-methoxybenzyl)-2-methylbut-3-yn-2-amine (1.0 eq., 1 mmol) was added dropwise and the mixture was stirred at room temperature. Upon completion, the reaction mixture was quenched with sat. NH$_4$Cl aq. and extracted three times with Et$_2$O. The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the desired starting material (**7a, 7b, 7d-7h, 7j**) in a high yield.

7c

The starting material **7c** was prepared according to the procedure of the literature.[55] To the solution of Pd(OAc)$_2$ (2 mol%, 0.04 mmol), Ph$_3$P (4.5 mol%, 0.045 mmol) and 4-iodoacetophenone (1.2 eq., 2.4 mmol) in Et$_3$N (3 mL), was added the solution of *N*-benzyl-2-methylbut-3-yn-2-amine in DMF (1 mL). The mixture was stirred at 50 °C for 5 h. After cooling to room temperature, the mixture was quenched with sat. NH$_4$Cl aq. and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the desired starting material **7c** (97% yield) as a pale yellow solid.

N-benzyl-2-methyl-4-(*p*-tolyl)but-3-yn-2-amine (7d)

Pale yellow solid; m.p. 43 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.49 (s, 6H), 2.35 (s, 3H), 3.95 (s, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 8.1 Hz, 4H), 7.38 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 29.7, 49.2, 50.6, 82.4, 93.7, 120.3, 126.9, 128.4, 129.0, 131.5, 137.8, 140.8; IR (KBr): 3305, 2973, 2848, 1508, 1453, 1375, 815; HRMS (ESI): [M+H]$^+$ calcd for C$_{19}$H$_{22}$N$^+$, 264.1747; found, m/z 264.1744.

N-benzyl-2-methyl-4-(naphthalene-2-yl)but-3-yn-2-amine (7f)

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.62 (s, 6H), 4.06 (s, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.40-7.44 (m, 3H), 7.51 (t, *J* = 6.7 Hz, 1H), 7.57 (t, *J* = 6.8 Hz, 1H), 7.67 (d, *J* = 6.1 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 8.35 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.9, 49.4, 51.0, 80.3, 99.6, 121.0, 125.2, 126.1, 126.3,

126.6, 127.0, 128.28, 128.30, 128.5, 130.2, 133.2, 133.3, 140.7; IR (KBr): 3311, 2978, 1602, 1454, 1395, 774; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{22}$N$^+$, 300.1747; found, m/z 300.1748.

N-benzyl-2-methyl-4-(naphthalene-1-yl)but-3-yn-2-amine (7g)

Pale yellow solid; m.p. 55 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.54 (s, 6H), 4.01 (s, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.46-7.50 (m, 3H), 7.76-7.82 (m, 3H), 7.95 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 49.2, 50.7, 82.7, 94.9, 120.7, 126.4, 126.5, 127.0, 127.6, 127.7, 127.9, 128.45, 128.48, 128.7, 131.2, 132.6, 133.0, 140.7; IR (KBr): 3311, 2974, 1593, 1497, 1381, 732; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{22}$N$^+$, 300.1747; found, m/z 264.1746.

N-benzyl-2-methyl-4-(thiophen-2-yl)but-3-yn-2-amine (7h)

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.49 (s, 6H), 3.93 (s, 2H), 6.97 (dd, *J* = 5.1 Hz, 3.7 Hz, 1H), 7.18 (d, *J* = 3.4 Hz, 1H), 7.22 (d, *J* = 5.4 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.5, 49.2, 50.9, 75.5, 98.4, 123.4, 126.4, 126.9, 127.0, 128.4, 128.5, 131.4, 140.6; IR (KBr): 3311, 2979, 1454, 1379, 852, 697; HRMS (ESI): [M+H]$^+$ calcd for C$_{16}$H$_{18}$NS$^+$, 256.1155; found, m/z 256.1154.

R^1 = CH$_2$CH$_2$Ph, R^2 = Et, R^3 = Bn (7i)
R^1 = Ph, R^2 = isobutyl, R^3 = PMB (7k)

The starting materials (**7i, 7k**) were synthesized according to the procedure of the literature.[56]

The solution of CuBr (20 mol%, 0.2 mmol), amine (1.5 eq., 1.5 mmol), acetylene (1.5 eq., 1.5 mmol) and aldehyde (1.0 eq., 1 mmol) in toluene (2 mL) was refluxed for 2 h. After cooling to room temperature, the reaction mixture was quenched with sat. NH$_4$Cl aq. The mixture was continued to stirr for further 2 h at room temperature and then resulting dark blue solution was extracted three times with toluene. The combined organic layers were washed three times with sat. NH$_4$Cl aq. and once with brine, and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (SiO$_2$, eluent: hexane/EtOAc) to afford the desired starting material **7i** (51% yield) or **7k** (70% yield).

N-benzyl-7-phenylhept-4-yn-3-amine (7i)

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3H), 1.37 (s, 1H), 1.50-1.69 (m, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.85 (t, *J* = 7.6 Hz,

2H), 3.25 (t, J = 6.8 Hz, 1H), 3.73 (d, J = 12.7 Hz, 1H), 3.93 (d, J = 12.7 Hz, 1H), 7.19-7.31 (m, 10 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 10.5, 20.9, 29.3, 35.4, 51.0, 51.4, 82.1, 83.1, 126.2, 126.9, 128.31, 128.34, 128.5, 140.3, 140.8; IR (KBr): 2930, 1454, 1340, 698; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{24}$N$^+$, 278.1904; found, m/z 278.1906.

R = Ph(**7l**), 4-MeC$_6$H$_4$(**7m**), 4-CF$_3$C$_6$H$_4$(**7n**)

The substrates **7l**-**7n** were synthesized from 2-methyl-3-butyn-2-amine by Sonogashira-coupling reaction.

To the solution of Pd$_2$Cl$_2$(PPh$_3$)$_2$ (2 mol%, 0.02 mmol), CuI (4 mol%, 0.04 mmol), Et$_3$N (2.0 eq., 2 mmol) and the corresponding aryl iodide (1.1 eq., 1.1 mmol) in THF (2 mL), 2-methyl-3-butyn-2-amine (1.0 eq., 1 mmol) was added dropwise and the mixture was stirred at room temperature. Upon completion, the reaction mixture was quenched with sat. NH$_4$Cl aq. and extracted three times with Et$_2$O. The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (SiO$_2$, eluent: from CHCl$_3$ to EtOAc) to afford the desired starting material (**7l**-**7n**) in high yield.

2-methyl-4-(p-tolyl)but-3-yn-2-amine (7m)

Pale orange solid; m.p. 30 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.48 (s, 6H), 1.74 (s, 2H), 2.33 (s, 3H), 7.09 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 31.8, 45.6, 80.0, 96.2, 120.2, 128.9, 131.3, 137.8; IR (KBr): 3364, 2972, 1509, 1380, 860, 817; HRMS (ESI): [M+H]$^+$ calcd for C$_{12}$H$_{16}$N$^+$, 174.1278; found, m/z 174.1282.

2-methyl-4-(4-(trifluoromethyl)phenyl)but-3-yn-2-amine (7n)

Pale yellow solid; m.p. 42 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.50 (s, 6H), 1.74 (s, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 31.6, 45.6, 78.8, 99.5, 123.9 (q, J = 271.9 Hz), 125.1 (q, J = 3.8 Hz), 127.2 (d, J = 1.9 Hz), 129.5 (q, J = 32.6), 131.7; IR (KBr): 3379, 2976, 2222, 1613, 1381, 1327, 842; HRMS (ESI): [M+H]$^+$ calcd for C$_{12}$H$_{13}$F$_3$N$^+$, 228.0995; found, m/z 228.0998.

5-4. オキサゾリジノン **8** の合成

The reaction was performed using a pressure test-tube equipped with a stirring bar in a 30 mL autoclave. To the mixture of AgOAc (2.5 mg, 10 mol%) and *N*-iodosuccinimide (33.8 mg, 1.0 eq.) in a pressure test-tube was added **7a** (37.4 mg, 0.15 mmol) in dry DMSO (1.0 mL). The pressure test-tube containing the reaction mixture was placed in the autoclave. The autoclave was purged with CO_2 and the reaction mixture was stirred at 25 °C for 24 h under CO_2 atmosphere (2.0 MPa). After CO_2 was vented, the reaction was quenched with $Na_2S_2O_3$ aq. and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (SiO_2, eluent: hexane/EtOAc) to produce the corresponding oxazolidinone **8a** (92%) as a colorless solid.

(*E*)-3-benzyl-5-(iodo(phenyl)methylene)-4,4-dimethyloxazolin-2-one (8a)

Colorless solid; m.p. 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 6H), 4.50 (s, 2H), 7.21-7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 44.1, 64.0, 68.8, 127.6, 127.8, 128.1, 128.2, 128.7, 129.4, 137.4, 139.8, 150.1, 153.3; IR (KBr): 2975, 1790, 1662, 1408, 1384, 1055, 751; HRMS (ESI): $[M+H]^+$ calcd for $C_{19}H_{19}INO_2^+$, 420.0455; found, m/z 420.0454.

(*E*)-3-benzyl-5-(iodo(4-(trifluoromethyl)phenyl)methylene)-4,4-dimethyloxazolin-2-one (8b)

Pale yellow solid; m.p. 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 6H), 4.50 (s, 2H), 7.30-7.35 (m, 5H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 44.2, 64.1, 66.1, 122.4, 125.1 (q, *J* = 3.4 Hz), 127.6, 127.9, 128.8, 129.9, 130.0 (q, *J* = 32.6 Hz), 137.1, 143.3, 151.3, 153.0; IR (KBr): 2981, 1790, 1658, 1407, 1385, 1319, 1057, 837; HRMS (ESI): $[M+H]^+$ calcd for $C_{20}H_{18}F_3INO_2^+$, 488.0329; found, m/z 488.0328.

(*E*)- 5-((4-acetylphenyl)iodomethylene)-3-benzyl-4,4-dimethyloxazolin-2-one (8c)

Pale yellow solid; m.p. 137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 6H), 2.61 (s, 3H), 4.50 (s, 2H), 7.29-7.35 (m, 5H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 26.7, 44.2, 64.1, 66.8, 127.6, 127.9, 128.2, 128.8, 129.9, 136.4, 137.2, 144.4, 151.1, 153.0, 197.4; IR (KBr): 2939, 1789, 1684, 1403, 1386, 1053, 741; HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{21}INO_3^+$, 462.0561; found, m/z 462.0561.

(*E*)-3-benzyl-5-(iodo(*p*-tolyl)methylene)-4,4-dimethyloxazolin-2-one (8d)

Pale yellow solid; m.p. 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 6H), 2.34 (s, 3H), 4.48 (s, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.28-7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 24.3, 44.1, 63.9, 69.1, 127.6,

127.7, 128.7, 128.8, 129.2, 137.0, 137.4, 138.1, 149.7, 153.3; IR (KBr): 2980, 1789, 1651, 1408, 1386, 1057, 707; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$INO$_2$$^+$, 434.0612; found, m/z 434.0613.
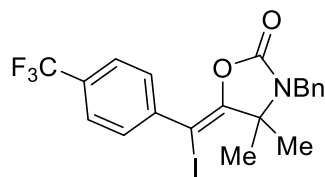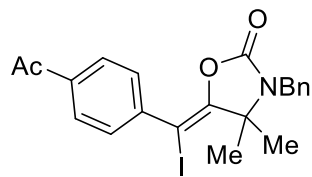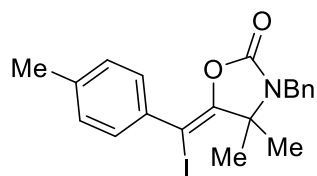
(*E*)-3-benzyl-5-(iodo(4-methoxyphenyl)methylene)-4,4-dimethyloxazolin-2-one (8e)
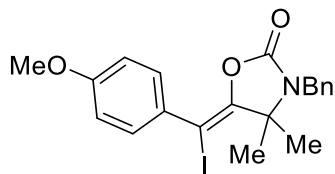
Pale yellow solid; m.p. 144 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.67 (s, 6H), 3.81 (s, 3H), 4.49 (s, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.28-7.36 (m, 7H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 24.4, 44.1, 55.3, 64.0, 69.1, 113.5, 127.6, 127.8, 128.7, 130.7, 132.2, 137.4, 149.5, 153.4, 159.2; IR (KBr): 2937, 1789, 1656, 1406, 1386, 1054, 740; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$INO$_3$$^+$, 450.0561; found, m/z 450.0560.

(*E*)-3-benzyl-5-(iodo(naphthalene-2-yl)methylene)-4,4-dimethyloxazolin-2-one (8f)

Pale yellow solid; m.p. 163 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.77 (s, 3H), 1.82 (s, 3H), 4.46 (d, *J* = 15.9 Hz, 1H), 4.53 (d, *J* = 15.9 Hz, 1H), 7.29-7.35 (m, 5H), 7.40-7.56 (m, 4H), 7.79 (d, *J* = 6.5 Hz, 1H), 7.86 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 24.5, 24.6, 44.2, 63.8, 64.8, 124.7, 125.5, 126.1, 126.3, 126.7, 127.7, 127.8, 128.5, 128.7, 128.9, 129.9, 134.0, 137.2, 137.3, 151.4, 153.3; IR (KBr): 2978, 1768, 1665, 1401, 1386, 1055, 776; HRMS (ESI): [M+H]$^+$ calcd for C$_{23}$H$_{21}$INO$_2$$^+$, 470.0612; found, m/z 470.0612.
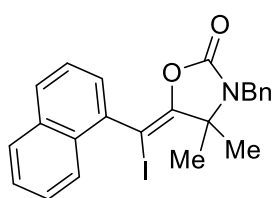
(*E*)-3-benzyl-5-(iodo(naphthalene-1-yl)methylene)-4,4-dimethyloxazolin-2-one (8g)
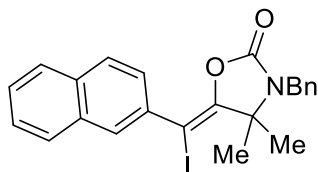
Pale yellow solid; m.p. 173 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.72 (s, 6H), 4.51 (s, 2H), 7.29-7.35 (m, 5H), 7.46-7.49 (m,3H), 7.78-7.82 (m, 3H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 24.4, 44.2, 64.0, 68.8, 126.3, 126.6, 127.1, 127.5, 127.6, 127.8, 128.2, 128.65, 128.72, 132.8, 132.9, 137.1, 137.3, 150.4, 153.3; IR (KBr): 2974, 1790, 1659, 1407, 1384, 1056, 739; HRMS (ESI): [M+H]$^+$ calcd for C$_{23}$H$_{21}$INO$_2$$^+$, 470.0612; found, m/z 470.0614.

(*E*)-3-benzyl-5-(iodo(thiophen-2-yl)methylene)-4,4-dimethyloxazolin-2-one (8h)
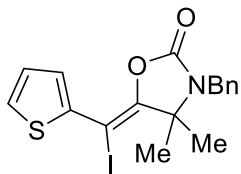
Pale yellow solid; m.p. 126 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.67 (s, 6H), 4.52 (s, 2H), 7.05 (dd, *J* = 5.2 Hz, 3.8 Hz, 1H), 7.28-7.35 (m, 5H), 7.41 (dd, *J* = 5.3 Hz, 1.2 Hz, 1H), 7.46 (dd, *J* = 3.7 Hz, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 24.5, 44.2, 62.8, 64.7, 126.3, 127.0, 127.6, 127.8, 128.7, 130.3, 137.2, 140.6, 149.4, 152.8; IR (KBr): 2970, 1766, 1618, 1402, 1367, 1046, 705; HRMS (ESI): [M+H]$^+$ calcd for C$_{17}$H$_{17}$INO$_2$S$^+$, 426.0020; found, m/z 426.0018.

(*E*)-3-benzyl-4-ethyl-5-(1-iodo-3-phenylpropylidene)oxazolin-2-one (8i)
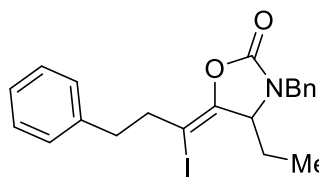
Pale yellow solid; m.p. 85 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.58 (t, *J* = 7.4 Hz, 3H), 1.57-1.67 (m, 1H), 2.08-2.18 (m, 1H), 2.72-2.86 (m, 3H), 2.98-3.07 (m, 1H), 3.93 (d, *J* = 15.3 Hz, 1H), 4.16 (t, *J* = 3.1 Hz, 1H), 4.88 (d, *J* = 15.3 Hz, 1H), 7.16-7.40 (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 5.9, 20.9, 35.0, 37.6, 45.2, 60.4, 78.2, 126.2, 128.0, 128.2, 128.3, 128.7, 128.9, 134.9, 139.8, 145.4, 155.0; IR (KBr): 3029, 2926, 1774, 1680, 1419, 1055, 711; HRMS (ESI): [M+H]$^+$ calcd for C$_{21}$H$_{23}$INO$_2{}^+$, 448.0768; found, m/z 448.0770.

(*E*)-5-(iodo(phenyl)methylene)-3-(4-methoxybenzyl)-4,4-dimethyloxazolin-2-one (8j)
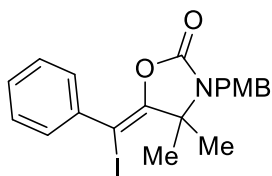
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.66 (s, 6H), 3.79 (s, 3H), 4.43 (s, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 24.3, 43.6, 55.2, 63.9, 68.6, 114.0, 128.06, 128.08, 129.0, 129.37, 129.39, 139.8, 150.1, 153.2, 159.1; IR (KBr): 2933, 2836, 1774, 1649, 1368, 1247, 1055, 762; HRMS (ESI): [M+H]$^+$ calcd for C$_{20}$H$_{21}$INO$_3{}^+$, 450.0561; found, m/z 450.0561.

(*E*)-5-(iodo(phenyl)methylene)-4-isobutyl-3-(4-methoxybenzyl)oxazolin-2-one (8k)
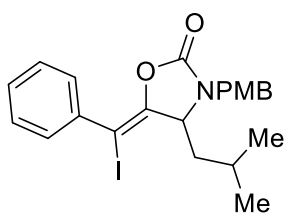
Pale brown oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.95 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H), 1.69-1.83 (m, 2H), 2.24-2.30 (m, 1H), 3.81 (s, 3H), 4.02 (d, *J* = 15.1 Hz, 1H), 4.39 (t, *J* = 3.9 Hz, 1H), 4.89 (d, *J* = 15.1 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.21-7.25 (m, 3H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.48 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 23.35, 23.44, 24.0, 36.8, 45.3, 55.3, 60.3, 73.9, 114.3, 126.8, 128.1, 128.3, 129.45, 129.51, 137.6, 146.4, 154.6, 159.5; IR (KBr): 2956, 1786, 1659, 1514, 1412, 1367, 1248, 1049, 767; HRMS (ESI): [M+H]$^+$ calcd for C$_{22}$H$_{25}$INO$_3{}^+$, 478.0874; found, m/z 478.0874.

5-(iodo(phenyl)methylene)-4,4-dimethyloxazolidin-2-one (*E:Z*=95:5) (8l)
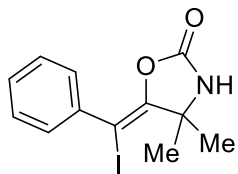
Colorless solid; m.p. 192 °C (decompose); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.20 (s, 0.3H, *Z* isomer), 1.78 (s, 5.7H, *E* isomer), 6.67 (s, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.8, 60.5, 69.1, 128.1, 128.2, 129.4, 139.5, 151.3, 153.0; IR (KBr):3251, 2977, 1774, 1662, 1384, 1342, 1024, 704; HRMS (ESI): [M+H]$^+$ calcd for C$_{12}$H$_{13}$INO$_2{}^+$, 329.9986; found, m/z 329.9983.

3-benzyl-5-(iodo(p-tolyl)methylene)-4,4-dimethyloxazolidin-2-one (*E:Z*=96:4) (8m)
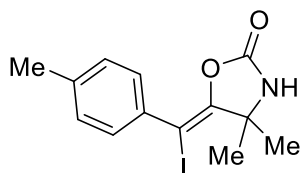
Colorless solid; m.p. 193 °C (decompose); ^{1}H NMR (400 MHz, CDCl$_3$): δ =1.22 (s, 0.2H, *Z* isomer), 1.79 (s, 5.8H, *E* isomer), 2.34 (s, 3H), 6.40 (s,

1H), 7.12 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.2, 26.8, 60.6, 69.4, 128.8, 129.2, 136.7, 138.1, 151.1, 153.4; IR (KBr): 3244, 2975, 1770, 1662, 1384, 1340, 1024, 801; HRMS (ESI): [M+H]$^+$ calcd for C$_{13}$H$_{15}$INO$_2^+$, 344.0142; found, m/z 344.0144.

3-benzyl-5-(iodo(4-(trifluoromethyl)phenyl)methylene)-4,4-dimethyloxazolidin-2-one (*E*:*Z*=97:3) (8n)
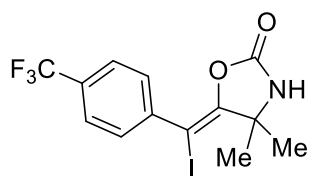
Colorless solid; m.p. 169 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.22 (s, 0.2H, *Z* isomer), 1.80 (s, 5.8H, *E* isomer), 6.53 (s, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.6, 60.8, 66.4, 119.8, 122.5, 125.2 (q, J = 3.9 Hz), 127.9, 129.6, 129.9, 130.3, 130.6, 143.1, 152.7, 153.1; IR (KBr): 3160, 2981, 1786, 1649, 1389, 1320, 1012, 852; HRMS (ESI): [M+H]$^+$ calcd for C$_{13}$H$_{12}$F$_3$INO$_2^+$, 397.9860; found, m/z 397.9861.

6. 銀触媒を用いるアリルケイ素化合物を求核種とする二酸化炭素固定化反応（第 3 章）

6-1. 溶媒

　テトラヒドロフランおよびジエチルエーテルは関東化学社から購入した有機合成用安定化無添加脱水溶媒をそのまま用いた（製品番号：THF 41001-85，Et$_2$O 14547-95）。N, N-ジメチルホルムアミドは和光純薬社から購入した有機合成用脱水溶媒をそのまま用いた（製品番号：DMF 046-26023）。

6-2. 試薬

　CsF は和光純薬社から購入した市販品をそのまま用いた（製品番号：031-17162）。(IPr)AgCl は東京化成工業社から購入した市販品をそのまま用いた（製品番号：C2373）。

6-3. 出発物質 11 の合成

R = （phenyl）-R^1　　R^1 = H(**11a**), p-Me(**11b**), m-Me(**11c**), o-Me(**11d**), p-OMe(**11e**), p-COOEt(**11f**), p-Ac(**11g**), p-CN(**11h**), p-CF$_3$(**11i**)

R =1-naph(**11j**), 2-naph(**11k**), 2-pyridyl(**11l**), ^{n}Bu(**11m**), CH$_2$CH$_2$Ph(**11n**), ^{t}Bu(**11o**)
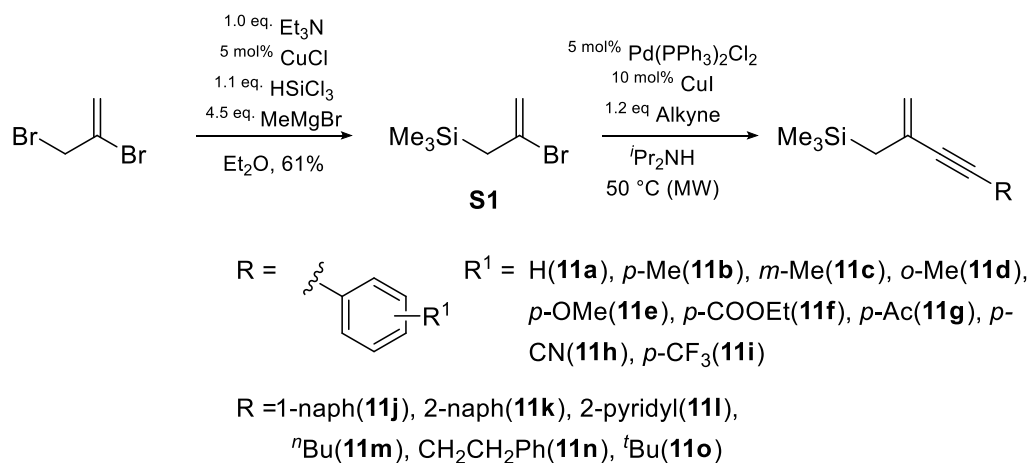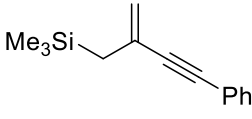
　　Substrates **11a-11o** were synthesized by the introduction of trimethylsilyl group followed by Sonogashira-coupling reaction. (2-bromo-allyl)-trimethyl-silane (**S1**) was synthesized according to the procedure in the literatures.[57] Et$_3$N (1.0 eq., 30 mmol) was added to CuCl (5 mol%, 1.5 mmol) in Et$_2$O (55 mL) in a two neck round bottom flask with reflux condenser. To the solution, the mixture of 2,3-dibromo-1-propene (1.0 eq., 30 mmol) and trichlorosilane (1.1 eq., 33 mmol) in Et$_2$O (5 mL) was slowly added and the solution was stirred for 6 h at room temperature. After cooling to 0 °C, MeMgBr (4.5 eq., 135 mmol, 3.0 M in Et$_2$O) was added over 10 min and the reaction mixture was stirred overnight at room temperature. The reaction was carefully quenched with sat. NH$_4$Cl aq. and poured onto water and Et$_2$O then extracted three times with Et$_2$O. The combined organic layers were washed with water and brine and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressre (250 hPa at 35 °C), the product was distilled under reduced pressure (32 mmHg, 58 °C) to give **S1** (61% yield) as a colorless oil.
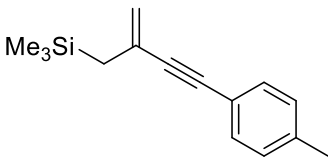
　　The corresponding alkyne (1.2 eq. 6 mmol) was added to the solution of Pd(PPh$_3$)$_2$Cl$_2$ (5 mol%, 0.025 mmol), CuI (10 mol%, 0.05 mmol) and **S1** (1 eq., 5 mmol) in ^{i}Pr$_2$NH (3 mL) in vial. The solution was heated at 50 °C with microwave. After stirred for 4 h, the reaction mixture was filtered then the solvent was removed under reduced pressure. The residue was purified by column

chromatography (SiO$_2$, eluent: hexane) to afford the desired starting material **11a-11o**, **11b-11d**, **11i-11k**, **11m-11q** could be purified by the bulb-to-bulb distillation.
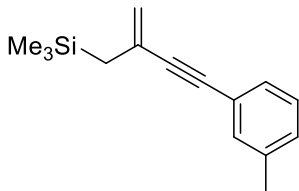
Trimethyl(2-methylene-4-phenylbut-3-ynyl)silane (11a)

The material data were in accordance with the previous literature.[58] Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.12 (s, 9H), 1.77 (d, J = 0.9 Hz, 2H), 5.08-5.10 (m, 1H), 5.28 (d, J = 2.0 Hz, 1H), 7.28-7.33 (m, 3H), 7.40-7.44 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 28.4, 88.4, 91.5, 119.0, 123.4, 128.0, 128.3, 128.9, 131.4.
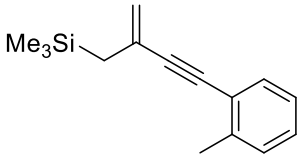
Trimethyl(2-methylene-4-(4-methylphenyl)but-3-ynyl)silane (11b)

Colorless oil; b.p. 145 °C (2.3 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.11 (s, 9H), 1.76 (s, 2H), 2.35 (s, 3H), 5.04-5.09 (m, 1H), 5.26 (d, J = 2.0 Hz, 1H), 7.11 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 21.5, 28.4, 88.6, 90.9, 118.6, 120.3, 128.98, 129.02, 131.3, 138.1; IR (KBr): 3093, 2955, 2210, 1597, 1510, 873, 854, 698; Anal. Calcd for C$_{15}$H$_{20}$Si: C, 78.88; H, 8.83. Found: C, 78.60; H, 8.67.
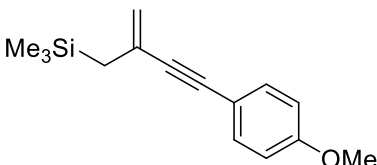
Trimethyl(2-methylene-4-(3-methylphenyl)but-3-ynyl)silane (11c)

Colorless oil; b.p. 125 °C (0.93 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.12 (s, 9H), 1.77 (s, 2H), 2.33 (s, 3H), 5.07-5.09 (m, 1H), 5.27 (d, J = 2.0 Hz, 1H), 7.08-7.13 (m, 1H), 7.16-7.27 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 21.2, 28.4, 88.5, 91.2, 118.9, 123.3, 128.2, 128.5, 128.9, 132.0, 137.9; IR (KBr): 3094, 2955, 2201, 1602, 1485, 854, 782, 690; Anal. Calcd for C$_{15}$H$_{20}$Si: C, 78.88; H, 8.83. Found: C, 79.07; H, 8.72.

Trimethyl(2-methylene-4-(2-methylphenyl)but-3-ynyl)silane (11d)

Colorless oil; b.p. 119 °C (0.79 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.11 (s, 9H), 1.78 (s, 2H), 2.44 (s, 3H), 5.06-5.10 (m, 1H), 5.29 (d, J = 2.0 Hz, 1H), 7.09-7.16 (m, 1H), 7.17-7.21 (m, 2H), 7.39 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 20.7, 28.3, 87.2, 95.5, 118.7, 123.2, 125.5, 128.0, 129.0, 129.4, 131.8, 140.0; IR (KBr):3094, 2955, 2209, 1594, 1485, 854, 700; Anal. Calcd for C$_{15}$H$_{20}$Si: C, 78.88; H, 8.83. Found: C, 78.34; H, 8.73.

Trimethyl(2-methylene-4-(4-methoxyphenyl)but-3-ynyl)silane (11e)

Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.11 (s, 9H), 1.76 (s, 2H), 3.81 (s, 3H), 5.03-5.07 (m, 1H), 5.23 (d, J = 2.0 Hz, 1H), 6.81-6.86 (m, 2H), 7.33-7.39 (m, 2H); ^{13}C NMR (100 MHz,

CDCl$_3$): δ = -1.6, 28.5, 55.3, 88.4, 90.2, 113.9, 115.6, 118.2, 129.0, 132.8, 159.4; IR (KBr): 3094, 2955, 2837, 2210, 1596, 854; HRMS (ESI): [M+Na]$^+$ calcd for C$_{15}$H$_{21}$OSiNa, 267.1176 ; found, m/z 267.1188.

Trimethyl(2-methylene-4-(4-ethoxycarbonylphenyl)but-3-ynyl)silane (11f)
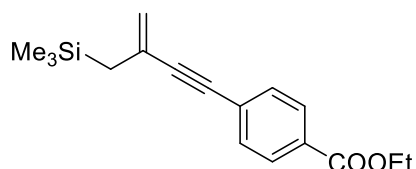
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.12 (s, 9H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.78 (d, *J* = 0.9 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 5.13-5.15 (m, 1H), 5.33 (d, *J* = 2.0 Hz, 1H), 7.47 (dt, *J* = 8.3, 1.7 Hz, 2H), 7.98 (dt, *J* = 8.5, 1.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 14.3, 28.2, 61.1, 87.6, 94.4, 120.0, 128.0, 128.6, 129.4, 129.6, 131.2, 166.1; IR (KBr): 3095, 2957, 2210, 1721, 1608, 856; HRMS (ESI): [M]$^+$ calcd for 287.1462; found, m/z 287.1452.

Trimethyl(2-methylene-4-(4-acetylphenyl)but-3-ynyl)silane (11g)
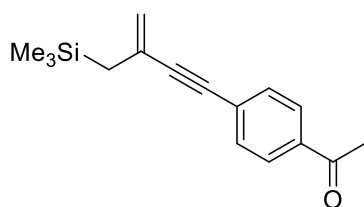
Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.12 (s, 9H), 1.78 (s, 2H), 2.60 (s, 3H), 5.14-5.17 (m, 1H), 5.34 (d, *J* = 1.8 Hz, 1H), 7.49 (dt, *J* = 1.7, 8.4 Hz, 2H), 7.90 (dt, *J* = 1.7, 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 26.6, 28.2, 87.6, 94.9, 120.2, 128.2, 128.4, 128.5, 131.5, 136.0, 197.3; IR (KBr): 3095, 2956, 2211, 1649, 1604, 1557, 851, 623; HRMS (ESI): [M+H]$^+$ calcd for C$_{16}$H$_{21}$OSi, 257.1357; found, m/z 257.1354.

Trimethyl(2-methylene-4-(4-cyanophenyl)but-3-ynyl)silane (11h)
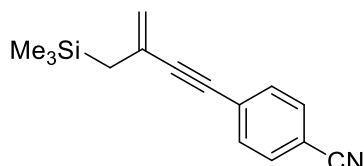
Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.11 (s, 9H), 1.77 (s, 2H), 5.17-5.19 (m, 1H), 5.35 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.7, 28.1, 86.7, 95.9, 11.23, 118.5, 120.7, 128.2, 128.4, 131.8, 132.0; IR (KBr):3095, 2954, 2227, 2213, 1605, 1501, 1249, 850; HRMS (ESI): [M+H]$^+$ calcd for C$_{15}$H$_{18}$NSi, 240.1204; found, m/z 240.1200.

Trimethyl(2-methylene-4-(4-trifluoromethylphenyl)but-3-ynyl)silane (11i)
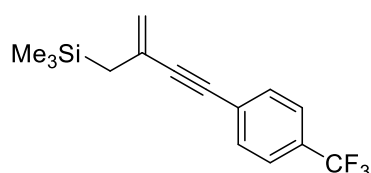
Colorless oil; b.p. 108 °C (0.28 Torr);^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.12 (s, 9H), 1.78 (d, *J* = 0.9 Hz, 2H), 5.14-5.16 (m, 1H), 5.33 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.7, 28.2, 87.0, 93.9, 120.2, 124.0 (q, *J* = 272.2 Hz), 125.2 (q, *J* = 3.8 Hz), 127.3 (q, *J* = 1.6 Hz), 128.5, 129.7 (q, *J* = 32.6 Hz) 131.6; IR (KBr): 3097, 2957, 2214, 1616, 1323, 841; Anal. Calcd for C$_{15}$H$_{17}$F$_3$Si: C, 63.80; H, 6.07. Found: C, 63.91; H, 6.20.

Trimethyl(2-methylene-4-(1-naphthyl)but-3-ynyl)silane (11j)
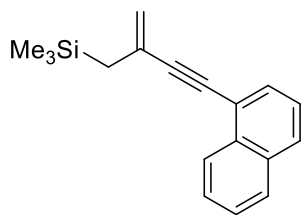
Colorless oil; b.p. 168 °C (0.41 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.15 (s, 9H), 1.87 (d, J = 1.1 Hz, 2H), 5.15-5.19 (m, 1H), 5.42 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 7.2, 8.1 Hz, 1H), 7.49-7.54 (m, 1H), 7.54-7.59 (m, 1H), 7.65 (dd, J = 1.1, 7.2 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.5, 28.4, 86.4, 96.5, 119.2, 121.1, 125.2, 126.2, 126.3, 126.6, 128.2, 128.5, 129.0, 130.2, 133.17, 133.19; IR (KBr): 3059, 2955, 2206, 1597, 851; Anal. Calcd for C$_{18}$H$_{20}$Si: C, 81.76; H, 7.62. Found: C, 81.99; H, 7.57.

Trimethyl(2-methylene-4-(2-naphthyl)but-3-ynyl)silane (11k)
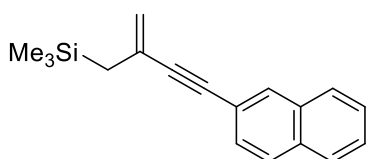
Colorless oil; b.p. 171 °C (0.46 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.15 (s, 9H), 1.81 (s, 2H), 5.11-5.13 (m, 1H), 5.33 (d, J = 2.0 Hz, 1H), 7.44-7.52 (m, 3H), 7.73-7.85 (m, 2H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 28.4, 88.8, 91.9, 119.2, 120.8, 126.46, 126.52, 127.7, 127.9, 128.3, 128.9, 131.1, 132.7, 133.0; IR (KBr): 3058, 2955, 2196, 1627, 855; Anal. Calcd for C$_{18}$H$_{20}$Si: C, 81.76; H, 7.62. Found: C, 82.02; H, 7.53.

Trimethyl(2-methylene-4-(2-pyridyl)but-3-ynyl)silane (11l)
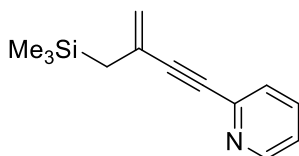
Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.12 (s, 9H), 1.79 (s, 2H), 5.16-5.22 (m, 1H), 5.40-5.46 (m, 1H), 7.17-7.25 (m, 1H), 7.38-7.44 (m, 1H), 7.60-7.67 (m, 1H), 8.56-8.62 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.7, 27.9, 87.6, 91.3, 121.0, 122.5, 126.9, 128.1, 136.0, 143.6, 150.0; IR (KBr): 3051, 2955, 2218, 1598, 1464, 854; HRMS (ESI): [M+H]$^+$ calcd for C$_{13}$H$_{18}$O, 216.1204; found, m/z 216.1206.

Trimethyl(2-methyleneoct-3-yn-1-yl)silane (11m)
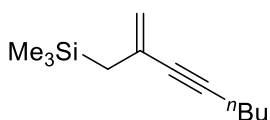
Colorless oil; b.p. 86 °C (2.5 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.06 (s, 9H), 0.91 (t, J = 7.2 Hz, 3H), 1.37-1.55 (m, 4H), 1.65 (d, J = 1.1 Hz, 2H), 2.28 (t, J = 7.0, 2H), 4.89-4.94 (m, 1H), 5.08 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 13.6, 18.9, 22.0, 28.7, 30.8, 82.6, 89.4, 117.3, 129.4; IR (KBr): 3094, 2958, 2934, 2223, 1599, 1249; Anal. Calcd for C$_{12}$H$_{22}$Si: C, 74.14; H, 11.41. Found: C, 72.79; H, 11.12.

Trimethyl(2-methylene-6-phenylhex-3-yn-1-yl)silane (11n)
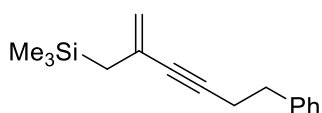
Colorless oil; b.p. 125 °C (0.59 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.04 (s, 9H), 1.63 (s, 2H), 2.57 (t, J = 7.6 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 4.91-4.95 (m, 1H), 5.09 (d, J = 2.0 Hz, 1H), 7.18-7.25 (m, 3H),

7.26-7.33 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.7, 21.5, 28.5, 35.1, 83.3, 88.4, 117.6, 126.2, 128.3, 128.4, 129.2, 140.7; IR (KBr): 3029, 2954, 2224, 1599, 855; Anal. Calcd for C$_{16}$H$_{22}$Si: C, 79.27; H, 9.15. Found: C, 79.31; H, 9.05.

Trimethyl (5,5-dimethyl-2-methylenehex-3-yn-1-yl) silane (11o)
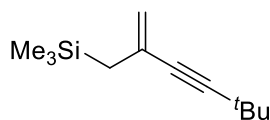
Colorless oil; b.p. 58 °C (1.0 Torr); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.07 (s, 9H), 1.23 (s, 9H), 1.65 (d, J = 1.1, 2H), 4.90-4.91 (m, 1H), 5.06 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 27.7, 28.9, 31.0, 81.1, 97.4, 117.2, 129.3; IR (KBr): 3095, 2970, 2226, 1599, 1363, 854; Anal. Calcd for C$_{12}$H$_{22}$Si: C, 74.14; H, 11.41. Found: C, 73.06; H, 11.16.
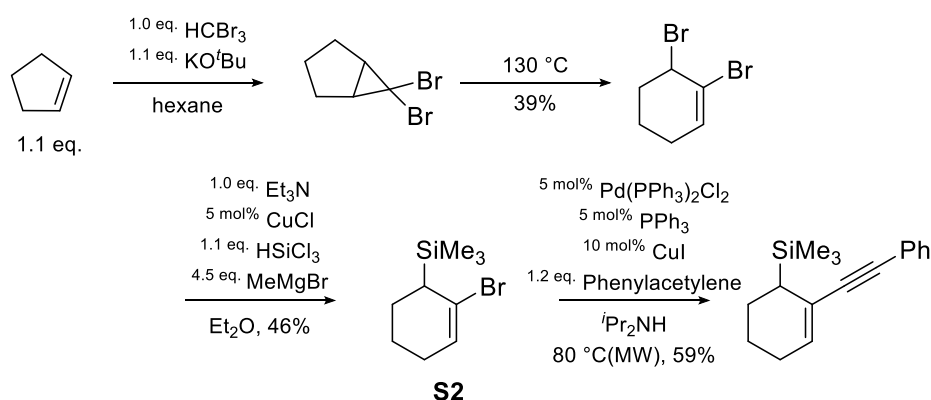
Compound **11p** was synthesized according to the previous literature.[59]

Bromoform (1.0 eq., 60 mmol) was added over 30 min at 0 °C to the mixture of cyclopentene (1.1 eq., 66 mmol) and KO^{t}Bu (1.1 eq., 66 mmol) in dry hexane (100 mL). The solution was stirred for 3 h at room temperature then poured onto ice. The mixture was extracted with hexane three times then the combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressure, the residue was heated to 130 °C until the reaction completed. The crude mixture was purified by column chromatography (SiO$_2$, eluent: hexane) to produce 2,3-dibromo-1-cyclohexene (39% yield) as a colorless oil.

Et$_3$N (1.0 eq., 22 mmol) was added to CuCl (5 mol%, 1.1 mmol) in Et$_2$O (38 mL) in a two neck round bottom flask with reflux condenser. To the solution, the mixture of 2,3-dibromo-1-cyclohexene (1.0 eq., 22 mmol) and trichlorosilane (1.1 eq., 24 mmol) in Et$_2$O (6 mL) was slowly added and the solution was stirred for 6 h at room temperature. After cooling to 0 °C, MeMgBr (4.5 eq., 99 mmol, 3.0 M in Et$_2$O) was added over 10 min (gently reflux) and the reaction mixture was stirred overnight at room temperature. The reaction was carefully quenched with sat. NH$_4$Cl aq. and poured onto water and Et$_2$O then extracted three times with Et$_2$O. The combined organic layers were washed with water and brine and dried over Na$_2$SO$_4$. After the solvent was removed under reduced pressre (250 hPa at 35 °C), the product was distilled under reduced pressure (10 mmHg, 90 °C) to give **S2** (46% yield) as a colorless oil.

Phenylacetylene (1.2 eq. 4 mmol) was added to the solution of Pd(PPh₃)₂Cl₂ (5 mol%, 0.1 mmol), PPh₃ (5 mol%, 0.1 mmol), CuI (10 mol%, 0.2 mmol) and **S2** (1.0 eq., 2 mmol) in ^{i}Pr₂NH (1 mL) in vial. The solution was heated at 80 °C with microwave. After stirred for 3 h, the reaction mixture was filtered then the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂, eluent: hexane) to afford the starting material **11p** (59% yield) as a colorless oil.

Trimethyl(2-(phenylethynyl)cyclohex-2-en-1-yl)silane (11p)

Colorless oil; b.p. 135 °C (0.28 Torr); ^{1}H NMR (400 MHz, CDCl₃): δ = 0.15 (s, 9H), 1.54-1.71 (m, 3H), 1.71-1.76 (m, 2H), 2.04-2.22 (m, 2H), 6.15-6.18 (m, 1H), 7.26-7.32 (m, 3H), 7.38-7.44 (m, 2H); ^{13}C NMR (100 MHz, CDCl₃): δ = -1.35, 21.0, 24.5, 25.7, 29.2, 87.2, 92.5, 122.7, 123.9, 127.6, 128.2, 131.2, 133.5; IR (KBr): 3020, 2937, 2204, 837; Anal. Calcd for C₁₇H₂₂Si: C, 80.25; H, 8.72. Found: C, 80.22; H, 8.56.
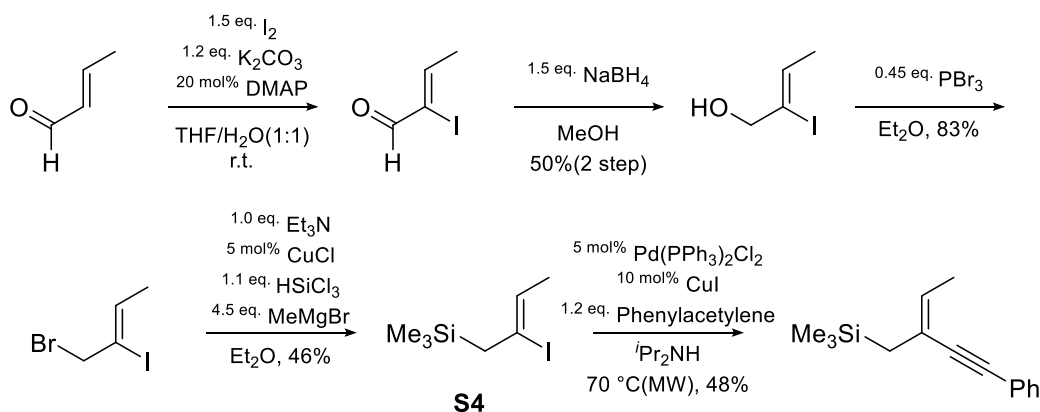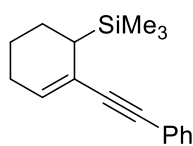
Compound **11q** was synthesized following the scheme shown above.

To the solution of crotonaldehyde (1.0 eq., 50 mmol) in THF/H₂O (1:1, 250 mL) was added K₂CO₃ (1.2 eq., 60 mmol), I₂ (1.5 eq., 75 mmol) and DMAP (20 mol%, 10 mmol). After stirred for 3 h at room temperature, the reaction was diluted with EtOAc and washed with sat. Na₂S₂O₃ aq. and 1N HCl aq.. The mixture was extracted three times with EtOAc then the combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressre to give the crude product **S3** which was used in the next step without further purification.[60]

NaBH₄ (1.5 eq., 75 mmol) was added to the solution of the crude compound **S3** in MeOH (20 mL). After **S3** was completely comsumed, the reaction mixture was quenched with 1N HCl aq. then extracted three times with EtOAc. The combined organic layers were washed with brine and dried over with Na₂SO₄. The solvent was removed under reduced pressre. The residue was purified with by column chromatography (SiO₂, eluent: hexane:EtOAc = 5:1) to afford 2-iodo-but-2-en-1-ol (50% yield).

To the solution of 2-iodo-but-2-en-1-ol (1.0 eq., 25 mmol) in Et₂O (80 mL) at 0 °C was added PBr₃ (0.45 eq., 11.3 mmol). The reaction mixture was stirred at 0 °C for 10 min then stired at room

temperature for another 10 min. The reaction was quenched with brine then extracted three times with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ aq. and brine then dried over Na_2SO_4. The solvent was removed under reduced pressre to give 1-bromo-2-iodo-2-butene (83% yield) which was pure enough to be used in the next step.

Et_3N (1.0 eq., 20.8 mmol) was added to CuCl (5 mol%, 1 mmol) in Et_2O (35 mL) in a two neck round bottom flask with reflux condenser. To the solution, the mixture of 1-bromo-2-iodo-2-butene (1.0 eq., 20.8 mmol) and trichlorosilane (1.1 eq., 22.9 mmol) in Et_2O (7 mL) was slowly added and the solution was stirred for 6 h at room temperature. After cooling to 0 °C, MeMgBr (4.5 eq., mmol, 3.0 M in Et_2O) was added over 10 min (gently reflux) and the reaction mixture was stirred overnight at room temperature. The reaction was carefully quenched with sat. NH_4Cl aq. and poured onto water and Et_2O then extracted three times with Et_2O. The combined organic layers were washed with water and brine and dried over Na_2SO_4. After the solvent was removed under reduced pressre (250 hPa at 35 °C), the product was distilled under reduced pressure (25 mmHg, 86 °C) to give **S4** (46% yield) as a colorless oil.

Phenylacetylene (1.2 eq. 2.4 mmol) was added to the solution of $Pd(PPh_3)_2Cl_2$ (5 mol%, 0.1 mmol), and CuI (10 mol%, 0.2 mmol) and **S4** (1 eq., 2 mmol) in ${}^i Pr_2NH$ (1 mL) in vial. The solution was heated at 70 °C with microwave. After stirred for 3 h, the reaction mixture was filtered then the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, eluent: hexane) to afford the starting material **11q** (48% yield) as a colorless oil.

(*E*)-Trimethyl(2-(phenylethynyl)but-2-en-1-yl)silane (11q)
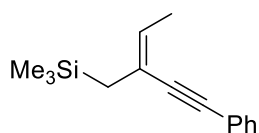
Colorless oil; b.p. 112 °C (0.45 Torr); ${}^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 9H), 1.68 (t, *J* = 1.0 Hz, 2H), 1.90 (dt, *J* = 1.0, 6.8 Hz, 3H), 5.56-5.63 (m, 1H), 7.27-7.34 (m, 3H), 7.41-7.47 (m, 2H); ${}^{13}C$ NMR (100 MHz, $CDCl_3$): δ = -1.5, 16.3, 27.3, 89.6, 93.4, 120.5, 124.0, 127.8, 128.2, 130.0, 131.2; IR (KBr): 3021, 2955, 2207, 1596, 1490, 1248, 854; Anal. Calcd for $C_{15}H_{20}Si$: C, 78.88; H, 8.83. Found: C, 78.78; H, 8.62.

6-4. フラン **12** およびピロン **13** の合成

The reaction was performed using a pressure test-tube equipped with a stirring bar in a 30 mL autoclave. To a mixture of (IPr)AgCl (8.0 mg, 0.015 mmol) and **11a** (32.2 mg, 0.15 mmol) in dry DMF (1.5 mL) in a test-tube was added CsF (34.2 mg, 0.225 mmol) and MeOH (7.3 μL, 0.18 mmol). The test-tube containing the reaction mixture was placed in the autoclave. The autoclave was purged with CO_2 and the reaction mixture was stirred at 40 °C for 24 h under CO_2 atmosphere (1.0 MPa). After CO_2 was vented, the reaction was quenched with water then the mixture was extracted with EtOAc three times. The combined organic layers was washed with brine and dried over Na_2SO_4. After the solvent was removed, the crude mixture was purified with column chromatography (SiO_2, eluent: hexane/EtOAc) to produce the corresponding lactone **12a** (21.9 mg, 78%) as a pale yellow

solid. 2-furanone and 2-pyrone could be isolated by column chromatography (SiO$_2$, eluent: hexane/EtOAc).

(Z)-5-Benzylidene-4-methylfuran-2(5H)-one (12a)
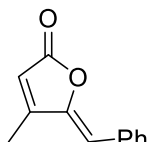
^{1}H NMR and ^{13}C NMR data were not consistent with a previously reported synthesis.[61] Based on HMBC, the compound was identified as a 5-membered ring lactone. Pale yellow solid; m.p. 88 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.26 (d, J = 1.3 Hz, 3H), 5.97-5.99 (m, 1H), 6.05 (s, 1H), 7.30-7.36 (m, 1H), 7.37-7.42 (m, 2H), 7.78-7.82 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 109.9, 115.5, 128.8, 129.0, 130.5, 132.7, 149.4, 156.0, 169.5; IR (KBr): 3062, 1744, 825; HRMS (ESI): [M+H]$^+$ calcd for C$_{12}$H$_{11}$O$_2^+$, 186.0754; found, m/z 187.0750.

4-Methyl-6-phenyl-2H-pyran-2-one (13a)
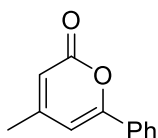
Characterization data were consistent with a previously reported synthesis.[62] Pale yellow solid; m.p. 84 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.23 (d, J = 1.1 Hz, 3H), 6.07-6.09 (m, 1H), 6.53 (d, J = 1.3 Hz, 1H), 7.42-7.47 (m, 3H), 7.79-7.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.6, 104.1, 111.6, 125.6, 128.8, 130.7, 131.3, 156.0, 159.4, 162.4; IR (KBr): 3056, 1698, 1637, 1551, 773; HRMS (ESI): [M+H]$^+$ calcd for C$_{12}$H$_{11}$O$_2^+$, 187. 0754; found, m/z 187.0752.

(Z)-5-(4-Methylbenzylidene)-4-methylfuran-2(5H)-one (12b)
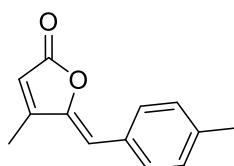
Pale yellow solid; m.p. 96 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.24 (d, J = 1.3 Hz, 3H), 2.37 (s, 3H), 5.95 (s, 1H), 6.02 (s, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 11.9, 21.4, 110.1, 115.1, 129.5, 130.0, 130.5, 139.4, 148.9, 156.0, 169.6; IR (KBr): 2922, 1770, 836; HRMS (ESI): [M]$^+$ calcd for C$_{13}$H$_{13}$O$_2^+$, 201.0911; found, m/z 201.912.

4-Methyl-6-(4-methylphenyl)-2H-pyran-2-one (13b)
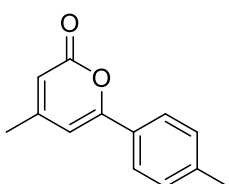
Pale yellow solid; m.p. 107 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.22 (d, J = 1.1 Hz, 3H), 6.04-6.07 (m, 1H), 6.49 (d, J = 1.1 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 21.7, 103.4, 111.2, 125.5, 128.6, 129.6, 141.2, 156.2, 159.7, 162.6; IR (KBr): 2956, 1704, 819; HRMS (ESI): [M]$^+$ calcd for C$_{13}$H$_{13}$O$_2^+$, 201.0911; found, m/z 201.0911.

(Z)-5-(3-Methylbenzylidene)-4-methylfuran-2(5H)-one (12c)
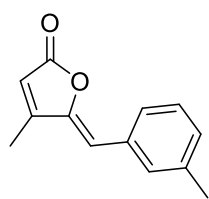
Pale yellow solid; m.p. 101 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.23-2.26 (m, 3H), 2.38 (s, 3H), 5.94-5.96 (m, 1H), 6.02 (s, 1H), 7.14 (d, J = 7.2 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.56-7.63 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 11.9, 21.4, 110.1, 115.3, 127.8, 128.6, 129.9, 131.0, 132.6, 138.4, 149.3, 156.0, 169.6; IR (KBr): 2969, 1759, 782; HRMS (ESI): [M]$^+$ calcd for C$_{13}$H$_{13}$O$_2$$^+$, 201.0911; found, m/z 201.0913.

4-Methyl-6-(3-methylphenyl)-2H-pyran-2-one (13c)

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.23 (d, J = 1.3 Hz, 3H), 2.40 (s, 3H), 6.06-6.09 (m, 1H), 6.52 (d, J = 1.3 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.33 (dd, J = 7.5, 7.7 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 21.6, 104.0, 111.5, 122.7, 126.2, 128.7, 131.2, 131.5, 138.7, 156.1, 159.6, 162.5; IR (KBr): 2921, 1717, 785; HRMS (ESI): [M]$^+$ calcd for C$_{13}$H$_{13}$O$_2$$^+$, 201.0911; found, m/z 201.0910.
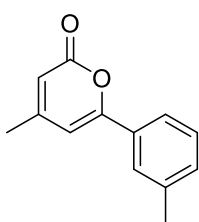
(Z)-5-(2-Methylbenzylidene)-4-methylfuran-2(5H)-one (12d)
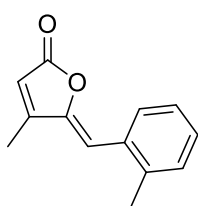
Characterization data were consistent with a previously reported synthesis.[61] Colorless solid; m.p. 109 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.28 (d, J = 1.3 Hz, 3H), 2.43 (s, 3H), 5.99 (s, 1H), 6.26 (s, 1H), 7.17-7.29 (m, 3H), 8.09.-8.13 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ =12.0, 20.1, 106.8, 115.6, 126.5, 129.0, 130.3, 130.7, 131.2, 137.2, 149.5, 156.0, 169.6; IR (KBr): 2972, 1762, 1603, 774; HRMS (ESI): [M+H]$^+$ calcd for C$_{32}$H$_{13}$O$_2$$^+$, 201.0911; found, m/z 201.0907.

4-Methyl-6-(2-methylphenyl)-2H-pyran-2-one (13d)

Colorless solid; m.p. 63 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.23 (d, J = 1.1 Hz, 3H), 2.47 (s, 3H), 6.08-6.10 (m, 1H), 6.19 (d, J = 1.3 Hz, 1H), 7.21-7.30 (m, 2H), 7.31-7.38 (m, 1H), 7.41-7.48 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 20.7, 21.6, 108.1, 111.4, 126.0, 129.0, 130.2, 131.2, 132.1, 136.7, 156.0, 161.7, 162.7; IR (KBr): 3066, 2927, 1718, 1556, 761; HRMS (ESI): [M+H]$^+$ calcd for C$_{32}$H$_{13}$O$_2$$^+$, 201.0911; found, m/z 201.0913.
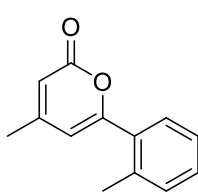
(Z)-5-(4-Methoxybezylidene)-4-methylfuran-2(5H)-one (12e)
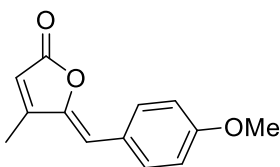
Pale yellow solid; m.p. 120 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.24 (d, J = 1.3 Hz, 3H), 3.85 (s, 3H), 5.92-5.94 (m, 1H), 6.01 (s, 1H), 6.92 (d, J = 2.5, 9.5 Hz, 2H), 7.76 (d, J = 2.5, 9.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 11.9, 55.3, 109.9, 114.3, 114.5, 125.6, 132.3, 148.0, 155.9, 160.3, 169.8; IR (KBr): 3066, 2968, 2841, 1742, 1598, 823; HRMS (ESI): [M+H]$^+$ calcd for

C$_{13}$H$_{13}$O$_3^+$, 217.0860; found, m/z 217.0862.

4-Methyl-6-(3-methoxyphenyl)-2*H*-pyran-2-one (13e)
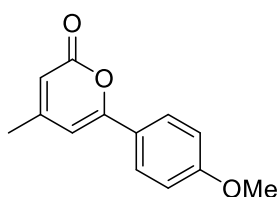
Pale yellow solid; m.p. 92 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.22 (s, 3H), 3.86 (s, 3H), 6.02 (s, 1H), 6.43 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.7, 55.4, 102.7, 110.5, 114.3, 123.8, 127.3, 156.4, 159.6, 161.6, 162.7; IR (KBr): 2998, 2924, 2846, 1729, 1262, 839; HRMS (ESI): [M+H]$^+$ calcd for C$_{13}$H$_{13}$O$_3^+$, 217.0860 ; found, m/z 217.0857.

(*Z*)-5-(4-Ethoxycarbonylbezylidene)-4-methylfuran-2(5*H*)-one (12f)
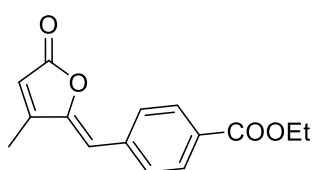
Pale yellow solid; m.p. 114 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3H), 2.27 (d, *J* = 1.3 Hz, 3H), 4.39 (t, *J* = 7.2 Hz, 3H), 6.02-6.05 (m, 1H), 6.07 (s, 1H), 7.81-7.87 (m, 2H), 8.02-8.07 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 14.3, 61.1, 108.5, 116.3, 129.8, 130.2, 136.9, 150.7, 156.0, 166.1, 169.0; IR (KBr): 3100, 2986, 1758, 1701, 1607, 821, 767; HRMS (ESI): [M+H]$^+$ calcd for C$_{15}$H$_{15}$O$_4^+$, 259.0965; found, m/z 259.0961.

(*Z*)-5-(4-Acetylbezylidene)-4-methylfuran-2(5*H*)-one (12g)
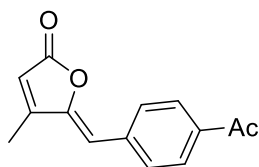
Colorless solid; m.p. 143 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.29 (d, *J* = 1.3 Hz, 3H), 2.62 (s, 3H), 6.05-6.08 (m, 1H), 6.08 (s, 1H), 7.86-7.89 (m, 2H), 7.95-7.99 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 26.7, 108.4, 116.4, 128.7, 130.5, 137.2, 150.9, 156.0, 169.0, 197.5; IR (KBr): 3089, 2927, 1778, 1672, 1277, 924; HRMS (ESI): [M+H]$^+$ calcd for C$_{14}$H$_{13}$O$_2^+$, 229.0860; found, m/z 229.0857.

(*Z*)-5-(4-Cyanobezylidene)-4-methylfuran-2(5*H*)-one (12h)
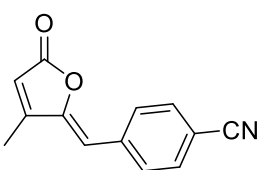
Colorless solid; m.p. 163 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.29 (d, *J* = 1.3 Hz, 3H), 6.03 (s, 1H), 6.07-6.10 (m, 1H), 7.65-7.69 (m, 2H), 7.85-7.90 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 107.4, 111.8, 116.9, 118.6, 130.1, 132.4, 137.2, 151.5, 155.8, 168.5; IR (KBr): 3095, 2222, 1774, 1608, 928, 555; HRMS (ESI): [M+H]$^+$ calcd for C$_{14}$H$_{13}$O$_3^+$, 212.0707; found, m/z 212.0703.

(*Z*)-5-(4-Trifluoromethylbezylidene)-4-methylfuran-2(5*H*)-one (12i)
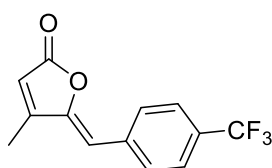
Pale brown solid; m.p. 116 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.28 (d, *J* = 1.3 Hz, 3H), 6.05 (bs, 1H), 6.06 (s, 1H), 7.63 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 107.9, 116.4, 123.9 (q, *J* = 272.5 Hz), 125.6 (q, *J* = 3.8 Hz), 130.2 (q, *J* = 32.6 Hz), 130.5, 136.1,

150.8, 156.0, 168.9; IR (KBr): 3132, 3055, 2968, 1751, 1328, 837; HRMS (ESI): $[M+H]^+$ calcd for $C_{13}H_{10}F_3O_2^+$, 255.0628; found, m/z 255.0624.

(*Z*)-4-Methyl-5-(naphthalen-1-ylmethylene)furan-2(5*H*)-one (12j)
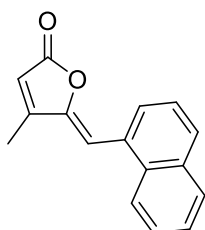
Pale yellow solid; m.p. 104 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.36 (d, *J* = 1.3 Hz, 3H), 6.03 (s, 1H), 6.82 (s, 1H), 7.49-7.59 (m, 3H), 7.82-7.89 (m, 2H), 8.10 (d, *J* = 8.3 Hz, 1H), 8.27 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.1, 105.6, 115.8, 122.8, 125.8, 125.9, 126.7, 128.4, 129.1, 129.6, 129.7, 131.5, 133.6, 150.4, 155.9, 169.6; IR (KBr):2925, 1764, 779; HRMS (ESI): $[M+H]^+$ calcd for $C_{16}H_{13}O_2^+$, 237.0911; found, m/z 237.0911.

4-Methyl-6-(naphthalen-1-yl)-2*H*-pyran-2-one (13j)
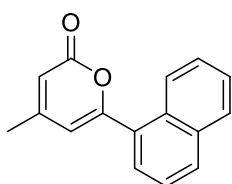
Pale yellow solid; m.p. 88 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.27 (d, *J* = 1.1 Hz, 3H), 6.16-6.19 (m, 1H), 6.39 (d, *J* = 1.3 Hz, 1H), 7.49-7.59 (m, 3H), 7.68 (dd, *J* = 7.2 Hz, 1.1 Hz, 1H), 7.88-7.92 (m, 1H), 7.95 (d, 8.3 Hz, 1H), 8.16-8.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.7, 109.3, 111.8, 124.88, 124.9, 126.4, 127.3, 127.7, 128.6, 130.2, 130.4, 131.0, 133.7, 156.0, 160.9, 162.7; IR (KBr): 3047, 1720, 1638, 779; HRMS (ESI): $[M+H]^+$ calcd for $C_{16}H_{13}O_2^+$, 237.0911; found, m/z 237.0909.

(*Z*)-4-Methyl-5-(naphthalen-2-ylmethylene)furan-2(5*H*)-one (12k)
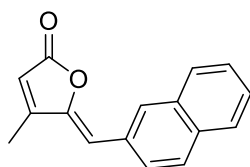
Pale yellow solid; m.p. 132 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.25 (d, *J* = 1.5 Hz, 3H), 5.97 (s, 1H), 6.17 (s, 1H), 7.45-7.54 (m, 2H), 7.77-7.90 (m, 3H), 7.93-7.98 (m, 1H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 110.0, 115.4, 126.4, 127.0, 127.3, 127.6, 128.4, 128.5, 130.4, 130.7, 133.2, 133.3, 149.6, 156.0, 169.5; IR (KBr): 3055, 1746, 1598, 936, 815; HRMS (ESI): $[M+H]^+$ calcd for $C_{16}H_{13}O_2^+$, 237.0911; found, m/z 237.0912.

## (*Z*)-4-Methyl-5-(pyridin-2-ylmethylene)furan-2(5*H*)-one (12l)
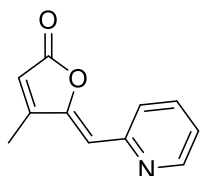
Characterization data were consistent with a previously reported synthesis.[61] Pale yellow solid; m.p. 127 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.29 (d, *J* = 1.3 Hz, 3H), 6.06 (s, 1H), 6.33 (s, 1H), 7.18-7.24 (m, 1H), 7.75 (td, *J* = 7.9, 1.7 Hz, 1H), 8.20-8.25 (m, 1H), 8.59-8.65 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 110.4, 116.5, 122.8, 125.8, 136.6, 149.6, 151.3, 152.1, 1566.5, 168.8; IR (KBr): 3064, 2990, 1765, 1750, 1466, 932; HRMS (ESI): $[M+H]^+$ calcd for $C_{11}H_{10}NO_2^+$, 188.0707; found, m/z 188.0703.

6-*n*-Butyl-4-methyl-2*H*-pyran-2-one (13m)
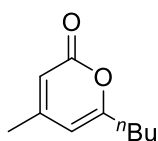
Characterization data were consistent with a previously reported synthesis.[63] Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3H), 1.31-1.42 (m, 2H), 1.58-1.69 (m, 2H), 2.12 (d, *J* = 1.0 Hz, 2H), 2.46 (t, *J* = 7.8 Hz, 3H), 5.85 (s, 1H), 5.94 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.7, 21.4, 22.1, 28.9, 33.3, 105.6, 110.5, 156.2, 163.3, 164.9; IR (KBr): 2961, 2934, 1732, 1561; HRMS (ESI): [M+H]$^+$ calcd for C$_{10}$H$_{15}$O$_2^+$, 167.1067; found, m/z 167.1067.

4-Methyl-6-phenethyl-2*H*-pyran-2-one (13n)
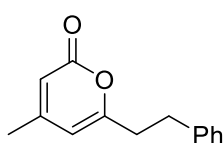
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.09 (s, 3H), 2.75 (t, *J* = 7.9 Hz, 2H), 2.97 (t, *J* = 7.9 Hz, 2H), 5.78 (s, 1H), 5.96 (s, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 7.0 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.4, 33.1, 35.5, 106.2, 110.8, 126.4, 128.3, 128.5, 140.0, 156.1, 163.1, 163.4; IR (KBr): 3063, 2931, 1725, 701; HRMS (ESI): [M+H]$^+$ calcd for C$_{14}$H$_{15}$O$_2^+$, 215.1067; found, m/z 215.1070.

(*Z*)-5-(2,2-Dimethylpropylidene)-4-methylfuran-2(5*H*)-one (12o)
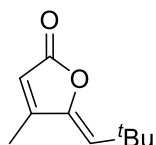
Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.25 (s, 9H), 2.11 (d, *J* = 1.3 Hz, 3H), 5.52 (s, 1H), 5.85 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.0, 30.3, 32.9, 115.1, 122.4, 148.4, 155.9, 169.7; IR (KBr): 2959, 1777; HRMS (ESI): [M+H]$^+$ calcd for C$_{10}$H$_{15}$O$_2^+$, 167.1067; found, m/z 167.1062.

6-*tert*-Butyl-4-methyl-2*H*-pyran-2-one (13o)
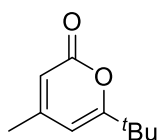
Characterization data were consistent with a previously reported synthesis.[62] Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.27 (s, 9H), 2.14 (d, *J* = 1.0 Hz, 3H), 5.89 (d, *J* = 1.5 Hz, 1H), 5.95 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.6, 27.9, 35.9, 102.3, 110.6, 156.2, 163.2, 171.6; IR (KBr): 2970, 2873, 1719, 1641, 1561; HRMS (ESI): [M+H]$^+$ calcd for C$_{10}$H$_{15}$O$_2^+$, 167.1067; found, m/z 167.1066.

(*Z*)-3-Benzylidene-4,5,6,7-tetrahydroisobenzofuran-1(3*H*)-one (12p)
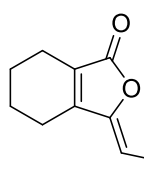
Characterization data were consistent with a previously reported synthesis.[64] Colorless solid; m.p. 112 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.73-1.85 (m, 4H), 2.30-2.40 (m, 2H), 2.44-2.54 (m, 2H), 5.85 (s, 1H), 7.25-7.32 (m, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 20.1, 21.1, 21.4, 21.6, 107.7, 126.6, 128.4, 128.7, 130.2, 133.1, 147.9, 152.5, 169.9; IR (KBr): 3066, 2940, 1760, 970, 691; HRMS (ESI): [M+H]$^+$ calcd for C$_{15}$H$_{15}$O$_2^+$, 227.1067; found, m/z 227.1067.

3-Phenyl-5,6,7,8-tetrahydro-1*H*-isochromen-1-one (13p)
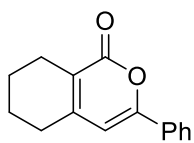
Characterization data were consistent with a previously reported synthesis.[65] Pale yellow solid; m.p. 106 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.74-1.83 (m, 4H), 2.48-2.59 (m, 4H), 6.43 (s, 1H), 7.40-7.46 (m, 3H), 7.77-7.82 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.6, 21.9, 23.3, 29.4, 104.1, 121.2, 125.2, 128.8, 130.1, 131.7, 151.2, 156.1, 163.2; IR (KBr): 3449, 2930, 2853, 1697; HRMS (ESI): [M+H]$^+$ calcd for C$_{15}$H$_{15}$O$_2^+$, 227.1067; found, m/z 227.1067.

Mixture of 12q-γ and 12q-α
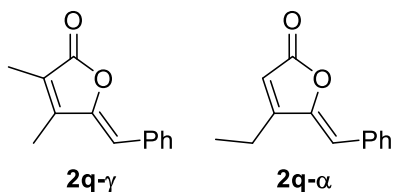
^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.31 (t, *J* = 7.3 Hz, 3H, 12q-α), 1.96 (s, 3H, 12q-γ), 2.15 (s, 3H, 12q-γ), 2.61 (q, *J* = 7.3 Hz, 2H, 2q-α), 5.97 (s, 1H, 12q-γ), 5.98 (s, 1H, 12q-α), 6.06 (s, 1H, 12q-α), 7.27-7.42 (m, 3H), 7.75-7.81 (m, 2H); [M+H]$^+$ calcd for C$_{13}$H$_{13}$O$_2^+$, 201.0911; found, m/z 201.0908.

4-Ethyl-6-phenyl-2*H*-pyran-2-one (13q-α)
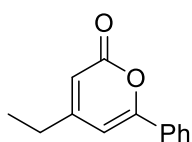
Pale yellow solid; m.p. 50 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3H), 2.53 (q, *J* = 7.5 Hz, 2H), 6.10 (s, 1H), 6.55 (s, 1H), 7.43-7.49 (m, 3H), 7.79-7.87 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.4, 28.5, 103.2, 110.1, 125.6, 128.9, 130.7, 131.4, 159.6, 161.4, 162.8; IR (KBr): 2972, 2937, 1713, 1637, 1551, 764; HRMS (ESI): [M+H]$^+$ calcd for C$_{13}$H$_{13}$O$_2^+$, 201.0911; found, m/z 201.0913.

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Silver Catalysis

C−C Bond Formation with Carbon Dioxide Promoted by a Silver Catalyst**

Satoshi Kikuchi, Kohei Sekine, Tomonobu Ishida, and Tohru Yamada*

A range of chemical reactions have been reported to produce useful chemicals from carbon dioxide, which is an ubiquitous, abundant, cheap, and nontoxic C1 feedstock.[1] Carbon dioxide is also used in industry to generate some useful materials. However, carbon dioxide is thermodynamically stable and much less reactive than other carbon derivatives owing to its high oxidation state. Therefore, strong nucleophiles and harsh reaction conditions have been required when carbon dioxide is used in organic syntheses. For example, Grignard reagents[2] and organolithium compounds[3] are well known to react with carbon dioxide to afford the corresponding carboxylic acids. Transition-metal catalyzed reactions of carbon dioxide to produce the corresponding carboxylic acid and ester derivatives have also been reported. In these systems, however, a boron- or halogen-containing reactant must be prepared in advance, or a stoichiometric amount of another metal-containing reducing agent is required.[4] Several reactions of CO_2 that are catalyzed by metal complexes under harsh reaction conditions have been reported to afford more-stable products.[5] In some reactions, the esterification of products with alkyl halides is required for stabilization or purification and this process generates waste salts. The reaction of enolates with CO_2 to provide the corresponding β-ketocarboxylic acids is a promising C−C bond-forming reaction. However, the β-ketocarboxylic acid products are thermodynamically unstable, therefore only limited types of substrates could be used, as otherwise the product readily converts back into the starting substrate by decarboxylation.[6]

Recently, we reported that a silver catalyst could effectively act as a π-Lewis acid to activate the C−C triple bond in propargylic alcohols and thus promote the reaction of carbon dioxide in the presence of a base to afford the corresponding cyclic carbonates (Scheme 1, path a)[7] or the corresponding α,β-unsaturated carbonyl compounds (Scheme 1, path b);[8] the product obtained depended on the polarity of solvent.[9]

Based on X-ray analysis and NOE experiments, it was suggested that all cyclic carbonates possessed a *Z* olefin. Theoretical analysis of the silver catalytic system with *N*-methylpyrimidine as a model base revealed that the transition state would provide the *Z-exo*-alkene product.[9] Consequently, it was confirmed that the activation of the C−C

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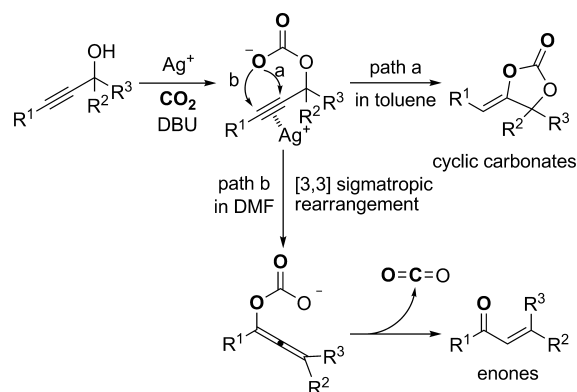
Scheme 1. Silver catalyst and DBU catalyzed the reaction of propargylic alcohol with carbon dioxide. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

triple bond by the silver catalyst, as a π-Lewis acid, was essential for these reactions. When the optically active Schiff base ligand for the silver catalyst was employed, symmetrical bispropargylic alcohols were converted into the cyclic carbonates through desymmetrization, in high yield and with high enantioselectivity.[9, 10]

In the reaction shown in Scheme 1, we believe the carbon dioxide would be captured by a hydroxy group to generate the carboxylate intermediate with formation of a new C−O bond. The resulting carboxylate could be trapped by the C−C triple bond, which had been activated by the silver catalyst, to afford the cyclic carbonate. Therefore, we postulated that when a ketone containing an alkyne group at an appropriate position is applied to the present reaction system, the derived enolate would capture carbon dioxide to generate the corresponding β-ketocarboxylate. The β-ketocarboxylate would then be trapped by the activated C−C triple bond to afford the corresponding stable lactone without the formation of any waste sideproducts (Scheme 2).[11] Herein, we report a catalytic C−C bond formation with carbon dioxide; this reaction involves C−C triple bond activation by a silver catalyst to afford the corresponding lactone under mild reaction conditions.

Several metal catalysts were initially investigated for the reaction of ketone **1a**, as the model substrate, in DMSO in the presence of DBU (2.0 equiv) under 1.0 MPa CO_2 pressure (Table 1). The reactions did not proceed in the absence of the metal salt (Table 1, entry 1). Palladium, copper, and gold(I) salts, which were expected to activate the C−C triple bond, hardly worked for this reaction (Table 1, entries 2–5). When a gold(III) salt was employed as the catalyst, the dihydrofuran
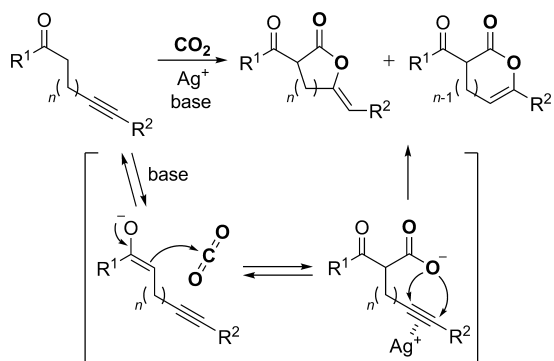
Scheme 2. The postulated reaction with carbon dioxide through C—C bond formation.

Table 1: Investigation of several metal salts.[a]
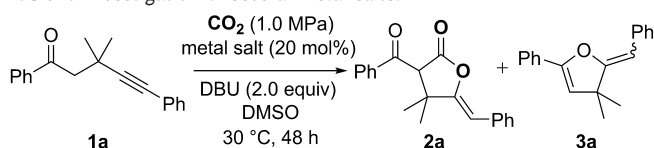
Entry	Metal Salt	Yield [%][b]	
		2a	**3a**
1	None	0	0
2	Pd(OAc)$_2$	trace	0
3	Cu(OTf)$_2$	0	0
4	AuCl	0	0
5	AuCl/AgOBz	0	0
6	AuCl$_3$	trace	13
7	AgOBz	40	5

[a] Reactions were carried out in 1.0 mL of solvent with 0.125 mmol of substrate **1a** under 1.0 MPa CO_2 pressure. [b] Yields of the isolated products. Bz = benzoyl, DMSO = dimethyl sulfoxide, Tf = trifluoromethanesulfonyl.

Table 2: Examination of various bases and solvents.[a]

Entry	Base	Solvent	Yield [%][b]	
			2a	**3a**
1	DMAP	DMSO	6	–
2	iPr$_2$NEt	DMSO	0	–
3	TBD	DMSO	7	–
4	MTBD	DMSO	48	6
5	MTBD	DMI	10	0
6	MTBD	DMA	59	4
7	MTBD	DMF	72	4
8	MTBD[c]	DMF	89	6
9[d]	MTBD[c]	DMF	91	4

[a] Reactions were carried out in 1.0 mL of solvent with 0.125 mmol of substrate **1a** in the presence of AgOBz (20 mol%) and 2.0 equivalents of base under 1.0 MPa CO_2 pressure. [b] Yields of the isolated products. [c] 4.0 equivalents of MTBD were used. [d] The reaction was performed at 25 °C. DMI = 1,3-dimethyl-2-imidazolidinone, DMA = N,N-dimethylacetamide.

derivative **3a**,[12] which would be formed by the direct intramolecular cyclization of the enol derived from ketone **1a**, was obtained in 13% yield although the desired product was not obtained at all (Table 1, entry 6). Among the catalysts tested, a silver salt was the most effective catalyst for this reaction to produce the γ-lactone **2a** (Table 1, entry 7).[13]

Taking into account the acidity of the α proton of **1a**, several bases were screened (Table 2).[13] When DMAP was used the corresponding product **2a** was obtained in 6% yield (Table 2, entry 1), but when Hünig's base was used no product was formed (Table 2, entry 2). In the previous work, amidine-type bases such as DBU were effectively employed to afford the cyclic carbonates in high yield. These observations were supported by DFT calculations on the reactions.[9] Based on these results, various amine bases, such as TBD and MTBD, were examined. When MTBD was employed as a base (Table 2, entry 4), the product **2a** was obtained in good yield (48%), whereas TBD was not an effective base for this reaction (Table 2, entry 3). In the preliminary examination of solvents, nonprotic polar solvents were found to promote the reaction smoothly.[13] Several different nonprotic polar solvents were next examined (Table 2, entries 5–7). The reaction in DMI afforded product **2a** was in low yield, whereas the reaction in DMA gave the product **2a** in moderate yield (Table 2, entries 5, 6). Among the solvents examined, DMF was found to be the most suitable as the reaction in this solvent afforded the product **2a** in the highest yield (Table 2, entry 7). 4.0 equivalents of MTBD were sufficient to promote the reaction to afford the corresponding β-ketolactone **2a** in 89% yield (Table 2, entry 8).[13] At lower reaction temperatures the formation of the by-product furan **3a** was suppressed, thus the yield of **3a** decreased although a longer reaction time was required.[13] Under the optimized conditions the product **2a** was obtained in 91% yield at 25 °C in 48 h (Table 2, entry 9).

The substrate scope of this reaction was investigated under the optimized catalytic reaction conditions (Table 3). Initially the reactions of substrates that were derived from acetophenone and had a range of alkyne substituents were examined (Table 3, entries 1, 3–8). The reactions of substrates having phenyl (**1a**), p-tolyl (**1b**), m-methoxyphenyl (**1c**), p-fluorophenyl (**1d**), and p-trifluoromethylphenyl (**1e**) groups on the alkyne proceeded under the optimized reaction conditions to achieve high yields, irrespective of the electron-withdrawing or electron-donating nature of the group on the phenyl ring. When the catalyst loading was decreased to from 20 mol% to 10 mol%, the reaction of ketone **1a** with carbon dioxide gave the lactone **2a** in good yield (Table 3, entry 2), although a longer reaction time was needed for the reaction to go to completion.[13] The reaction of substrates **1f** and **1g**, which bear an alkyl substituent on the alkyne, were also catalyzed in the presence of 6.0 equivalents of MTBD to afford the corresponding product **2f** and **2g** in good yields (Table 3, entries 7 and 8) under 2.0 MPa CO_2 pressure. Substrates derived from aromatic ketones were subjected to this catalytic system under the optimized reaction conditions (Table 3, entries 9–14). The p-tolyl ketone derivative **1h** was

Table 3: AgOBz and MTBD system was applied to the reaction of several substrates (**1a–1o**).[a]

Entry	Product			t [h]	Yield [%][b]
1		$R^1 =$	H (**2a**)	48	91
2[c]			H (**2a**)	240	85
3			*p*-Me (**2b**)	96	90
4			*m*-MeO (**2c**)	96	87
5			*p*-F (**2d**)	72	79
6			*p*-CF$_3$ (**2e**)	48	90
7[d]		$R^2 =$	Ph (**2f**)	70	77
8[d]			CH$_2$CH$_3$ (**2g**)	72	83
9		$R^3 =$	*p*-Me (**2h**)	72	84
10[e]			*p*-CF$_3$ (**2i**)	192	79
11[f]			*p*-MeO (**2j**)	144	69
12[f,g]			*m*-MeO (**2k**)	144	77
13[f,g]			*o*-MeO (**2l**)	220	76
14[d]			(**2m**)	120	77
15[h]			$n = 1$ (**2n**)	120	74
16[h,i]			$n = 2$ (**2o**)	48	36[j]

[a] The reaction was performed with AgOBz (20 mol%) and MTBD (4.0 equiv) in 1.0 mL of DMF with 0.125 mmol of substrate **1** at 25 °C under 1.0 MPa CO$_2$ pressure. [b] Yield of the isolated products. [c] The amount of silver catalyst was decreased from 20 mol% to 10 mol%. [d] The reaction was carried out with 6.0 equivalents of MTBD under 2.0 MPa CO$_2$ pressure. [e] The reaction temperature was 5 °C. [f] The reaction was performed at 10 °C under 2.0 MPa CO$_2$ pressure. [g] AgOBz (40 mol%) was used. [h] The reaction was carried out under 2.0 MPa CO$_2$ pressure. [i] AgOAc (40 mol%) was used instead of AgOBz at 60 °C. [j] 47% of ketone **1o** was recovered and the corresponding furan was obtained in 6% yield.

a good substrate for this reaction and the corresponding product **2h** was obtained in good yield (Table 3, entry 9). The substrate bearing a *p*-trifluoromethylbenzoyl group **1i** was also a good substrate, producing the corresponding product **2i** in good yield, although a longer reaction time and low reaction temperature were required (Table 3, entry 10). This catalytic system catalyzed reaction of methoxy-substituted ketone derivative **1j**, but the yield was not satisfactory. The yield of the product **2j** was improved to 69% at lower temperature (10 °C) under 2.0 MPa CO$_2$ pressure (Table 3, entry 11). The reactions of other methoxyacetophenone derivatives **1k** and **1l** proceeded in the presence of AgOBz (40 mol%) at 10 °C under 2.0 MPa CO$_2$ pressure and the corresponding products (**2k** and **2l**) were obtained in good yields (Table 3, entries 12–13). The 1-naphtyl derivative (**1m**) was transformed into the corresponding lactone derivative

(**2m**) in 77% yield when 6.0 equivalents of MTBD were used (Table 3, entry 14). The ketone having a cyclobutyl substituent (**1n**) was also converted efficiently into the corresponding product (**2n**) in good yield under the same catalytic system with 2.0 MPa CO$_2$ pressure (Table 3, entry 15). The substrate bearing a cyclopentyl group (**1o**) was also applied to this catalytic system and the product (**2o**) was obtained in 36% yield (Table 3, entry 16).

The present catalytic system was also applied to aliphatic ketone derivatives (**1p**, **1q**, and **1r**; Scheme 3) at 50 °C under 2.0 MPa CO$_2$ pressure. Substrate **1p** was converted into the corresponding γ-lactone **2p** in 58% yield. The yield of γ-
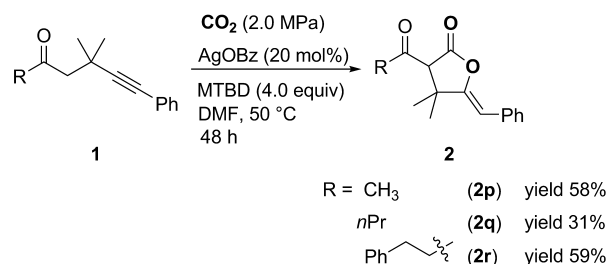
Scheme 3. The reaction of aliphatic ketone derivatives (**2p–2r**).[14] DMF = *N*,*N*-dimethylformamide.

lactone **2q** was not satisfactory (31% yield), but the reaction of ketone **1r** with carbon dioxide afforded the corresponding γ-lactone **2r** in 59% yield. These ketones possess two different protons α and α′ to the carbonyl group and thus two different enolates can be generated, but the γ-lactone was selectively obtained without the formation of any other lactone derivatives. The reaction to form the five-membered lactone is the productive pathway,[13] and the corresponding γ-lactone was selectively obtained without any need for control of the enolization.

The geometry of the C−C double bond in the lactone derivative **2h** was confirmed by X-ray analysis to reveal the *Z* isomer as the sole product (Figure 1). All other lactone derivatives were also selectively obtained as the *Z* isomers based on NOE experiments.
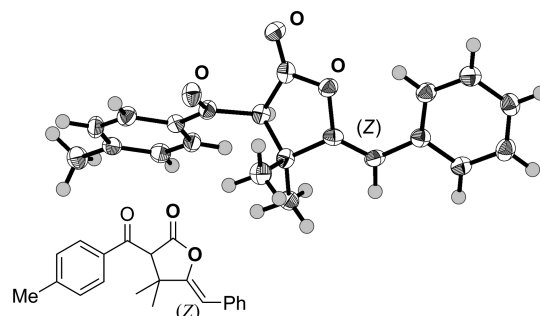
Figure 1. Single-crystal structure of **2h**.[15] Thermal ellipsoids are shown at 50% probability.

In this study, we successfully developed a catalytic C–C bond-forming reaction with carbon dioxide; this reaction employed catalytic silver benzoate in the presence of MTBD to afford lactone derivatives in good-to-high yields under mild reaction conditions. This reaction system could be applied to aliphatic ketone derivatives and the corresponding lactone was obtained without any control of the formation of enolate. The geometry of the C–C double bond of the products was confirmed to be Z based on X-ray analysis and NOE experiments. Further applications of the silver-catalyzed C–C bond-forming reaction with carbon dioxide are underway with various organic compounds.

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[11] This hypothesis was based on the theoretical study of the reaction of propargylic alcohol with carbon dioxide, see Ref. [9].

[12] It was reported that the dihydrofuran derivatives were formed in the presence of an acid catalyst at high temperature. See: Z. P. Zhan, S. P. Wang, X. B. Cai, H. J. Liu, J. L. Yu, Y. Y. Cuia, *Adv. Synth. Catal.* **2007**, *349*, 2097–2102.

[13] See the Supporting Information.

[14] The other products were furan derivatives and the recovered starting ketone **1**.

[15] CCDC 827765 (**2h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Silver-catalyzed C–C bond formation with carbon dioxide: significant synthesis of dihydroisobenzofurans†

Kohei Sekine, Ayano Takayanagi, Satoshi Kikuchi and Tohru Yamada*

The silver salt catalyzed the C–C bond forming reaction of *o*-alkynyl-acetophenone derivatives and carbon dioxide. In this reaction, a carbonyl group and a furan skeleton were successively constructed to afford the corresponding dihydroisobenzofuran derivatives.

Carbon dioxide has drawn much attention as a C1 resource due to its abundant supply from industries, low toxic properties and easy handling.[1] The Kolbe–Schmitt reaction, found in any organic chemistry textbook, has been employed for the commercial production of salicylic acid. On the other hand, the transition-metal-catalyzed carboxylation reactions of various carbon nucleophiles have been actively researched for the preparation of fine chemicals.[2] The synthesis of value-added chemicals, for example medicinal supplies, agrichemicals and functional materials, requires toxic C1 sources such as carbon monoxide and phosgene. In this paper, it was noted that instead of using these toxic reagents, safe and inexpensive carbon dioxide could be effectively employed to produce dihydroisobenzofuran derivatives which would be useful frameworks for synthesizing natural products and medicines.

Dihydroisobenzofuran(phthalan) is a class of characteristic structures used as a building block for natural product synthesis or a key mother nucleus of significant bioactive compounds (Fig. 1).[3] For example, Pestacin displays antioxidant activity and moderate antifungal properties.[3a] Escitalopram is known as an antidepressant of the selective serotonin reuptake inhibitor class.[3b] Compound **1** having a benzylidene structure shows a potential tyrosine-kinase inhibitory effect.[3c] Among the various synthetic reactions for the phthalan derivatives, the transition-metal-catalyzed cyclization reactions of *o*-alkynylbenzylalcohol[4] or *o*-alkynylbenzaldehyde[5] are particularly useful with respect to atom economy. In many cases, however, phthalan and isochromene were obtained through the 5-*exo*-dig and 6-*endo*-dig cyclizations, respectively. Though the selective synthesis of phthalan derivatives

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc47221c
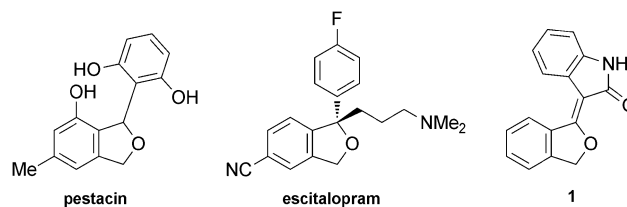
Fig. 1 Bioactive compounds bearing dihydroisobenzofuran structure.

by the transition-metal-catalyzed cyclization has been achieved,[4a,e,f,h,5g] substituents of phthalans were limited and in some cases high temperature was required.

Enolate has been a promising reagent for the C–C bond forming reactions. The reactions of carbon dioxide with an enolate to produce the corresponding β-ketocarboxylic acid have been examined.[6] Due to its thermodynamic instability, however, the product would easily return back to the starting material. Therefore, careful treatment or subsequent reduction of the product was required. A tandem reaction for the conversion of β-ketocarboxylic acid into a stable compound is one of the most reasonable methods for the reaction of an enolate and carbon dioxide.

Recently, we reported that the combination of a silver salt and base effectively promoted the incorporation of carbon dioxide into propargylic alcohols, propargylic amines and *o*-alkynylanilines.[7] In these reactions, the geometry of the *exo*-olefin in every product was confirmed as the *Z* isomer by X-ray analysis or an NOE experiment. These results and DFT calculations supported the fact that the alkyne activation by a silver catalyst should be essential.[7e] The silver-catalyzed C–C bond forming reaction of alkyne-containing ketones and carbon dioxide was also successfully developed to provide the corresponding 5-membered ring lactone derivatives.[8] Interestingly, during the reaction optimization of the alkyne-containing aliphatic ketones, not only the corresponding lactone derivatives, but also furan derivatives containing a carboxyl group were detected. Based on the structure of the furan, it was assumed that the ketone carbonyl of the β-ketocarboxylic acid was trapped on the C–C triple bond activated by the silver catalyst unlike in our previous studies.[9]
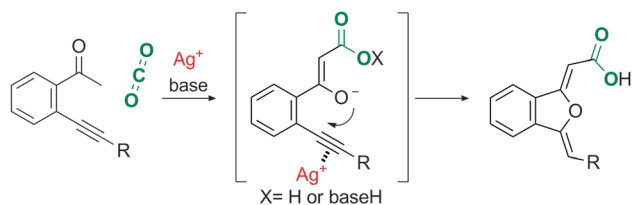
Scheme 1 Silver-catalyzed cyclization affords dihydroisobenzofuran derivatives.

This result inspired us to examine the C–C bond forming reaction with carbon dioxide to successively construct a carboxyl group and a furan skeleton. It was postulated that dihydroisobenzofuran derivatives bearing a carboxyl group could be obtained by the 5-*exo*-dig regioselective cyclization of *o*-alkynylacetophenone and carbon dioxide using the silver-catalytic system (Scheme 1). In the literature, these compounds were synthesized by the coupling–cyclization of 3-(2-iodophenyl)-3-oxopropanoic acid derivatives and terminal alkynes[10] or the functionalization of 1-alkylidene-1,3-dihydroisobenzofurans,[11] but the yields were unsatisfactory or the scope of the substrates was limited. We now report the silver-catalyzed C–C bond formation using carbon dioxide to afford dihydroisobenzofuran derivatives *via* the 5-*exo*-dig cyclization.

In an initial study, compound **2a** was employed as a model substrate and various metal salts were examined in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_3CN under a 1.0 MPa CO_2 atmosphere (Table 1). In the absence of a metal salt, a trace amount of the desired product **3a** was observed in the ^1H NMR spectrum (Table 1, entry 1). Although Au^I, Cu^I, and Pd^{II} were expected to activate the C–C triple bond to catalyze the cyclization reaction of *o*-alkynylbenzyl alcohol or *o*-alkynylbenzaldehyde, these metals did not effectively work in the present reaction (Table 1, entries 2–4). On the other hand, when a catalytic amount of a Ag^I salt was employed, the reaction smoothly proceeded to afford dihydroisobenzofuran **3a** in an excellent yield (Table 1, entry 5). When $AgNO_3$, AgBr

and AgOAc were used, in every case, the dihydroisobenzofuran **3a** was exclusively produced *via* the 5-*exo*-dig cyclization (Table 1, entries 5–7). Under a 1 atm (balloon) CO_2 atmosphere, this reaction also proceeded but a longer reaction time was required (Table 1, entry 8). In DMF and DMSO, **3a** was obtained in 94% and 91% yields, respectively (Table 1, entries 9 and 10). Other bases were also examined, but DBU was found to be the most suitable base in this reaction.[9] Unfortunately, the purification of **3a** was not successful using the standard methods, such as back extraction and silica gel column chromatography, though **3a** could be isolated by recrystallization in 66% yield (Table 1, entry 7). In order to obtain the corresponding ester of **3a**, esterification was attempted. It was found that **3a** could be esterified with methyl iodide in a one-pot synthesis to give the corresponding methyl ester **4a** in 92% yield (Table 2).

The substrate scope of the silver-catalyzed cyclization under the optimized reaction conditions was investigated (Table 2). Substituents on the phenyl ring in the R^1 group were evaluated. The reactions of substrates having 4,5-OMe (**2b**), 4-F (**2c**), or 5-Cl (**2d**) were efficiently catalyzed to give the corresponding products **4b**–**4d** in high yields. As for **2e** bearing 2-naphthylketone, the product **4e** was obtained in 69% yield. The reactions were

Table 1 Investigation of several metal salts and solvents

Entry[a]	Catalyst	Solvent	Yield[b]/%
1	None	CH_3CN	<1
2	$(PPh_3)AuCl$	CH_3CN	0
3[c]	CuBr	CH_3CN	7
4	$Pd(OAc)_2$	CH_3CN	3
5	AgBr	CH_3CN	89
6	$AgNO_3$	CH_3CN	91
7	AgOAc	CH_3CN	99 (66)[d]
8[e]	AgOAc	CH_3CN	98
9	AgOAc	DMF	94
10	AgOAc	DMSO	91

[a] The reaction was carried out with 0.15 mmol of the substrate, 30 °C, 1 h. [b] Yields were determined by ^1H NMR using trimethylphenylsilane as the internal standard. [c] 21 h. [d] Isolated yield. Purified by recrystallization. [e] Under a 1 atm (balloon) CO_2 atmosphere, 24 h.

Table 2 Silver-catalyzed cyclization of various *o*-alkynylacetophenones[a]

4a, 92% (3 h)   **4b**, 91% (6 h)   **4c**, 90% (6 h)

4d, 95% (6 h)   **4e**, 69% (24 h)   **4f**, R = Me, 87% (1 h)
4g, R = CF_3, 87% (1 h)
4h, R = COMe, 89% (6 h)
4i, R = CHO, 70% (6 h)

4j, 91% (4 h)   **4k**, R = *n*Bu, 95% (8 h), *Z*:*E* = 95:5[b]
4l, R = CH_2CH_2Ph, 97% (6 h), *Z*:*E* = 93:7[b]
4m, R = CH_2OMe, 94% (6 h), *Z*:*E* = 93:7[b]
4n, R = H, 62% (3 h), *Z*:*E* = 88:12[b]

4o, 51% (24 h)   **4p**, 55% (24 h, in DMSO)   **4q**, 47% (24 h, in DMSO)
71% (24 h, in DMF)
73% (24 h, in DMSO)

[a] Isolated yield. [b] The ratio of *Z* and *E* isomers about the C–C double bond adjacent to the carbonyl group. Determined by ^1H NMR.

suitable when the phenyl ring in the R^2 group was substituted with p-Me (**2f**), p-CF$_3$ (**2g**), p-COMe (**2h**), p-CHO (**2i**), and o-CO$_2$Me (**2j**) regardless of the electron-withdrawing or electron-donating groups. The alkyl-substituted alkynes were also good substrates, and the corresponding products **4k**, **4l**, and **4m** were obtained in 95%, 97%, and 94% yields, respectively. The reaction of the substrate **2n** bearing the terminal alkyne gave the corresponding product **4n** in 62% yield. The silver-catalyzed system was applied to α-substituted ketones. However, even if the reaction time was 24 h, substrate **2o** was not completely transformed and produced the product **4o** in only 51% yield. Aprotic polar solvents were examined expecting the effective solvation to promote the generation of the enolate. As a result, DMSO was found to be suitable as the solvent to afford the product **4o** in the highest yield. The reaction of substrates **2o–2q** in DMSO afforded the corresponding products **4o–4p** in 73%, 55% and 47% yields, respectively. For the purified products **4k–4n**, as for the geometry of the C–C double bond adjacent to the carbonyl group, Z/E isomers were observed based on the ^{1}H NMR spectrum (Table 2). Similar Z/E isomerization of 1-(alkoxycarbonyl)methylenephthalan derivatives was detected in a previous study[12] which suggested that the Z/E isomerization occurs in silica gel or under slightly acidic conditions. The products **4a–4j**, **4o–4q** were obtained as a single isomer. The geometries of the two C–C double bonds were suggested to be Z isomers based on NOE experiments.[13]

It is noted that the silver-catalyzed system effectively promoted the C–C bond forming reaction of the o-alkynylacetophenone derivatives and carbon dioxide to afford the dihydroisobenzofuran derivatives bearing a carboxyl group or a methoxycarbonyl group in high-to-excellent yields. Furan derivatives were selectively obtained via the 5-exo-dig cyclization. Further investigations are currently underway in our laboratory.

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13 As for the geometry of the C–C double bond adjacent to the carbonyl group, a trace amount of E isomer was sometimes detected by ^{1}H NMR (Z : E = >99 : 1). For the isomerization of 1-(alkoxycarbonyl)-methylenephthalan derivatives, see ESI†.

Silver-catalyzed Three-component Reaction of Propargylic Amines, Carbon Dioxide, and N-Iodosuccinimide for Stereoselective Preparation of (E)-Iodovinyloxazolidinones

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The silver-catalyzed three-component reaction of propargylic amines, carbon dioxide, and N-iodosuccinimide for the stereoselective synthesis of (E)-iodovinyloxazolidinones was developed. The silver-catalytic system could be applied to various propargylic amines to afford the corresponding iodovinyloxazolidinones in high yields. The structure of the oxazolidinone was confirmed by X-ray structure analysis to be the E-isomer for the geometry of the exo-olefin. The silver-catalyzed cyclization and replacement of silver with the iodine group in the intermediate were thought to be crucial steps.

Carbon dioxide is one of the most attractive carbon sources due to its low toxicity, ease of handling, and abundance to displace toxic reagents such as phosgene and carbon monoxide. For the incorporation of carbon dioxide in fine chemicals, much effort has been actively made;[1] three- or four-component reactions using aryne,[2] allene,[3] alkyne,[4] or others[5] have been recently developed to afford diverse building blocks such as carboxylic acid, lactone, carbonate, and carbamate derivatives. Sequential reactions in a one-pot operation would provide promising methods to form various important frameworks in the pharmaceutical and material science fields. Our group has reported that carbon dioxide incorporation into propargylic amines was effectively catalyzed by silver salts under mild conditions to selectively afford (Z)-alkenyloxazolidinones (Scheme 1, eq 1).[6] Through the reaction, a vinylsilver intermediate was expected to be stereoselectively generated as a result of the anti-addition of carbamate to the C–C triple bond activated by silver salts. This assumption was supported by DFT calculations of the silver-catalyzed carbon dioxide incorporation into propargylic alcohols.[6b] It is reasonable to assume that the silver ion in the intermediate would be stereospecifically replaced by a proton to produce (Z)-alkenyloxazolidinone and regenerate the silver catalyst. This plausible mechanism suggested that in the presence of appropriate electrophiles (E+), the C(vinyl)–Ag bond could be stereospecifically trapped by the electrophiles instead of the proton to afford the corresponding oxazolidinones containing the C(vinyl)–E bond with high geometry control (Scheme 1, eq 2). The exchange reaction of
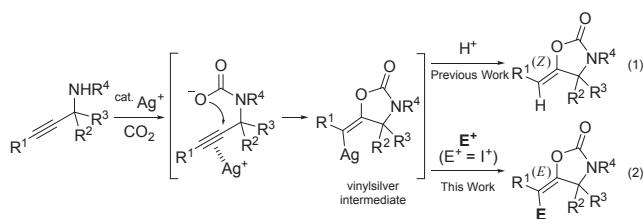
silver with electrophiles would be persuasive evidence for the vinylsilver intermediates in the present silver-catalytic systems.[6] In recent publications, the transformation of the C(vinyl)–Ag bond following the silver-catalyzed cyclization of allenylamine, o-alkynylaniline or alkynyl silyl enol ether has been developed to form the C(vinyl)–Cl bond,[7a] C(vinyl)–F bond,[7b,7c] C(vinyl)–I bond,[7d] and C(vinyl)–SnBu₃ bond.[7e]

The halovinyl component is one of the most reliable structures for metal-catalyzed coupling reactions to form new carbon frameworks. Thus, the successive introduction of carbon dioxide and a halogen group into propargylic amines was investigated to afford oxazolidinones bearing (E)-halovinyl moieties. As an example for the sequential introduction of carbon dioxide and a halogen group, the iodo-cyclization of primary propargylic amines and carbon dioxide with t-BuOI was reported,[8] but the yields of the products and variations of the substituents at the terminal position are not sufficient. According to previous studies,[6] it was expected that the silver-catalytic system could be applied to various propargylic amines bearing internal alkynes at around room temperature. In this communication, we report the silver-catalyzed three-component reaction of propargylic amine, carbon dioxide, and halonium ions to provide the corresponding oxazolidinone derivatives with an (E)-halovinyl group.

For the initial screening, the propargylic amine **1a** was employed as the starting material using 10 mol% AgOAc in DMSO under a 2.0 MPa CO_2 atmosphere (Table 1, Entries 1–3). The halonium ions were first examined using the corresponding

Table 1. Examination of halonium ion sources as electrophile

Entry	E⁺ source	Solvent	CO_2 pressure /MPa	Time /h	Yield[a] **2** /%
1	NCS	DMSO	2.0	24	0[b]
2	NBS	DMSO	2.0	24	0
3	NIS	DMSO	2.0	24	92(**2a**)
4	I₂	DMSO	2.0	24	trace
5	I-Cl	DMSO	2.0	24	0
6	I⁺ c	DMSO	2.0	24	0
7	NIS	DMSO	1.0	60	92(**2a**)
8	NIS	DMF	2.0	24	71(**2a**)
9	NIS	CH₃CN	2.0	24	57(**2a**)
10	NIS	CH₂Cl₂	2.0	24	3(**2a**)
11	NIS	Toluene	2.0	24	trace

[a]Isolated yield. [b]The corresponding oxazolidinone **3a** was obtained in 15% yield. [c]Bis(2,4,6-trimethylpyridine)iodonium hexafluorophosphate was employed.

Scheme 1. Incorporation of carbon dioxide into propargylic amines.

Table 2. Comparative experiments

Entry	Cat.	I⁺ source	Yield[a] 2a/%	4a/%	1a/%
1	AgOAc	NIS	92	trace	0
2	none	NIS	10	20	26
3	none	I₂	0	5	71

[a]Isolated yield.

Table 3. Three-component reaction for secondary propargylic amines

Entry	Product		Yield[a]/%
1	(2a)	R^1 = Ph	92
2	(2b)	R^1 = (p-CF₃-phenyl)	89
3	(2c)	R^1 = (p-Ac-phenyl)	82
4[b]	(2d)	R^1 = (p-Me-phenyl)	91
5[b]	(2e)	R^1 = (p-OMe-phenyl)	91
6	(2f)	R^1 = 2-naphthyl	96
7[b]	(2g)	R^1 = 1-naphthyl	95
8	(2h)	R^1 = 2-thienyl	90
9[b]	(2i)		86
10[b,c]	(2j)	R^2 = Me, R^3 = Me	92
11	(2k)	R^2 = CH₂CH(Me)Me, R^3 = H	92

[a]Isolated yield. *E*-Isomer was selectively obtained in every case. [b]The reaction was carried out for 48 h. [c]The reaction was carried out under 1.0 MPa CO₂.

succinimides. In the case of *N*-chlorosuccinimide and *N*-bromosuccinimide, the corresponding oxazolidinone **2** was not obtained (Table 1, Entries 1 and 2). On the other hand, when *N*-iodosuccinimide (NIS) was employed, the propargylic amine **1a** was completely consumed in 24 h to produce the oxazolidinone **2a** bearing the iodovinyl group in 92% yield (Table 1, Entry 3). According to the ¹H NMR spectroscopic analysis, the oxazolidinone **2a** was obtained as the sole isomer. The structure of the oxazolidinone **2a** was confirmed by X-ray analysis, and the geometry of the *exo*-olefin in **2a** was suggested to be the *E*-isomer (Figure S1). To our surprise, the oxazolidinone **3a** was not observed at all, which suggested that the silver ion was effectively replaced with the iodonium ion prior to the proton derived from the amino group. Several iodine sources were then examined to determine variations in the effective iodonium sources. It was revealed that iodine, iodine monochloride, or bis(2,4,6-trimethylpyridine)iodonium hexafluorophosphate were not effective (Table 1, Entries 4–6). When the carbon dioxide pressure was reduced to 1.0 MPa, the corresponding iodovinyl derivative **2a** was produced in 92% yield, though a longer reaction time was required (Table 1, Entry 7). After evaluation of the solvents (Table 1, Entries 8–11), aprotic polar solvents, such as CH₃CN, DMF, and DMSO, turned out to be suitable to produce the oxazolidinone **2a** in good yields.

For a detailed study of the reaction, some comparative experiments were carried out (Table 2). The halonium ion is typically employed as an activator for alkenes and alkynes for halocyclization, such as halolactonization.[9] Therefore, it was a concern that, without silver catalysts, NIS itself promoted the cyclization to afford the oxazolidinone **2a**. In the absence of AgOAc, the oxazolidinone **2a** was obtained in 10% yield along with a 20% yield of the imine **4a**. The imine **4a** was supposed to be produced by the oxidation of benzylamine by the iodonium ion (Table 2, Entry 2).[10] When iodine was employed instead of NIS, the reaction did not afford the oxazolidinone **2a** at all (Table 2, Entry 3). It was assumed that the iodo-cyclization pathway was not dominant in the present silver-catalyzed reaction and that the vinylsilver intermediate could be trapped by the iodonium ion to stereoselectively afford corresponding (*E*)-oxazolidinones. In addition, it was notable that the silver catalysts were necessary to promote the cyclization reaction prior to oxidation of benzylamine by the iodonium ion. Next, the oxazolidinone **3a**, which was synthesized under the previous conditions,[6] was exposed to the reaction conditions in order to confirm whether the oxazolidinone **3a** was transformed into the iodine-introduced **2a** (Scheme S1). As a result, the vinyl iodine **2a** was not detected at all and the starting oxazolidinone **3a** was recovered in 99% yield, which suggested that the iodovinyl moiety did not form through the oxazolidinone **3a**.

The scope of the substrates was investigated under the optimized reaction conditions (Table 3). First, substituents on the aromatics were evaluated using secondary propargylic amines. In the case of the substrates **1b** (*p*-CF₃) and **1c** (*p*-Ac) bearing electron-withdrawing groups, the corresponding (*E*)-oxazolidinones **2b** and **2c** were obtained in 89% and 82% yields, respectively. Propargylic amines **1d** (*p*-Me) and **1e** (*p*-OMe) were transformed into the corresponding oxazolidinones **2d** and **2e** in 91% and 91% yields, respectively. The reaction of the propargylic amines **1f** and **1g** having a 1-naphthyl or 2-naphthyl group proceeded to give the oxazolidinones **2f** and **2g** in high yields, respectively. The 2-thienyl- and alkyl-substituted alkynes substrates **1h** and **1i** were also suitable for the reaction to furnish the corresponding products **2h** and **2i** in 90% and 86% yields, respectively. The *p*-methoxybenzyl propargylic amines **1j**–**1l** were found to be good substrates. Substrates **1j** and **1k** were converted to oxazolidinones **2j** and **2k** in 92% yields,

Table 4. Evaluation of primary amine derivatives

Entry	R	Cat.	X /equiv	Conc. /M	Yield[a] /%	$E:Z$[b]
1	Ph (**1l**)	AgOAc	1.2	0.30	86	58:42
2	Ph (**1l**)	none	1.2	0.30	79[c]	22:78
3	Ph (**1l**)	AgOAc	1.0	0.15	95	83:17
4	Ph (**1l**)	AgSbF$_6$	1.0	0.15	95	88:12
5	Ph (**1l**)	AgNO$_3$	1.0	0.15	90	91:9
6	Ph (**1l**)	AgNO$_3$	1.0	0.05	94	95:5
7	4-MeC$_6$H$_4$ (**1m**)	AgNO$_3$	1.0	0.05	91	96:4
8[d]	4-CF$_3$C$_6$H$_4$ (**1n**)	AgNO$_3$	1.0	0.05	98	97:3

[a]Isolated yield. [b]Determined by ^{1}H NMR. [c]Undesired and unseparated compound was detected by ^{1}H NMR. [d]2.0 MPa CO$_2$ pressure.

respectively. In every case, the *E*-isomer was selectively obtained as the sole isomer.[11]

The optimized reaction system was also applied to primary amine derivatives. The reaction of substrate **1l** smoothly proceeded, but unfortunately, the *E* and *Z* isomers of the oxazolidinones were obtained with the *E*/*Z* ratio 58:42 (Table 4, Entry 1). Though the iodonium ion was not effective for secondary propargylic amines as shown in Table 2, according to a previous report,[8] it was considered that the iodo-cyclization of primary propargylic amines and carbon dioxide occurred as a background reaction. Actually, the reaction conditions without AgOAc gave the corresponding oxazolidinone. Interestingly, the oxazolidinone (*Z*)-**2l** was obtained as a major product (Table 4, Entry 2), which should be caused by the equilibration in the iodonium intermediate.[12] The background reaction could cause the poor stereoselectivity for the *E*-isomer in Table 4, Entry 1. It was found that a low concentration depressed the background reaction (Table 4, Entry 3). If the silver-catalyzed cyclization proceeded prior to the background iodo-cyclization, the oxazolidinone **2l** was supposed to be obtained with high *E*-selectivity. After examination of the several counter anions of silver salts to promote the cyclization step, AgNO$_3$ turned out to be suitable for the high *E*-selective synthesis of oxazolizinones (Table 4, Entries 3–5). Finally, when the concentration was reduced to 0.05 M, the oxazolidinones (*E*)-**2l** and (*Z*)-**2l** were produced in 94% yield with the ratios of 95:5 (Table 4, Entry 6). Substrates containing an electron-donating group **1m** (*p*-Me) and an electron-withdrawing group **1n** (*p*-CF$_3$) on the aromatics were transformed into corresponding the oxazolidinones **2m** and **2n** in high yields with the ratios of 96:4 and 97:3, respectively (Table 4, Entries 7 and 8).

In conclusion, the silver-catalyzed three-component reaction of propargylic amines, carbon dioxide, and NIS for the stereo-selective synthesis of (*E*)-iodovinyloxazolidinones was developed. The silver-catalytic system could be applied to various secondary propargylic amines to afford the corresponding iodovinyloxazolidinones in high yields. It should be noted that prior to the other possibility of oxidation and protodeauration, silver catalysts could control the reaction to selectively afford (*E*)-iodovinyloxazolidinones. In the case of primary amines, a low concentration was found to be suitable for the highly

E-selective synthesis. The structure of the oxazolidinone **2a** was confirmed by an X-ray structure analysis to be the *E*-isomer for the geometry of the *exo*-olefin. The silver-catalyzed cyclization and replacement of silver with the iodine group in the intermediate were supposed to be crucial steps. The transformation should provide persuasive evidence for the vinylsilver intermediates for the previously reported silver-catalytic incorporation of carbon dioxide.

Supporting Information is available electronically on J-STAGE.

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Silver-Catalyzed Cascade Carboxylation and Cyclization of Trimethyl(2-methylenebut-3-yn-1-yl)silane Derivatives

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S *Supporting Information*
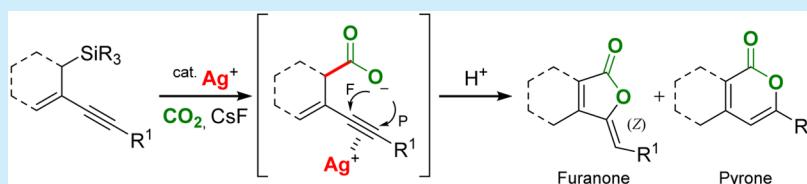
ABSTRACT: C−C bond-forming carboxylation and cyclization of trimethyl(2-methylenebut-3-yn-1-yl)silane derivatives and carbon dioxide was developed. Silver catalysts and CsF promoted the reaction to afford the corresponding 2-furanone and 2-pyrone derivatives in good-to-high yields. The structure of the 2-furanone was confirmed by single-crystal X-ray crystallography, which revealed that the geometry of the *exo*-olefin was that of a Z-isomer. When an aromatic ring-substituted alkyne was used, 2-furanone derivatives were selectively obtained via 5-*exo-dig* cyclization, whereas the reaction of alkyl-substituted alkynes produced 2-pyrone derivatives with high selectivity.

Carbon dioxide has been utilized as a carbon source for the synthesis of fine chemicals due to its abundant supply and easy handling, despite its thermodynamic stability. Methods to transform carbon dioxide into high-value chemicals have been developed,[1] and carbon dioxide has been incorporated into alkyne derivatives during the synthesis of heterocyclic compounds.[2] Propargyl alcohols[3] and propargyl amines[4] were converted to the corresponding cyclic carbonates and oxazolidinones in the presence of a transition metal, organic base, phosphine, or carbene catalyst. Though cyclic carbonates and oxazolidinones are important structures in materials and pharmaceutical sciences, their hydrolysis would readily promote decarboxylation. To incorporate carbon dioxide into organic molecules, formation of C−C bonds between the substrate and carbon dioxide is important. Cyclization following C−C bond-forming carboxylation can afford the corresponding lactones that are not easily decarboxylated. However, few examples of cyclization following carboxylation of alkyne derivatives with C−C bond formation have been reported.[5,7g]

Organosilane compounds, such as allylsilane, arylsilane, and vinylsilane, are useful reagents for new C−C bond formation. For example, Hosomi−Sakurai allylation[6] has been used to provide homoallyl alcohols, which are an important framework for the total synthesis of natural products and medicinal compounds. Studies related to the carboxylation of organosilane compounds using carbon dioxide have been reported; fluoride-mediated or Lewis acid mediated carboxylation afforded the corresponding carboxylic acids or esters.[7] However, for allylsilane compounds, only one system involving Lewis acid mediated carboxylation has been reported.[6c] Therefore, allylsilane compounds have additional potential for carbon dioxide incorporation.

Recently, carbon dioxide incorporation into propargyl alcohols,[8a,b,e] propargylamines,[8c−e] and *o*-alkynylanilines[8f,g] using silver catalysts and base was reported. In these reactions, silver catalysts, acting as a π-Lewis acid, activate C−C triple bonds to promote cyclization of the intermediates, such as carbonates and carbamates. Activation of C−C triple bonds by silver salts was a crucial step; otherwise, the intermediates would readily revert back to starting materials. The silver catalytic system was applied to ketone-containing alkynes to give the corresponding lactones[9a] or furans having a carboxyl group[9b] in good-to-high yields via C−C bond formation between the substrates and carbon dioxide. Next, organosilane compounds were utilized as a nucleophile for carbon dioxide, which led to C−C bond-forming carboxylation and cyclization.

On the basis of previous studies, 5-membered ring lactones and 6-membered ring lactones were expected from the reaction of carbon dioxide and an allylsilane containing a C−C triple bond (Scheme 1). The present report describes a silver-catalyzed cyclization following carboxylation of trimethyl(2-methylenebut-3-yn-1-yl)silane derivatives with carbon dioxide.

Scheme 1. Cyclization Following Carboxylation of Allylsilanes Containing Alkynes
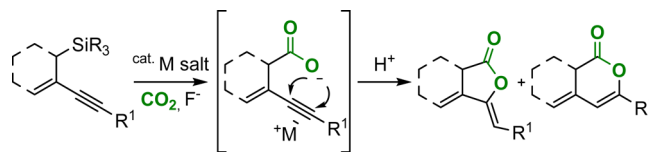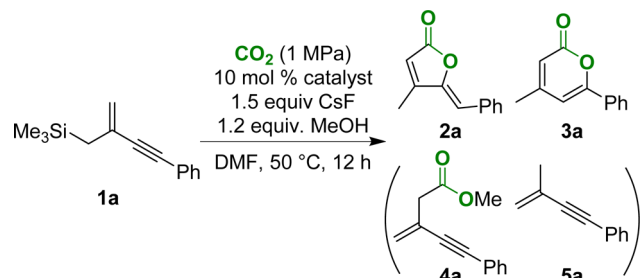
Enyne compound **1a** containing an allylsilane moiety was employed as a model substrate in the presence of CsF and MeOH in DMF under 1 MPa CO_2 atmosphere. Methanol was added as a proton source for complete turnover of the catalytic cycle. Initially, various metal salts were examined (Table 1).

Table 1. Examination of Metal Salts

entry[a]	catalyst	yield **2 + 3**[b] (%)	**2:3**[c]
1	none	trace[d]	
2	CuI	trace[e]	
3	$(PPh_3)AuCl$	17	95:5
4	$Pd(OAc)_2$	49	89:11
5	AgF	70	77:23
6	AgOTf	79	88:12
7[f]	AgOTf	28	87:13
8[g]	AgOTf	73	83:19
9	AgOAc	73	89:11
10	$AgBF_4$	73	91:9
11	(IMes)AgCl	80	93:7
12	(IPr)AgCl	80	94:6
13[h]	**(IPr)AgCl**	**78**	> 95:5

[a]The reaction was carried out with 0.15 mmol of substrate in 1.5 mL of solvent. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]**4a** was obtained in 54% yield after methylation. [e]**4a** was produced in 63% yield after methylation. [f]KF was used intsead of CsF. [g]TBAT (tetrabutylammonium difluorotriphenylsilicate) was used intsead of CsF. [h]40 °C for 24 h.

Without any catalysts or with CuI, a trace amount of 2-furanone **2a** was detected, although methyl ester **4a** was obtained after methylation by trimethylsilyldiazomethane (Table 1, entries 1 and 2). The results indicated that carboxylation of **1a** proceeded; in contrast, cyclization was minimal. The metal salts $(PPh_3)AuCl$ and $Pd(OAc)_2$ promoted the reaction to give 2-furanone **2a** and 2-pyrone **3a** in 17% and 49% yields, respectively (Table 1, entries 3 and 4). In the presence of AgF, the reaction proceeded smoothly to afford a 70% yield of a mixture of 77:23 furanone **2a**/pyrone **3a** (Table 1, entry 5). In this case, (3-methylbut-3-en-1-yn-1-yl)benzene **5a** was obtained in 8% yield, which was produced by protonation of a carbanion equivalent generated from substrate and CsF. For fluoride sources, CsF was the most suitable for this reaction (Table 1, entries 6−8).[10] Various silver salts were screened to improve the selectivity for **2a** (Table 1, entries 5, 6, and 9−12). The results indicated that an N-heterocyclic carbene ligand slightly improved selectivity for the furanone **2a**; (IMes)AgCl and (IPr)AgCl produced **2a** and **3a** in ratios of 93:7 and 94:6, respectively (Table 1, entries 11 and 12). Examination of the reaction temperature[10] revealed that the ratio of furanone **2a** to pyrone **3a** was >95:5 if the reaction was conducted at 40 °C, which afforded a mixture of **2a** and **3a** in 78% yield (Table 1, entry 13).

Various alkynylaromatics were next explored under the optimized conditions (Table 2, entries 1−12). Electron-

Table 2. Substrate Scope Using the Silver Catalytic System
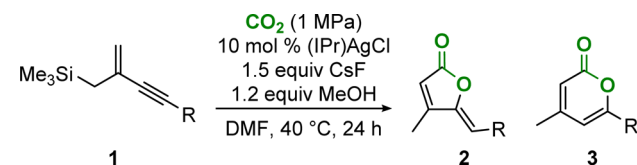
| entry[a]	substrate			yield[b] **2** / %	**3** / %	(**2:3**)[c]
1	R =	R^1 = H(**1a**)		78	trace	
2		*p*-Me(**1b**)		76	5	(94:6)
3		*m*-Me(**1c**)		78	4	(95:5)
4[d,e]		*o*-Me(**1d**)		43	29	(60:40)
5		*p*-OMe(**1e**)		66	9	(88:12)
6[d]		*p*-COOEt(**1f**)		74	ND[f]	
7		*p*-Ac(**1g**)		72	ND[f]	
8		*p*-CN(**1h**)		92	ND[f]	
9		*p*-CF_3(**1i**)		78	ND[f]	
10	R =	1-naph	(**1j**)	18	15	(56:44)
11		2-naph	(**1k**)	80	trace	
12			(**1l**)	73	ND[f]	
13[d]		*n*Bu	(**1m**)	ND[f]	77	
14[d,g]		CH_2CH_2Ph	(**1n**)	ND[f]	65	
15[d]		*t*Bu	(**1o**)	14	43	(25:75)

[a]The reaction was carried out with 0.15 mmol of substrate in 1.5 mL of DMF. [b]Isolated yield. [c]The ratio was calculated based on isolated yields. [d]50 °C. [e]20 mol % (IPr)AgCl was employed. 48 h. [f]Not detected. [g]Using AgOTf instead of (IPr)AgCl.

donating groups induced production of the pyrone **3**. For substrates **1b** (*p*-Me), **1c** (*m*-Me), and **1e** (*p*-OMe), the corresponding furanones **2b**, **2c**, and **2e**, and pyrones **3b**, **3c**, and **3e** were obtained with ratios of 94:6, 95:5, and 88:12, respectively (Table 2, entries 2, 3, and 5). The reaction of substrate **1d** (*o*-Me) required higher temperatures, compared to the optimized conditions, to afford the corresponding furanone **2d** and pyrone **3d** in 43% and 29% yields, respectively. A methyl group at the *ortho*-position should hinder the approach of silver catalysts, therefore requiring a greater amount of catalyst, higher temperatures, and a longer reaction time (Table 2, entry 4). In contrast, substrates containing electron-withdrawing groups such as *p*-COOEt (**1f**), *p*-Ac (**1g**), *p*-CN (**1h**), and *p*-CF_3 (**1i**) gave the corresponding furanones **2f−i** selectively in high yields, while pyrone derivatives **3f−i** were not observed (Table 2, entries 6−9). 1-Naphthyl and 2-naphthyl isomers affected yield and selectivity; substrate **1j** (1-naphthyl) could be converted to furanone **2j** and pyrone **3j** in 18% and 15% yields, respectively (Table 2, entry 10). In contrast, 2-naphthyl-substituted furanone **2k** (2-naphthyl) was produced selectively in 80% yield (Table 2, entry 11). The regioselectivity for substrates **1b** (*p*-Me), **1c** (*m*-Me), **1d** (*o*-Me), **1j** (1-naphthyl), and **1k** (2-naphthyl) was assumed to be due to steric effects from the substituent at the *ortho*-position; silver catalysts were hindered from occupying the appropriate position for 5-*exo* cyclization to promote 6-*endo* cyclization. For 2-pyridyl-substituted substrate **1l**, the reaction afforded only the

furanone **2l** in 73% yield. The reaction of the alkyl-substituted alkynes substrates **1m** and **1n** also proceeded (Table 2, entries 13−15). Interestingly, the corresponding pyrones **3m** and **3n** were obtained exclusively in 77% and 65% yields, respectively (Table 2, entries 13 and 14). For *tert*-butyl (**1o**), pyrone **3o** was produced in a greater yield than that of the furanone **2o** (Table 2, entry 15). Selectivity for pyrone **3** when using alkyl-substituted substrates **1m**, **1n**, and **1o** was due to the electron-donating properties of the alkyl groups. A similar tendency was noticed upon introduction of electron-donating groups into alkynylaromatics (Table 2, entries 2−5).

Alkyl-substituted allylsilane **1p** also was investigated (Scheme 2). The reaction required a higher temperature to provide an

Scheme 2. Reactions of Alkyl-Substituted Allylsilanes
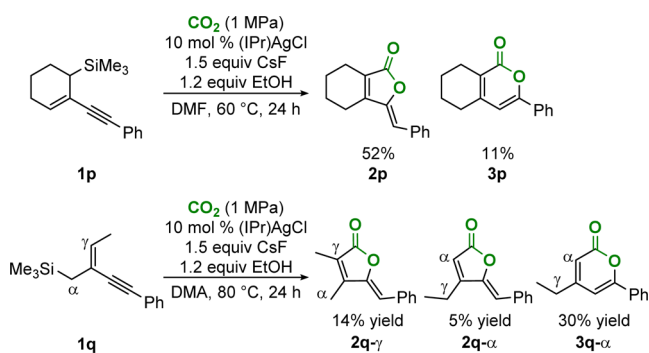
adequate yield of furanone **2p** and pyrone **3p**. Only trace amounts of furanone **2p** and pyrone **3p** were observed at 40 °C. However, raising the temperature to 60 °C increased the yields of furanone **2p** and pyrone **3p** to 52% and 11%, respectively.

Next, we investigated the nucleophilic addition to carbon dioxide of substrate **1q**, which contains a trisubstituted alkene moiety (Scheme 2). Previous studies on fluoride-activated allylation[6c] indicated that a carbanion (ion pair or equivalent) was generated via Si−F bond formation. This was supported by the result that nucleophilic addition of multisubstituted allylsilanes occurred preferably from the less substituted carbon atom, which gave homoallylalcohols with loss of regioselectivity. In this case, **1q** was transformed to three isomers, **2q**-γ produced by attack from the γ-carbon, and **2q**-α and **3q**-α were produced by the addition from the α-carbon. These observations suggest that nucleophilic addition of a carbanion (ion pair or equivalent) to carbon dioxide occurred to produce the carboxylate. The structure of **2d** was confirmed by single-crystal X-ray crystallography (Figure 1). The geometry of the
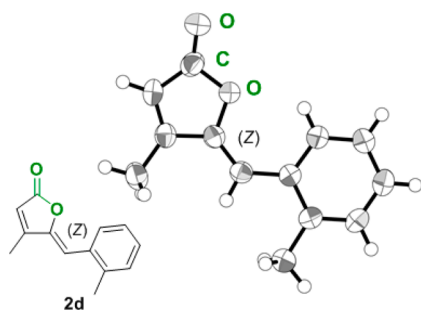
exo-olefin of **2d** was that of a Z isomer. The structure based on heteronuclear multiple bond correlation (HMBC) (see the Supporting Information for details) also agreed with that suggested by the X-ray analysis.

In conclusion, a C−C bond-forming cyclization following carboxylation of trimethyl(2-methylenebut-3-yn-1-yl)silane derivatives and carbon dioxide was promoted by silver catalysts and CsF. It afforded the corresponding 2-furanone and 2-pyrone derivatives in good-to-high yields. The structure of the 2-furanone was confirmed by single-crystal X-ray crystallography and HMBC, which revealed that the geometry of the *exo*-olefin was that of a Z-isomer. Results also showed that, when using an aromatic ring-substituted alkyne, 2-furanone derivatives were selectively obtained via 5-*exo-dig* cyclization, whereas the reaction of alkyl-substituted alkynes produced 2-pyrone derivatives with high selectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03023.

> Experimental procedures and analytical data for new compounds (PDF)
> X-ray crystallographic data for **2d** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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Figure 1

Figure 1. X-ray structure analysis of **2d**. Thermal ellipsoids are shown at 50% probability.[11]

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(10) See the Supporting Information for details.

(11) CCDC 1424535 (**2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data_request/cif.